2. Synthesis of the ABC Ring System of Azaspiracid: A Systematic Study into the Effect of C_{16} and C_{17} Substitution on Bisspirocyclization.

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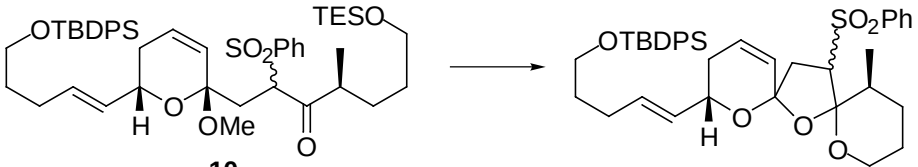
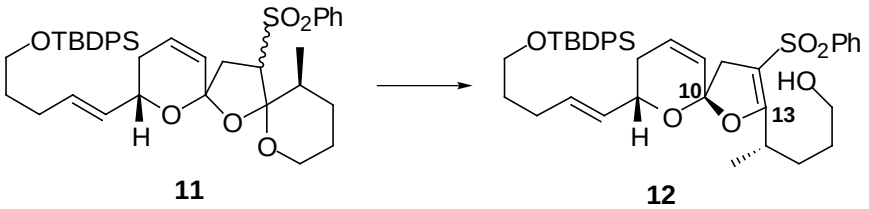
Electronic Supplementary Information

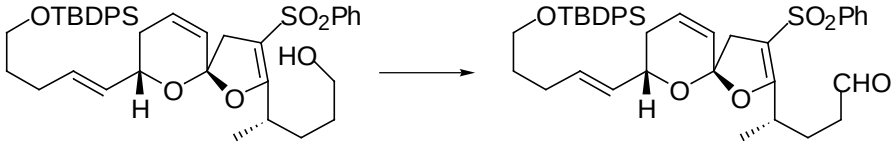


Sulfone Spirocycle 11: To a stirred solution of **10** (68 mg, 0.083 mmol) in MeCN (9 mL) at r.t. was added CSA (8.8 mg, 0.038 mmol). After 2 h, the reaction was quenched with solid $NaHCO_3$ (250 mg). The mixture was diluted with 35% EtOAc / hexanes (50 mL), filtered through a small plug of silica gel (35% EtOAc / hexanes rinse), and concentrated *in vacuo*. The resultant oil was purified by chromatography over silica gel, eluting with 6-40% EtOAc / hexanes, to give **11** (52 mg, 0.076 mmol, 91%) as a colorless oil: IR (neat) 3069, 3046, 2930, 2857, 1471, 1446, 1427, 1307, 1150, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.93 (m, 2H), 7.59-7.67 (m, 5H), 7.48-7.55 (m, 2H), 7.32-7.44 (m, 6H), 6.03-6.09 (m, 1H of a diastereomer), 5.88 - 5.93 (m, 1H of a diastereomer), 5.41-5.70 (m, 3H), 4.33-4.47 (m, 1H), 4.15 (dd, J = 7.0, 13.2 Hz, 1H of a diastereomer), 3.35-3.82 (m, 2H & 1H of a diastereomer), 2.70 (dd, J = 12.4, 12.4 Hz, 1H of a diastereomer), 2.52-2.60 (m 1H of a diastereomer), 2.3-2.43 (m, 1H), 1.90-2.20 (m, 5H), 1.40-1.80 (m, 7H), 1.14 (d, J = 5.9 Hz, 3H of a diastereomer), 1.04 (s, 9H of a diastereomer), 1.03 (s, 9H of a diastereomer), 0.90 (d, J = 6.7 Hz, 3H of a diastereomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 139.3, 135.7, 134.2, 133.9, 133.8, 133.2, 132.1, 130.8, 130.1, 130.0, 129.8, 129.4, 128.4, 128.2, 127.8, 127.3, 126.8, 109.9, 107.3, 102.53, 102.46, 73.8, 70.8, 69.3, 66.6, 63.5, 63.4, 61.3, 41.2, 38.7, 35.4, 34.8, 32.1, 32.0, 30.1, 29.9, 29.4, 28.9, 28.8, 28.5, 27.1, 26.0, 25.3, 19.4, 18.2, 16.4, 15.5; HRMS (FAB+) calcd. for $C_{40}H_{51}O_6SSi$ (M+H) 687.3176, found 687.3154.



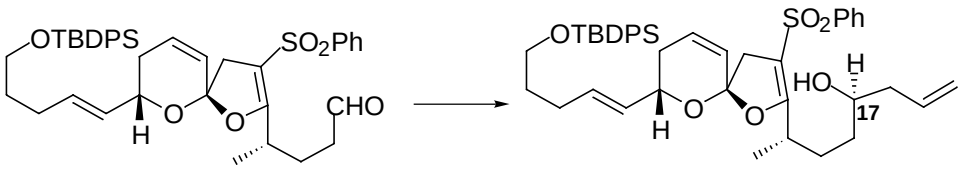
Sulfone Enol Ether 12: To a stirred solution of **11** (51 mg, 0.75 mmol) in THF (2.3 mL) at -78°C was added dropwise *n*-BuLi (35 µL, 0.0875 mmol, 2.5 M in hexanes). An additional portion of *n*-BuLi (6 µL, 0.015 mmol, 2.5 M in hexanes) was added during the course of the reaction. After 70 min, the reaction was quenched with solid SiO_2 (500 mg). After 5 min, the mixture was further diluted with sat. aq. NH_4Cl (20 mL) and extracted with Et_2O (4 X 25 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 6-50% EtOAc / hexanes, to give **12** (35.8 mg, 0.0.22 mmol, 70%) followed by C_{10}-epi **12** (5.0 mg, 0.0.073, 10%) as

