Palladium Catalyzed Cross Coupling of Terminal Alkynes With 4-Trifloyl Oxazole: Studies Toward the Construction of the C26-C31 Subunit of Phorboxazole A

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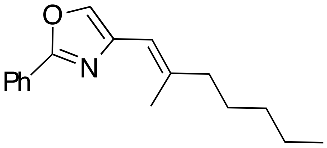
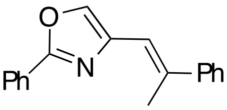
Supporting Information

^{1}H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature, unless otherwise stated. ^{13}C NMR were recorded on a 75.5 Hz spectrometer at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.24; ^{13}C, δ 77.0). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad). All ^{13}C NMR were recorded with complete proton decoupling. Infrared spectra were recorded on a FT-spectrophotometer. High resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described.[1] When specified as "anhydrous", solvents were distilled and / or stored over 4 Å molecular sieves prior to use. Yields refer to chromatographically pure materials, unless otherwise stated. Tetrahydrofuran was freshly distilled under argon from sodium / benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use. *N*-Methyl pyrrolidine (NMP) was distilled from calcium hydride. $Pd(PPh_3)_4$ was prepared as described in "Palladium Reagents in Oganic Syntheses," p 2, Richard F. Heck, *Academic Press, New York*, 1985. DMPU was distilled over 4Å molecular sieves. Methyl iodide (MeI) was passed through a plug of neutral Al_2O_3 before use. All other reagents were used as supplied by Strem Chemicals, Aldrich and Alfa Aesar. All reactions were performed under a dry argon or nitrogen atmosphere in flame dried glassware.

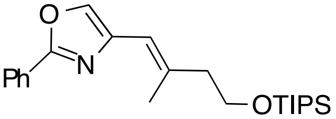
General Procedure for the Carboalumination illustrated for: 4-(*E*-2-Methyl-1-heptenyl)-2-phenyl-oxazole (4a).



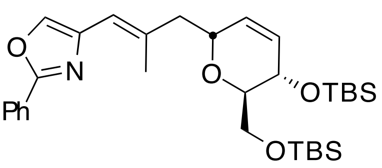
To a flame-dried 10 mL round bottom flask equipped with a stir bar was added zirconocene dichloride (5 mg, 0.017 mmol), and THF (0.5 mL). The solution was cooled to 0 °C and $AlMe_3$ (0.1 mL, 2.0 **M** in hexanes) was slowly added. The reaction mixture was stirred at 0 °C for 0.5 h and 1 h at rt. A solution of 1-heptyne (22 μL, 0.17 mmol) in THF (0.1 mL) was added, and the reaction was stirred at rt for 3 h. The solvents were remove under high vacuum and the residual was redissolved in THF (1 mL). A solution of triflate **2** (50 mg, 0.17 mmol) and Pd(PPh$_3$)$_4$ (20 mg, 0.017 mmol) in THF (1.7 mL) was then added via cannula. The reaction mixture was placed in an oil bath at 60 °C and stirred at constant temperature for 1.5 h. The reaction mixture was then cooled to rt, diluted with H$_2$O (10 mL), and extracted with CHCl$_3$ (3 x 5 mL). The combined organic layers were washed with saturated brine (5 mL), dried over MgSO$_4$, filtered, and concentrated *in vaccuo*. Purification by flash chromatography on SiO$_2$ provided the desired coupling product **4a** as a clear oil in 75% yield (33 mg, 0.129 mmol). ^{1}H NMR (CDCl$_3$) δ: 8.03 (m, 2H), 7.55 (s, 1H); 7.43 (m, 3H); 6.12 (s, 1H); 2.17 (t, 2H, J1 = 7.6 Hz, J2 = 7.6 Hz); 1.96 (s, 3H); 1.50 (t, 2H, J1 = 7.2 Hz, J2 = 7.6 Hz); 1.30 (m, 4H); 0.88 (t, 3H, J1 = 6.8 Hz, J2 = 7.2 Hz). ^{13}C NMR (CDCl$_3$) δ:160.6; 142.3; 139.9; 134.7; 130.2; 128.8; 126.4; 114.5; 40.5; 31.5; 27.5; 22.6; 18.8; 14.0. IR: 3061; 2956; 2929; 2857; 1558; 1488; 1449; 1339; 1105; 1025; 934. CIMS+NH$_4$ (NH$_3$ gas): 256, 255, 212, 199, 105. CIHRMS+NH$_4$ calculated for C$_{17}$H$_{21}$NO+H= 256.16; found 256.1690.



