The Use of Thiazoles in the Halogen Dance Reaction: Application to the Total Synthesis of WS75624 B

Supporting Info

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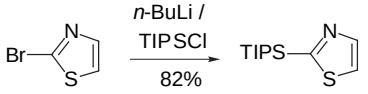
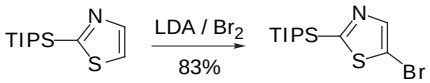
General: All moisture sensitive reactions were conducted under a nitrogen atmosphere in oven-dried glassware using solvents purified according to standard procedures.[1] ^{1}H NMR spectra were obtained at 500 MHz, ^{13}C NMR spectra at 125 MHz with ^{1}H decoupling (WALTZ) in chloroform-*d*, with chemical shifts reported in parts per million referenced to residual chloroform (δ = 7.24 for ^{1}H and 77.00 for ^{13}C). Infrared spectra were recorded as thin films on NaCl plates. Melting points are uncorrected.



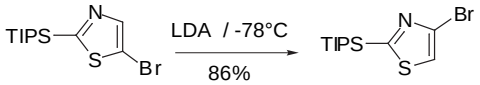
6 **10**

2-Triisopropylsilylthiazole (10). 2-Bromothiazole (**6**, 492 mg, 3.0 x 10^{-3} mol, 1 equiv) was added dropwise to *n*-BuLi (2.26 mL, 1.46 M in hexanes, 1.1 equiv) in THF (8 mL) at –78 °C. The solution was allowed to stir for 1 hour, and then triisopropylsilyl triflate (1.29 mL, 3.9 x 10^{-3} mol, 1.3 equiv) was added dropwise over 1 minute. The solution was stirred at –78 °C for 1 hour, and allowed to come to room temperature. The reaction was diluted with ethyl acetate, and washed with saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 2/1 hexanes/chloroform) provided 2-triisopropylthiazole (**10**) (480 mg, 66%); *Rf* = 0.5 (10/1 hexanes/ethyl acetate); IR: 2945, 2867, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.12 (d, *J* = 7.4 Hz, 18H), 1.44 (sept, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 3.0 Hz, 1H), 8.14 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.68, 18.45, 120.96, 145.38, 169.90. Anal. Calcd for $C_{12}H_{23}NSSi$ C, 59.69; H, 9.60; N, 5.80; S, 13.28. Found C, 59.73; H, 9.86; N, 5.68; S, 13.68.



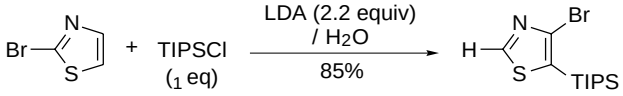
10 **11**

5-Bromo-2-triisopropylsilyl Thiazole (11). *n*-BuLi (0.71 mL, 1.60 M in hexanes, 1.6 equiv) was added dropwise to 2-triisopropylsilyl thiazole (**10**, 170 mg, 7.0 x 10-4 mol, 1 equiv) in THF (8 mL) at –78 °C. The solution was allowed to stir for 2 hours, and then bromine (108 µL, 2.1 x 10^{-3} mol, 3 equiv) was added dropwise over 1 minute. The solution was stirred at –78 °C for 1 hour, and then allowed to come to room temperature. The reaction was diluted with ethyl acetate, and washed with saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, hexanes then 100/1 hexanes/ethyl acetate) provided 5-bromo-2-triisopropylthiazole (**11**) (187 mg, 83%); *Rf* = 0.8 (50/1 hexanes/ethyl acetate); IR: 2949, 2867, 1462, 1444 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.10 (d, *J* = 7.4 Hz, 18H), 1.39 (sept, *J* = 7.4 Hz, 1H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.54, 18.39, 111.59, 146.49, 173.44. Anal. Calcd for $C_{12}H_{22}BrNSSi$ C, 44.99; H, 6.92; N, 4.37. Found C, 44.94; H, 7.10; N, 4.28.



