Supplementary Information
for
"Investigations of β-Siloxy Epoxide Ring Expansions Forming 1-Azaspirocylic Ketones "

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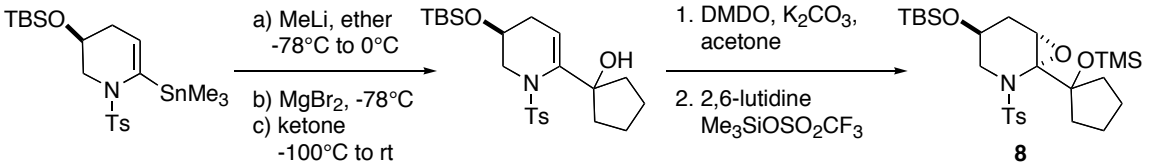
Experimental

General

All reactions were performed under an atmosphere of dry nitrogen. Glassware was flame-dried prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Dichloromethane and toluene were distilled from calcium hydride prior to use. Common reagents or materials were purchased from commercial sources and purified by standard distillation or recrystallization prior to use. Dimethyldioxirane (DMDO) was prepared according to literature procedures: (a) Murray, R. W. *Chem. Rev*. **1989**, *89*, 1187. (b) Adam, W.; Hadjiarapoglou, L. *Topics in Current Chemistry* **1993**, *164*, 45. (c) Murray, R. W.; Singh, M. *Org. Syn. Coll. Vol. IX*, **1998**, 288. Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV_{254} pre-coated TLC plates. The stationary phase for HPLC consisted of an Agilent Eclipse XDB-C8 reverse phase column of dimensions 4.6 mm x 150mm. Melting points are uncorrected. Optical rotations of samples were measured using either at 589 nm (sodium 'D' line). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterochloroform. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform unless otherwise indicated. Chemical shifts are reported in parts per million (ppm) and are referenced to the centerline of deuterochloroform (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}) and tin-carbon coupling (J_{Sn-C}) are reported as an average of the ^{117}Sn and ^{119}Sn values.

Part A: Expansions of Cyclopentanol Trimethylsilyl Ethers
1. Construction of and Ring Expansion of 8



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

To a solution of (+)-(3*S*)-3-(*tert*-butyldimethylsilyloxy)-1-(toluene-4-sulfonyl)-6-trimethylstannyl-1,2,3,4-tetrahydropyridine (2.93 g, 5.52 mmol) in diethyl ether (100 mL) at –78 °C was added MeLi (7.60 mL, 12.2 mmol) 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) in diethyl ether (100 mL) was added. The mixture was stirred for 0.5 h and then was cooled to –100 °C and a solution of cyclopentanone (1.30 mL, 14.7 mmol) 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 silica gel yielded 2.22 g (89%) of a white solid.

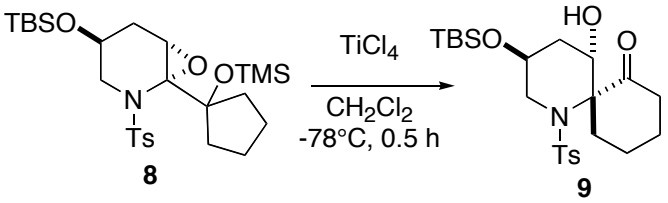
mp: 87-88 °C (methanol-hexanes). $[\alpha]_D^{23}$ = +218 ± 1 (c 0.16, $CHCl_3$). IR (KBr): 3520, 2951, 1339, 1159 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J*=8.2 Hz, 2H), 7.28 (d, *J*=8.5 Hz, 2H), 5.74 (t, *J*=4.1 Hz, 1H), 4.38 (s, 1H), 3.85 (dd, *J*=13.7, 5.2 Hz, 1H), 3.34-3.25 (m, 1H), 2.77 (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, $CDCl_3$): δ 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*-Butyldimethylsilyloxy)-2-(toluene-4-sulfonyl)-1-(1-trimethylsilyloxycyclopentyl)-7-oxa-2-azabicyclo[4.1.0]heptane (8)

To (+)-(5*S*)-1-[5-(*tert*-butyldimethylsilyloxy)-1-(toluene-4-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclopentanol **(10)** (1.08 g, 2.39 mmol) and potassium carbonate (3.40 g, 24.6 mmol) 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 trimethylsilyl triflate (720 μL, 3.97 mmol, 1.7 equiv.) and 2,6-lutidine (720 μL, 6.22 mmol, 2.6 equiv.) in THF (60 mL) was added. 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 silica gel afforded 1.07 g (83%) of a white solid.

mp = 94-95 °C (methanol-hexanes). $[\alpha]_D^{26}$ = -12.3 ± 0.5 (c 0.23, $CHCl_3$). IR (KBr): 2954, 2859, 1353, 1250, 1164, 839 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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.



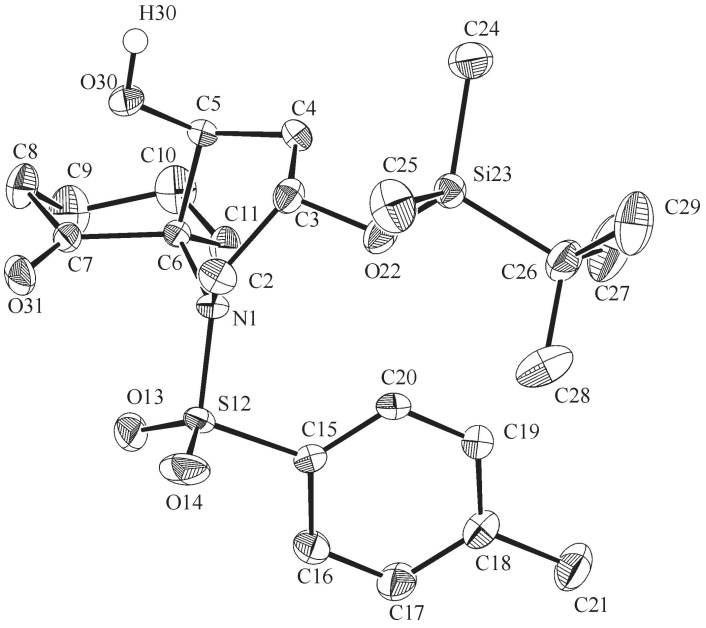
(-)-(3*S*, 5*S*, 6*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undecan-7-one (9)

To a solution of epoxide **8** (89 mg, 0.17 mmol) in dichloromethane (8.0 mL) was added 180 μL 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.

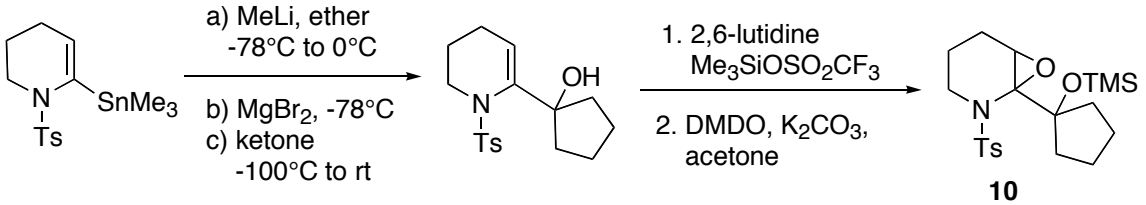
mp = 137-138 °C (methanol). $[\alpha]_D^{26}$ = -8.6 ± 0.5 (c 0.25, $CHCl_3$). IR (KBr): 3505, 2941, 2858, 1718, 1329, 1149 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J*=8.4 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 4.13-4.00 (m, 2H), 3.58 (s, 1H), 3.32 (dd, *J*=12.0, 8.0 Hz, 1H), 3.06-2.86 (m, 2H), 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, $CDCl_3$): □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.

Figure A. ORTEP representation of the crystal structure of **9**



2. Construction of and Expansion of 10



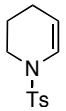
10

1-[1'-(Toluene-4''-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclopentanol
A solution (1.25 mL) of methyllithium in ether (1.88 mmol, 2.2 equiv.,1.5 M) was added to a cold (-78 ˚C) solution of 1-(toluene-4'-sulfonyl)-6-trimethylstannyl-1,2,3,4-tetrahydropyridine (335 mg, 0.837 mmol, 1.0 equiv) in diethyl ether (13.5 mL). The solution was warmed to 0˚C, stirred for 10 min, and recooled to -78 ˚C. A solution of magnesium bromide diethyl etherate (570 mg, 2.21 mmol, 2.6 equiv) in diethyl ether (11.5 mL) was added, and the mixture was stirred at -78 ˚C for 0.5 h. The mixture was cooled to -100 ˚C, and a cold (-100 ˚C) solution of cyclobutanone (200 □L, 2.26 mmol, 2.7 equiv) in diethyl ether (9.5 mL) was added. The mixture was stirred at -100 ˚C for 2 h, then warmed to rt as it was stirred overnight. The solvent was removed by concentration *in vacuo*. Purification by column chromatography (1/5 ethyl acetate-hexanes) on silica gel

gave 6.1 mg (3%) of 1-(toluene-4'-sulfonyl)-1,2,3,4-tetrahydropyridine as a colorless oil and 228 mg (84%) of 1-[1'-(toluene-4''-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclopentanol as a white solid.

mp = 109-110 °C (ethyl acetates-hexanes). IR (KBr): 3514, 2956, 1646, 1598, 1333, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □7.77 (d, *J*=8.2 Hz, 2H), 7.26 (d, *J*=8.2 Hz, 2H), 5.81 (t, *J*=4.0 Hz, 1H), 4.47 (s, 1H), 3.43 (t, *J*=6.1 Hz, 2H), 2.40 (s, 3H), 2.24-2.13 (m, 2H), 1.96-1.84 (m, 2H), 1.83-1.71 (m, 4H), 1.70-1.62 (m, 2H), 1.26-1.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): □144.0, 143.8, 136.7, 129.7, 127.7, 122.0, 83.2, 47.7, 39.7, 23.0, 21.6, 21.4, 19.2. HRMS (EI+): Calcd for $C_{17}H_{23}NO_3S$ (M^+): 321.1399. Found 321.1390.

1-(Toluene-4'-sulfonyl)-1,2,3,4-tetrahydropyridine[1]



IR (KBr): 2931, 2851, 1649, 1339, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □7.64 (d, *J*=8.2 Hz, 2H), 7.28 (d, *J*=7.6, 2H), 6.61 (dt, *J*=8.4, 1.9 Hz, 1H), 4.97-4.91 (m, 1H), 3.34 (t, *J*=5.5 Hz, 2H), 2.40 (s, 3H), 1.92-1.85 (m, 2H), 1.67-1.59 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): □143.5, 135.1, 129.7, 127.1, 125.1, 108.2, 43.8, 21.5, 20.9, 20.9.

1-(Toluene-4'-sulfonyl)-6-(1''-trimethylsilyloxycyclopentyl)-1,2,3,4-tetrahydropyridine

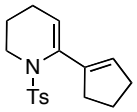
To a solution of freshly distilled 2,6-lutidine (25.0 □L, 0.216 mmol, 4.0 equiv) in 1 mL of THF was added 25.0 □L of freshly distilled trimethylsilyl trifluoromethanesulfonate (0.138 mmol, 2.6 equiv). The mixture was allowed to stir for 10 min and then added to a solution of 17.2 mg of 1-[1'-(toluene-4''-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclopentanol (0.0535 mmol, 1.0 equiv) in 1 mL of THF. The mixture was stirred at rt for 0.5 h and then poured into a saturated solution of aqueous sodium bicarbonate, and extracted with diethyl ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by column chromatography (1/11 to 1/20 ethyl acetate-hexanes; 1% triethylamine) on silica gel afforded 14.3 mg (68%) of 1-(toluene-4'-sulfonyl)-6-(1''-trimethylsilyloxycyclopentyl)-1,2,3,4-tetrahydropyridine as a white solid and 5.4 mg (33%) of 6-cyclopent-1'-enyl-1-(toluene-4''-sulfonyl)-1,2,3,4-tetrahydropyridine as a colorless oil.

mp = 71-72 °C (ethyl acetate-hexanes). IR (KBr): 2955, 1599, 1346, 1163 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □ 7.74 (d, *J*=8.2 Hz, 2H), 7.25 (d, *J*=8.2 Hz, 2H), 6.05 (t, *J*=4.6 Hz, 1H), 3.39 (t, *J*=6.7 Hz, 2H), 2.40 (s, 3H), 2.25-2.11 (m, 2H),

[1] Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes F. P. J. T. *Org. Lett.* **2001**, *3*, 2045.

1.83-1.69 (m, 4H), 1.68-1.56 (m, 2H), 1.48 (quin, *J*=6.7 HZ, 2H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 145.1, 143.1, 138.0, 129.2, 127.4, 124.1, 87.2, 47.8, 39.9, 22.9, 21.3, 20.6, 1.9. HRMS (DCI+, ammonia/isobutane): Calcd for $C_{20}H_{31}NO_3SSi$ (M^+): 393.1794. Found 393.1804. Anal. Calcd for $C_{20}H_{31}NO_3SSi$: C, 61.03; H, 7.94; N, 3.56. Found: C, 60.84; H, 7.80; N, 3.65.

6-Cyclopent-1'-enyl-1-(toluene-4''-sulfonyl)-1,2,3,4-tetrahydropyridine

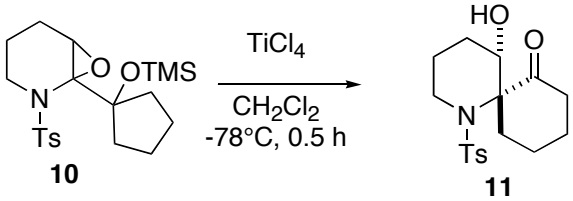


^{1}H NMR (300 MHz, $CDCl_3$): 7.64 (d, *J*=8.5 Hz, 2H), 7.25 (d, *J*=8.1 Hz, 2H), 5.73 (br s, 1H), 5.39 (t, *J*=4.0 Hz, 1H), 3.55 (t, *J*=5.8 Hz, 2H), 2.56-2.45 (m, 2H), 2.41-2.31 (m, 2H), 2.40 (s, 3H), 1.96-1.83 (m, 4H), 1.37-1.26 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 143.2, 142.6, 137.2, 137.0, 129.4, 127.9, 117.4, 46.6, 33.9, 32.7, 23.6, 22.2, 21.5, 20.1.