4-(*E*-2-methyl-styryl)-2-phenyl-oxazole (4b): Purification on SiO$_2$ (EtOAc: Hexanes) provided **4b** as a clear oil in 72 % yield. ^{1}H NMR (CDCl$_3$) δ: 8.07 (m, 2H); 7.72 (s, 1H); 7.35 (m, 10H) 6.60 (s, 1H); 2.45 (s, 3H). ^{13}C NMR (CDCl$_3$) δ: 160.9; 143.6; 140.0; 139.2; 135.9; 130.4; 128.7; 128.3; 127.3; 126.4; 125.9; 116.9; 18.4. IR: 3440; 2360; 2342; 2107; 1643. CIMS+NH$_4$ (NH$_3$ gas): 262, 232, 129, 105. CIHRMS+NH$_4$ calculated for C$_{18}$H$_{15}$NO+H= 262.12; found 262.1216.

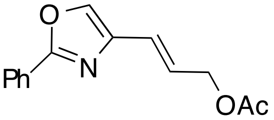


4-(*E*-2-Methyl-4-triisopropylsilyloxy-1-butenyl)-2-phenyl oxazole (4c): Purification on SiO$_2$ (EtOAc: Hexanes) provided **4c** as a clear oil in 72 % yield. ^{1}H NMR (CDCl$_3$) δ: 8.03 (m, 2H); 7.55 (s, 1H); 7.43 (m, 3H); 6.15 (s, 1H); 3.84 (2H, t, J1 = 7.2 Hz, J2 = 7.2 Hz); 2.44 (2H, t, J1 = 7.2 Hz, J2 = 7.2 Hz); 2. 02 (s, 3H); 1.07 (m, 3H); 1.04 (d, 18H, J = 5.2 Hz). ^{13} C NMR (CDCl$_3$) δ: 160.5; 139.7; 139.0; 134.9; 130.2; 128.7; 127.5; 126.3; 116.2; 62.6; 44.0; 19.4; 18.0; 11.9. IR: 3443; 2945; 1653; 1464; 1103. CIMS+NH$_4$ (NH$_3$ gas): 428, 342, 280, 207. CIHRMS+NH$_4$ calculated for C$_{26}$H$_{41}$NO$_2$Si+H = 428.29; found 428.2930.



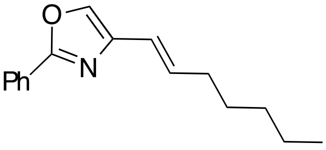
4-[(4*S*, 7*S*, 8*R*)-*E*, *Z*-4,8-epoxy-7,9-(di(tert-butyldimethylsilyloxy))-2-methyl-non-1,5-dienyl]-2-phenyl-oxazole (4d): Purification on SiO$_2$ (EtOAc: Hexanes) provided **4d** as a clear oil in 68 % yield. ^{1}H NMR (CDCl$_3$) δ: 8.01 (m, 2H); 7.43 (m, 4H), 5.88 (m, 3H), 4.36 (t, 1H, J = 7.2 Hz); 4.09 (m, 1H); 3.75 (m, 3H); 2.45 (m, 2H), 2.24 (s, 3H); 0.87 (m, 18H); 0.05 (m, 12H). ^{13}C NMR (CDCl$_3$) δ: 134.2, 130.2, 130.0, 128.7, 127.9, 126.5, 126.1, 80.5, 74.4, 70.2, 69.9, 62.8, 61.4, 25.9, 25.8,, 23.5, 18.1, 11.6, -4.4, -4.9, -5.4, -5.6. IR: 2950, 2929, 2862, 1717, 1465, 1394, 1361, 1105, 930. CIMS+NH_4 (NH_3 gas): 556, 397, 357, 339, 117. CIHRMS+NH_4 calculated for $C_{31}H_{49}NO_4Si_2$+H= 556.3212; found 556.3288.