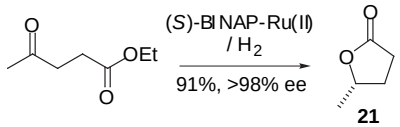
11 **14**

4-Bromo-2-Triisopropylsilylthiazole (14). 5-Bromo-2-triisopropylsilyl thiazole (**11**, 77 mg, 2.4 x 10^{-4} mol, 1 equiv) in THF (3 mL) was added dropwise to a solution of LDA in THF (5 mL) prepared from diisopropylamine (50 mL, 3.6 x 10^{-4} mol, 1.5 equiv) and *n*-BuLi (0.18 mL, 1.6 M in hexanes, 1.2 equiv) at –78 °C. The solution was allowed to stir for 3 hours, and then quenched with water. The reaction was diluted with ethyl acetate, and the organic layer was washed with saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (SiO2, hexanes then 100/1 hexanes/ethyl acetate) provided 4-bromo-2-triisopropylthiazole (**14**) (66 mg, 86%); *Rf* = 0.9 (50/1 hexanes/ethyl acetate); IR (neat): 2945, 2867, 1462, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11 (d, *J* = 7.4 Hz, 18H), 1.43 (sept, *J* = 7.4 Hz, 1H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.54, 18.40, 119.05, 127.96, 172.05. Anal. Calcd for $C_{12}H_{22}BrNSSi$ C, 44.99; H, 6.92; N, 4.37; S, 10.01. Found C, 45.28; H, 7.18; N, 3.97; S, 10.01.



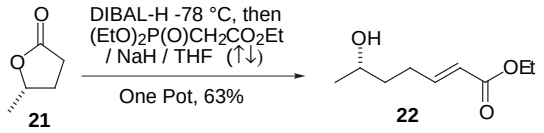
6 **15**

4-Bromo-5-triisopropylsilylthiazole (15). *n*-BuLi (0.85 mL, 1.58 M in hexanes, 2.2 equiv) was added dropwise to diisopropylamine (0.21 mL, 1.46 x 10^{-3} mol, 2.4 equiv) in THF (8 mL) at 0 °C. After stirring for 15 minutes, the solution was cooled to -78 °C. Triisopropylsilyl chloride (0.14 mL, 6.7 x 10^{-4} mol, 1.1 equiv) was added to the vigorously stirring LDA solution via syringe followed by 2-bromothiazole (**6**, 55 μL, 6.1 x 10^{-4} mol, 1 equiv) via syringe over 5 seconds. The light yellow solution was stirred for 2 hours at -78 °C. The reaction was then quenched with water at -78 °C, and allowed to come to room temperature. The reaction was diluted with ethyl acetate, and the organic layer was washed with 1 M NH_4OH, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 100/1 hexanes/diethyl ether) provided 4-bromo-5-triisopropylsilyl thiazole (**15**) (166 mg, 85% yield). *Rf* = 0.6 (10:1 hexanes/ethyl acetate); IR (neat): 2942, 1434 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11 (d, *J* = 7.6 Hz, 18H), 1.56 (sept, *J* = 7.6 Hz, 1H), 8.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) d 12.34, 18.59, 124.39, 133.15, 157.52.

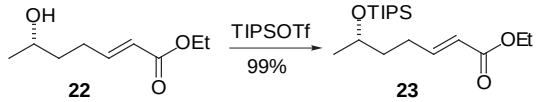


21

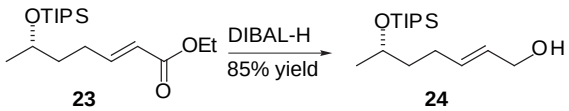
(*S*)-4-Methyl-γ-butyrolactone (21).[2] Ethyl levulinate (14.84 g, 0.103 mol, 1.0 equiv), ethanol (15 mL), and HCl (512 μL, 1.0 M aqueous, 0.5%) were degassed with nitrogen for 1 hour then transferred to a flask containing $RuCl_2$-(*S*)-BINAP•Et_3N (46 mg, 5.1 x 10^{-5} mol, 0.05%). After the catalyst had dissolved, the solution was transferred via cannula under nitrogen atmosphere to a stainless steel bomb reactor equipped with a glass insert. The reactor was purged 3x with hydrogen, and placed under 1400 psi hydrogen pressure and brought to 50 ˚C for 5 days, with occasional recharging of hydrogen pressure. After 5 days, the pressure was released and the reaction was concentrated to an oil. Kugelrhor distillation (48 ˚C, 0.5 mmHg) provided (*S*)-4-methyl-γ-butyrolactone (**21**) (9.38 g, 9.37 x 10^{-2} mol, 91% yield, >98% ee by GC using Supleco β-dex column). $[\alpha]_D$ –35.03˚ (c 15.3 mg/mL, CH_2Cl_2); IR (neat): 2978, 1774, 1197 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.38 (d, *J* = 6.2 Hz, 3H), 1.80 (m, 1H), 2.33 (m, 1H), 2.52 (m, 2H), 4.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.04, 29.06, 29.69, 77.21, 177.17.



