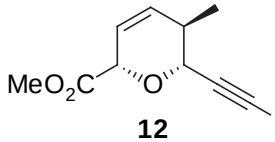
Supporting Information:

Formal [4+2]-Annulation of Chiral Crotylsilane: Synthesis of the C19-C28 Fragment of Phorboxazole

Hongbing Huang and James S. Panek*
Department of Chemsitry, and Center for Streamlined Synthesis
Metcalf Center for Science and Engineering,
590 Commonwealth Avenue, Boston University,
Boston, Massachusetts 02215

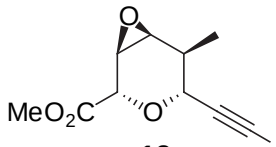
General Information: ^{1}H- and ^{13}C-NMR were taken in $CDCl_3$ at 400 MHz and 75.0 MHz respectively unless specified otherwise. Chemical shifts are reported in parts per million using the solvent resonance internal standard (chloroform, 7.24 and 77.0 ppm, unless specified otherwise). Data are reported as follows: chemical shift, multiplicity (app = apparent, par obsc = partially obscured, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, abq = ab quartet), coupling constant, and integration. Ratios of diastereomers (dr) were determined by ^{1}H-NMR (400 MHz) operating at a signal/noise ratio of >200:1. Infrared Resonance spectra were recorded on a Nicolet Impact 400 FT-IR spectrometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589nm, and are reported as $[\alpha]_D$ (concentration in grams/100 mL solvent). High resolution mass spectra (HRMS) were obtained on a Fingan MAT-90 spectrometer on the Boston University Mass Spectrometry Laboratory. Tetrahydrofuran (THF) and ethyl ether (Et_2O) were distilled under nitrogen from sodium-benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled under nitrogen from CaH_2. All other reagents were used as supplied. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted. Analytical thin layer chromatography was performed on Whatman Reagent silica gel 60-A plates. Flash chromatography was performed on E. Merck silica gel 230-400 mesh.



12

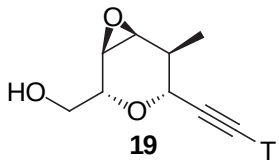
General procedure for the TMSOTf catalyzed [4+2]-annualtion illustrated for (**12**): A solution of crotylsilane **6** (8.3 g, 0.021 mol, 1.0 equiv) and 3-triisopropylsilyl-α,β -acetylenic aldehyde **11** (4.4 g, 0.021

mol, 1.0 equiv) in CH_2Cl_2 (0.05 **M**) at 20 °C was treated with TMSOTf (1.9 mL, 0.011 mol, 0.5 equiv). The solution was stirred at room temperature for 12h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel (5%, EtOAc/hexane eluant) gave 4.3 g of pale yellow oil. $[\alpha]_D^{20}$ –96.1° (c 1.3 , $CHCl_3$). IR (neat) 2944, 2866, 1768, 1738, 1086, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77-5.75 (m, 2H), 4.77 (m, 1H), 3.99 (d, J = 9.2 Hz, 1H), 3.74 (s, 1H), 2.55-2.5 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 1.04 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 132.7, 123.3, 104.9, 87.5, 74.7, 71.6, 52.5, 35.7, 18.7, 17.2, 11.3; HRMS (CI/NH_3) m/z calcd for $C_{19}H_{33}SiO_3$ 337.2199, found 337.2242.



18

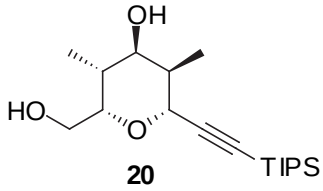
Typical procedure for the epoxidation of dihydropyrans illustrated for epoxide (**18**): To a solution of **12** (2.1 g, 6.25 mmol, 1.0 equiv) in CCl_4 (0.05 **M**) was added m-CPBA (3.6 g, 12.5mmol, 2.0 equiv). The reaction was stirred at room temperature for 12 hours. The reaction was quenched by the addition of saturated $Na_2S_2O_3$, followed by the addition of saturated $NaHCO_3$, and was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel (10%, EtOAc/hexane eluant) gave 1.9 g of colorless oil. $[\alpha]_D^{20}$ –44.9° (c 1.2 , $CHCl_3$). IR (neat) 2944, 2866, 1767, 1741, 1463, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.42 (s, 1H), 3.86 (d, J = 10.2 Hz , 1H), 3.80 (s, 3H), 3.52 (d, J = 4.0 Hz, 1H), 3.24 (br s, 1H), 2.23 (m, 1H), 1.18 (d, J = 6.9 Hz, 3H), 1.03 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 104.1, 88.0, 74.7, 67.4, 55.4, 54.2, 52.8, 36.0, 18.7, 14.0, 11.3; HRMS (CI/NH_3) m/z calcd for $C_{19}H_{33}SiO_4$ 353.2148, found 353.2162.