colorless oils. **12**: $[\alpha]_D^{23}$ +62.4° (c 180, $CHCl_3$); IR (neat) 3444, 2929, 2856, 1624, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.6 Hz, 2H), 7.66 (d, J = 6.7 Hz, 4H) 7.49-7.60 (m, 3H), 7.36-7.41 (m, 6H), 6.06-6.12 (m, 1H), 5.69 (d, J = 10.9 Hz, 1H), 5.65 (dt, J = 6.6, 15.7 Hz, 1H), 5.46 (dd, J = 6.0, 15.7 Hz, 1H), 4.35-4.43 (m, 1H), 3.65 (t, J = 6.2 Hz, 2H), 3.55 (t, J = 5.7 Hz, 2H), 2.91 (d, J = 15.1 Hz, 1H), 2.83 (d, J = 15.1 Hz, 1H), 2.00-2.17 (m, 4H), 1.49-1.67 (m, 7H), 1.14 (d, J = 6.9 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 142.5, 135.8, 134.2, 133.1, 133.0, 130.4, 129.8, 129.4, 129.3, 127.8, 127.0, 126.0, 108.7, 106.4, 70.6, 63.4, 62.9, 42.1, 32.0, 31.4, 30.6, 30.4, 28.8, 27.0, 19.4, 18.6, 15.5; HRMS (FAB+) calcd. for $C_{40}H_{51}O_6SSi$ (M+H) 687.3176, found 687.3158.



12 **23**

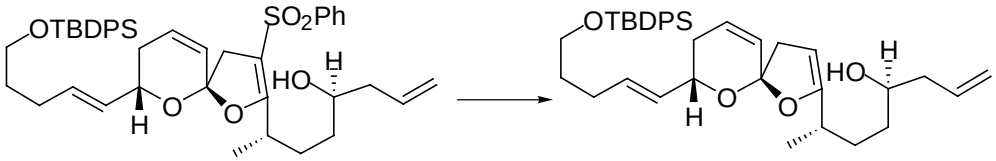
Aldehyde 23: To a stirred solution of **12** (21.6 mg, 0.0320 mmol) in CH_2Cl_2 (1.0 mL) with powdered 4 Å mol. sieves (250 mg) was sequentially added TPAP (2.5 mg, 6.3 μmol) and NMO (9.0 mg, 0.077 mmol) at r.t. After 30 min, the reaction was diluted with 33% EtOAc / hexanes (10 mL), filtered through a small plug of silica gel (33% EtOAc / hexanes rinse), and concentrated *in vacuo* to give **23** (21.0 mg, 0.031 mmol, 97%) as a colorless oil: $[\alpha]_D^{23}$ +52.4° (c 1.03, $CHCl_3$); IR (neat) 2928, 28.55, 1724, 1627, 1110, 599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.87 (d, J = 6.8 Hz, 2H), 7.65 (dd, J = 1.5 , 6.0 Hz, 4H), 7.50-7.65 (m, 3H), 7.35-7.43 (m, 6H), 6.07-6.13 (m 1H), 5.68 (d, J = 10.5 Hz, 1H), 5.60 (dt, J = 6.5, 15.7 Hz, 1H), 5.41, (dd, J = 6.5, 15.7 Hz, 1H), 4.29-4.36 (m, 1H), 3.64 (t, J = 6.2 Hz, 2H), 3.51-3.59 (m, 1H), 2.84 (s, 2H), 2.32-2.43 (m, 2H), 1.95-2.15 (m, 4H) , 1.73-1.83 (m, 2H), 1.58-1.68 (m, 4H), 1.15 (d, J = 6.8 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 170.0, 135.8, 134.1, 133.2, 130.7, 129.8, 129.4, 129.2, 127.8, 127.0, 125.7, 109.9, 106.6, 70.9, 63.4, 42.0, 41.0, 41.7, 32.0, 30.0, 29.9, 28.8, 27.1, 26.3, 19.4, 18.5; HRMS (FAB+) calcd. for $C_{40}H_{49}O_6SSi$ (M+H) 685.3019, found 685.3020.



23 **13**

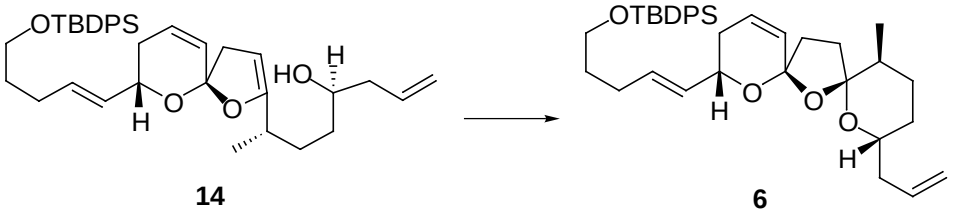
Homoallylic Alcohol 13: To a stirred solution of **23** (20.0 mg, 0.0292 mmol) in Et_2O (1.1 mL) at -100°C was added dropwise precooled $(Ipc)_2Ballyl$[1] (140 μL, 0.035