(*S*)-Ethyl-6-hydroxy-hept-2-enoate (22). (*S*)-4-Methyl-γ-butyrolactone (**21**) (6.0 g, 6.0 x 10^{-2} mol, 1.0 equiv) was dissolved in THF (240 mL) under a nitrogen atmosphere and cooled to -78 ˚C. Diisobutylaluminum hydride (63 mL, 1.0 M in hexanes, 1.05 equiv) was added dropwise over a period of 20 minutes, and the reaction was stirred an additional hour. To a separate flask containing a slurry of sodium hydride (2.87 g, 1.2 x 10^{-1} mol, 2.0 equiv) in THF (400 mL) under a nitrogen atmosphere, triethyl phosphonoactetate (13.08 mL, 6.6 x 10^{-2} mol, 1.2 equiv) was added dropwise over a period of 1 hour with vigorous H_2 evolution. This mixture was then transferred to the reaction flask via cannula over a period of 30 minutes. The reaction was allowed to come to room temperature and stirred for 18 hours or until the lactol was no longer observed by TLC (lactol: *Rf* = 0.5, UV, product: *Rf* = 0.6, UV; 3:2 ethyl acetate/hexanes). The reaction was diluted with hexanes (300 mL) and NaOH (3 mL, 10 M) was added dropwise by pipet. The reaction was allowed to stir at room temperature for 1 hour at which time a large amount of aluminum salts had precipitated. The reaction mixture was dried with $MgSO_4$, filtered and washed with hexanes, and the filtrate concentrated under reduced pressure. Flash chromatography (SiO_2, 2/1 hexanes/ ethyl acetate) provied (*S*)-ethyl-6-hydroxy-hept-2-enoate (**22**) (6.59 g, 63%). *Rf* 0.6 (4:6 hexanes/ ethyl acetate); $[\alpha]_D$ +13.17˚ (c 12.0 mg/mL, CH_2Cl_2); IR (neat): 3436, 2970, 1718, 1653, 1204, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ1.19 (d, *J* = 6.2 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.42 (bs, 1H), 1.58 (m, 2H), 2.29 (m, 2H), 3.80 (sextet, *J* = 6.3 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 5.81 (d, *J* = 15.6 Hz, 1H), 6.95 (dt, *J* = 6.9, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.24, 23.62, 28.46, 37.25, 60.18, 67.26, 121.55, 148.64, 166.63**.** Anal. Calcd for $C_9H_{16}O_3$ C, 62.77; H, 9.36. Found: C, 63.13; H, 9.76