(1*S, 6*R**)-2-(Toluene-4'-sulfonyl)-1-(1''-trimethylsilyloxycyclopentyl)-7-oxa-2-azabicyclo[4.1.0]heptane (10)**

To 1-(toluene-4'-sulfonyl)-6-(1''-trimethylsilyloxycyclopentyl)-1,2,3,4-tetrahydropyridine (54.4 mg, 0.138 mmol, 1.0 equiv) and potassium carbonate (192 mg, 1.39 mmol, 10 equiv) was added a 0.07 M acetone solution of dimethyldioxirane (10 mL, 0.70 mmol, 5.1 equiv) and the mixture was stirred at rt for 5 h. The reaction mixture was then poured into a saturated solution of sodium 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 concentrated *in vacuo*. Purification by column chromatography (1/6 diethyl ether-petroleum ether; 1% triethylamine) on silica gel afforded 55.6 mg (98%) of **10** as a white solid.

mp = 74-75 °C (hexanes). IR (KBr): 2953, 1351, 1162 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.88 (d, *J*=8.2 Hz, 2H), 7.25 (d, *J*=9.8 Hz, 2H), 3.43 (dt, *J*=14.6, 3.1 Hz, 1H), 3.22 (d, *J*=2.4 Hz, 1H), 2.79 (td, *J*=12.5, 2.4 Hz, 1H), 2.40 (s, 3H), 2.19-2.06 (m, 1H), 1.97-1.48 (m, 9H), 1.14-1.02 (m, 1H), 0.93-0.77 (m, 1H), 0.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 143.5 (Q), 137.4 (Q), 129.3 (CH), 128.7 (CH), 86.2 (Q), 72.3 (Q), 53.5 (CH), 45.1 (CH_2), 40.0 (CH_2), 35.9 (CH_2), 23.5 (CH_2), 21.7 (CH_2), 21.6 (CH_2), 21.5 (CH_3), 17.8 (CH_2), 2.0 (CH_3). HRMS (DCI+, ammonia/methane): Calcd for $C_{20}H_{32}NO_4SSi$ (M^+ + 1): 410.1821. Found 410.1826.



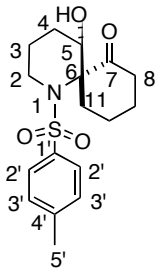
10 **11**

(5*S, 6*R**)-5-Hydroxy-1-(toluene-4'-sulfonyl)-1-azaspiro[5.5]undecan-7-one (11)**

To a solution of 22.1 mg of (1*S**, 6*R**)-2-(toluene-4'-sulfonyl)-1-(1''-trimethylsilyloxycyclopentyl)-7-oxa-2-azabicyclo[4.1.0]heptane (epoxide **10**) (0.0540 mmol, 1.0 equiv) in 2.5 mL of dichloromethane was added a 1.0 M dichloromethane solution of titanium tetrachloride (60 μL, 0.060 mmol, 1.1 equiv) 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 (2/1 ethyl acetate-hexanes) on silica gel yielded 75 mg (96%) of a viscous oil.

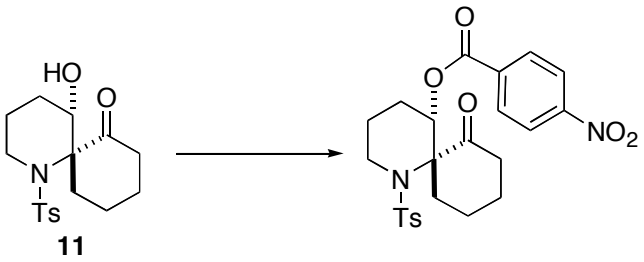
IR (KBr): 3516, 2936, 1707, 1325, 1153 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=8.8 Hz, 2H), 3.93 (dd, *J*=6.2, 3.0 Hz, 1H), 3.38 (d, *J*=3.0, 1H), 3.27-3.13 (m, 2H), 2.98-2.89 (m, 1H), 2.55-2.41 (m, 2H), 2.39 (s, 3H), 2.39 (s, 3H), 2.09-1.71 (m, 7H), 1.65-1.53 (m, 1H), 1.34 (dt, *J*=13.4, 3.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.3, 143.4, 137.5, 129.4, 127.8, 69.5, 66.9, 42.3, 40.4, 33.2, 25.2, 25.1, 21.5, 20.8, 17.8. HRMS (EI+): Calcd for $C_{17}H_{23}NO_4S$ (M^+): 337.1348. Found 337.1355.

Table A: Selected NMR Data for (5*S, 6*R**)-5-Hydroxy-1-(toluene-4'-sulfonyl)-1-azaspiro[5.5]undecan-7-one (11)**



Carbon No.	^{13}C δ (ppm)[a]	APT[a]	^{1}H δ (ppm) (mult J (Hz))[b,c,d]	HMBC Correlations[e]
2	42.3	CH_2	H-2: 3.27-3.13 (m)	
5	66.9	CH	H-5: 3.93 (dd, 6.2, 3.0)	OH
6	69.5	Q		H-2, H-5, H-8a, H-8b, OH
7	210.3	Q		H-8a, H-8b
8	40.2	CH	H-8a: 2.98-2.89 (m) H-8b: part of m at 2.55-2.41	
1'	137.5	Q		H-3'
2'	127.8	CH	H-2': 7.84 (d, 8.4)	
3'	129.4	CH	H-3': 7.27 (d, 8.8)	H-5'
4'	143.4	Q		H-2', H-5'
5'	21.5	CH_3	H-5': 2.39 (s)	H-3'

[a] Recorded at 75 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC data.
[d] Methylene protons are arbitrarily designated H-Xa and H-Xb.
[e] Only those correlations which could be unambiguously assigned are recorded

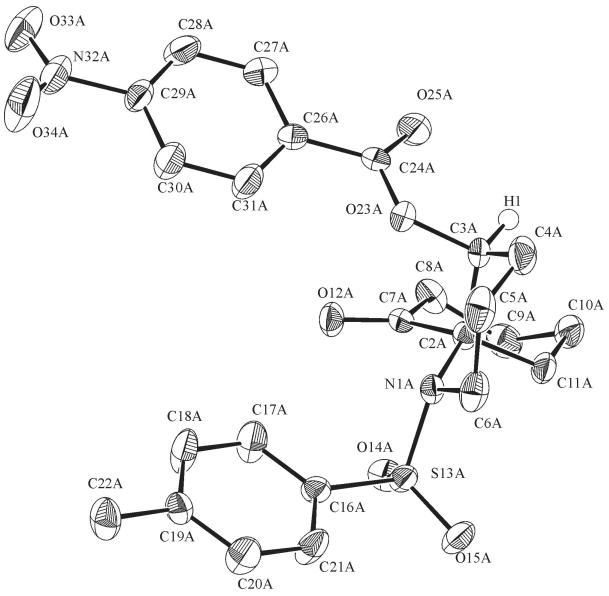


(5'*S, 6'*R**)-4-Nitrobenzoic acid 7'-oxo-1'-(toluene-4''-sulfonyl)-1'-azaspiro[5.5]undec-5'-yl ester**

To a solution of 10.8 mg of (5*S**, 6*R**)-5-hydroxy-1-(toluene-4'-sulfonyl)-1-azaspiro[5.5]undecan-7-one (**11**) (0.0320, 1.0 equiv) and 15.4 mg of 4-dimethylaminopyridine (0.126 mmol, 4.0 equiv) in dichloromethane (0.5 mL) at 0 °C was added a solution of 14.6 mg of 4-nitrobenzoyl chloride (0.0787 mmol, 2.5 equiv) in 1.0 mL of dichloromethane. The reaction mixture was stirred at rt for 4 h and poured into a saturated solution of sodium bicarbonate. The two layers were separated and the organic layer was washed consecutively with a saturated solution of sodium bicarbonate and a saturated solution of sodium chloride. The

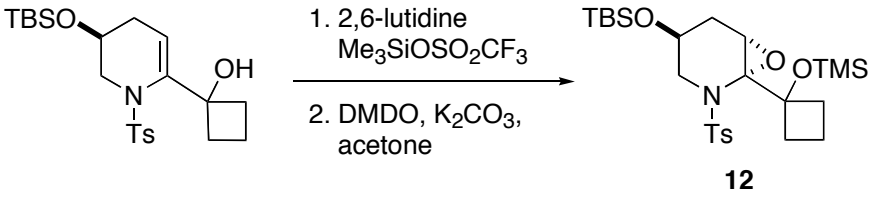
organic layer was dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (3/1 diethyl ether-petroleum ether) on silica gel yielded 15.6 mg (100%) of a white solid. mp = 203-204 °C (methanol). IR (KBr): 2945, 1719, 1528, 1324, 1154, 1104 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): □8.29 (d, *J*=8.7 Hz, 2H), 8.23 (d, *J*=8.7 Hz, 2H), 7.93 (d, *J*=8.2 Hz, 2H), 7.33 (d, *J*=8.2 Hz, 2H), 5.56 (t, *J*=3.0 Hz, 1H), 3.42 (dt, *J*=14.2, 3.8 Hz, 1H), 3.30 (td, *J*=14.2, 3.8 Hz, 1H), 2.84 (m, 1H), 2.67 (m, 1H), 2.45 (s, 3H), 2.44-2.38 (m, 1H), 2.18-1.94 (m, 5H), 1.91-1.66 (m, 3H), 1.61-1.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): □204.1, 164.1, 150.5, 143.6, 138.1, 135.6, 131.3, 129.6, 127.4, 123.4, 69.9, 69.7, 65.8, 42.2, 40.3, 34.7, 26.5, 23.5, 21.5, 21.1, 18.7, 15.3. HRMS (DCI, ammonia/isobutane): Calcd for $C_{24}H_{27}N_2O_7S$ (M^+ + 1): 487.1539. Found 487.1530.

Figure B. ORTEP representation of the crystal structure of (5'*S**, 6'*R**)-4-Nitrobenzoic acid 7'-oxo-1'-(toluene-4''-sulfonyl)-1'-azaspiro[5.5]undec-5'-yl ester



Part B: Expansions of Cyclobutanol Trimethylsilyl Ethers

1. Construction of 12



12

(+)-(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-(toluene-4'-sulfonyl)-6-(1''-trimethylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine

Freshly distilled 2,6-lutidine (32.0 μL, 0.276 mmol, 2.5 equiv) was added to a THF (2.0 mL) solution followed by the addition of freshly distilled trimethylsilyl trifluoromethanesulfonate (32.0 μL, 0.176 mmol, 1.6 equiv). The mixture was allowed to stir for 10 min and then added to a solution of (+)-(5*S*)-1-[5-(*tert*-butyldimethylsilyloxy)-1-(toluene-4'-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclobutanol (48.3 mg, 0.110 mmol, 1.0 equiv) in THF (2.0 mL). The mixture was stirred at rt for 0.5 h and then poured into a saturated solution of aqueous sodium bicarbonate, and extracted with diethyl ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by column chromatography (1/25 ethyl acetate-hexanes; 1% triethylamine) on SiO_2 afforded 51.0 mg (91%) of a white solid.
mp = 38-40 °C (ethyl acetates-hexanes). $[\alpha]_D^{25}$ = +116.8 ± 0.8 (c 0.20, $CHCl_3$). IR (KBr): 2954, 1362, 1169 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=7.9 HZ, 2H), 5.59 (t, *J*=4.1 Hz, 1H), 3.88 (dd, *J*=13.1, 5.0 Hz, 1H), 3.57-3.47 (m, 1H), 2.70 (dd, *J*=13.4, 10.7 Hz, 1H), 2.65-2.54 (m, 1H), 2.53-2.43 (m, 1H), 2.39 (s, 3H), 2.38-2.28 (m, 1H), 2.25-2.13 (m, 2H), 1.89-1.75 (m, 2H), 1.56-1.45 (m, 1H), 0.80 (s, 9H), 0.12 (s, 9H), -0.06 (s, 3H), -0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 143.2, 137.8, 129.3, 127.8, 117.3, 79.6, 63.6, 53.1, 40.0, 36.1, 33.5, 25.7, 21.5, 17.9, 13.8, 2.1, -4.8, -4.9. HRMS (DCI+, ammonia/isobutane): Calcd for $C_{25}H_{44}NO_4SSi_2$ (M^+ + 1): 510.2530. Found 510.2510.

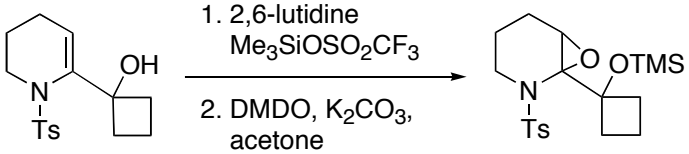
(-)-(1*S*, 4*S*, 6*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-(toluene-4'-sulfonyl)-1-(1''-trimethylsilyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane (12)

To (+)-(3*S*)-3-(*tert*-butyldimethylsilyloxy)-1-(toluene-4'-sulfonyl)-6-(1''-trimethylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine (49.7 mg, 0.0975 mmol, 1.0 equiv) and potassium carbonate (141 mg, 1.02 mmol, 10 equiv) was added a 0.05-0.10 M acetone solution of dimethyldioxirane (10 mL, 0.5-1.0 mmol, 5.0-10 equiv) in acetone and the mixture was stirred overnight at rt. The reaction mixture was then poured into a saturated solution of sodium 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 concentrated *in* vacuo. Purification by column chromatography (1/20 ethyl acetate-hexanes; 1% triethylamine) on SiO_2 afforded 49.5 mg (97%) of a colorless oil.

$[\alpha]_D^{24}$ = -6.0 ± 0.4 (c 0.30, $CHCl_3$). IR (NaCl): 2954, 1599, 1354, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J*=8.5 Hz, 2H), 7.26 (d, *J*=8.5 Hz, 2H), 3.55-3.44 (m, 1H), 3.36 (dd, *J*=13.7, 4.0 Hz, 1H), 3.16 (d, *J*=2.7 Hz, 1H), 2.80-2.70 (m, 1H), 2.61 (dd, *J*=13.7, 10.7 Hz, 1H), 2.39 (s, 3H), 2.35 (d, *J*=6.4 Hz, 1H), 2.29-2.15 (m, 1H), 2.10-2.00 (m, 1H), 1.99-1.80 (m, 2H), 1.68-1.52 (m, 2H), 0.78 (s, 9H), 0.17 (s, 9H), -0.12 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 137.8, 129.4, 128.1, 81.3, 72.1, 64.0, 56.3, 51.3, 34.9, 33.3, 31.9, 25.6, 21.5, 17.8, 14.8, 2.0, -4.9, -5.0. HRMS (DCI+, ammonia/isobutane): Calcd for $C_{25}H_{44}NO_5SSi_2$ (M^+ + 1): 526.2479. Found 526.2482.

2. Construction of 13



13

1-(Toluene-4'-sulfonyl)-6-(1''-trimethylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine

A mixture of freshly distilled 2,6-lutidine (110 μL, 0.950 mmol, 2.5 equiv) and trimethylsilyl trifluoromethanesulfonate (110 μL, 0.606 mmol, 1.6 equiv) in 5 mL of THF was stirred for 10 min, then added to a solution of 1-[1'-(toluene-4''-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclobutanol (117 mg, 0.382 mmol, 1.0 equiv) in 10 mL of THF. The mixture was stirred at rt for 0.5 h and then poured into a saturated solution of aqueous sodium bicarbonate, and extracted with diethyl ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by column chromatography (1/11 ethyl acetate-hexanes; 1% triethylamine) on SiO_2 afforded 139 mg (96%) of a white solid.

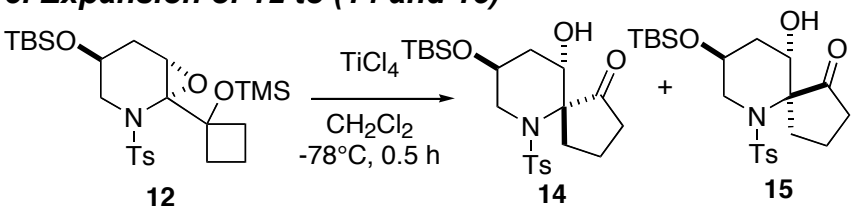
mp = 75-76 °C (ethyl acetates-hexanes). IR (KBr): 3068, 2955, 1646, 1600, 1351, 1138 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.5 Hz, 2H), 5.68 (t, *J*=4.0 Hz, 1H), 3.43 (t, *J*=5.8 Hz, 2H), 2.62-2.51 (m, 2H), 2.39 (s, 3H), 2.32-2.20 (m, 2H), 1.94-1.74 (m, 3H), 1.56-1.43 (m, 1H), 1.39-1.28 (m, 2H), 0.15 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 143.0, 137.9, 129.2, 127.9, 119.0, 79.9, 47.6, 38.0, 21.9, 21.5, 20.2, 13.7, 2.1. HRMS (DCI, ammonia/isobutane): Calcd for $C_{19}H_{30}NO_3SSi$ (M^+ + 1): 380.1716. Found 380.1718.