mmol, 0.25 M in pentane) *via* syringe. After 30 min, the reaction was quenched with MeOH (50µL) and warmed to r.t. The solution was further quenched with aq. phosphate buffer (800 µL, pH 7) and H_2O_2 (200 µL, 30% in H_2O). After 30 min, the solution was diluted with sat. aq. NaCl (25 mL) and extracted with Et_2O (4 X 25 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 7-40% EtOAc / hexanes, to give **13** (15.0 mg, 0.0.21 mmol, 71%) as a colorless oil. $[\alpha]_D^{23}$ +14.1° (c 0.68, $CHCl_3$); IR (neat) 3566, 2928, 2855, 2625, 1427, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85-7.90 (m, 2H), 7.65 (dd, J = 1.4, 7.4 Hz, 4H) 7.47-7.61 (m, 3H), 7.34-7.45 (m, 6H), 6.06-6.12 (m, 1H), 5.70-5.82 (m, 1H), 5.69 (d, J = 9.5 Hz, 1H), 5.66 (dt, J = 6.1, 15.7 Hz, 1H), 5.45 (dd, J = 5.4, 15.7 Hz, 1H), 5.04-5.10 (m, 2H), 4.37-4.45 (m, 1H), 3.64 (t, J = 6.3 Hz, 2H), 3.52-3.62 (m, 1H), 2.92 (d, J = 15.2 Hz, 1H), 2.84 (d, J = 15.2 Hz, 1H), 2.00-2.19 (m, 6H), 1.30-1.67 (m, 9H), 1.15 (d, J = 7.0 Hz, 3H), 1.05 (s, 9H); (75 MHz, $CDCl_3$) δ 170.3, 142.6, 135.8, 135.0, 134.1, 132.9, 132.7, 130.3, 129.8, 129.5, 129.3, 127.8, 126.9, 126.0, 118.2, 108.6, 106.4, 70.6, 70.4, 63.4, 42.2, 42.1, 34.5, 32.0, 31.4, 30.2, 30.0, 28.8, 27.0, 19.4, 18.9; HRMS (FAB+) calcd. for $C_{43}H_{55}O_6SSi$ (M+H) 727.3489, found 727.3504.



13 **14**

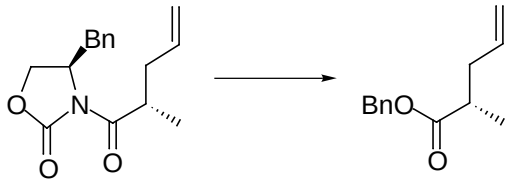
Desulfonylated Enol Ether 14: To a stirred solution of **13** (12.5 mg, 0.0175 mmol) in THF (0.3 mL) and MeOH (0.6 mL) at -10°C was sequentially added Na_2HPO_4 (36 mg) and Na / Hg (224 mg, 5% in Hg). After 20 min, the reaction was warmed to 0°C. After 1 h, the reaction was diluted with Et_2O, filtered through a small pad of celite® (Et_2O rinse) and concentrated *in vacuo*. The crude product **14** was used immediately in subsequent manipulations.



14 **6**

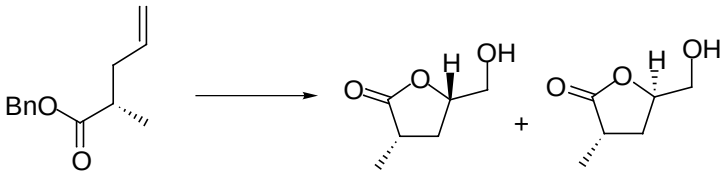
C_{17} Spirocycle 6: To a stirred solution of crude **14** (0.0175 mmol) in PhMe (1.0 mL) and *t*-BuOH (1.0 mL) was added CSA (17.1 mg, 0.0737 mmol) at r.t. After 14.5 h, the reaction was quenched with solid $NaHCO_3$ (250 mg). After 10 min, the solution was diluted with 25% EtOAc / hexanes (25 mL), filtered through a small plug of silica gel (25% EtOAc / hexanes rinse), and concentrated *in vacuo*. The resultant oil was purified

using preparative thin layer chromatography over silica gel, eluting with 20% EtOAc / hexanes, to give **6** (7.6 mg, 0.013 mmol, 76% over 2 steps) as a colorless oil: $[\alpha]_D^{23}$ -50.0° (c 0.38, $CHCl_3$); IR (neat) 3037, 2928, 2865, 1461, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.68 (m, 4H), 7.34-7.42 (m, 6H), 5.93-6.97 (m, 1H), 5.59-5.93 (m, 4H), 4.94-5.04 (m, 2H), 4.38-4.43 (m, 1H), 3.80-3.86 (m, 1H), 3.66 (t, J = 6.2 Hz, 2H), 1.99 - 2.25 (m, 12H), 1.5-1.78 (m, 5H), 1.04 (s, 9H), 0.87 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 134.4, 132.0, 131.0, 129.9, 129.0, 128.2, 128.0, 116.5, 110.1, 105.4, 70.9, 70.0, 63.8, 41.1, 37.9, 36.0, 32.4, 31.5, 30.6, 30.1, 29.2, 28.9, 27.3, 19.6, 16.7; HRMS (FAB+) calcd. for $C_{37}H_{49}O_4Si$ (M+H) 585.3400, found 585.3397.



15 **16**

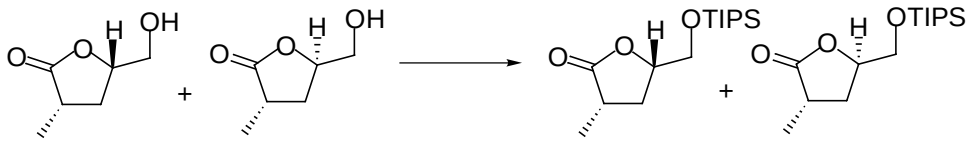
Benzyl ester 16: To a stirred solution of BnOH (4.49 g, 4.3 mL, 41.6 mmol) in THF (100 mL) at 0°C was added dropwise *n*-BuLi (11.5 mL, 28.8 mmol, 2.5 M in hexanes) *via* syringe. After 20 min, a solution of **15** (6.263 g, 22.9 mmol) in THF (15 mL) was added *via* cannula to the benzyl alcohol solution. Additional portion of THF (2 X 2.5 mL) was used to rinse the auxiliary flask. After 35 min, the reaction was quenched with sat. aq. NH_4Cl (100 mL) and concentrated *in vacuo* to remove the THF. The aqueous solution was extracted with Et_2O (4 X 200 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5-30% EtOAc / hexanes, to give **16** (4.665 g, 22.9 mmol, 99%) as a colorless oil. $[\alpha]_D^{23}$ +2.5° (c 4.32, $CHCl_3$); IR (neat) 3033, 2976, 1734, 1456, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.38 (m, 5H), 5.68-5.79 (m, 1H), 5.00-5.12 (m, 4H), 2.56-2.63 (m, 1H), 2.40-2.49 (m, 1H), 2.16-2.26 (m, 1H), 1.18 (d, J = 4.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 136.3, 135.6, 128.7, 128.34, 128.30, 117.1, 66.3, 39.5, 38.0, 16.7; HRMS (FAB+) calcd. for $C_{13}H_{17}O_2$ (M+H) 205.1229, found 205.1225.