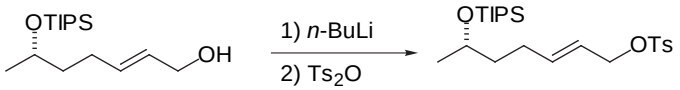


***(S)*-Ethyl-6-(triisopropylsiloxy)-hept-2-enoate (23)**. (*S*)-Ethyl-6-hydroxy-hept-2-enoate (**22**, 6.59 g, 3.82 x 10^{-2} mol, 1.0 equiv) and ethyl diisopropyl amine (13.3 mL, 7.64 x 10^{-2} mol, 2.0 equiv) were dissolved in THF (200 mL). Triisopropylsilyl triflate (10.79 mL, 4.01 x 10^{-3} mol, 1.05 equiv) was added dropwise over a period of 1 minute, and then stirred an additional hour. The reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (SiO_2, 3/1 hexanes/ethyl acetate) provided (*S*)-ethyl-6-(triisopropylsiloxy)-hept-2-enoate (**23**) (12.43 g, 99%). *Rf* 0.6 (4:6 hexanes/ ethyl acetate); $[\alpha]_D$ +5.83˚ (c 9.6 mg/mL, CH_2Cl_2); IR (neat): 2942, 1724, 1655, 1463, 1205, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ1.03 (s, 21H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.59 (m, 2H), 2.25 (q, *J* = 7.0 Hz, 2H), 3.97 (sextet, *J* = 6.0 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 5.79 (d, *J* = 15.6 Hz, 1H), 6.97 (dt, *J* = 6.8, 15.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.48, 14.28, 18.12, 23.36, 27.87, 37.92, 60.13, 67.74, 121.16, 149.39, 166.73; Anal. Calcd for $C_{18}H_{36}O_3Si$; C, 65.80; H, 11.04. Found: C, 65.68; H, 10.82.



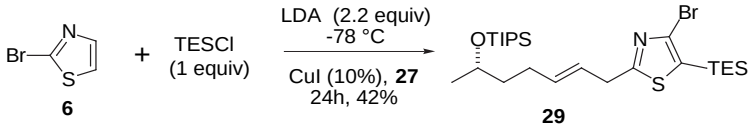
(*S*)-6-(triisopropylsiloxy)-hept-2-en-1-ol (24). Diisobutylaluminum hydride (25.3 mL, 1.0 M in hexanes, 3.0 equiv) was added dropwise over a period of 10 minutes to a solution of (*S*)-ethyl-6-(triisopropylsiloxy)-hept-2-enoate (**23**, 2.77 g, 8.42 x 10^{-3} mol, 1.0 equiv) in THF (50 mL) at 0 ˚C, and then stirred for 1 hour. The reaction was quenched with water, stirred 1 hour, and then diluted with ethyl acetate. The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (SiO_2, 10/1

hexanes/ethyl acetate) provided (*S*)-ethyl-6-(triisopropylsiloxy)-hept-2-enol (**24**) (2.06 g, 85%). *Rf* 0.2 (10:1 hexanes/ethyl acetate); $[\alpha]_D$ +5.00˚ (c 8.3 mg/mL, CH_2Cl_2); IR (neat): 3323, 2962, 1463, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 21H), 1.14 (d, *J* = 5.9 Hz, 3H), 1.24 (bs, 1H), 1.53 (m, 2H), 2.08 (q, *J* = 7.5 Hz, 2H), 3.93 (sextet, *J* = 5.9 Hz, 1H), 4.07 (d, *J* = 4.8 Hz, 2H), 5.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.52, 18.15, 23.43, 27.99, 39.22, 63.84, 68.02, 128.84, 133.39; Anal. Calcd for $C_{16}H_{34}O_2Si$; C, 67.07; H, 11.96. Found: C, 67.07; H, 12.23.



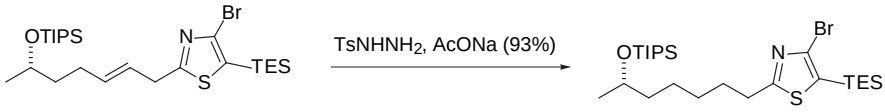
24 **27**

(*S*)-6-(triisopropylsiloxy)-hept-2-en-1-*para*-toluenesulfonate (27). *n*-BuLi (7.53 mL, 1.46 M, 1.05 equiv) was added dropwise to a solution of (*S*)-ethyl-6-(triisopropylsiloxy)-hept-2-en-1-ol (**24**, 3.0 g, 1.05 x 10^{-2} mol, 1.0 equiv) in THF (45 mL) at 0 ˚C. After 5 minutes, the solution was transfered via cannula to a solution of *p*-toluenesulfonic anhydride (3.76 g, 1.16 x 10^{-3} mol, 1.1 equiv) in THF (45 mL) over a period of 10 minutes. After an additional 15 minutes of stirring, CuI (54 mg, 2.88 x 10^{-3} mol, 0.1 equiv) was added while purging with nitrogen, and the solution was cannulated directly to the following reaction mixture without isolation.