(1*S, 6*R**)-2-(Toluene-4'-sulfonyl)-1-(1''-trimethylsilyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane (13)**

To 1-(toluene-4'-sulfonyl)-6-(1''-trimethylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine (118 mg, 0.310 mmol, 1.0 equiv) and potassium carbonate (450 mg, 3.26 mmol, 11 equiv) was added a solution of dimethyldioxirane (0.05 M, 31 mL, 1.55 mmol, 5.0 equiv) in acetone and the mixture was stirred at rt for 2 h. The reaction mixture was then poured into a saturated solution of sodium 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 concentrated *in vacuo*. Purification by column chromatography (1/7 diethyl ether-petroleum ether; 1% triethylamine) on SiO_2 yielded 113 mg (92%) of a colorless oil.

mp = 72-73 °C (ethyl acetates-hexanes). IR (KBr): 2998, 2950, 1600, 1337, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □7.88 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=8.5 Hz, 2H), 3.51 (dt, *J*=14.4, 3.1 Hz, 1H), 3.09 (d, *J*=3.4 Hz, 1H), 2.84-2.66 (m, 2H), 2.39 (s, 3H), 2.31-2.21 (m, 1H), 2.15-2.04 (m, 1H), 2.02-1.89 (m, 2H), 1.89-.180 (m, 1H), 1.78-1.59 (m, 2H), 1.28-1.06 (m, 2H), 0.18 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): □143.2, 137.8, 129.2, 128.2, 81.7, 71.8, 54.2, 45.3, 34.8, 31.8, 22.1, 21.5, 18.8, 14.7, 2.0. HRMS (DCI+, ammonia/isobutane): Calcd for $C_{19}H_{30}NO_4SSi$ (M^+ + 1): 396.1665. Found 396.1663.

3. Expansion of 12 to (14 and 15)

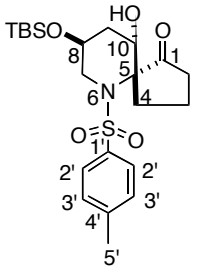


To a solution of epoxide **12** (24.8 mg, 0.0472 mmol) in dichloromethane (2.0 mL) was added 52 □L of a 1.0 M solution of titanium tetrachloride (0.052 mmol) at –78 °C. The reaction mixture was stirred for 0.5 h at –78 °C and then warmed to rt and poured into a saturated aqueous sodium chloride solution. 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) yielded 10.6 mg (50%) of **14** as a white solid and 9.5 mg (45%) of **15** as a clear oil.

(-)-(5*R*, 8*S*, 10*S*)-8-(*tert*-Butyldimethylsilyloxy)-10-hydroxy-6-(toluene-4'-sulfonyl)-6-azaspiro[5.4]decan-1-one (14)

mp = 104-105 °C (ethyl acetate-hexanes). $[\alpha]_D^{20.6}$ = -28.7 ± 0.4 (c 0.131, $CHCl_3$). IR (NaCl): 3504, 2928, 1730, 1333, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J*=8.2 Hz, 2H), 7.28 (d, *J*=8.2 Hz, 2H), 4.29 (d, *J*=2.1 Hz, 1H), 3.96-3.85 (m, 1H), 3.74-3.68 (m, 1H), 3.34 (ddd, *J*=12.8, 5.3, 1.5 Hz, 1H), 2.95-2.85 (m, 1H), 2.82 (dd, *J*=12.5, 10.7 Hz, 1H), 2.55-2.45 (m, 1H), 2.40 (s, 3H), 2.37-2.20 (m, 2H), 2.09-2.00 (m, 1H), 2.00-1.93 (m, 1H), 1.89-1.79 (m, 1H), 1.50-1.41 (m, 1H), 0.79 (s, 9H), -0.08 (s, 3H), -0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.6, 143.7, 136.8, 129.5, 127.5, 69.8, 66.0, 62.5, 49.7, 38.2, 35.9, 32.4, 25.7, 21.6, 18.6, 18.0, -4.9, -5.0. LRMS (CI+, ammonia) *m/z* (relative intensity): 454 (M^+ + 1, 2), 166 (11), 150 (14), 149 (11), 148 (100).

Table B: NMR Data for (-)-(5*R*, 8*S*, 10*S*)-8-(*tert*-Butyldimethylsilyloxy)-10-hydroxy-6-(toluene-4'-sulfonyl)-6-azaspiro[5.4]decan-1-one (14)



Carbon No.	^{13}C δ (ppm)[a]	APT[a]	^1H δ (ppm) (mult J (Hz))[b,c,d]	HMBC Correlations[e]
1	218.6	Q		H-2b, H-3b, H-4a, H-4b
2	38.2	CH_2	H-2a: 2.95-2.85 (m) H-2b: part of 2.37-2.20 (m)	H-3a, H-3b, H-4a, H-4b
3	18.6	CH_2	H-3a: part of 2.37-2.20 H-3b: 1.89-1.79 (m)	H-2a, H-2b, H-4a, H-4b
4	32.4	CH_2	H-4a: 2.55-2.45 (m) H-4b: 2.00-1.93 (m)	H-2a, H-2b, H-3a, H-3b
5	66.0	Q		H-3a, H-3b, H-4a, H-4b H-7eq
7	49.7		H-7eq: 3.34 (ddd, 12.8, 5.3, 1.5) H-7ax: 2.82 (dd, 12.5, 10.7)	H-8, H-9eq
8	62.5	CH	H-8: 3.96-3.85 (m)	H-7eq, H-7ax, H-9eq
9	35.9	CH_2	H-9eq: 2.09-2.00 (m) H-9ax: 1.46 (ddt, 13.3, 10.7, 2.4)	H-7eq, H-7ax, H-8
10	69.8	CH	3.74-3.68 (m)	H-4eq, H-4ax, H-8
1'	136.8	Q		H-3'
2'	127.5	CH	7.74 (d, 8.2)	H-3'
3'	129.5	CH	7.28 (d, 8.2)	H-5'
4'	143.7	Q		H-2', H-5'
5'	21.6	CH_3	H-5': 2.40 (s)	H-3'

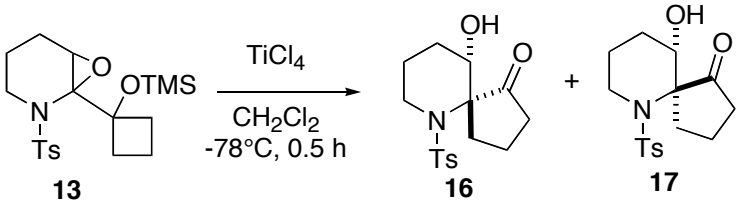
[a] Recorded at 75 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC data.
[d] Methylene protons are arbitrarily designated H-Xa and H-Xb or are designated H-Xeq and H-Xax if they are known to occupy axial and equatorial position, respectively.

[e] Only those correlations which could be unambiguously assigned are recorded.

(+)-(5*S*, 8*S*, 10*S*)-8-(*tert*-Butyldimethylsilyloxy)-10-hydroxy-6-(toluene-4'-sulfonyl)-6-azaspiro[5.4]decan-1-one (15)

$[\alpha]_D^{20.6}$ = +52.6 ± 0.2 (c 0.114, $CHCl_3$). IR (NaCl): 3625, 2956, 2857, 1748, 1334, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J*=8.2 Hz, 2H), 7.21 (d, *J*=8.2 Hz, 2H), 4.41-4.32 (m, 1H), 3.94 (t, *J*=2.4 Hz, 1H), 3.11 (dt, *J*=13.4, 2.0 Hz, 1H), 3.04 (dd, *J*=13.4, 2.0 Hz, 1H), 2.83-2.73 (m, 1H), 2.42-2.12 (m, 3H), 2.36 (s, 3H), 2.03-1.93 (m, 1H), 1.85-1.77 (m, 1H), 1.68-1.62 (m, 2H), 0.65 (s, 9H), -0.10 (s, 3H), -0.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.3, 143.3, 136.7, 129.3, 128.0, 69.5, 64.7, 49.9, 38.6, 36.8, 26.8, 25.6, 21.5, 18.8, 17.8, -5.2, -5.4. LRMS (CI+, ammonia) *m/z* (relative intensity): 454 (M^+ + 1, 20), 299 (31), 282 (25), 280 (17), 166 (25), 150 (11), 149 (11), 148 (100).

4. Expansion of 13 to (16 and 17)



13 **16** **17**

To a solution of epoxide **13** (30.1 mg, 0.0761 mmol) in dichloromethane (3.5 mL) was added 84 μL of a 1.0 M solution of titanium tetrachloride (0.084 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 aqueous sodium chloride solution. 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 on silica gel (5/8 ethyl acetate-hexanes) yielded 17.0 mg (69%) of **16** as a white solid and 6.6 mg (27%) of **17** as a white solid.

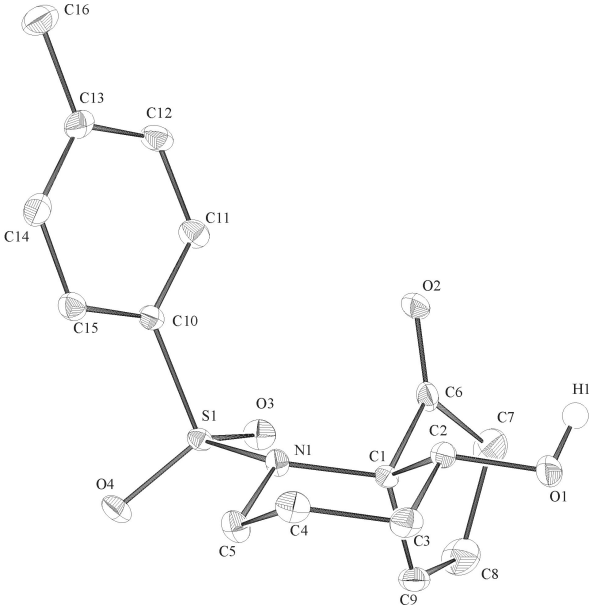
(5*R, 10*S**)-10-Hydroxy-6-(toluene-4'-sulfonyl)-6-azaspiro[5.4]decan-1-one (16):**

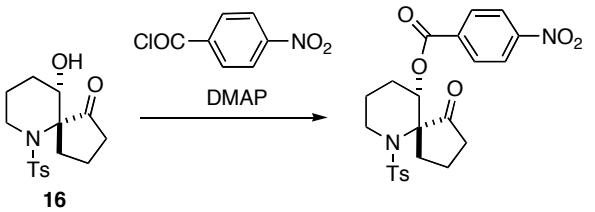
mp = 82-83 °C (ethyl acetate-hexanes). IR (KBr): 3468, 2959, 2870, 1728, 1326, 1155 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J*=8.2 Hz, 2H), 7.25 (d, *J*=8.2 Hz, 2H), 4.20 (d, *J*=2.1 Hz, 1H), 3.64-3.61 (m, 1H), 3.28-3.21 (m, 1H), 3.02 (td, *J*=13.0, 3.3 Hz, 1H), 2.90-2.79 (m, 1H), 2.48 (quin, *J*=7.0 Hz, 1H), 2.40-2.15 (m, 2H), 2.37 (s, 3H), 2.05 (quin, *J*=6.8 Hz, 1H), 1.94-1.73 (m, 3H), 1.60-1.49 (m, 1H), 1.38-1.28 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.6, 143.6, 136.9, 129.5, 127.6, 67.7, 66.4, 43.8, 37.6, 32.4, 25.6, 21.5, 18.5, 17.9. HRMS (DCI+, ammonia/isobutane): Calcd for $C_{16}H_{22}NO_4S$ (M^+): 324.1270. Found 324.1264.

(5*S, 10*S**)-10-Hydroxy-6-(toluene-4'-sulfonyl)-6-azaspiro[5.4]decan-1-one (17):**

mp = 157-159 °C (ethyl acetate-hexanes). IR (KBr): 3436, 2951, 1730, 1326, 1155 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □7.77 (d, *J*=8.2 Hz, 2H), 7.26 (d, *J* =8.2 Hz, 2H), 3.82 (dd, *J*=11.9, 4.0 Hz, 1H), 3.26-3.14 (m, 1H), 2.89 (td, *J*=13.0, 2.8 Hz, 1H), 2.84-2.74 (m, 1H), 2.39 (s, 3H), 2.44-2.13 (m, 4H), 2.04-1.92 (m, 1H), 1.83-1.72 (m, 1H), 1.64-1.51 (m, 1H), 1.44 (ddd, *J*=25.0, 12.5, 3.7 Hz, 1H), 1.38-1.19 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): □217.6, 143.6, 137.0, 129.5, 127.8, 73.4, 69.7, 43.6, 38.3, 29.3, 27.3, 22.8, 21.5, 18.7. HRMS (EI+): Calcd for $C_{16}H_{21}NO_4S$ (M^+): 323.1191. Found 323.1192.

Figure C. ORTEP representation of the crystal structure of **17**





16

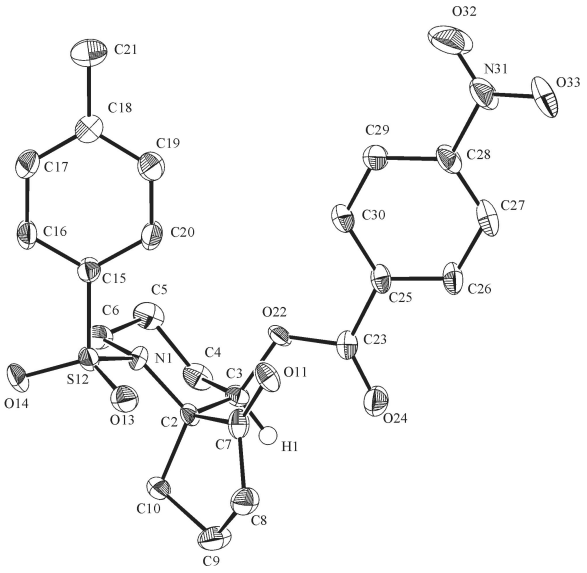
(5*S, 10*S**)-4-Nitrobenzoic acid 1'-oxo-6'-(toluene-4''-sulfonyl)-6-azaspiro[5.4]dec-10'-yl ester**

To a solution of 67.4 mg of (5*R**, 10*S**)-10-hydroxy-6-(toluene-4'-sulfonyl)-6-azaspiro[5.4]decan-1-one (**16**) (0.208 mmol) and 107 mg of 4-dimethylaminopyridine (0.876 mmol) in 5.0 mL of dichloromethane was added a solution of 97.3 mg of 4-nitrobenzoyl chloride (0.524 mmol) in 5.0 mL of

dichloromethane. The mixture was stirred overnight at rt and then at reflux for 4 h. Sequential addition of 103 mg of 4-dimethylaminopyridine (0.843 mmol) and 106 mg of 4-nitrobenzoyl chloride (0.571 mmol) was followed by stirring at reflux for 1 h. The reaction mixture was cooled 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 on silica gel (1/2 ethyl acetate-hexanes) yielded 21.6 mg (22%) of a white solid.

mp = 263-265 °C (CH_2Cl_2). IR (KBr): 2973, 1750, 1723, 1525, 1326, 1158 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 8.21 (d, *J*=8.9 Hz, 2H), 8.05 (d, *J*=8.9 Hz, 2H), 7.88 (d, *J*=8.3 Hz, 2H), 7.29 (d, *J*=8.3 Hz, 2H), 5.33-5.26 (m, 1H), 3.56-3.45 (m, 1H), 3.21 (td, *J*=13.0, 3.3 Hz, 1H), 2.78-2.59 (m, 1H), 2.58-2.49 (m, 1H), 2.48 (s, 3H), 2.46-2.30 (m, 2H), 2.27-2.12 (m, 1H), 1.98-1.73 (m, 4H), 1.69-1.57 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 210.8, 163.8, 150.5, 143.6, 137.9, 135.6, 131.0, 129.3, 127.7, 123.4, 68.3, 67.8, 44.2, 36.3, 33.5, 29.7, 24.7, 21.6, 19.2, 17.9. HRMS (CI+, ammonia/methane): Calcd for $C_{23}H_{25}N_2O_7S$ ($M^+ + 1$): 473.1382. Found 473.1389.
An X-ray crystal structure was obtained.