General Procedure for Stille Coupling illustrated for: 4-(3-acetoxy-1-propenyl)-2-phenyl-oxazole (6c).



A 10 mL round bottom flask under nitogen was charged with LiCl (0.044 g, 1.06 mmol), stannane **5c** (0.144 g, 0.36 mmol), triflate **2** (0.10 g, 0.341 mmol) and DMF (3 mL, 0.1 **M**). Pd(PPh_3)$_4$ (16 mg, 0.013 mmol) was added as a solid and the flask was equipped with a water condenser. The reaction mixture was warmed to 60 °C and stirred at constant temperature for 2 h. The reaction mixture was allowed to cool to rt, diluted with H_2O (10mL), and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with H_2O (5 x 5mL) then brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 (EtOAc/PE 5:95) afforded **6c** as a clear oil (0.056 g, 0.28 mmol). ^{1}H NMR ($CDCl_3$) δ: 8.05 (m, 2H); 7.54 (s, 1H); 7.44 (m, 3H); (6.52, m, 2H); 6.34 (d, 1H, J = 16Hz); 4.18 (t, 2H, J_1 = 6.8 Hz, J_2 = 6.4 Hz); 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 171.1; 160.5; 134.3; 130.1; 128.7; 128.4; 128.1; 126.5; 120.5; 63.7; 32.0; 21.0. IR: 2960; 1738; 1366; 1037. CIMS+NH_4 (NH_3 gas): 258, 227, 197, 168, 122, 105. CIHRMS+NH_4 calculated for $C_{15}H_{15}NO_3$+H= 258.11; found 258.1113.

2-Phenyl-4-styryl-oxazole (6a): The crude product was obtained as a solid which was triturated with cold pentane to provide pure **6a** as a buff powder in 80% yield ^{1}H NMR ($CDCl_3$) δ: (270 MHz) 8.10 (m, 2H); 7.70 (s, 1H); 7.426 (m, 10H); 7.38 (d, 1H, J = 23.6) 6.96 (d, 1H, J = 21.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 161.7; 140.3; 136.8; 135.3; 130.6; 130.5; 128.7; 128.6; 127.7; 126.5; 116.4. IR: 3405, 2360, 2342, 1684, 1448, 1265. CIMS+NH_4 (NH_3 gas): 262, 248, 115, 105. CIHRMS+NH_4 calculated for $C_{17}H_{13}NO$+H= 247.10; found 247.1053.

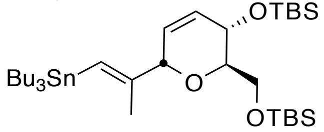


4-(1-Heptenyl)-2-phenyl-oxazole (6b): Purification on SiO_2 (EtOAc: Hexanes) provided **6b** as a clear oil in 80 % yield.^{1}H NMR ($CDCl_3$) δ: 8.03 (m, 2H); 7.50 (s, 1H); 7.43 (m, 3H); 6.53 (m, 1H); 6.24 (d, 1H, J = 15.6 Hz); 2.20 (dd, 2H, J1 = 6 Hz, J2 = 7.6 Hz); 1.45 (m, 2 H), 1.19 (m, 4H); 0.88 (m, 3 Hz). ^{13}C NMR ($CDCl_3$) δ: 133.7; 131.5; 130.3; 128.9; 128.6; 126.6; 126.4; 126.2; 117.9; 32.8; 31.4; 28.7; 22.6; 14.0. IR: 2956; 2928; 2857; 1696;