6 **29**

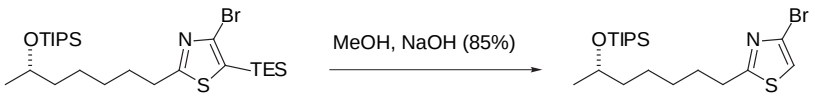
1-(4-Bromo-5-triethylsilyl-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-hept-2-ene (29). *n*-BuLi (25.8 mL, 1.46 M in hexanes, 3.6 equiv) was added dropwise to diisopropylamine (5.87 mL, 4.2 x 10^{-2} mol, 4.0 equiv) in THF (100 mL) at 0 ˚C. After stirring for 15 minutes, the solution was cooled to -78 ˚C. Triethylsilylchloride (3.07 mL, 1.83 x 10^{-3} mol, 1.75 equiv) was added to the vigorously stirred LDA via syringe followed by 2-bromothiazole (**6**, 1.60 mL, 1.8 x 10^{-2} mol, 1.7 equiv) via syringe over a period of 5 seconds. The light yellow solution was stirred for 2 hours at -78 ˚C. The (*S*)-6-(triisopropylsiloxy)-hept-2-en-1-tosylate (**27**) solution as prepared above was then transferred via cannula to the reaction mixture and stirred for 18 hours at -78 ˚C. The reaction was quenched with water at -78 ˚C, and allowed to come to room temperature. The reaction mixture was diluted with ethyl acetate, washed with 1 M NH_4OH, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (SiO_2, 100/1 hexanes/diethyl ether) provided 1-(4-bromo-5-triethylsilyl-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-hept-2-ene (**29**) (2.41 g, 42% yield from (*S*)-ethyl-6-(triisopropylsiloxy)-hept-2-enol, **24**). *Rf* 0.4 (50:1 Hexanes/Diethyl ether); $[\alpha]_D$ +3.11˚ (c 11.9 mg/mL, CH_2Cl_2); IR (neat): 2956, 1465, 1016 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (m, 6H), 0.96 (m, 9H), 1.04 (s, 21H), 1.15 (d, *J* = 5.9 Hz, 3H), 1.53 (m, 2H), 2.11 (m, 2H), 3.67 (d, *J* = 6.7 Hz, 2H), 3.94 (sextet, *J* = 5.9 Hz, 1H), 6.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.72, 7.28, 12.50, 18.15, 23.39, 28.24, 36.62, 39.16, 67.97, 124.38, 125.26, 130.48, 135.53, 175.61; Anal. Calcd for $C_{25}H_{48}BrNOSSi_2$; C, 54.91; H, 8.85; N, 2.56; S, 5.86. Found: C, 54.86; H, 8.73; N, 2.54; S, 5.75.



29

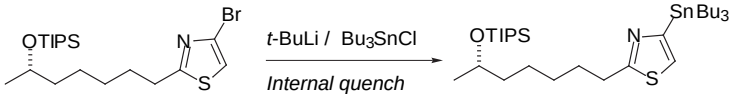
1-(4-Bromo-5-triethylsilyl-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-heptane. 1-(4-Bromo-5-triethylsilyl-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-hept-2-ene (**29**) (1.50 g, 2.74 x 10^{-3} mol, 1.0 equiv) was placed in a round bottom flask with *p*-toluenesulfonohydrazine (5.11 g, 2.74 x 10^{-2} mol, 10 equiv) and DME (50 mL). The solution was brought to reflux, then sodium acetate (7.46 g, 5.5 x 10^{-2} mol, 20 equiv) in water (30 mL), was added dropwise over a period of 6 hours via cannula. The solution was heated to reflux for 18 hours, cooled, and diluted with ethyl acetate (50 mL). The

organic layer was washed with saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (SiO_2, 100/1 hexanes/diethyl ether) provided 1-(4-Bromo-5-triethylsilyl-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-heptane (1.40 g, 93%). *Rf* 0.4 (50:1 hexanes/diethyl ether); $[\alpha]_D$ +1.73˚ (c 11.0 mg/mL, CH_2Cl_2); IR (neat): 2940, 1463, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (m, 6H), 0.96 (m, 9H), 1.03 (s, 21H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.40 (m, 6H), 1.76 (m, 2H), 2.96 (t, *J* = 7.8 Hz, 2H), 3.89 (sextet, *J* = 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.74, 7.28, 12.49, 18.14, 23.49, 24.90, 29.36, 29.83, 33.30, 39.71, 68.43, 124.51, 130.28, 176.43; Anal. Calcd for $C_{25}H_{50}BrNOSSi_2$; C, 54.71; H, 9.18; N, 2.55; S, 5.84. Found: C, 54.89; H, 9.08; N, 2.39; S, 6.19.