Figure D. ORTEP representation of the crystal structure of 5*S**, 10*S**)-4-Nitrobenzoic acid 1'-oxo-6'-(toluene-4''-sulfonyl)-6-azaspiro[5.4]dec-10'-yl ester



5. Reequilibration Experiments

To a cold solution (-78 °C) of 10.9 mg of (5*R**, 10*S**)-10-Hydroxy-6-(toluene-4'-sulfonyl)-6-azaspiro[5.4]decan-1-one (**16**) (0.034 mmol) in 1.5 mL of dichloromethane was added 37 L of a solution of titanium tetrachloride in

dichloromethane (0.037 mmol, 1.0 M (Aldrich)). The mixture was stirred at -78 ˚C for 0.5 h and then at rt for 2 h. No equilibration was observed by TLC.

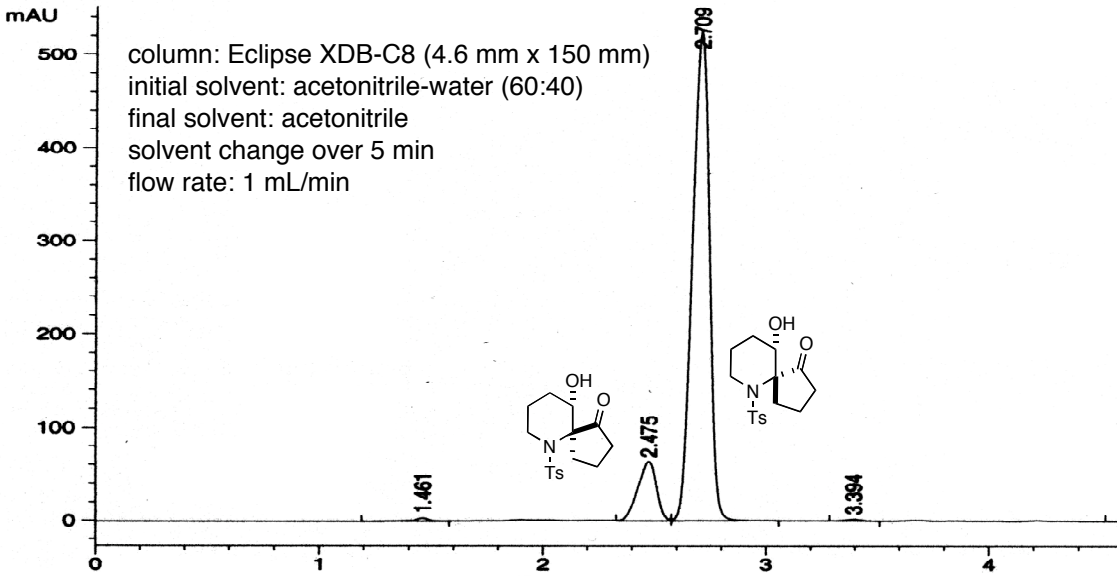
To a cold solution (-78 ˚C) of 9.8 mg of (5*S**, 10*S**)-10-Hydroxy-6-(toluene-4'-sulfonyl)-6-azaspiro[5.4]decan-1-one (**17**) (0.030 mmol) in 1.3 mL of dichloromethane was added 33 μL of a solution of titanium tetrachloride in dichloromethane (0.033 mmol, 1.0 M (Aldrich)). The mixture was stirred at -78 ˚C for 0.5 h and then at rt for 2 h. No equilibration was observed by TLC.

6. Examples of Lewis Acid Screen of Expansions of 13 to (16 and 17)

Procedure Using $Yb(OTf)_3$

Ytterbium (III) trifluoromethanesulfonate was weighed in the glove box and was dried under vacuum for 48 h at 200 ˚C prior to use. A solution of 9.8 mg of (1*S**, **13** (0.025 mmol, 1.0 equiv) in 1.2 mL of dichloromethane was added to 21 mg of ytterbium (III) trifluoromethanesulfonate (0.034 mmol, 1.4 equiv, precooled at –78 °C). The mixture was stirred at –78 °C for 0.5 h, at -42 ˚C for 5 h, and then at 0 ˚C for 2 h. Analysis, using HPLC (Figure E), of an aliquot of the reaction mixture showed the presence of a 7.4:1 mixture of diastereomers **16** and **17**. The reaction mixture was 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 (1/1 ethyl acetate-hexanes) on silica gel yielded 7.9 mg (99%) of a colorless oil consisting of a mixture of the two diastereomeric products.

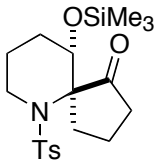
Figure E. Sample HPLC trace of diastereomers **16** and **17**



Procedure Using Et_2AlCl

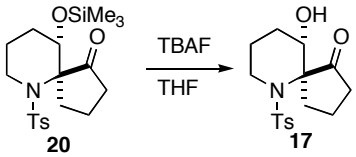
To a cold solution (-78 ˚C) of 16.2 mg of (1*S**, 6*R**)-2-(toluene-4'-sulfonyl)-1-(1''-trimethylsilyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane (**13**) (0.041 mmol) in 2.0 mL of dichloromethane was added 50 μL of a solution of diethylaluminum chloride in heptane (0.050 mmol, 1.0 M (Aldrich)). The mixture was stirred at -78 ˚C for 2 h, at -42 ˚C for 0.5 h, at -15 ˚C for 0.5 h, at 0 ˚C for 0.5 h, and then overnight at rt. The reaction mixture was 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 on silica gel (1/1 ethyl acetate-hexanes) yielded 6.0 mg (37%) of a yellow oil (**20**) and 6.8 mg (51%) of colorless oil. Analysis, using HPLC (Figure E), of an aliquot of the colorless oil showed the colorless oil to consist of a 5.9:1 mixture of diastereomers (**16**) and (**17**).

(5S*, 10S*)-6-(Toluene-4'-sulfonyl)-10-trimethylsilyloxy-6-azaspiro[4.5]decan-1-one (20)



20

IR (CCl_4): 2967, 2868, 1733, 1331, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J*=8.2 Hz, 2H), 7.25 (d, *J*=7.0 Hz, 2H), 3.85 (dd, *J*=7.6, 3.4 Hz, 1H), 3.37 (dt, *J*=12.9, 5.3 Hz,1H), 3.27-3.17 (m, 1H), 2.59 (dt, *J*=13.7, 8.9 Hz, 1H), 2.54-2.42 (m, 1H), 2.39 (s, 3H), 2.29-2.17 (m, 2H), 2.11-1.99 (m, 2H), 1.89-1.74 (m, 2H), 1.72-1.63 (m, 1H), 1.49-1.40 (m, 1H), 0.07 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.5 (Q), 143.0 (Q), 138.4 (Q), 129.2 (CH), 127.7 (CH), 72.2 (CH), 68.6 (Q), 42.8 (CH_2), 37.2 (CH_2), 34.8 (CH_2), 26.9 (CH_2), 21.5 (CH_3), 19.7 (CH_2), 18.2 (CH_2), 0.1 (CH_3). HRMS (CI+, ammonia): Calcd for $C_{19}H_{30}NO_4SSi$ (M^+ + 1): 396.1665. Found 396.1667.



20 **17**

(5*S, 10*S**)-10-Hydroxy-6-(toluene-4'-sulfonyl)-6-azaspiro[4.5]decan-1-one (17)**

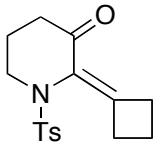
To a solution of 3.3 mg of (5*S**, 10*S**)-6-(toluene-4'-sulfonyl)-10-trimethylsilyloxy-6-azaspiro[5.4]decan-1-one (**20**) (0.0083 mmol) in 0.5 mL of THF was added 12 μL of a solution of tetrabutylammonium fluriode in THF (0.012 mmol, 1.0 M (Aldrich)). The mixture was stirred at rt for 0.5 h. The reaction mixture was poured into a saturated solution of sodium 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 concentrated by evaporation *in vacuo*. Purification by column chromatography on silica gel (1/1 ethyl acetate-hexanes) yielded 2.2 mg (82%) of **17** as a white solid.

Procedure Using $MgBr_2 \bullet Et_2O$

To a cold solution (-78 ˚C) of 16.3 mg of (1*S**, 6*R**)-2-(toluene-4'-sulfonyl)-1-(1''-trimethylsilyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane (**13**) (0.041 mmol) in 1.0 mL of dichloromethane was added of a solution of 14 mg of magnesium bromide diethyl etherate (0.054 mmol) in 1.0 mL of dichloromethane. The mixture was stirred at -78 ˚C for 0.5 h, at -42 ˚C for 0.5 h, and at 0 ˚C for 2.5 h. The reaction mixture was 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 on silica gel (1/1 ethyl acetate-hexanes) yielded 3.0 mg (24%) of a semisolid (**21**) and 9.0 mg (68%) of colorless oil. Analysis, using HPLC (Figure E), of an aliquot of the colorless oil showed the colorless oil to consist of a 10:1 mixture of diastereomers (**16**) and (**17**).

2-Cyclobutylidene-1-(toluene-4'-sulfonyl)-piperidin-3-one (21)

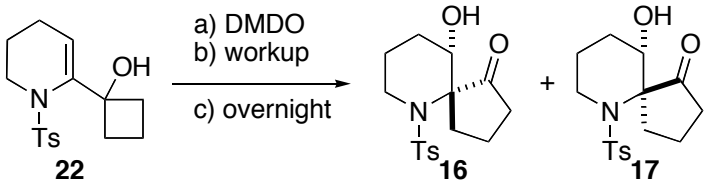


21

IR (CCl_4): 2927, 1708, 1641, 1362, 1168 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □7.61 (d, *J*=8.2 Hz, 2H), 7.26 (d, *J*=7.9 Hz, 2H), 3.66-3.55 (m, 2H), 3.11 (dd, *J*=16.9, 8.1 Hz, 4H), 2.39 (s, 3H), 2.16-2.00 (m, 2H), 1.65 (d, *J*=3.6 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): □196.7 (Q), 165.5 (Q), 143.9 (Q), 135.8 (Q), 129.9 (CH), 127.2 (CH), 125.4 (Q), 45.7 (CH_2), 36.8 (CH_2), 34.3 (CH_2), 33.1 (CH_3), 20.0 (CH_2), 18.3 (CH_2). HRMS (DCI+, ammonia/isobutane): Calcd for $C_{16}H_{19}NO_3S$ (M^+): 305.1086. Found 305.1086.

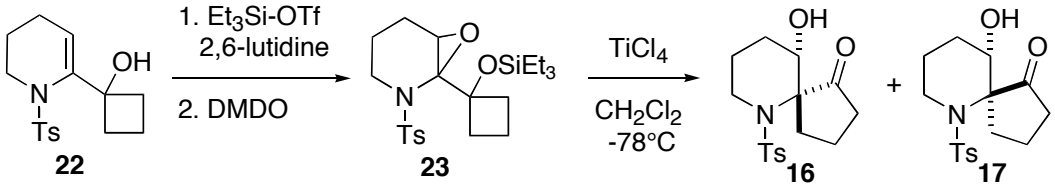
Part C: Effect of Silicon Protecting Group

1. No Protecting Group



To 1-[1'-(toluene-4''-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclobutanol (**22**) (9.6 mg, 0.031 mmol, 1.0 equiv) was added a solution of dimethyldioxirane (0.05-0.1 M, 5.0 mL, 0.25-0.50 mmol, 8.0-16 equiv) in acetone and the mixture was stirred at rt for 0.5 h. The reaction mixture was then poured into water. 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 *in vacuo* to afford 9.0 mg (89%) of a colorless oil. Analysis using HPLC (using the conditions described in Figure X.XX) showed the oil to consist of a 13.2:1 mixture of diastereomers **16** and **17**.

2. Triethylsilyl Ether



1-(Toluene-4'-sulfonyl)-6-(1''-triethylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine

A mixture of freshly distilled 2,6-lutidine (28.0 μL, 0.242 mmol, 2.5 equiv) and trimethylsilyl trifluoromethanesulfonate (35.0 μL, 0.155 mmol, 1.6 equiv) in 2 mL of THF was stirred for 10 min, then added to a solution of 30 mg of **22** (0.0979 mmol, 1.0 equiv) in 2 mL of THF. The mixture was stirred at rt overnight and then poured into a saturated solution of aqueous sodium bicarbonate, and extracted with diethyl ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by column chromatography (1/12 diethyl ether-petroleum ether) on SiO_2 afforded 40.7 mg (99%) of a pale yellow oil.

IR (CCl_4): 2957, 2877, 1555, 1359, 1166 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=8.2 Hz, 2H), 3.50 (dt, *J*=14.3, 3.1, 1H), 3.08 (d,

J=2.4 Hz, 1H), 2.93-2.83 (m, 1H), 2.75 (dd, *J*=12.2, 2.7 Hz, 1H), 2.39 (s, 3H), 2.31-2.19 (m, 1H), 2.14-2.03 (m, 1H), 2.00-1.77 (m, 3H), 1.76-1.59 (m, 2H), 1.25-1.03 (m, 2H), 1.25-1.03 (m, 2H), 0.96 (t, *J*=7.9 Hz, 9H), 0.66 (q, *J*=7.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 143.3, 138.0, 129.2, 128.2, 81.4, 72.1, 54.1, 45.5, 35.0, 32.2, 22.2, 21.5, 18.7, 14.1, 7.1, 6.4. LRMS (CI+, ammonia) *m/z* (relative intensity): 438 (M^+ + 1, 100).