16 **24** epi-**24**

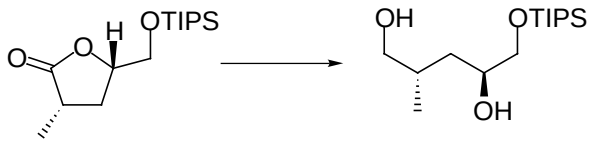
Lactone 24: To a stirred solution of **16** (285 mg, 1.40 mmol) in *t*-BuOH (6.1 mL) and H_2O (6.1 mL) at 0°C was sequentially added $NaHCO_3$ (564 mg, 6.71 mmol),

DHQ_2(PHAL) (32.0 mg, 0.041 mmol), $K_3Fe(CN)_6$ (1.336g, 4.06 mmol), K_2CO_3 (530 mg, 3.84 mmol) and $K_2OsO_2 \cdot 2H_2O$ (5.2 mg, 0.014 mmol). The solution was allowed to warm to 5°C. After 22.5 h, the reaction was quenched with solid $Na_2S_2O_3$ (1 g). After stirring for an additional 15 min, the solution was diluted with sat. aq. NaCl (200 mL) and extracted with EtOAc (4X 200 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and used without any further purification.



24 epi-**24** **17** epi-**17**

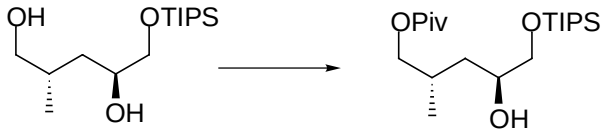
TIPS Ester 17: To a stirred solution of crude **24** (1.4 mmol) in CH_2Cl_2 (8 mL) at -78°C was sequentially added 2,6-lutidine (478 mg, 520 µL, 4.46 mmol) and TIPSOTf (1.12 g, 980 µL, 3.6 mmol). After 15 min, the reaction was quenched with NH_4Cl (50 mL) and extracted with Et_2O (3 X 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 2-14% EtOAc / hexanes, to give **17** and epi-**17** (265 mg, 66% overall yield from **16**). The more polar epimer **17** (165 mg, 0.58 mmol, 42% isolated yield) was isolated as a colorless oil. $[\alpha]_D^{23}$ +4.7° (c 3.35, $CHCl_3$); IR (neat) 2942, 2892, 1778, 1462, 1170, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42-4.47 (m ,1H), 4.93 (dd, J = 3.8, 11.0 Hz, 1H), 3.82 (dd, J = 4.1, 11.0, Hz, 1H), 2.65-2.75 (m, 1H), 2.37-2.45 (m, 1H), 1.81-1.93 (m, 1H), 1.29 (d, J = 7.1 Hz, 3H), 1.02-1.12 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 78.5, 64.5, 35.6, 32.2, 18.1, 15.6, 12.1; HRMS (FAB+) calcd. for $C_{15}H_{31}O_3Si$ (M+H) 287.2043, found 287.2045.



17 **18**

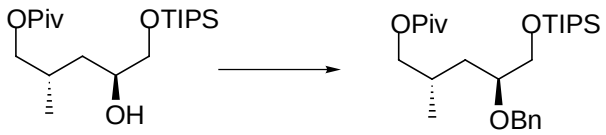
Diol 18: To a stirred solution of **17** (320 mg, 1.12 mmol) in THF (5.3 mL) at 0°C was sequentially added MeOH (42.7 mg, 54 µL, 1.33 mmol) and $LiBH_4$ (760 µL, 1.52 mmol, 2.0 M in THF). After 4 h, the reaction was quenched with sat. aq. NH_4Cl (50 mL) and extracted with Et_2O (4 X 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give **18** (325 mg, 1.12 mmol, 99%) as a colorless oil. $[\alpha]_D^{23}$ -4.1° (c 1.05, $CHCl_3$); IR (neat) 3344, 2862, 1463, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75-3.84 (m, 1H), 3.68 (dd, J = 3.6, 9.3 Hz, 1H), 3.58 (dd, J = 4.3, 11.0 Hz, 1H), 3.39-3.49 (m, 2H), 3.20 (bs, OH), 1.81-1.92 (m, 1H), 1.66 (bs, OH), 1.34-1.39 (m, 2H), 0.98-1.12

(m, 21H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.5, 69.0, 68.0, 38.4, 34.9, 18.4, 18.1, 12.1; HRMS (FAB+) calcd. for $C_{15}H_{35}O_3Si$ (M+H) 291.2356, found 291.2354.