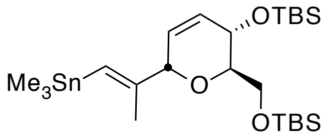
1558; 1450; 1270; 1105; 967 CIMS+NH_4 (NH_3 gas): 242, 241, 198, 105. CIHRMS+NH_4 calculated for $C_{16}H_{19}NO$+H= 242.15; found 242.1544.

Procedure for the Generation of $(Me_3Sn)_2CuCNLi_2$: In a 10 mL round bottom flask was syringed hexamethylditin (0.177 mL, 0.86 mmol) and THF (1.7 mL). The solution was cooled to -78 °C and MeLi (0.614 mL, 0.86 mmol, 1,4 **M** in hexanes) was slowly added. The reaction was stirred at -78 °C for o.5 h. In a 25 mL Schlenk flask was charged CuCN (39 mg, 0.43 mmol). After flame drying the CuCN, the Schlenk was cool to rt under argon and THF (*c*. 0.05 mL) was added to make a slurry. The slurry was was cooled to 0 °C and the previous solution was added via cannula. The reaction mixture was stirred at 0 °C for 20 minutes before using in subsequent reactions.

General Procedures for the Addition of Higher Order Stannyl Cuprate to Alkynes illustrated for (2*S*, 5*S*, 6*R*)-6(tertbutylsilyloxy)methyl-5(tertbutylsilyloxy)-5,6 dihydro-2-(*E* -(1'methyl-2'-tributylstannyl-ethenyl)-'2*H*-pyran (8).



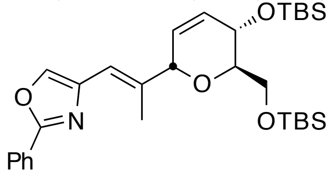
To a solution of stannyl cuprate (5.7 mmol) in THF (16 mL) at -78 °C was added pyran **7** (2.0 g, 5.3 mmol) in THF (*c* 0.5 mL). The reaction mixture was stirred for 15 minutes at -78 °C. MeI (6.9 mL, 100 mmol) and DMPU (1.6 mL) were sequently added. The reaction mixture was stirred for 3.5 h at -78°C and then poured into a saturated solution of NH_4Cl (40 mL). The solution was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatograhy on SiO_2, treated with 3% Et_3N in hexanes, eluting with 100% hexanes, yielded stannane **8** in 80% (2.88 g, 4.18 mmol). ^1H NMR ($CDCl_3$) δ: 5.78 (m, 3H), 4.52 (b, 1H), 4.05 (m, 1H), 3.82 (m, 1H), 2.33 (m, 1H), 3.38 (m, 1H), 1.84 (s, 3H), 1.36 (m, 27H), 0.872 (m, 18H), 0.05 (m, 12H). ^{13}C NMR ($CDCl_3$) δ: 151.9, 130.1, 128.8, 126.8, 74.5, 64.6, 63.3, 28.9, 29.2, 27.3, 26.0, 25.8,13.7, 10.1, -4.4, -4.9, -5.4, -5.6. IR: 2957, 2927, 2856, 1464, 1376, 1252, 1092, 837. CIMS+NH_4 (NH_3 gas): 648.6, 631.3, 457.1, 291.0, 249.2, 159.0. CIHRMS+NH_4 calculated for $C_{33}H_{68}O_3Si_2Sn$+H= 687.3725; found 687.3629.