19

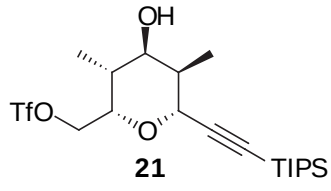
Experimental procedure for the $LiAlH_4$ reduction of methyl ester (**18**): To a slurry of $LiAlH_4$ (94 mg, 2.4 mmol, 0.65 equiv) in THF (0.1 **M**) was added a solution of **18** (1.34 g, 3.8 mmol, 1.0 equiv) in THF dropwise at 0 °C. The reaction was stirred at this temperature for 20

min, followed by the addition of 5% HCl (10 mL), and was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography on silica gel (35%, EtOAc/hexane eluant) gave 1.2 g of colorless oil; $[\alpha]_D^{20}$ –20.9° (c 0.9, $CHCl_3$). IR (neat) 3435, 2943, 2866, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (app d, J = 10.2, 3H), 3.72 (m, 1H), 3.22 (app d, J = 4.3 Hz, 1H), 3.20 (app d, J = 4.3 Hz, 1H), 2.16-2.08 (m, 1H), 2.03 (br s, 1H), 1.18 (d, J = 6.9 Hz, 3H), 1.04 (s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.7, 87.6, 76.0, 67.8, 64.5, 55.9, 54.9, 37.1, 19.2, 14.5, 11.8; HRMS (CI/NH_3) m/z calcd for $C_{18}H_{33}SiO_3$ 325.2199, found 325.2194.



20

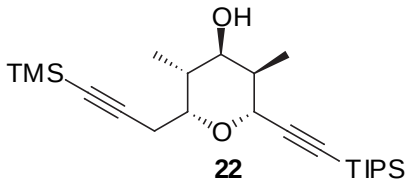
Experimental procedure for epoxide ring opening: To a suspension of CuI (1.5 g, 7.2 mmol, 2.5 equiv) in THF (0.1 **M**) at 0 °C was added CH_3MgBr dropwise (3 **M** in ether, 5.1 mL, 15.5 mmol, 5 equiv). To the resulted gray color solution was added a solution of **19** in 4 mL of THF. The reaction was stirred at 0 °C for 4 hours, and was quenched by the addition of saturated NH_4Cl. The aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel (50%, EtOAc/hexane eluant) gave 0.95 g of colorless oil. $[\alpha]_D^{20}$ +0.053° (c 0.3, $CHCl_3$). IR (neat) 3407, 2943, 2866, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (d, J = 10.9 Hz, 1H), 3.94 (dt, J = 3.0, 8.9 Hz, 1H), 3.69 (dt, J = 3.0, 13.0 Hz, 1H), 3.63 (app d, J = 2.6 Hz, 1H), 3.43 (dt, J = 3.3 Hz, 9.0 Hz, 1H), 1.9 (m, 1H), 1.73 (m, 1H), 1.46 (d, J = 3.0 Hz, 1H), 1.04 (s, 21H), 0.91 (d, J = 7.25 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.4, 86.5, 75.3, 74.3, 69.5, 64.2, 37.5, 36.3, 18.8, 14.4, 13.8, 11.4; HRMS (CI/NH_3) m/z calcd for $C_{19}H_{37}SiO_3$ 341.2512, found 341.2552.



21

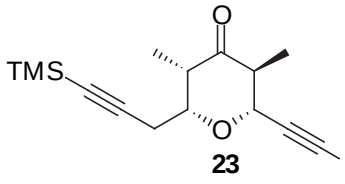
Experimental procedure for selective trifilation: To a solution of diol **20** (0.9 g, 2.65 mmol, 1.0 equiv) and pyridine (0.43 mL, 5.30 mmol, 2.0 equiv) in CH_2Cl_2 (0.04 **M**) was added Tf_2O at –15 °C. The reaction was stirred at this temperature for 12 hours, after which time the CH_2Cl_2 was removed under reduced pressure. Purification of the resultant