18 **25**

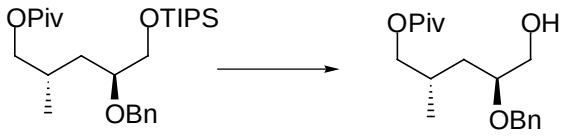
Pivolylated Alcohol 25: To a stirred solution of **18** (200 mg, 0.69 mmol) in CH_2Cl_2 (2.6 mL) at -78°C was sequentially added DMAP (9.0 mg, 0.074 mmol), Et_3N (87.4 mg, 120 µL, 0.864 mmol) and PivCl (98 mg, 100 µL, 0.822 mmol). The solution was allowed to warm to -30°C over a period of 2 h. The solution was then recooled to -78°C and an additional portions of PivCl (49 mg, 50µL, 0.41 mmol) and Et_3N (36.4 mg, 50µL, 0.36 mmol) were added to the solution. The reaction was allowed to warm to r.t. over a period of 45 min. The reaction was quenched with sat. aq. NH4Cl (50 mL) and extracted with Et_2O (4 X 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 4-40% EtOAc / hexanes, to give **25** (171 mg, 0.457 mmol, 66%) as a colorless oil: $[\alpha]_D^{23}$ -2.3° (c 1.56, $CHCl_3$); IR (neat) 3500, 2942, 2865, 1730, 1462, 1165 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (dd, J = 5.9, 10.8 Hz, 1H), 3.90 (dd, J = 9.3, 10.6 Hz, 1H), 3.67-3.81 (m, 2H), 3.48 (dd, J = 7.0, 9.5 Hz, 1H), 2.49 (bd, OH), 2.08-2.15 (m, 1H), 1.49-1.59 (m, 2H), 1.20 (s, 9H), 1.02-1.12 (m, 21H), 0.97 (m, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 69.8, 69.6, 68.2, 39.0, 36.6, 39.6, 27.4, 18.1, 16.7, 12.1; HRMS (FAB+) calcd. for $C_{20}H_{43}O_4Si$ (M+H) 375.2931, found 375.2935.



25 **19**

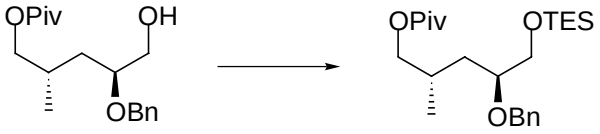
Benzyl ether 19: To a stirred solution of **25** (550 mg, 1.47 mmol) in DMF (6.8 mL) and BnBr (3.4 mL) at -50°C was added NaH (97.0 mg, 2.42 mmol, 60% in mineral oil). After 10 min, the reaction was warmed to -10°C over a period of 50 min. After an additional 1 h, the reaction was further warmed to r.t. After 30 min, the reaction was quenched with sat. aq. NH_4Cl (5 mL), diluted with sat. aq. NaCl (70 mL) and extracted with Et_2O (4 X 70 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 2-10% EtOAc / hexanes, to give **19** (661 mg, 1.42 mmol, 97%) as a colorless oil. The product **19** contained a small

amount of impurities (<15%) resulting from protecting group migration during the benzylation which were removed after desilylation.



19 **26**

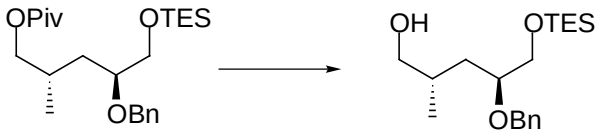
Alcohol 26: To a stirred solution of **19** (650 mg, 1.40 mmol) in THF (2.0 mL) was added TBAF (4.5 mL, 4.5 mmol, 1.0 M in THF) *via* syringe. After 1 h, the reaction was quenched with sat. aq. NH_4Cl (30 mL) and concentrated *in vacuo* to remove the THF. The aqueous solution was extracted with Et_2O (4 X 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5-50% EtOAc / hexanes, to give **26** (340 mg, 1.10 mmol, 79%) as a colorless oil: $[\alpha]_D^{23}$ +2.1° (c 0.87, $CHCl_3$); IR (neat) 3457, 2962, 1732, 1480, 1285, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.39 (m, 5H), 4.60 (s, 2H), 3.95 (dd, J = 5.9, 10.9 Hz, 1H), 3.88 (dd, J = 6.2, 10.9 Hz, 1H), 2.77 (dd, J = 3.1, 11.1 Hz, 1H, 3.52-3.65 (m, 2H), 1.97-2.05 (m, 1H), 1.89 (bs, OH), 1.73-1.82 (m, 1H), 1.26-1.35 (m, 1H), 1.21 (s, 9H), 0.94 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 138.5, 128.7, 128.1, 128.0, 77.5, 71.8, 69.4, 64.5, 39.1, 35.3, 29.6, 27.4, 17.2; HRMS (FAB+) calcd. for $C_{18}H_{29}O_4$ (M+H) 309.2066, found 309.2060.



26 **20**

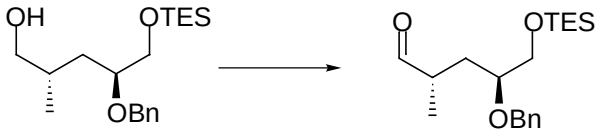
TES Ether 20: To a stirred solution of **26** (331 mg, 1.07 mmol) in CH_2Cl_2 (4.0 mL) at 0°C was sequentially added DMAP (12.3 mg, 0.10 mmol), Et_3N (152.5 mg, 210 µL, 1.51 mmol) and TESCl (197.6 mg, 220 µL, 1.31 mmol). After 45 min, the reaction was quenched with sat. aq. NH_4Cl (50 mL) and extracted with Et_2O (4 X 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 1-15% EtOAc / hexanes, to give **20** (429 mg, 1.02 mmol, 95%) as a colorless oil: $[\alpha]_D^{23}$ -24.7° (c 1.67, $CHCl_3$); IR (neat) 3030, 2956, 1730, 1455, 1155, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.35 (m, 5H), 4.75 (d, J = 11.6 Hz, 1H), 4.55 (d, J = 11.6 Hz, 1H), 3.94 (dd, J = 5.6, 10.7 Hz, 1H), 3.87 (dd, J= 5.1, 10.6 Hz, 1H), 3.71-3.78 (m, 1H), 3.53-3.60 (m, 2H), 2.02-2.10 (m, 1H), 1.54-1.63 (m, 1H), 1.29-1.41 (m, 1H), 1.20 (s, 9H), 0.97 (t, J = 8.0 Hz, 9H), 0.87 (d, J = 6.7 Hz, 3H), 0.61 (q, J= 8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 139.0, 128.5, 128.1, 127.7, 77.5, 72.5,

69.9, 66.0, 39.1, 36.0, 29.4, 27.4, 16.7, 7.0, 4.6; HRMS (FAB+) calcd. for $C_{23}H_{43}O_4Si$ (M+H) 423.2931, found 423.2923.