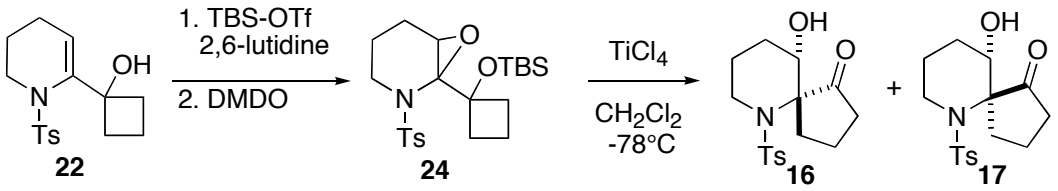
(1*S, 6*R**)-2-(Toluene-4'-sulfonyl)-1-(1''-triethylsilyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane (23)**

To 1-(toluene-4'-sulfonyl)-6-(1''-triethylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine (40.7 mg, 0.0965 mmol, 1.0 equiv) and potassium carbonate (140 mg, 1.01 mmol, 11 equiv) was added a solution of dimethyldioxirane (0.05-0.10 M, 10 mL, 0.5-1.0 mmol, 5-10 equiv) in acetone and the mixture was stirred at rt for 1 h. The reaction mixture was then poured into a saturated solution of sodium 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 concentrated *in vacuo*. Purification by column chromatography (1/9 diethyl ether-petroleum ether) on SiO_2 yielded 33.6 mg (80%) of a colorless oil.
IR (CCl_4): 2957, 2877, 1555, 1359, 1166 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=8.2 Hz, 2H), 3.50 (dt, *J*=14.3, 3.1 Hz, 1H), 3.08 (d, *J*=2.4 Hz, 1H), 2.93-2.83 (m, 1H), 2.75 (dd, *J*=12.2, 2.7 Hz, 1H), 2.39 (s, 3H), 2.31-2.19 (m, 1H), 2.14-2.03 (m, 1H), 2.00-1.77 (m, 3H), 1.76-1.59 (m, 2H), 1.25-1.03 (m, 2H), 0.96 (t, *J*=7.9 Hz, 9H), 0.66 (q, *J*=7.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 143.3, 138.0, 129.2, 128.2, 81.4, 72.1, 54.1, 45.5, 35.0, 32.2, 22.2, 21.5, 18.7, 14.1, 7.1, 6.4. LRMS (CI+, ammonia) *m/z* (relative intensity): 438 (M^+ + 1, 100).

Expansion of 23 to (16 and 17)

To a solution of 24.5 mg of epoxide **23** (0.0560 mmol, 1.0 equiv) in 2.7 mL of dichloromethane was added 65 L of a 1.0 M solution of titanium tetrachloride (0.065 mmol, 1.2 equiv) in dichloromethane at -78 °C. The reaction mixture was stirred for 0.5 h at -78 °C and then warmed to rt. HPLC analysis (using the conditions described in Figure E), of an aliquot of the reaction mixture showed the presence of a 2.5:1 mixture of diastereomers **16** and **17**. The reaction mixture was 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 (5/8 ethyl acetate-hexanes) on SiO_2 yielded 17.9 mg (99%) of a colorless oil consisting of a mixture of the two diastereomeric products.

3. tert-Butyldimethylsilyl Ether



22 24 16 17

6-[1'-(*tert*-Butyldimethylsilyloxy)-cyclobutyl]-1-(toluene-4''-sulfonyl)-1,2,3,4-tetrahydropyridine

This reaction was carried out as described for **22** to **23** using 2,6-lutidine (38.0 μL, 0.328 mmol, 2.5 equiv), *tert*-butyldimethylsilyl trifluoromethanesulfonate (49.0 μL, 0.280 mmol, 2.1 equiv), and **22** (40.7 mg, 0.132 mmol, 1.0 equiv). Purification by column chromatography (1/9 diethyl ether-petroleum ether) on SiO_2 afforded 47.3 mg (85%) of a white solid.

mp = 75-76 °C (ethyl acetate-hexanes). IR (KBr): 2954, 2857, 1599, 1348, 1165 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=8.2 Hz, 2H), 3.51 (dt, *J*=14.3, 2.7 Hz, 1H), 3.06 (d, *J*=2.1 Hz, 1H), 3.06 (d, *J*=2.1 Hz, 1H), 2.88-2.71 (m, 2H), 2.39 (s, 3H), 2.32-2.21 (m, 1H), 2.15-2.05 (m, 1H), 2.03-1.79 (m, 3H), 1.75-1.59 (m, 2H), 1.24-1.15 (m, 1H), 1.14-0.99 (m, 1H), 0.87 (s, 9H), 0.21 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 137.9, 129.2, 128.2, 81.7, 72.1, 54.0, 45.5, 34.9, 31.9, 25.9, 22.3, 21.5, 18.6, 18.2, 14.4, -2.8. LRMS (CI+, ammonia) *m/z* (relative intensity): 438 (M^+ + 1, 100).

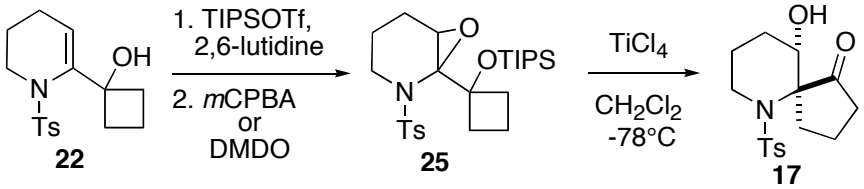
(1*S, 6*R**)-1-[1'-(*tert*-Butyldimethylsilyloxy)-cyclobutyl]-2-(toluene-4''-sulfonyl)-7-oxa-2-azabicyclo[4.1.0]heptane (24)**

This reaction was carried out as described for **22** to **23** using 6-[1'-(*tert*-butyldimethylsilyloxy)-cyclobutyl]-1-(toluene-4''-sulfonyl)-1,2,3,4-tetrahydropyridine (47.3 mg, 0.112 mmol, 1.0 equiv), potassium carbonate (160 mg, 1.16 mmol, 10 equiv), and dimethyldioxirane (0.05-0.10 M, 12 mL, 0.6-1.2 mmol, 5-11 equiv). The reaction was stirred overnight at rt. Purification by column chromatography (1/9 diethyl ether-petroleum ether) on SiO_2 afforded 45.5 mg (93%) of a white solid.
mp = 75-76 °C (ethyl acetate-hexanes). IR (KBr): 2954, 2857, 1599, 1348, 1165 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=8.2 Hz, 2H), 3.51 (dt, *J*=14.3, 2.7 Hz, 1H), 3.06 (d, *J*=2.1 Hz, 1H), 2.88-2.71 (m, 2H), 2.39 (s, 3H), 2.32-2.21 (m, 1H), 2.15-2.05 (m, 1H), 2.03-1.79 (m, 3H), 1.75-1.59 (m, 2H), 1.24-1.15 (m, 1H), 1.14-0.99 (m, 1H), 0.87 (s, 9H), 0.21 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 137.9, 129.2, 128.2, 81.7, 72.1, 54.0, 45.5, 34.9, 31.9, 25.9, 22.3, 21.5, 18.6, 18.2, 14.4, -2.8. LRMS (CI+, ammonia) *m/z* (relative intensity): 438 (M^+ + 1, 100).

Expansion of 24 to (16 and 17)

This reaction was carried out as described for **23** using 32 mg (0.0752 mmol) of (1*S**, 6*R**)-1-[1'-(*tert*-butyldimethylsilyloxy)-cyclobutyl]-2-(toluene-4''-sulfonyl)-7-oxa-2-azabicyclo[4.1.0]heptane (**24**), and 86 μL of a 1.0 M (dichloromethane) solution of titanium tetrachloride (0.0860 mmol, 1.1 equiv) at –78 °C in 3.6 mL of dichloromethane. HPLC analysis (using the conditions described in Figure E), of an aliquot of the reaction mixture showed the presence of a 1.3:1 mixture of diastereomers **16** and **17**. Column chromatography (5/8 ethyl acetate-hexanes) on silica gel gave 21.6 mg (89%) of a clear oil.

4. Triisopropylsilyl Ether



1-(Toluene-4-sulfonyl)-6-(1-triisopropylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine

A solution of 50 μL of triisopropylsilyl triflate (0.16 mmol) and 50 μL (0.25 mmoL) 2,6-lutidine in 2.0 mL of THF was added to a solution of 35 mg of **22** (0.114 mmol) in 3 mL of THF. The reaction mixture was stirred for 14 h at rt and poured into a saturated aqueous sodium bicarbonate solution. 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 on silica gel (5% ethyl acetate-hexanes) yielded 62 mg (99%) of a white solid.

mp=68-69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J*=8.2 Hz, 2H), 7.23 (d, *J*=8.2 Hz, 2H), 5.82 (t, *J*=5.8 Hz, 1H), 3.47-3.43 (m, 2H), 2.73-2.66 (m, 2H), 2.40 (s, 3H), 2.36-2.30 (m, 2H), 1.89-1.83 (m, 2H), 1.77-1.70 (m, 1H), 1.53-1.45 (m, 1H), 1.28-1.21 (m, 2H), 1.11 (s, 21H).

(1*S, 6*R**)-2-(Toluene-4'-sulfonyl)-1-(1''-triisopropylsilanyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane (25)**

Method A: Use of DMDO

This reaction was carried out as described for **22** to **23** in the sample procedure using 1-(toluene-4'-sulfonyl)-6-(1''-triisopropylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine (244 mg, 0.526 mmol, 1.0 equiv), potassium carbonate (802 mg, 5.80 mmol, 11 equiv), and dimethyldioxirane (0.05-0.10 M, 60 mL, 3.0-6.0

mmol, 6-11 equiv). The reaction was stirred at rt for 1 h. Purification by column chromatography (1/11 ethyl acetate-hexanes; 1% triethylamine) on SiO_2 afforded 222 mg (88%) of a white solid, mp=98-99 °C.

Method B: Use of *m*-CPBA

To a solution of 58 mg of 1-(toluene-4-sulfonyl)-6-(1-triisopropylsilyloxy-cyclobutyl)-1,2,3,4-tetrahydropyridine (0.125 mmoL) in 5.0 mL of CH_2Cl_2 at –5 °C was added slowly 43 mg of *m*-chloroperbenzoic acid (0.250 mmol). The reaction mixture was stirred for 4 h at rt. Two other portions of 43 mg of *m*-chloroperbenzoic acid (0.250 mmol) were added. The reaction mixture was stirred for 14 h at rt and poured into a solution of 0.5M aqueous sodium hydroxide solution. 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 on silica gel (5% ethyl acetate-hexanes) yielded 53 mg (88%) of a white solid, mp=98-99 °C.

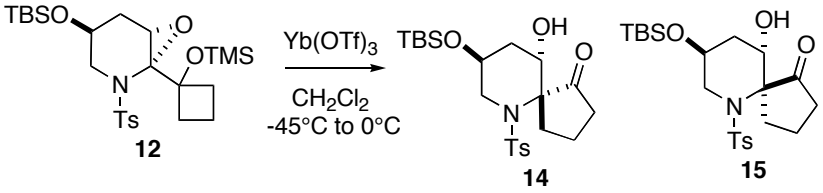
mp = 98-99 °C (ethyl acetate-hexanes). IR (NaCl): 2944, 2867, 1464, 1340, 1158 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □7.86 (d, *J*=8.1 Hz, 2H), 7.24 (d, *J*=8.1 Hz, 2H), 3.51 (dt, *J*=14.6, 3.1 Hz, 1H), 3.15-3.03 (m, 2H), 2.84 (ddd, *J*=14.6, 12.3, 2.7 Hz, 1H), 2.39 (s, 3H), 2.30-2.13 (m, 2H), 2.00-1.55 (m, 7H), 1.16-1.04 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): □143.3, 138.0, 129.2, 128.3, 80.8, 72.6, 54.1, 45.5, 35.6, 33.1, 21.9, 21.5, 18.4, 18.2, 13.5, 12.8. Anal. Calcd for $C_{25}H_{41}NO_4SSi$: C, 62.59; H, 8.61; N, 2.92. Found: C, 62.67; H, 8.83; N, 3.08.

Expansion of 25 to 17

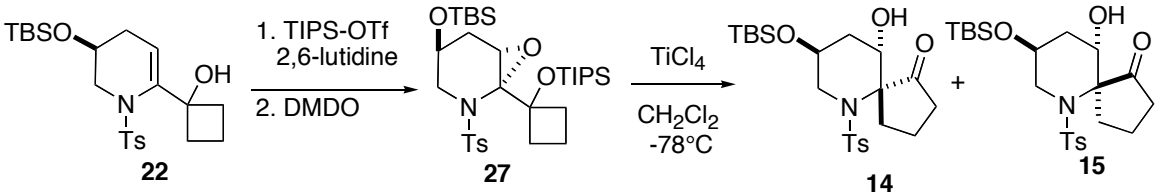
(5S*,10S*)-10-Hydroxy-6-(toluene-4-sulfonyl)-6-azaspiro[4.5]decan-1-one (17)

To a –78°C solution of 25 mg (0.052 mmoL) of 1-(toluene-4-sulfonyl)-1-(1-triisopropylsilyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane 25 in 2.0 mL of CH_2Cl_2 was added 57 □L of a 1.0 M solution (0.057 mmol) of titanium tetrachloride. The reaction mixture was stirred for 0.5 h at –78 °C and then warmed to rt and poured into a saturated aqueous NaCl solution. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography on silica gel (30% ethyl acetate-hexanes) yielded 16 mg (95%) of a white solid (mp=157-159°C).

5. Selective Formation of 14 or 15



Ytterbium (III) trifluoromethanesulfonate was weighed in the glove box and was dried under vacuum for 48 h at 200 °C prior to use. A solution of 23.8 mg of **12** **(**0.0453 mmol, 1.0 equiv) in dichloromethane (2.2 mL) at –78 °C was added to a flask containing 38.1 mg of ytterbium (III) trifluoromethanesulfonate (0.0614 mmol, 1.4 equiv) at –78 °C. The mixture was stirred at –78 °C for 0.5 h, at -42 ˚C for 5 h, at -15 ˚C for 0.5 h, and then at 0 ˚C for 1 h. The reaction mixture was 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 silica gel yielded 14.5 mg (71%) of **14** as a colorless oil and 3.2 mg (16%) of **15** as a colorless oil.



(+)-(3*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-(toluene-4'-sulfonyl)-6-(1''-triisopropylsilyloxycyclobutyl)-1,2,3,4-tetrahydropyridine

This reaction was carried out as described for **22** to **23** using 2,6-lutidine (25.0 □L, 0.216 mmol, 2.5 equiv), triisopropylsilyl trifluoromethanesulfonate (38.0 □L, 0.141 mmol, 1.6 equiv), and 37.8 mg of **22** (0.0864 mmol, 1.0 equiv). The reaction mixture was stirred overnight at rt. 2,6-Lutidine (25.0 □L, 0.216 mmol, 2.5 equiv) and triisopropylsilyl trifluoromethanesulfonate (70.0 □L, 0.260 mmol, 3.0 equiv) were added once more. The reaction mixture was stirred at rt for 7 h. 2,6-Lutidine (25.0 □L, 0.216 mmol, 2.5 equiv) and triisopropylsilyl trifluoromethanesulfonate (38.0 □L, 0.141 mmol, 1.6 equiv) were added once more. The reaction mixture was stirred at rt for 4 h. Purification by column chromatography (1/25 ethyl acetate-hexanes) on silica gel afforded 48.0 mg (94%) of a colorless oil.