crude residue by chromatography (10% EtOAc/hexane eluant) gave 1.2 g of colorless oil. $[\alpha]_D^{20}$ +24.6° (c 0.5 $CHCl_3$). IR (neat) 3462, 2944, 2867, 1417 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (d, J = 10.2, 7.9 Hz, 1H), 4.33 (dd, J = 10.5, 4.6 Hz, 1H), 4.23 (d, J = 10.5 Hz, 1H), 4.20 (overlp m, 1H), 3.68 (app d, J = 2.6 Hz, 1H), 1.95-1.90 (m, 1H), 1.84-1.80 (m, 1H), 1.55 (d, J = 2.9 Hz, H), 1.04 (app s, 24H), 0.95 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.3, 87.7, 77.5, 74.6, 72.2, 70.3, 37.8, 36.8, 19.6, 14.5, 12.2, 11.7; HRMS (CI/NH_3) m/z calcd for $C_{20}H_{35}SiSF_3O_5$ 472.1927, found 472.1958.



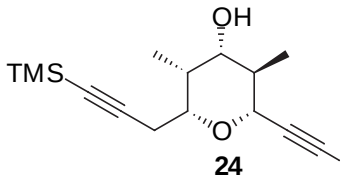
22

Nucleophilic displacement of 1° triflate: To a solution of DIPA (68 μL, 0.47 mmol, 1.1 equiv) HMPA (82μL, 0.47 mmol, 1.1 equiv) in THF (0.05 **M)** at –78 °C was added nBuLi (2.5 **M** in hexane, 0.19 mL, 0.47 mmol, 1.1 equiv). The solution was warmed to 0°C and stirred for 30 min. The reaction was cooled to –78 °C and (trimethylsilyl)acetylene (66 μL, 0.47 mmol, 1.1 equiv) was added via syringe. The reaction was stirred for 15 min, after which time a solution of triflate **21** (0.23 g, 0.43 mmol, 1.0 equiv) in THF (1 mL) was added. After stirring for 5 min at –78°C**,** the reaction was warmed to –10 °C and stirred at this temperature for an additional 2 hours. The reaction was then quenched with 5% HCl. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel (2%, EtOAc/hexane eluant) gave 145 mg of colorless oil. $[\alpha]_D^{20}$ +16.0° (c 0.4 $CHCl_3$). IR (neat) 2943, 2866, 2177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (d, J = 10.2 Hz, 1H), 3.98-3.93 (m, 1H), 3.69 (br s, 1H), 2.55 (dd, J = 16.8, 5.9 Hz, 1H), 2.31 (dd, J = 16.8, 9.9 Hz, 1H), 1.97-1.87 (m, 2H), 1.40 (d, J = 2.6 Hz, 1H), 1.03 (app s, 24 H), 0.94 (d, J = 7.3 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.5, 103.1, 86.3, 74.4, 72.5, 69.6, 37.8, 36.0, 23.6, 18.9, 13.8, 11.5, 10.4, 0.3; HRMS (CI/NH_3) m/z calcd for $C_{23}H_{44}O_2Si_2$ 420.2880, found 420.2887.



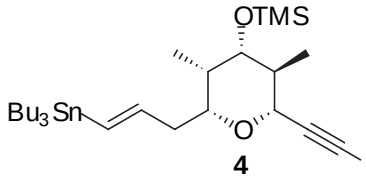
23

Experimental procedure for oxidation of 2° alcohol: To a solution of Dess-Martin periodinane[1] (270 mg, 0.6 mmol, 2.2 equiv) in CH_2Cl_2 (0.3 **M**) at 0 °C was added alcohol **22** (120 mg, 0.29 mmol, 1.0 equiv). The reaction was stirred at this temperature for 3 hours, after which time the reaction was diluted with ether (3 mL), followed by the addition of 2 mL of saturated $Na_2S_2O_3$ and 2 mL of saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 3 mL). The combined organic layers were washed with saturated $NaHCO_3$ (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel (1%, EtOAc/hexane eluant) gave 115 mg of keto-pyran **23**. $[\alpha]_D^{20}$ +41.8° (c 0.4 $CHCl_3$). IR (neat) 2959, 2866, 2180, 1716, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (d, J = 10.9 Hz, 1H), 3.76-3.72 (m, 1H), 2.71-2.64 (m, 3H), 2.48 (dd, J = 16.8, 9.9 Hz, 1H), 1.17 (d, J = 7.3 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H), 1.05 (s, 21H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ210.7, 104.2, 101.1 88.3, 87.5, 77.4, 74.3, 47.6, 46.7, 23.0, 18.8, 11.4, 10.9, 9.9, 0.20; HRMS (CI/NH_3) m/z calcd for $C_{24}H_{42}O_2Si_2$ 418.2723, found 418.2726.