20 **27**

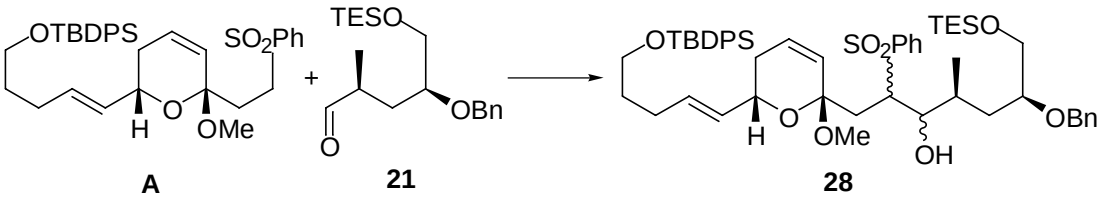
Alcohol 27: To a stirred solution of **20** (117 mg, 0.277 mmol) in THF (0.6 mL) at 0°C was sequentially added H_2O (10 mg, 10 µL, 0.55 mmol) and $LiBH_4$ (280 µL, 560 mmol, 2.0 M in THF). The reaction was warmed to r.t. and sat. aq. NH_4Cl (15 µL) was added dropwise. An additional portion of $LiBH_4$ (150 µL, 0.30 mmol, 2.0 M in THF) was added during the course of the reaction. After 2.5 h, the reaction as quenched with sat. aq. NH_4Cl (20 mL) and extracted with Et_2O (4 X 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give **27** (93 mg, 0.277 mmol, 99%) as a colorless oil: $[\alpha]_D^{23}$ -41.5° (c 1.31, $CHCl_3$); IR (neat) 3407, 2953, 2875, 1457, 1104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.36 (m, 5H), 4.77 (d, J = 11.4 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 3.76 (dd, J = 7.5, 12.4 Hz, 1H), 3.54-3.62 (m, 2H), 3.48 (dd, J = 5.6, 10.7 Hz, 1H), 3.41 (dd, J = 6.1, 10.7 Hz, 1H), 2.19 (bs, OH), 1.79-1.91 (m, 1H), 1.52-1.62 (m ,1H), 1.36-1.44 (m, 1H), 0.98 (t, J = 7.9 Hz, 9H), 0.89 (d, 6.8 Hz, 3H), 0.62 (q, J = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.6, 128.2, 127.9, 78.6, 72.6, 68.8, 66.0, 36.5, 33.3, 17.5, 7.0, 4.6; HRMS (FAB+) calcd. for $C_{19}H_{35}O_3Si$ (M+H) 339.2359, found 339.2359 .



27 **21**

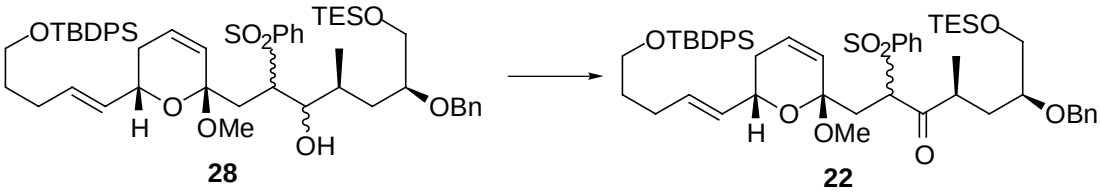
Aldehyde 21: To a stirred solution of **21** (77 mg, 0.228 mmol) in CH_2Cl_2 (1.35 mL) with powdered 4 Å mol. sieves (250 mg) was sequentially added NMO (34.6 mg, 0.296 mmol) and TPAP (4.6 mg, 0.013 mmol) at r.t. An additional portion of TPAP (3.4 mg, 0.0097 mmol) was added during the course of the reaction. After 30 min, the reaction was diluted with 25% EtOAc / hexanes (5 mL), filtered through a small plug of silica gel (25% EtOAc / hexanes rinse) and concentrated *in vacuo* to give **21** (67 mg, 0.199 mmol, 87%) as a colorless oil: $[\alpha]_D^{23}$ -21.2° (c 0.755, $CHCl_3$); IR (neat) 3064, 2954, 2912, 1726, 1454, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (d, J = 2.4 Hz, 1H), 7.28-7.38 (m, 5H), 4.69 (d, J = 11.3 Hz, 1H), 3.49 (d, J = 11.3 Hz, 1H), 3.74 (dd, J = 5.2, 10.1 Hz, 1H), 3.48-3.61 (m, 2H), 2.47-2.57 (m, 1H), 1.88-1.99 (m, 1H), 1.48-156 (m,

1H), 1.01 (d, J = 6.8 Hz, 3H), 0.966 (t, J = 8.0 Hz, 9H), 0.61 (q, J = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 138.5, 128.6, 128.3, 127.9, 77.4, 72.6, 65.4, 44.0, 33.9, 13.8, 7.0, 4.5; HRMS (FAB+) calcd. for $C_{19}H_{33}O_3Si$ (M+H) 337.2199, found 337.2187 .