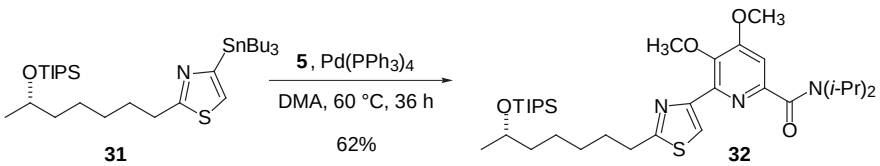
30

1-(4-Bromo-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-heptane. 1-(4-Bromo-5-triethylsilyl-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-heptane (1.33 g, 2.42 x 10^{-3} mol, 1.0 equiv) was dissolved in 20 mL methanol and 10 M NaOH (2.4 mL, 2.4 x 10^{-2} mol, 10 equiv) and stirred for 18 hours at room temperature. The reaction was diluted with 25 mL ethyl acetate and washed with saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (SiO_2, 100/1 hexanes/diethyl ether) provided 1-(4-Bromo-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-hept-2-ene (1.01 g, 85%). *Rf* 0.4 (50:1 hexanes/diethyl Ether); $[\alpha]_D$ -1.09˚ (c 12.9 mg/mL, CH_2Cl_2); IR (neat): 2940, 1482, 1050, 884 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 21H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.40 (m, 6H), 1.77 (m, 2H), 2.97 (t, *J* = 7.5 Hz, 2H), 3.89 (sextet, *J* = 6.2 Hz, 1H), 7.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.49, 18.15, 23.50, 24.89, 29.23, 29.84, 33.56, 39.70, 68.41, 115.62, 124.11, 172.73; Anal. Calcd for $C_{25}H_{50}BrNOSSi_2$; C, 52.51; H, 8.35; N, 3.22; S, 3.68. Found: C, 52.47; H, 8.22; N, 3.05; S, 7.69.



30 **31**

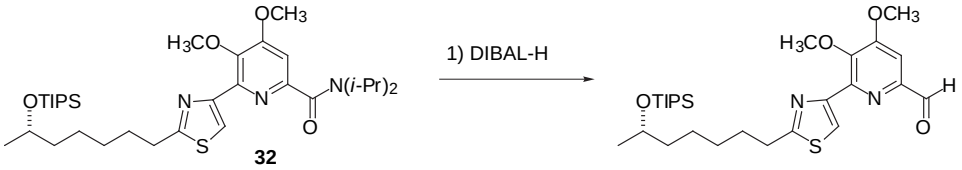
1-(4-Tributyltin-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-heptane. *t*-BuLi (981 µL, 1.7 M in pentane, 1.1 equiv) was added dropwise to a solution of 1-(4-Bromo-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-heptane (**30**, 659 mg, 1.52 x 10^{-3} mol, 1.0 equiv) and tributyltin chloride (354 µL, 2.13 x 10^{-3} mol, 1.4 equiv) in THF (15 mL) at -78 ˚C. The solution was stirred for 1 hour at -78 ˚C, and then allowed to come to room temperature. The reaction was diluted with ethyl acetate (15 mL) and stirred for 1 hour with saturated aqueous KF (3 mL). The organic layer was washed with saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to provide 843 mg of crude 1-(4-tributyltin-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-heptane (**31**) which was used without purification (attempted flash chromatography resulted in significant amounts of destannylation) in the following reaction.