$[\square]_D^{20.7}$ = +97.2 ± 0.2 (c 0.32, $CHCl_3$). IR (CCl_4): 2959, 1171 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □ 7.76 (d, *J*=8.2 Hz, 2H), 7.23 (d, *J*=8.2 Hz, 2H), 5.72 (dd, *J*=4.6, 3.7 Hz, 1H), 3.88 (dd, *J*=13.4, 5.2 Hz, 1H), 3.40-3.29 (m, 1H), 2.76 (dd, *J*=13.4,

10.4 Hz, 1H), 2.75-2.69 (m, 1H), 2.63-2.52 (m, 1H), 2.37-2.23 (m, 2H), 2.39 (s, 3H), 2.12 (ddd, *J*=18.3, 7.5, 3.5 Hz, 1H), 1.80 (ddd, *J*=18.3, 7.5, 3.5 Hz, 1H), 1.75-1.65 (m, 1H), 1.55-1.39 (m, 1H), 1.09 (s, 18H), 1.04 (s, 3H), 0.77 (s, 9H), -0.12 (s, 3H), -0.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): □ 144.6, 143.2, 138.2, 129.4, 127.5, 118.0, 78.3, 63.5, 53.3, 40.7, 37.5, 33.4, 25.7, 21.5, 18.4, 17.9, 13.7, 12.7, -4.9, -4.9. LRMS (CI+, ammonia) *m/z* (relative intensity): 610 (M^+ + 1, 100).

(-)-(1*R*, 4*S*, 6*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-(toluene-4'-sulfonyl)-1-(1''-triisopropylsilyloxycyclobutyl)-7-oxa-2-azabicyclo[4.1.0]heptane (27)

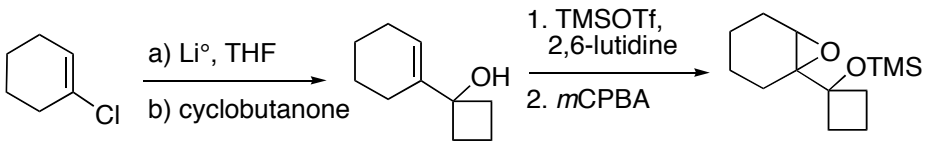
This reaction was carried out as described for **22** to **23** using 42.4 mg of (+)-(3*S*)-3-(*tert*-butyldimethylsilyloxy)-1-(toluene-4'-sulfonyl)-6-(1''-triisopropylsilyloxy-cyclobutyl)-1,2,3,4-tetrahydropyridine (0.0714 mmol, 1.0 equiv), potassium carbonate (101 mg, 0.732 mmol, 10 equiv), and dimethyldioxirane (0.05-0.10 M, 10 mL, 0.5-1.0 mmol, 7-14 equiv). The reaction was stirred at rt overnight. Purification by column chromatography (1/30 ethyl acetate-hexanes; 1% triethylamine) on SiO_2 afforded 37.4 mg (86%) of a pale yellow oil.

$[□]_D^{21.2}$ = -8.1 ± 0.2 (c 0.141, $CHCl_3$). IR (CCl_4): 2948, 2867, 1464, 1362, 1166 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): □ 7.87 (d, *J*=8.2 Hz, 2H), 7.25 (d, *J*=8.2 Hz, 2H), 3.45-3.33 (m, 2H), 3.22 (d, *J*=3.1 Hz, 1H), 3.09-2.98 (m, 1H), 2.80-2.70 (m, 1H), 2.39 (s, 3H), 2.36-2.13 (m, 3H), 2.01-1.91 (m, 1H), 1.81-1.52 (m, 3H), 1.18-1.03 (m, 21H), 0.77 (s, 9H), -0.15 (s, 3H), -0.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): □ 143.5, 137.9, 129.4, 128.2, 80.3, 72.8, 63.4, 56.2, 51.6, 35.7, 33.3, 33.2, 25.6, 21.5, 18.4, 17.8, 13.5, 12.8, -4.9, -5.0. LRMS (CI, ammonia) *m/z* (relative intensity): 610 (M^+ + 1, 100).

Expansion of 27 to (14 and 15)

To a solution of 22.3 mg of **27** (0.0366 mmol, 1.0 equiv) in 1.6 mL of dichloromethane was added a 40 mL of a 1.0 M solution of titanium tetrachloride in dichloromethane (0.040 mmol, 1.1 equiv) at -78 °C. The reaction mixture was stirred for 0.5 h at -78 °C 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 2.2 mg (13%) of **14** as a colorless oil and 13.4 mg (81%) of **15** as a colorless oil.

Part D: Carbocyclic Versions



18

1-Cyclohex-1-enylcyclobutanol

To a suspension of 50 mg (7.25 mmol) of finely cut lithium (pre-washed with pentane) in 3.0 mL of Et_2O was added 370 μL (3.3 mmol) of cyclohexenyl chloride. The reaction mixture was heated to reflux for 12 h and then cooled to rt. The solution was transferred into an empty dry round bottom flask to remove the metal and salt impurities. The solution was cooled to –100 °C, after which a precooled (-100 °C) solution of 247 μL (3.3 mmol) of cyclobutanone in 1.0 mL of Et_2O was added. The resulting mixture was stirred at –100 °C for 90 min then warmed to rt for 1 h. The reaction mixture was poured into a saturated aqueous ammonium chloride solution. The two layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography on prewashed silica gel with 1% Et_3N / hexane (20% ethyl acetate-hexanes) yielded 365 mg (73%) of a clear liquid.

IR (NaCl): 3336, 2931, 1440, 1248, 1139 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ 5.59 (m, 1H), 2.25-2.15 (m, 2H), 2.07-1.77 (m, 6H), 1.58-1.41 (m, 6H). ^{13}C NMR (75 MHz, C_6D_6): δ 140.0, 119.9, 77.9, 34.5, 25.4, 23.25, 23.20, 23.16, 22.8, 13.6. LRMS (EI+) *m/z* (relative intensity): 134 (M^+-H_2O).

1-(Cyclohex-1-enylcyclobutoxy)-trimethylsilane

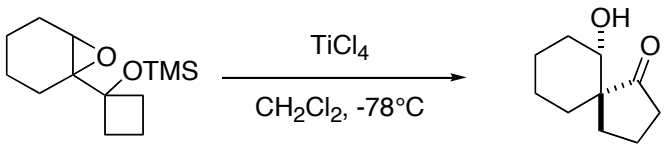
A solution of 134 μL (1.6 mmoL) of trimethylsilyl triflate and 134 μL (2.5 mmoL) 2,6-lutidine in 5.0 mL of THF was added to a solution of 70 mg (0.46 mmoL) of 1-cyclohex-1-enylcyclobutanol in 5.0 mL of THF. The reaction mixture was stirred for 0.5 h at rt and poured into a saturated aqueous sodium bicarbonate solution. The two layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography on silica gel (5% ethyl acetate-hexanes) yielded 80 mg (81%) of a clear liquid.

IR (NaCl): 2935, 1249, 1139 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ 5.65-5.63 (m, 1H), 2.28-2.15 (m, 4H), 2.14-2.09 (m, 2H),1.98-1.93 (m, 2H), 1.74-1.65 (m, 1H), 1.60-1.54 (m, 2H), 1.52-1.36 (m, 3H), 0.15 (s, 9H). ^{13}C NMR (75 MHz, C_6D_6): δ 140.3, 120.2, 79.4, 35.6, 25.5, 23.20, 23.18, 22.8, 13.8, 1.9. LRMS (EI+) *m/z* (relative intensity): 224 (M^+).

(1S*,6R*)-Trimethyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane (18)

To a solution of 20 mg (0.089 mmoL) of (1-cyclohex-1-enylcyclobutoxy)-trimethylsilane in 2.0 mL of CH_2Cl_2 at –5 °C was added slowly 18.4 mg (0.107 mmol) of *m*-chloroperbenzoic acid. The reaction mixture was stirred for 4 h at rt. Two additional portions of 18.4 mg (0.107 mmol) of *m*-chloroperbenzoic acid were added. The reaction mixture was stirred for 14 h at rt and poured into an aqueous 0.5M sodium hydroxide solution. 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 on silica gel (5% ethyl acetate-hexanes) yielded 20 mg (94%) of a clear liquid.

IR (NaCl): 2941, 1447, 1251, 1158 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2CO$): □3.11 (s, 1H), 2.15-1.88 (m, 6H), 1.86-1.66 (m, 3H), 1.48-1.16 (m, 5H), 0.10 (s, 9H). ^{13}C NMR (75 MHz, $CD_3)_2CO$): □79.0, 60.8, 54.7, 32.4, 32.0, 24.6, 22.8, 20.6, 19.2, 12.6, 1.2. LRMS (EI+) *m/z* (relative intensity): 240 (M^+, 4), 212 (20), 197 (17), 171 (12), 170 (59), 169 (70), 155 (27), 143 (10), 141 (14), 129 (17), 79 (15), 77 (11), 75 (49), 73 (100), 55 (11).



18 **19**

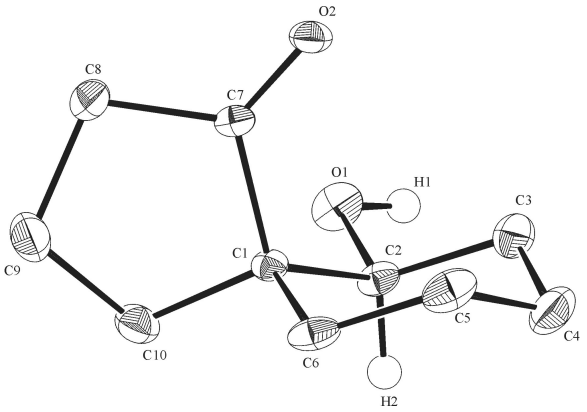
(5S*,6S*)-6-Hydroxyspiro[4.5]decan-1-one (19)

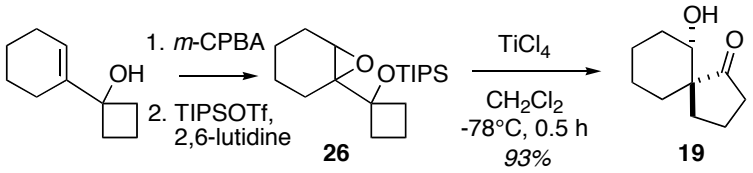
To a solution of 17.6 mg (0.073 mmol) of trimethyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane **18** in 2.0 mL of CH_2Cl_2 at –78 °C was added 80 □L of a 1.0 M solution (0.08 mmol) of titanium tetrachloride. The reaction mixture was stirred for 0.5 h at –78 °C and then warmed to rt and poured into a saturated aqueous sodium chloride solution. 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 on silica gel (20% ethyl acetate-hexanes) yielded 7.6 mg (62%) of a white solid, mp=55-57 ^oC.

IR (NaCl): 3488, 2932, 2852, 1723, 1447, 1166, 1048 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): □3.71 (bs, 1H), 3.61 (m, 1H), 2.38-2.15 (m, 2H), 2.03-1.67 (m, 7H), 1.60-1.20 (m, 5H). ^1H NMR (400 MHz, CD_3OD): □4.79 (s, 1H), 3.51 (dd, *J*=9.2, 4.3 Hz, 1H), 2.36-2.18 (m, 2H), 2.01-1.71 (m, 6H), 1.66-1.58 (m, 2H), 1.43-1.16 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): d 225.9, 70.9, 51.6, 38.4, 32.6, 28.8, 26.9, 20.8, 19.6, 18.7. LRMS (EI+) *m/z* (relative intensity): 168 (M, 21), 150 (56), 132 (21),

122 (12), 108 (39), 97 (100), 91 (12), 81 (53), 67 (33), 55 (39). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.87; H, 9.76.

Figure F. ORTEP representation of the crystal structure of **19**





(1S*,6R*)-Triisopropyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane (26)

To a solution of 150 mg (0.98 mmol) of 1-cyclohex-1-enylcyclobutanol and 130 mg of sodium bicarbonate in 10 mL of a 3:2 mixture of dichloromethane-water was added 320 mg (2.16 mmol) of *m*-chloroperbenzoic acid. The mixture was stirred for 1 h at rt. Saturated aqueous sodium bicarbonate solution was added and the mixture extracted with dichloromethane. The organic extracts were dried (sodium sulfate), filtered and concentrated *in vacuo*. Column chromatography on silica gel (10% ethyl acetate-hexanes to 20% ethyl acetate-hexanes) gave 162 mg (99%) of a colorless oil that was carried on to the next reaction.

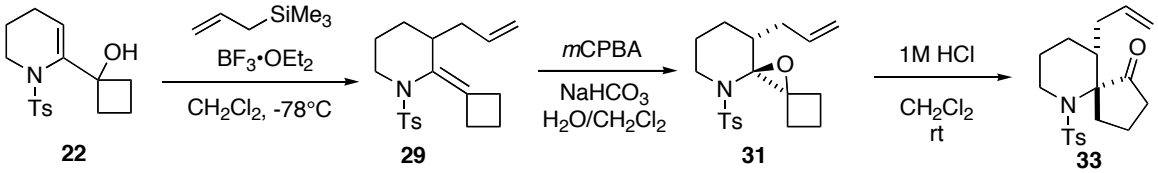
A solution of 103 □L (0.384 mmol) of triisopropylsilyl triflate and 70 □L (0.6 mmoL) of 2,6-lutidine in 2.0 mL of THF was stirred for 10 min, then added to a solution of 40 mg (0.24 mmoL) of 1-(7-oxa-bicyclo[4.1.0]hept-1-yl) **2.13** in 5.0 mL of THF was added. The reaction mixture was stirred for 14 h at rt and poured into an aqueous saturated $NaHCO_3$ solution. 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 on silica gel (5% ethyl acetate-hexanes) yielded 48 mg (62% after 3 purifications) of a clear liquid.

IR (NaCl): 2943, 2867, 1463, 1252, 1163, 1038 cm^{-1}. ^1H NMR (300 MHz, $(CD_3)_2CO$): □ 3.15 (bs, 1H), 2.26-2.19 (m, 1H), 2.17-1.92 (m, 5H), 1.84-1.60 (m, 3H), 1.55-1.42 (m, 2H), 1.35-1.24 (m, 3H), 1.10 (bs, 21H). ^{13}C NMR (75 MHz, $CD_3)_2CO$): □ 79.9, 62.5, 55.7, 34.1, 33.8, 24.8, 22.3, 20.5, 19.2, 14.6, 13.3. LRMS (EI+) *m/z* (relative intensity): 296 (M^+), 281 (M^+-CH_3).

(5S*,6S*)-6-Hydroxyspiro[4.5]decan-1-one (19)

To a solution of 6.3 mg (0.019 mmol) of triisopropyl[1-(7-oxa-bicyclo[4.1.0]hept-1-yl)cyclobutoxy]silane **26** in 2.0 mL of CH_2Cl_2 at –78 °C was added 21.4 □L of a 1.0 M solution (0.021 mmol) of titanium tetrachloride. The reaction mixture was stirred for 0.5 h at –78 °C and then warmed to rt and poured into a saturated aqueous sodium chloride solution. 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 on silica gel (20% ethyl acetate-hexanes) yielded 6 mg (95%) of a white solid.