A **21** **28**

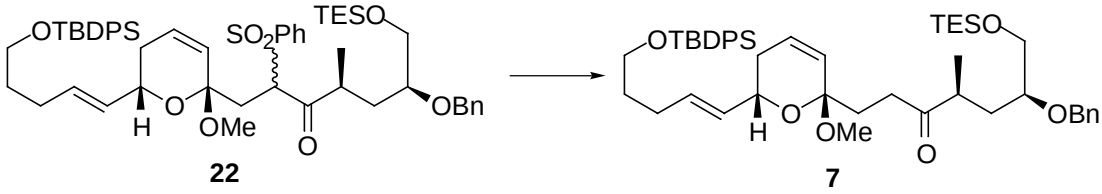
To a stirred solution of sulfone **A** (76.0 mg, 0.126 mmol) in THF (0.8 mL) at -78°C was added LDA[2] (140µL, 1.0 M in THF) dropwise. After 25 min, a solution of the aldehyde **21** (53.9 mg, 0.160 mmol) in precooled THF (0.2 mL) was added *via* cannula to the orange sulfone solution. After 25 min, the reaction was removed from the cooling bath. After 2 min, the reaction was quenched with sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (4 X 30 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give the crude **28** (125 mg) as a colorless oil. The crude hydroxy sulfone **28** was used immediately; chromatography of the crude mixture results in spirocyclization at C_{10} to a complex mixture of isomers.



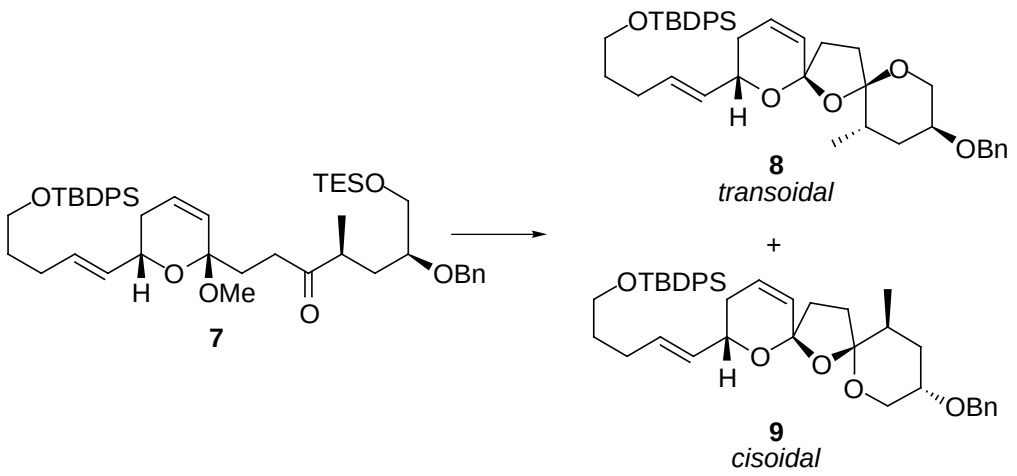
28 **22**

Keto sulfone 22: To a stirred solution of crude **28** (0.126 mmol) in CH_2Cl_2 (1.0 mL) with powdered 4 Å mol. sieves (100 mg) was sequentially added NMO (19.0 mg, 0.162 mmol) and TPAP (18.0 mg, 0.0512 mmol). An additional portion of TPAP (17.8 mg, 0.0506 mmol) was added during the course of the reaction. After 3.25 h, the reaction was diluted with 25% EtOAc / hexanes (5 mL), filtered through a small plug of silica gel (25% EtOAc / hexanes rinse) and concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 7-40% EtOAc / hexanes (with 0.5% Et_3N), to give **22** (70.4 mg, 0.0751 mmol, 60 % over 2 steps) as a colorless oil: IR (neat) 2931, 1721, 1448, 1310, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.78 (m, 2H), 7.60-7.70 (m, 5H), 7.45-7.53 (m, 2H), 7.27-7.43 (m, 11H), 5.86-5.96 (m, 1H), 5.33-5.63 (m, 3H), 4.80-4.86 (m, 1H), 4.47-4.66 (m, 2H), 4.13-4.18 (m, 1H), 3.50-3.85 (m, 6H), 3.16-3.23 (m, 1H of a diastereomer), 3.10 (s, 3H of a diastereomer), 3.07 (s, 3H of a diastereomer), 3.00-3.10 (m, 1H of a diastereomer), 2.65 (dd, J = 10.0, 13.8 Hz, 1H of a diastereomer), 1.72-2.32 (m, 7H), 1.55-1.70 (m, 3H), 1.3-1.52 (m, 4H), 1.09 (s, 9H of a diastereomer), 1.07 (s, 9H of a diastereomer), 1.05-1.10 (m, 3H), 0.99 (t, J = 9.4 Hz, 6H of 1 diastereomer), 0.97 (t,

J = 9.4 Hz, 6H of 1 diastereomer), 0.58-0.72 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 204.7, 139.2, 139.0, 137.1, 136.9, 135.7, 134.24, 134.17, 132.9, 132.3, 130.5, 129.8, 129.6, 129.5, 129.14, 129.06, 128.53, 128.48, 128.3, 128.1, 127.8, 127.7, 127.6, 97.5, 96.5, 73.0, 72.3, 69.8, 69.3, 69.1, 68.7, 66.5, 66.2, 63.51, 63.47, 49.4, 49.0, 44.6, 44.5, 35.3, 34.7, 34.4, 33.6, 32.2, 32.1, 30.1, 28.9, 28.8, 27.1, 19.4, 15.6, 14.5, 7.04, 7.02, 4.6; HRMS (FAB+) calcd. for $C_{53}H_{71}O_7SSi_2$ (M-MeOH) 907.4459, found 907.4452.