31 **32**

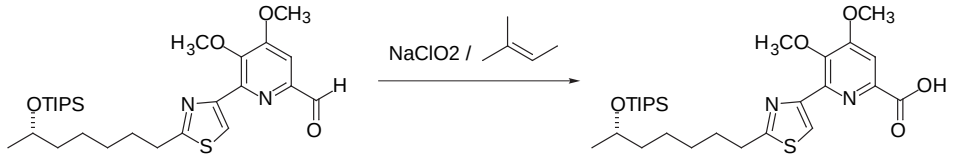
6-(2-(6-(*S*)-Triisopropylsiloxy-heptane)-4-thiazolyl)-4,5-dimethoxy-2-pyridine Carboxylic Acid *N*,*N*-Diisopropylamide (32). A solution of crude 1-(4-tributyltin-2-thiazolyl)-6-(*S*)-triisopropylsiloxy-heptane (**31**, 843 mg) and 6-iodo-4,5-dimethoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**5**)[3] (535 mg, 1.37 x 10^{-3} mol, 0.9 equiv) in dimethylacetamide (DMA) (15 mL) was added to tetrakistriphenylphosphine palladium (175 mg, 1.52 x 10^{-4} mol, 0.1 equiv), CuI (29 mg, 1.52 x 10^{-4} mol, 0.1 equiv), and LiCl (128 mg, 3.04 x 10^{-}

^{3} mol, 2.0 equiv) under nitrogen. The solution was brought to 70 ˚C for 24 hours in an oil bath. Upon cooling, the DMA was distilled off under reduced pressure. The residue was dissolved in ethyl acetate (10 mL), and stirred for 1 hour with saturateed aqueous KF (15 mL). The organic layer was washed with saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (SiO_2, 9/1 chloroform/ethyl acetate) provided 6-(2-(6-(*S*)-triisopropylsiloxy-heptane)-4-thiazolyl)-4,5-dimethoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**32**, 447 mg, 6 x 10^{-4} mol, 53%). *Rf* 0.2 (9/1 chloroform/ethyl acetate); $[\alpha]_D$ -1.58˚ (c 13.9 mg/mL, chloroform); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 21H), 1.13 (d, *J* = 6.1 Hz, 3H), 1.23 (d, *J* = 6.5 Hz, 6H), 1.34-1.54 (m, 6H), 1.53 (d, *J* = 6.7 Hz, 6H) 1.84 (m, 2H), 3.04 (t, *J* = 7.7 Hz, 2H), 3.55 (septet, *J* = 6.7 Hz, 1H), 3.85 (s, 3H), 3.55 (sextet, *J* = 5.8 Hz, 1H), 3.95 (s, 3H), 4.30 (septet, *J* = 6.5 Hz, 1H), 7.16 (s, 1H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.49, 18.15, 20.60, 20.94, 23.52, 25.06, 29.39, 29.80, 33.56, 39.79, 46.30, 50.78, 56.07, 60.89, 68.50, 106.94, 119.40, 143.78, 144.60, 151.68, 152.35, 160.21, 168.07, 170.21. Anal. Calcd for $C_{33}H_{57}N_3O_4SSi$: C, 63.93; H, 9.27; N, 6.78; S, 5.17. Found: C, 64.11; H, 9.44; N, 6.46; S, 5.11.