Part E: Substrates with Substituents at the 3-Position



3-Allyl-2-cyclobutylidene-1-(toluene-4-sulfonyl)-piperidine (29)
To a solution of 100 mg (0.325 mmol) of **22** in 5.0 mL of CH_2Cl_2 at rt was added slowly 103 □L (0.650 mmol) of allyltrimethylsilane. The reaction mixture was cooled to –78 °C and 124 □L (0.975 mmol) of boron trifluoride-diethyl etherate was slowly added. The reaction mixture was stirred at –78 °C for 45 min. Silica gel and 2.0 mL of Et_2O were added and the mixture was concentrated to dryness by evaporation *in vacuo*. Purification by column chromatography on silica gel (10% ethyl acetate-hexanes) yielded 90 mg (84%) of a clear oil.

IR (NaCl): 2928, 1336, 1154 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □ 7.75 (d, *J*=8.2 Hz, 2H), 7.26 (d, *J*=8.2 Hz, 2H), 5.85-5.74 (m, 1H), 5.02-4.96 (m, 2H),3.59 (dt, *J*=12.8, 3.3 Hz, 1H), 3.14-3.07 (m, 1H), 2.91-2.53 (m, 4H), 2.41 (s, 3H), 2.34-2.25 (m, 2H), 2.00-1.86 (m, 3H), 1.68-1.52 (m, 3H), 1.35-1.29 (m, 1H). ^{13}C NMR (75 MHz, ($CDCl_3$): □ 142.8, 138.7, 138.3, 137.4, 129.3, 128.7, 127.3, 115.7, 48.5, 36.1, 36.0, 30.4, 29.4, 29.3, 21.4, 20.6, 16.5. LRMS (EI+) *m/z* (relative intensity): 331 (M). Anal. Calcd for $C_{19}H_{25}NO_2S$: C, 68.85; H, 7.60; N, 4.23. Found: C, 68.69; H, 7.68; N, 4.35.

(5S*,10R*)-10-Allyl-6-(toluene-4-sulfonyl)-11-oxa-6-aza-dispiro[3.0.5.1]undecane (31)

To a solution of 71 mg (0.214 mmol) of **29** in 6.0 mL of CH_2Cl_2 and 4.0 mL of water at rt was added 28 mg (0.30 mmol) of sodium bicarbonate and 117 mg (0.428 mmol) of *m*-chloroperbenzoic acid. The reaction mixture was stirred for 4 h and was incomplete. Additional portions of 28 mg (0.30 mmol) of sodium bicarbonate and 117 mg (0.428mmol) of *m*-chloroperbenzoic acid were added. The reaction mixture was stirred for 14 h at rt and poured into a saturated aqueous $NaHCO_3$ solution. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography on silica gel pre-treated with 5% Et_3N in hexane (10% ethyl acetate-hexanes) yielded 57 mg (77%) of a white solid (mp=decomposition under heat).

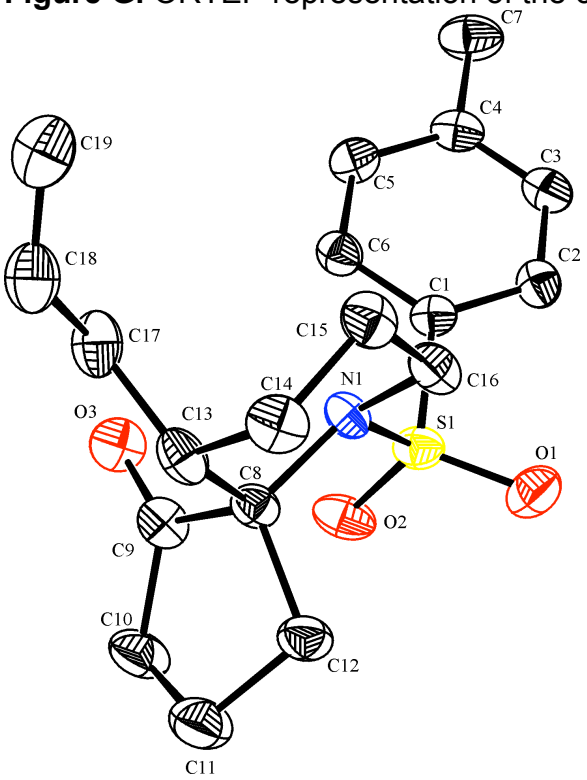
IR (NaCl): 2940, 1330, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □7.57 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.2 Hz, 2H), 5.84-5.73 (m, 1H), 5.13-5.01 (m, 2H), 3.50-3.32 (m, 2H), 2.56-2.41 (m, 4H), 2.37 (s, 3H), 2.35-2.25 (m, 1H), 2.19-2.10 (m, 1H), 2.03-1.94 (m, 2H), 1.86-1.70 (m, 3H), 1.64-1.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): □142.8, 138.9, 136.3, 129.3, 126.3, 116.5, 76.2, 72.5, 47.0, 39.3, 32.7, 30.7, 30.0, 25.4, 21.3, 20.9, 13.2. LRMS (EI+) *m/z* (relative intensity): 347 (M^+).

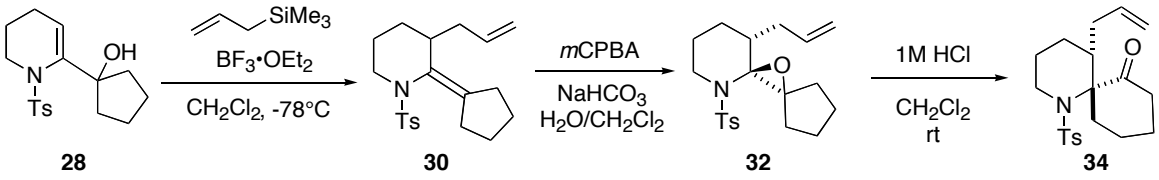
10-Allyl-6-(toluene-4-sulfonyl)-6-aza-spiro[4.5]decane-1-one (33)

To a solution of 10 mg (0.0288 mmol) of **31** in 1.0 mL of CH_2Cl_2 was added 29 □L (0.0288 mmol) of 1M HCl at rt. The reaction mixture was stirred for 10 min. The reaction mixture was poured into water. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography on silica gel (10% ethyl acetate-hexanes) yielded 9 mg (90%) of a white solid (mp~0 °C).

IR (NaCl): 2952, 1744, 1326, 1155 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □7.88 (d, *J*=7.9 Hz, 2H), 7.29 (d, *J*=7.9 Hz, 2H), 5.65-5.54 (m, 1H), 4.98 (bs, 1H), 4.94 (d, *J*=6.1 Hz, 1H), 3.26 (dt, *J*=10.4, 3.0 Hz, 1H), 3.11 (td, *J*=12.2, 3.6 Hz, 1H), 2.68 (qu, *J*=9.5 Hz, 1H), 2.56-2.46 (m, 2H), 2.42 (s, 3H), 2.38-2.24 (m, 2H), 2.20-2.11 (m, 1H), 2.05-1.95 (m, 1H), 1.85-1.70 (m, 3H), 1.68-1.48 (m, 2H), 1.38-1.25 (m, 1H). ^{13}C NMR (75 MHz, ($CDCl_3$): □214.3, 143.2, 137.7, 136.8, 129.3, 127.8, 116.3, 77.2, 69.0, 43.9, 37.9, 36.6, 34.8, 31.8, 21.5, 19.0, 17.9. LRMS (EI+) *m/z* (relative intensity): 347 (M^+).

Figure G. ORTEP representation of the crystal structure of **33**





28 **30** **32** **34**

3-Allyl-2-cyclopentylidene-1-(toluene-4-sulfonyl)-piperidine (30)

To a solution of 100 mg (0.311 mmol) of **28** in 5.0 mL of CH_2Cl_2 at rt was added slowly 99 μL (0.622 mmol) of allyltrimethylsilane. The reaction mixture was cooled to -78°C and 118 μL (0.933 mmol) of boron trifluoride diethyl etherate was slowly added. The reaction mixture was stirred at -78°C for 45 min. Silica gel and 2.0 mL of Et_2O were added and the mixture was concentrated to dryness by evaporation *in vacuo*. Purification by column chromatography (10% ethyl acetate-hexanes) yielded 96 mg (89%) of a clear oil.

IR (NaCl): 2947, 1335, 1155 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J*=8.2 Hz, 2H), 7.27 (d, *J*=8.2 Hz, 2H), 5.92-5.81 (m, 1H), 5.05-4.96 (m, 2H), 3.73-3.63 (m, 1H), 2.95-2.88 (m, 1H), 2.57-2.21 (m, 6H), 2.41 (s, 3H), 2.13-2.05 (m, 1H), 1.81-1.56 (m, 7H), 1.50-1.40 (m, 1H), 1.30-1.23 (m, 1H). ^{13}C NMR (75 MHz,

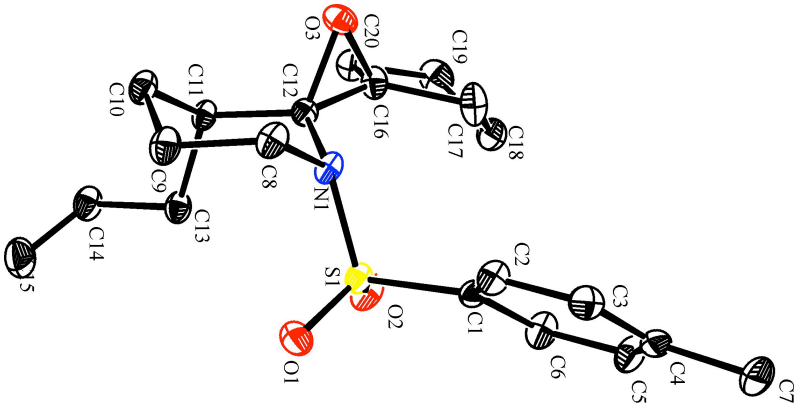
($CDCl_3$): □143.0, 142.6, 138.2, 137.4, 129.1, 128.3, 127.2, 115.4, 76.4, 48.1, 37.3, 35.5, 32.0, 30.1, 28.5, 26.2, 21.2, 19.4. LRMS (EI) *m/z* (relative intensity): 346 (M^+ + 1). 345 (M^+),

(6S*,11R*)-11-Allyl-7-(toluene-4-sulfonyl)-12-oxa-7-aza-dispiro[4.0.5.1]dodecane (32)

To a solution of 28 mg (0.081 mmol) of **30** in 3.0 mL of CH_2Cl_2 and 2.0 mL of H_2O at rt were added 11 mg (0.13 mmol) of $NaHCO_3$ and 44 mg (0.162 mmol) of *m*-chloroperbenzoic acid. The reaction mixture was stirred for 4 h. A second portion of 11 mg (0.13 mmol) of $NaHCO_3$ and 44 mg (0.162 mmol) of *m*-chloroperbenzoic acid was added. The reaction mixture was stirred for 14 h at rt and poured into a saturated aqueous $NaHCO_3$ solution. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography on silica gel (10% ethyl acetate-hexanes) yielded 24 mg (82%) of a white solid, mp=89-91 °C.

IR (NaCl): 2951, 1329, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □7.64 (d, *J*=8.2 Hz, 2H), 7.25 (d, *J*=8.2 Hz, 2H), 5.87-5.74 (m, 1H), 5.18-5.00 (m, 2H), 3.56-3.48 (m, 1H), 3.32-3.22 (m, 1H), 2.70-2.55 (m, 2H), 2.39 (s, 3H), 2.32-2.21 (m, 1H), 2.19-2.05 (m, 2H), 2.03-1.39 (m, 10H). ^{13}C NMR (75 MHz, ($CDCl_3$): □143.0, 138.4, 136.5, 129.5, 126.4, 116.5, 79.9, 46.7, 40.1, 33.1, 32.2, 30.7, 25.0, 24.1, 21.4, 19.3. LRMS (EI+) *m/z* (relative intensity): 361 (M^+). Anal. Calcd for $C_{20}H_{27}NO_3S$: C, 66.45; H, 7.53; N, 3.87. Found: C, 66.85; H, 7.65; N, 4.03.

Figure H. ORTEP representation of the crystal structure of **32**

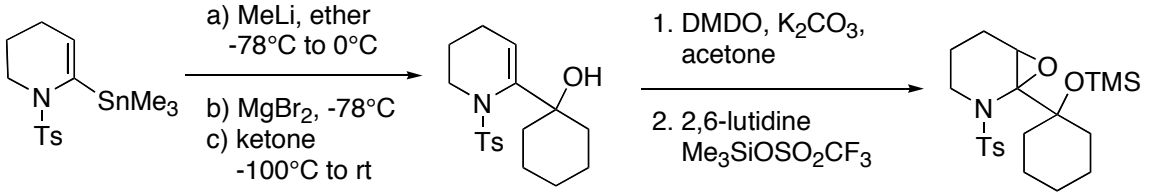


(6*R,11*R**)-11-Allyl-6-(toluene-4-sulfonyl)-7-aza-spiro[5.5]undecane-1-one (34)**

To a solution of 13 mg (0.0366 mmol) of **32** in 1.0 mL of CH_2Cl_2 at rt was added 36 μL (0.0366 mmol) of 1M HCl. The reaction mixture was stirred for 2 h, then poured into water. The organic and aqueous layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography on silica gel (10% ethyl acetate-hexanes) yielded 12 mg (91%) of a white solid (mp~0 °C).

IR (NaCl): 2948, 2870, 1715, 1454, 1322, 1154 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J*=7.9 Hz, 2H), 7.29 (d, *J*=7.9 Hz, 2H), 5.70-5.58 (m, 1H), 5.00 (d, *J*=6.1 Hz, 1H), 4.97 (bs, 1H), 3.23 (t, *J*=9.5 Hz, 1H), 3.21 (d, *J*=9.5 Hz, 1H), 2.69 (dm, *J*=9.5 Hz, 1H), 2.53 (t, *J*=9.5 Hz, 2H), 2.42 (s, 3H), 2.28-2.19 (m, 1H), 2.10-1.84 (m, 5H), 1.76-1.70 (m, 2H), 1.69-1.54 (m, 3H), 1.48-1.44 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 138.9, 136.3, 129.3, 126.3, 116.5, 76.2, 72.5, 47.0, 39.3, 32.7, 30.7, 30.0, 25.4, 21.3, 20.9, 13.2. LRMS (EI+) *m/z* (relative intensity): 361 (M^+).

Part F: Construction of 35 and Attempts to Ring Expand



35

1-[1'-(Toluene-4''-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclohexanol

A 1.40 M etheral solution of methyllithium (1.25 mL, 1.75 mmol, 2.2 equiv) was added to a solution of 1-(toluene-4'-sulfonyl)-6-trimethylstannyl-1,2,3,4-tetrahydropyridine (317 mg, 0.791 mmol, 1.0 equiv) in 12 mL of diethyl ether at –78 °C. The solution was warmed to 0 °C, stirred for 10 min, and recooled to -78 °C. A solution of magnesium bromide diethyl etherate (522 mg, 2.02 mmol, 2.6 equiv) in 10 mL of diethyl ether was added, and the mixture was stirred at -78 °C for 0.5 h. The mixture was cooled to -100 °C, and a cold (-100 °C) solution of freshly distilled cyclohexanone (215 mL, 2.07 mmol, 2.6 equiv) in diethyl ether (10 mL) was added. The mixture was stirred at -100 °C for 2 h, then warmed to rt as it was stirred overnight. The solvent was removed by concentration *in vacuo*. Purification by column chromatography (2/9 ethyl acetate-hexanes) on SiO_2 gave 233 mg (88%) of a white solid.

mp = 109-110 ˚C (ethyl acetate-hexanes). IR (KBr): 3512, 2942, 1593, 1330, 1159 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d 7.78 (d, *J*=8.2 Hz, 2H), 7.25 (d, *J*=8.2 Hz, 2H), 5.82 (t, *J*=4.3 Hz, 1H), 4.65 (s, 1H), 3.44 (t, *J*=6.3 Hz, 2H), 2.40 (s, 3H), 1.99-1.24 (14H). ^{13}C NMR (75 MHz, $CDCl_3$): d 144.0, 143.8, 136.9, 129.6, 127.7, 124.1, 72.8, 48.2, 37.2, 25.9, 22.7, 21.6, 21.1, 19.7. HRMS (EI+): Calcd for $C_{18}H_{25}NO_3S$ (M^+): 335.1555. Found 335.1554.