24

Experimental procedure for the LAH reduction: To a slurry of $LiAlH_4$ (8 mg, 0.22 mmol, 1.0 equiv) in THF (0.1 **M**) was added a solution of **23** (90 mg, 0.22 mmol, 1.0 equiv) in THF dropwise at 0 °C. The reaction was stirred at this temperature for 15 min, followed by the addition of 5% HCl (10 mL), and was extracted with Et_2O (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on silica gel (1%, EtOAc/hexane eluant) gave 81 mg of alcohol **24**. $[\alpha]_D^{20}$ +31.0° (c 0.6 $CHCl_3$). IR (neat) 3397, 2944, 2866, 2179, 1463cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (d, J = 10.6 Hz, 1H), 3.52-3.48 (m, 1H), 3.41-3.48 (m, 1H), 2.57 (dd, J = 16.8, 5.3 Hz, 1H), 2.41 (dd, J = 16.8, 10.2 Hz, 1H), 2.17-2.14 (m, 1H), 1.71-1.66 (m, 1H), 1.52 (br s, 1H), 1.07 (d, J = 6.6 Hz, 3H), 1.03 (s, 21H), 0.91(d, J =6.9 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ105.3, 102.7, 86.7, 86.5, 77.4, 76.5, 73.7, 38.8, 36.9, 23.7, 18.8, 14.0, 11.4, 5.2, 0.3; HRMS (CI/NH_3) m/z calcd for $C_{24}H_{44}O_2Si_2$ 420.2880, found 420.2921.



4

Experimental procedure for introduction of the E-vinyl stannane: To a solution of the alcohol **24** (40 mg, 0.10 mmol, 1.0 equiv) and 2, 6-luitidine (17 μL, 0.14 mmol, 1.5 equiv) in CH_2Cl_2 (0.2 **M)** was added TMSOTf (21 μL, 0.11 mmol, 1.2 equiv) at –20 °C. The reaction was stirred at this temperature for 4 hours, after which time the solution was filtered through a pad of silica gel and the solvent was removed under reduced pressure. The resultant residue was then dissolved in 1 mL of acetone. To the above solution was added N-bromosuccinimide (20 mg, 0.11 mmol, 1.1 equiv) and silver nitrate (2 mg, 0.01 mmol, 0.1 equiv).[2] The mixture was stirred at room temperature for 45 min. The mixtrure was diluted with light petroleum (5 mL) and then washed with water (2 x 2 mL). The separated aqueous layer was extracted with Et_2O-light petroleum ether (1:1, 5 mL), and the combined organic extracts were dried over $MgSO_4$ and filtered through a pad of silica gel. Evaporation of the solvent under reduced pressure left the 1-bromoalkyne in a high state of purity, which was used directly in the next step without further purification.

To a THF (1 mL) solution of 1-bromoalkyne (50 mg, 0.10 mmol, 1.0 equiv) and $PdCl_2(PPh_3)$ (3.5 mg, 0.005 mmol, 0.05 equiv) was added tributyltin hydride (60 μL, 0.22 mmol, 2.2 equiv) over 20 min.[3] The reaction was allowed to stir for another 10 min before the solvent THF was removed under reduced pressure. The oily residue was purified by column chromatography (neutral Al_2O_3, hexane eluant) to give 50 mg of colorless oil. $[\alpha]_D^{20}$ +37.0° (c 0.4 $CHCl_3$). IR (neat) 2959, 2926, 2866, 1463cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (d, J = 18.8 Hz, 1H), 5.86 (m, 1H), 3.71 (d, J = 10.6 Hz, 1H), 3.33-3.28 (m, 2H), 2.53-2.47 (m, 1H), 2.27-2.19 (m, 1H), 1.76-1.68 (m, 2H), 1.48-1.36 (m, 6H), 1.30-1.18 (m, 6H), 1.03 (app s, 24H), 0.97(d, J = 6.6 Hz, 3H), 0.90-0.80 (m, 15H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ145.4, 131.4, 106.5 86.3, 79.5, 74.3, 41.6, 39.3, 39.0, 29.7, 28.1, 19.3, 15.0, 14.3, 11.9, 10.1, 6.3, 0.9; HRMS (CI/NH_3) m/z calcd for $C_{36}H_{72}O_2Si_2$ 712.4094, found 712.4117.

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[1] Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

[2] Boden, C. D.J.; Pattenden, G.; Ye, T. *J. Chem. Soc. Perkin Trans.* 1 **1996**, 2417-2419.

[3] Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857-1867.