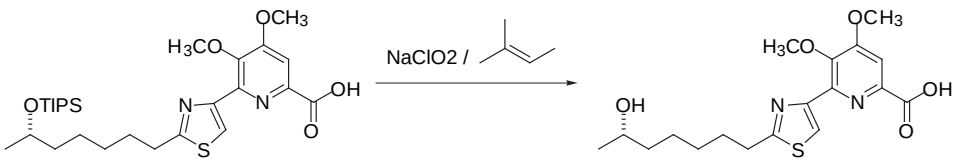


32

6-(2-(6-(*S*)-Triisopropylsiloxy-heptane)-4-thiazolyl)-4,5-dimethoxy-2-pyridine Carboxaldehyde. Diisobutylaluminum hydride (778 µL, 1.0 M in hexanes, 1.3 equiv) was added to a solution of 6-(2-(6-(*S*)-triisopropylsiloxy-heptane)-4-thiazolyl)-4,5-dimethoxy-2-pyridine carboxylic acid *N*,*N*-diisopropylamide (**32**, 371 mg, 6.0 x 10^{-4} mol, 1.0 equiv) in THF (10 mL) at 0 ˚C, and then stirred for 1 hour. The reaction was diluted with hexanes (3 mL) and NaOH (600 µL, 10 M) was added dropwise by syringe. The reaction was allowed to stir at room temperature for 1 hour at which time a large amount of aluminum salts had precipitated. The reaction mixture was dried with $MgSO_4$, filtered and concentrated under reduced pressure to provide 6-(2-(6-(*S*)-triisopropylsiloxy-heptane)-4-thiazolyl)-4,5-dimethoxy-2-pyridine carboxaldehyde (295 mg, 95%) which was used without purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (s, 21H), 1.13 (d, *J* = 6.1 Hz, 3H), 1.37-1.52 (m, 6H), 1.85 (m, 2H), 3.13 (t, *J* = 7.9 Hz, 2H), 3.90 (s, 3H), 3.90 (m, 1H), 4.01 (s, 3H), 7.53 (s, 1H), 7.97 (s, 1H), 10.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.52, 18.15, 23.43, 27.99, 39.22, 63.84, 68.02, 128.84, 133.39.



6-(2-(6-(*S*)-Triisopropylsiloxy-heptane)-4-thiazolyl)-4,5-dimethoxy-2-pyridine Carboxylic Acid. 6-(2-(6-(*S*)-Triisopropylsiloxy-heptane)-4-thiazolyl)-4,5-dimethoxy-2-pyridine carboxaldehyde (167 mg, 3.2 x 10^{-4} mol, 1.0 equiv), and NaH_2PO_4 (192 mg, 1.6 x 10^{-4} mol, 5.0 equiv) were dissolved in *t*-BuOH (2 mL), water (2 mL) and 2-methyl-2-butene (4 mL). Sodium chlorite (192 mg, 1.6 x 10^{-4} mol, 5.0 equiv) was added in three portions over a period of one minute. The reaction was allowed to stir at room temperature for 2 hours, and then diluted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was used without purification in the following reaction.



(+)-(*S*)-WS75624 B, **2b**

(+)-(*S*)-WS75624 B (2b). 6-(2-(6-(*S*)-Triisopropylsiloxy-heptane)-4-thiazolyl)-4,5-dimethoxy-2-pyridine carboxylic acid (3.2×10^{-4} mol, 1.0 equiv) and tetrabutylamonium flouride (251 mg, 9.6×10^{-4} mol, 3.0 equiv) were dissolved in THF (5 mL) and allowed to stir at room temperature overnight. The reaction mixture was diluted with ethyl acetate, and the organic layer was washed with saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting solid was then recrystallized from hot ethyl acetate to obtain (+)-(*S*)-WS75624B (**2b**) (85 mg, 70% yield from 6-(2-(6-(*S*)-triisopropylsiloxy-heptane)-4-thiazolyl)-4,5-dimethoxy-2-pyridine carboxaldehyde) $[\alpha]_D$ +3.1˚ (c 8.0 mg/mL, CH_3OH); ^1H NMR (CD_3OD, 500 MHz) δ 1.13 (d, *J* = 6.2 Hz, 3H), 1.39-1.49 (m, 6H), 1.86 (pent, *J* = 7.5 Hz, 2H), 3.12 (t, *J* = 7.6 Hz, 2H), 3.70 (sextet, *J* = 6.3 Hz, 1H), 4.01 (s, 3H), 4.10 (s, 3H), 7.83 (s, 1H), 8.35 (s, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 23.52, 26.53, 30.21, 31.34, 34.00, 39.98, 57.44, 61.02, 68.44, 109.17, 123.83 142.89, 144.75, 147.36, 148.36, 163.37, 166.63, 173.55. Anal. Calcd for $C_{18}H_{24}N_2O_5S$ C, 56.82; H, 6.36; N, 7.36; S, 8.43. Found: C, 56.46; H, 6.23; N, 7.18; S, 8.47. The spectral properties for **2b** are identical to those reported in the literature.[4]

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3 For the synthesis of this compound, see: Sammakia, T.; Stangeland, E. L.; Whitcomb, M. C. *Org. Lett.* **2002**; *4*; 2385

4 Yoshimura, S.; Tsurumi, T.; Takase, S.; Okuhara, M. J. *Antibiotics* **1995**, *48*, 1073.