1-(Toluene-4'-sulfonyl)-6-(1''-trimethylsilyloxycyclohexyl)-1,2,3,4-tetrahydropyridine

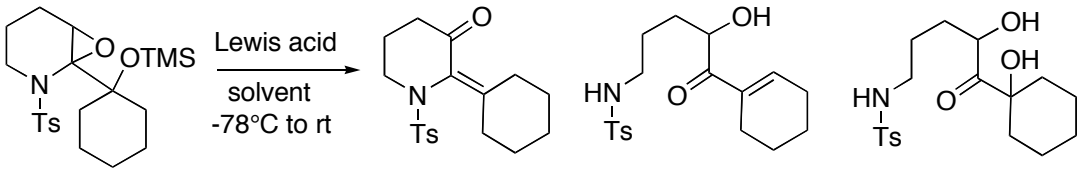
A solution of freshly distilled 2,6-lutidine (64.0 mL, 0.553 mmol, 2.5 equiv) and trimethylsilyl trifluoromethanesulfonate (64.0 mL, 0.353 mmol, 1.6 equiv) in 4 mL of THF was stirred for 10 min, then added to a solution of 74.1 mg of 1-[1'-(toluene-4''-sulfonyl)-1,4,5,6-tetrahydropyridin-2-yl]-cyclohexanol (0.221 mmol, 1.0 equiv) in 3 mL of THF. The mixture was stirred at rt for 0.5 h and then poured into a saturated solution of aqueous sodium bicarbonate, and extracted with diethyl ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by column chromatography (1/12 ethyl acetate-hexanes; 1% triethylamine) on SiO_2 afforded 70.1 mg (78%) of a white solid.

mp=71-73 ˚C (ethyl acetate-hexanes). IR (KBr): 2954, 2861, 1445, 1346, 1164 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): □7.76 (d, *J*=8.2 Hz, 2H), 7.23 (d, *J*=7.9 Hz, 2H), 6.00 (t, *J*=4.6 Hz, 1H), 3.43 (t, *J*=6.5 Hz, 2H), 2.39 (s, 3H), 2.35-2.26 (m, 2H), 1.71-1.51 (m, 6H), 1.50-1.19 (m, 6H), 0.11 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): □146.7, 143.0, 137.6, 129.1, 127.6, 125.6, 48.1, 37.3, 25.1, 22.7, 21.3, 20.3, 20.1, 2.5. HRMS (DCI+, ammonia/isobutane): Calcd for $C_{21}H_{33}NO_3SSi$ (M^+): 407.1950. Found 407.1956.

(1*S, 6*R**)-2-(Toluene-4'-sulfonyl)-1-(1''-trimethylsilyloxycyclohexyl)-7-oxa-2-azabicyclo[4.1.0]heptane (35)**

To a solution of 1-(toluene-4'-sulfonyl)-6-(1''-trimethylsilanyloxycyclohexyl)-1,2,3,4-tetrahydropyridine (464 mg, 1.14 mmol, 1.0 equiv) in dichloromethane (30 mL) was sequentially added an aqueous solution of sodium bicarbonate (0.50 M, 7.0 mL, 3.5 mmol, 3.1 equiv) and 3-chloroperoxybenzoic acid (394 mg, 2.28 mmol, 2.0 equiv) at rt. The reaction mixture was stirred for 5 h and poured into a saturated solution of aqueous sodium bicarbonate. The two layers were separated and the organic layer was washed with a saturated solution of aqueous sodium bicarbonate. This procedure was repeated twice more. The organic layer was dried over magnesium sulfate, filtered, and concentrated by evaporation *in vacuo*. Purification by column chromatography (1/9 ethyl acetate-hexanes; 1% triethylamine) on SiO_2 yielded 400 mg (83%) of a semisolid.

IR (CCl_4): 2935, 2861, 1356, 1165 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.86 (d, *J*=8.3 Hz, 2H), 7.26 (d, *J*=8.3 Hz, 2H), 3.42 (dt, *J*=14.6, 3.9 Hz, 1H), 3.19 (t, *J*=2.8 Hz, 1H), 2.85-2.74 (m, 1H), 2.40 (s, 3H), 2.23-2.16 (m, 1H), 1.86 (td, *J*=13.4, 3.9 Hz, 1H), 1.77-1.68 (m, 2H), 1.67-0.80 (m, 10H), 0.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 143.6 (Q), 137.4 (Q), 129.3 (CH), 128.7 (CH), 77.1 (Q), 75.1 (Q), 52.4 (CH), 45.0 (CH_2), 37.5 (CH_2), 33.3 (CH_2), 25.5 (CH_2), 21.9 (CH_2), 21.5 (CH_3), 21.3 (CH_2), 17.5 (CH_2), 2.3 (CH_3). HRMS (DCI+, ammonia/isobutane): Calcd for $C_{21}H_{34}NO_4SSi$ (M^+ + 1): 424.1978. Found 424.1973.



35 **36** **37** **38**

$MgBr_2$, CH_2Cl_2	*73%*	*trace*	*trace*
TMSOTf, CH_2Cl_2	—	*77%*	*trace*
BF_3•OEt_2, MeOH	*14%*	—	*85%*

2-Cyclohexylidene-1-(toluene-4'-sulfonyl)-piperidin-3-one (36)

***N*-(5'-Cyclohex-1''-enyl-4'-hydroxy-5'-oxopentyl)-4-methylbenzenesulfonamide (37)**

***N*-[4'-Hydroxy-5'-(1''-hydroxycyclohexyl)-5'-oxopentyl]-4-methylbenzenesulfonamide (38)**

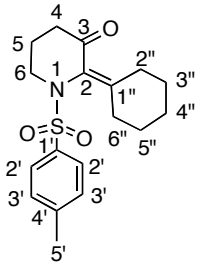
Protocol Using Magnesium Bromide-Diethyl Etherate

A cold (-78 °C) solution of 23.0 mg of (1*S**, 6*R**)-2-(toluene-4'-sulfonyl)-1-(1''-trimethylsilyloxycyclohexyl)-7-oxa-2-azabicyclo[4.1.0]heptane (**35**) (0.0543 mmol) in 2.8 mL of dichloromethane was added to a cold round bottom (-78 °C) containing 15.3 mg of magnesium bromide diethyl etherate (0.0831 mmol). The mixture was stirred at -78 °C for 0.5 h, at -42 °C for 0.5 h, at -15 °C for 0.5 h, at 0 °C for 7h, and overnight at rt. The reaction mixture was 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 on silica gel (1/3 to 4/5 ethyl acetate-hexanes) yielded 13.2 mg (73%) of **36** as a clear oil.

IR (CCl_4): 2936, 2857, 1697, 1614, 1360, 1166 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.59 (d, *J*=8.2 Hz, 2H), 7.25 (d, *J*=8.9 Hz, 2H), 3.70 (ddd, *J*=12.8, 10.1, 6.6 Hz,

1H), 3.59-3.51 (m, 1H), 2.85-2.76 (m, 1H), 2.71-2.62 (m, 1H), 2.61-2.53 (m, 1H), 2.47 (ddd, *J*=13.7, 8.9, 4.9 Hz, 1H), 2.38 (s, 3H), 2.04 (dt, *J*=17.1, 4.1 Hz, 1H), 1.91-1.80 (m, 1H), 1.79-1.65 (m, 2H), 1.64-1.45 (m, 5H), 1.20 (ddd, *J*=17.1, 12.2, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 199.2, 160.5, 143.8, 135.7, 129.8, 127.5, 125.3, 46.2, 38.2, 31.9, 29.9, 28.0, 27.9, 26.0, 21.5, 19.9. LRMS (EI+) *m/z* (relative intensity): 333 (M^+, 15).

Table C: Selected NMR Data for 2-Cyclohexylidene-1-(toluene-4'-sulfonyl)-piperidin-3-one (36)



Carbon No.	^{13}C (ppm)[a]	APT[a]	^{1}H (ppm) (mult J (Hz))[b,c,d]	HMBC Correlations[e]
2	125.3	Q		
3	199.2	Q		H-4eq, H-4ax, H-5
4	38.2	CH_2	H-4eq: 2.04 (dt, 17.1, 4.1) H-4ax: 1.20 (ddd, 17.1, 12.2, 4.9)	H-6a, H-6b
5	19.9	CH_2	H-5: 1.79-1.65 (m)	H-4ax H-6a, H-6b
6	46.2	CH_2	H-6a: 3.70 (ddd, 12.8, 10.1, 6.6) H-6b: 3.59-3.51 (m)	H-4a, H-4b
1'	135.7	Q		H-3'
2'	127.5	CH	H-2': 7.59 (d, 8.2)	
3'	129.8	CH	H-3': 7.25 (d, 8.9)	H-2', H-5'
4'	143.8	Q		H-2', H-5'
5'	21.5	CH_3	H-5': 2.38 (s)	H-3'
1''	160.5	Q		

[a] Recorded at 75 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC data.
[d] Methylene protons are arbitrarily designated H-Xa and H-Xb or are designated H-Xeq and H-Xax if they are known to occupy axial and equatorial position, respectively.
[e] Only those correlations which could be unambiguously assigned are recorded.

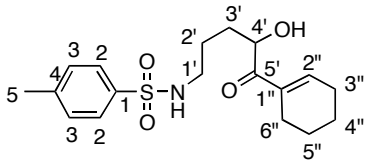
Protocol Using Trimethylsilyl Triflate

To a cooled (-78 °C) solution of 29.7 mg of (1*S**, 6*R**)-2-(toluene-4'-sulfonyl)-1-(1''-trimethylsilyloxycyclohexyl)-7-oxa-2-azabicyclo[4.1.0]heptane (**35**) (0.0701 mmol) in 3.5 mL of dichloromethane was added 15 L of freshly distilled trimethylsilyltrifluoromethanesulfonate (0.0827 mmol). The mixture was stirred at -78 °C for 0.5 h. Water was added and the solution was warmed to rt. The mixture was 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 on silica gel (4/5 ethyl acetate-hexanes) yielded 19.0 mg (77%) of **37** as a clear oil.

IR (CCl_4): 3471, 3279, 2938, 2864, 1664, 1636, 1332, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.70 (d, *J*=8.3 Hz, 2H), 7.28 (d, *J*=8.3 Hz, 2H), 6.87-6.82 (m, 1H), 4.73-4.67 m, 2H), 3.85-3.40 (m, 1H), 3.02-2.87 (m, 2H), 2.40 (s, 3H), 2.31-2.24 (m, 3H), 2.12-2.01 (m, 1H), 1.88-1.78 (m, 1H), 1.71-1.48 (m, 5H), 1.44-1.33 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 201.9, 143.4, 142.9, 137.0, 135.9, 129.7, 127.0, 71.1, 42.8, 33.5, 26.2, 25.4, 23.2, 21.7, 21.5, 21.4. LRMS (EI+) *m/z* (relative intensity): 351 (M^+, 1.8).

Table D. Selected NMR Data for (±)-*N*-(5'-Cyclohex-1''-enyl-4'-hydroxy-5'-oxopentyl)-4-methylbenzenesulfonamide (37)



Carbon No.	^{13}C (ppm)[a]	APT[a]	^1H (ppm) (mult J (Hz))[b,c,d]	HMBC Correlations[e]
1	137.0	Q		H-2, H-3
2	127.0	CH	H-2: 7.70 (d, 8.3)	H-3
3	129.7	CH	H-3: 7.28 (d, 8.3)	H-2, H-5
4	143.4	Q		H-2, H-5
5	21.5	CH_3	H-5: 2.40 (s)	H-3,
1'	42.8	CH_2	H-1': 3.02-2.87 (m)	
2'	25.4	CH_2	H-2': part of m at 1.71-1.48	H-1', H-4'
3'	33.5	CH_2	H-3'a: 1.88-1.78 (m)	H-1', H-4'
			H-3'b: 1.44-1.33 (m)	
4'	71.1	CH	H-4'': part of m at 4.73-4.67	H-3'a, H-3'b
5'	201.9	Q		H-2'', H-4', H-3'
1''	135.9	Q		
2''	142.9	CH	H-2'': 6.87-6.82 (m)	

[a] Recorded at 75 MHz. [b] Recorded at 400 MHz. [c] Assignments based on HMQC data.
[d] Methylene protons are arbitrarily designated H-Xa and H-Xb.
[e] Only those correlations which could be unambiguously assigned are recorded.

Protocol Using Boron Trifluoride·Etherate

To a cooled (-78 °C) solution of (1*S**, 6*R**)-2-(toluene-4'-sulfonyl)-1-(1''-trimethylsilyloxycyclohexyl)-7-oxa-2-azabicyclo[4.1.0]heptane (**35**) (22.8 mg, 0.0538 mmol, 1.0 equiv) in freshly distilled methanol (2.7 mL) was added boron trifluoride dimethyl etherate (9.5 L, 0.0750 mmol, 1.4 equiv). The mixture was stirred at -78 °C for 3 h, warmed to -42 °C and stirred for 6 h, and warmed to rt and stirred overnight. The reaction mixture was poured into a saturated solution

of sodium 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 concentrated by evaporation *in vacuo*. Purification by column chromatography (4/5 ethyl acetate-hexanes) on SiO_2 yielded 2.6 mg (14%) of 2-cyclohexylidene-1-(toluene-4'-sulfonyl)-piperidin-3-one (**36**) as a clear oil and 16.1 mg (81%) of *N*-[4'-Hydroxy-5'-(1''-hydroxycyclohexyl)-5'-oxopentyl]-4-methylbenzenesulfonamide (**38**) as a clear oil.

IR (CCl_4): 3500, 3283, 2935, 2859, 1706, 1327, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): □7.72 (d, *J*=8.2 Hz, 2H), 7.28 (d, *J*=7.9 Hz, 2H), 5.09-5.02 (m, 1H), 4.61 (ddd, *J*=8.5, 7.0, 2.7 Hz, 1H), 3.28 (d, *J*=7.0 Hz, 1H), 2.98 (dd, *J*=12.8, 6.4 Hz, 2H), 2.78 (s, 1H), 2.40 (s, 3H), 2.06-1.96 (m, 1H), 1.80-1.49 (m, 11H), 1.46-1.35 (m, 1H), 1.32-1.19 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): □216.5 (Q), 143.5 (Q), 136.8 (Q), 129.7 (CH), 127.1 (CH), 79.0 (Q), 72.7 (CH), 42.5 (CH_2), 34.5 (CH_2), 34.0 (CH_2), 30.9 (CH_2), 25.4 (CH_2), 24.9 (CH_2), 21.5 (CH_3), 20.5 (CH_2). LRMS (EI+) *m/z* (relative intensity): 392 ($M^+ + Na^+$, 100).