Ketone 7: To a stirred solution of **22** (16.0 mg, 0.017 mmol) in THF (0.3 mL) and MeOH (1.0 mL) at -10°C was added Na_2HPO_4 (16 mg, 0.112 mmol). After 5 min, Na / Hg amalgam (118 mg, 0.257 mmol, 5% in Hg) was added. After 2 h, the reaction was diluted with 20% EtOAc / hexanes, filtered through a small plug of SiO2 (20% EtOAc / hexanes rinse) and concentrated *in vacuo* to yield crude **7** (0.017 mmol) which was used without any further purification. $[\alpha]_D^{23}$ -0.5° (c 2.55, $CHCl_3$); IR (neat) 2931, 1714, 1393, 1109 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.70 (m, 4H), 7.20-7.45 (m, 11H), 5.93-6.00 (m, 1H), 5.63-6.81 (dt, J = 6.4, 15.5 Hz, 1H), 5.48-5.60 (m, 2H), 4.73 (d, J = 11.7 Hz, 1H), 4.52 (d, J = 11.7 Hz, 1H), 4.21-4.28 (m, 1H), 3.65-3.75 (m, 3H), 3.58 (dd, J = 5.2, 10.3 Hz, 1H), 3.44-3.51 (m, 1H), 3.21 (s, 3H), 2.64-2.80 (m, 1H), 2.43-2.55 (m, 2H), 1.65-2.20 (m, 9H), 1.47-1.55 (m, 1H), 1.27 (s, 9H), 1.00 (d, J = 6.8 Hz, 3H), 0.98 (t, J = 7.8 Hz, 9H), 0.62 (q, J = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 138.9, 135.8, 134.2, 132.7, 130.3, 129.8, 128.5, 128.4, 128.2, 127.8, 98.2, 77.8, 72.5, 68.9, 65.9, 63.5, 48.4, 43.2, 35.7, 35.4, 32.1, 30.6, 29.5, 28.9, 27.1, 19.4, 16.5, 7.0, 4.6; HRMS (FAB+) calcd. for $C_{47}H_{67}O_5Si_2$ (M-MeOH) 767.4527, found 767.4512.



C_{16} Spirocycles 8 and 9: To a stirred solution of crude **7** (0.017 mmol) in PhMe (1.1 mL) and *t*-BuOH (1.1 mL) was added CSA (19 mg, 0.0818 mmol). After 17 h, the reaction was quenched with solid $NaHCO_3$ (200 mg). After 5 min, the solution was diluted with 40% EtOAc / hexanes, filtered through a small plug of SiO_2 (40% EtOAc / hexanes rinse) and concentrated *in vacuo*. The crude oil was purified by preparative TLC (15% EtOAc / hexanes) to give the less polar **8** (3.3 mg, 0.0051 mmol, 30%) and more polar **9** (5.5 mg, 0.0084 mmol, 50%) as colorless oils.

8: $[\alpha]_D^{23}$ -34.7° (c 0.265, $CHCl_3$); IR (neat) 2960, 2926, 2853, 1427, 1110, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 6.1 Hz, 4H), 7.26-7.43 (m, 11H), 5.93-5.97 (m, 1H), 5.61-5.69 (m, 2H); 5.50 (dd, J = 6.0, 15.8 Hz, 1H); 4.51-4.55 (m, 2H), 4.35-4.39 (m, 1H), 3.68-3.83 (m, 3H); 3.66 (t, J = 6.2 Hz, 2H), 1.59-2.17 (m, 13H); 1.05 (s, 9H), 1.03 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 135.8, 134.2, 132.3, 130.7, 129.74, 129.66, 128.6, 128.0, 127.81, 127.76, 108.9, 104.7, 70.7, 69.5, 69.2, 64.2, 63.4, 36.5, 33.6, 33.14, 33.08, 32.1, 30.3, 28.9, 27.0, 19.4, 16.3; HRMS (FAB+) calcd. for $C_{41}H_{53}O_5Si$ (M+H) 653.3662, found 653.3658 .

9: $[\alpha]_D^{23}$ -58.0° (c 0.40, $CHCl_3$); IR (neat) 3069, 3032, 2961, 2921, 2851, 1467, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, J = 1.7, 7.5 Hz, 4H); 7.26-7.45 (m, 11H), 5.94-6.00 (m, 1H), 5.52-5.82 (m, 3H); 4.61 (d, J = 12.4 Hz, 1H), 4.52 (d, J = 12.4 Hz, 1H); 4.36-4.42 (m, 1H); 3.79-3.90 (m, 2H); 3.66 (t, J = 6.2 Hz, 2H); 3.41-3.43 (m, 1H); 1.60-2.24 (m, 13H); 1.04 (s 9H); 0.87 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 135.8, 134.2, 132.2, 130.5, 129.7, 128.7, 128.5, 127.9, 127.8, 127.6, 109.5, 105.3, 77.4, 72.0, 70.1, 63.5, 63.2, 37.4, 35.1, 32.6, 32.2, 32.0, 30.2, 28.9, 27.0, 19.4, 16.4; HRMS (FAB+) calcd. for $C_{41}H_{53}O_5Si$ (M+H) 652.3662, found 653.3672.

Equilibration of C_{16} Spirocycles 8 and 9: To a stirred solution of cisoidal spirocycle **9** (8.8 mg, 0.0135 mmol) in PhMe (0.9 mL) and *t*-BuOH (0.9 mL) was added

CSA (16.6 mg, 0.0715 mmol). After 18 h, the reaction was quenched with solid $NaHCO_3$ (200 mg). After 5 min, the solution was diluted with 30% EtOAc / hexanes, filtered through a small plug of SiO_2 (33% EtOAc / hexanes rinse) and concentrated *in vacuo*. The crude oil was purified by chromatography over silica gel, eluting with 1-9% EtOAc / hexanes, to give sequentially **8** (3.1 mg, 0.0476 mmol, 35%) followed by recovered **9** (5.0 mg, 0.0767 mmol, 57%) as colorless oils.

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(1) The $(Ipc)_2$Ballyl was prepared as a stock solution in pentane from the commercially available (-)-Ipc_2BOMe and allylMgBr in accord with the low salt protocol developed by Brown and co-workers. Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(2) The 1.0 M LDA solution was prepared fresh immediately prior to use: To a stirred solution of *N*, *N*-diispropyl amine (404 mg, 560 µL, 4.0 mmol) in THF (1.84 mL) at -78°C was added *n*-BuLi (1.6 mL, 4.0 mmol, 2.5 M in hexanes) dropwise. After 5 min, the white suspension was warmed to -10°C. After 30 min, the solution was employed in the relevant reaction.