(2*S*, 5*S*, 6*R*)-6(tertbutylsilyloxy)methyl-5(tertbutylsilyloxy)-5,6 dihydro-2-(*E* -(1'methyl-2'-trimethylstannyl-ethenyl)-'2*H*-pyran (9). Purification on deactivated SiO_2 (3%Et_3N:hexanes, eluting with 100% hexanes) provided **9** as a clear oil in 70 % yield. ^1H NMR ($CDCl_3$) δ: 5.75 (m, 4H), 4.50 (bd, 1H, J=10.4 Hz), 4.19 (d, 1H, J=7.6 Hz), 3.85 (m, 1H), 3.64 (m, 1H), 3.40 (m, 1H), 1.85 (s, 3H), 0.88 (s, 18H), 0.11 (m, 12H). ^{13}C

NMR (CDCl$_3$) δ: 151.7, 130.5, 129.2, 127.0, 75.6, 64.5, 63.2, 27.0, 25.8, -4.4, -4.9, -5.4, -5.6. IR: 2957, 2885, 2360, 2342, 2653, 1463, 1388, 1361, 1316, 1186, 1155, 1018, 939. CIMS+NH$_4$ (NH$_3$ gas): 547.2, 505.1, 400.2, 341.1, 325.1, 209.1, 193.0. CIHRMS+NH$_4$ calculated for $C_{24}H_{50}O_3Si_2Sn$+H= 562.5192; found 562.4685.

Stille coupling of 2 and 11: 4-[(4*S*, 7*S*, 8*R*)-*E*, *Z*-3,7-epoxy-6,8-(di(tert-butyldimethylsilyloxy))-2-methyl-octa-1,4-dienyl]2-phenyl-oxazole (10).



In a 10 mL Schlenk flask LiCl (25 mg, 0.6 mmol) was added and flame dried. After cooling the flask to rt under argon, Pd$_2$(dba)$_3$•CHCl$_3$ (7 mg, 0.0067 mmol) was added. A solution of triflate **2** (33 mg, 0.11 mmol) in NMP (0.1 mL) and one of stannane **9** (0.1 g, 0.17 mmol) in NMP (0.1 mL) were added sequentially. ^{t}Bu$_3$P (3 mL, 0.015 mmol) was added via syringe. The reaction mixture was placed in an oil bath at 60 °C for 5 h. The reaction mixture was cooled to rt, diluted with CH$_2$Cl$_2$ (5 mL) and H$_2$O (10 mL). The layers were separated, and the aqueous layer extracted with CH$_2$Cl$_2$ (3 x 3 mL). The combined organic layers were washed with H$_2$O (3 x 15 mL) then saturated brine (15 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on SiO$_2$ provided **10** (34 mg, 0.006 mmol) as a clear oil in 60% yield. ^{1}H NMR (CDCl$_3$) δ: 8.02 (m, 2H), 7.62 (s, 1H), 7.42 (m, 3H), 6.36 (s, 1H), 5.85 (m, 2H), 4.61 (b, 1H), 4.09 (m, 1H), 3.82 (dd, 1H, J1 = 2.4 Hz, 8.8 Hz), 3.66 (m, 1H), 3.43 (m, 1H), 2.07 (s, 3H), 0.86 (m, 18 H), 0.054 (m, 12H). ^{13}C NMR (CDCl$_3$) δ: 139.3, 135.8, 133.6, 131.3, 130.3, 128.7, 128.5, 127.5, 126.4, 117.7, 47.5, 63.5, 62.65, 25.9, 25.7, -4.4, -4.9, -5.4, -5.6. IR: 2956, 2929, 2857, 1717, 1472, 1463, 1389, 1361, 1257, 1092, 1006, 909. CIMS+NH$_4$ (NH$_3$ gas): 551.1, 484.1, 368.2, 264.0. CIHRMS+NH$_4$ calculated for $C_{30}H_{47}NO_4Si_2$+H= 542.3043; found 542.3157 .

Additional Notes and References

(1) Still, W. C.; Kahn, M; Mitra, A.*J. Org. Chem.* **1978**, 43, 2923-2925.