Synthesis of the C22-C26 Tetrahydropyran Segment of Phorboxazole by a Stereoselective Prins Cyclization

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Experimental Section

General Procedure. All moisture and air-sensitive reactions were carried out in flame-dried glassware using magnetic stirring under a positive pressure of argon. Standard syringe/septa techniques were employed. Concentration of organic solutions was accomplished by rotary evaporation. Thin layer chromatography was performed on Whatman silica gel PE SIL G/UV (0.25 mm) plates. Flash column chromatography was performed on EM Science 230-400 mesh silica gel. Capillary GC analysis was performed on a Hewlett Packard Model 6890 instrument with a 30 m x 0.25 μM Alltech EC-5 (SE-54) capillary column. A flame ionization detector and a Hewlett Packard computer interfaced integrator were employed for analysis. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Infrared spectra were recorded on a MIDAC Grams/Prospect FT-IR. NMR spectra were recorded on Bruker DRX400, Bruker GN500 and Bruker Omega500 MHz FT-NMR instruments. Proton NMR spectra were recorded in ppm and were referenced to residual solvent: $CDCl_3$ (7.26 ppm). Data are presented as follows: chemical shift, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet), integration and coupling constant(s) in Hertz (Hz). Multiplets (m) are reported over the range (ppm) at which they appear at the indicated field strength. Carbon NMR spectra were recorded in ppm relative to the solvent signal: $CDCl_3$ (77.0 ppm). Mass spectral data was obtained on a Micromass 7070E-HF or a Micromass autospec spectrometer. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ).

3-*O*-(*tert*-Butyldiphenylsilyloxy)-propanal (2). A sample of 33.85 mL (67.7 mmol, 2.0 M solution in dichloromethane, 1.1 equiv) oxalylchloride was dissolved in 150 mL dichloromethane and the solution was cooled to −78 °C. A sample of 9.60 mL (10.57 g, 135.3 mmol, 2.2 equiv) DMSO, diluted in 30 mL dichloromethane, was slowly added to the solution. After 5 min, 19.35 g (61.5 mmol) 3-*O*-(*tert*-butyldiphenylsilyloxy)-propan-1,3-diol, diluted in 50 mL dichloromethane were added slowly and stirring was continued for an additional 15 min. Triethylamine (43 mL, 309 mmol, 5.0 equiv) was added and the solution

was warmed to 23 °C. The aqueous layer was reextracted with additional dichloromethane. The organic layers were combined, washed with saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The filtered solution was concentrated under reduced pressure to a volume of ca. 100 mL and used without further purification.

(3*R*,4*R*)-3-*O*-(*tert*-Butyldiphenylsilyl)-4-methylhepten-1,3-diol (9). The solution of the aldehyde was added all at once to to solution of 24.2 g (ca. 73.7 mmol, 1.2 equiv) of boronate **8**[1] in 200 mL hexanes. The resulting solution was immediately cooled to 0 °C in a thermostated bath and stirred for 3 d. Then 10.44 g (9.32 mL, 70 mmol) triethanolamine were added, and the mixture was stirred for 1 h at 23 °C. The solution was refluxed for 3 h, then cooled to 23 °C, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (5% ethyl acetate/hexanes) to give 20.92 g **9** as a clear oil that was still contamined with ca. 14 mol% of aldehyde **2**. Compound **9** was a clear oil: $\mathbf{R_f}$ (5% ethyl acetate /hexanes): 0.18; **IR** (neat) 3521, 1428, 1111 cm^{-1}; **^{1}H** NMR (500 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 9H), 1.67 (m, 5 H), 2.21 (m, 1H), 3.67 (d/d/d, *J* = 2.3 Hz, 7.7 Hz, 8.4 Hz, 1 H), 3.86 (m, 2H), 5.36 (d/d/q, *J* = 1.5 Hz, 7.8 Hz, 15.3 Hz, 1H), 5.47 (d/d/q, *J* = 0.7 Hz, 6.3 Hz, 15.3 Hz, 1H) 7.39-7.45 (m, 6H), 7.67-7.68 (m, 4H) ppm; **^{13}C** NMR (125 MHz, $CDCl_3$): δ = 15.9, 18.1, 19.0, 26.8, 35.5, 43.0, 63.7, 75.3, 125.5, 127.7, 129.8, 133.0, 133.7, 135.5 ppm; **MS** (HRCI-isobutane) calcd. for $C_{24}H_{35}O_2Si$ (M + H): 383.2406, found 383.2413. **HPLC** (Chiralcel OD-H, 2% ethyl acetate/hexanes, flow: 1.0 mL/min) 23 °C: 8.002 min for (*S*,*S*)-**9**, 6.854 min for (*R*,*R*)-**9**; *ee*=98%.

Ester 10. A solution of 11.36 g (63 mmol, 1.5 equiv) *O*-benzyl (*S*)-lactic acid in 150 mL dichloromethane was cooled to 0°C. A sample of 12.99 g DCC (63 mmol, 1.5 equiv) was added in several portions and a white precipitate formed quickly. After 5 min stirring, 16.07 g (42 mmol) alcohol (*S*,*S*)-**9** (as a mixture with aldehyde **2**) was added as a solution in 100 mL dichloromethane along with a small amount of DMAP . The cooling bath was removed and stirring was continued for 24 h. The solution was filtered and the solvent was removed under reduced pressure. The resulting oil was chromatographed several times with 5% ethyl acetate /hexanes. The resulting oil was heated to 50 °C for 3 h under high vacuum to give 17.72 g (32.53 mmol, 53% over 3 steps) of **4** as a colorless oil: $[\alpha]_D$ (T=24°C): −32.9

[1] The boronate **8** was isolated as a 92:8 mixture of **8** and (4*R*,5*R*)-4,5-dicyclohexyl-2-(*Z*-propenyl)-1,3,2-dioxaborolane. The later does not react with aldehydes under the reaction conditions. Hoffmann, R. W.; Ditrich, K.; Köester, G.; Stüermer, R. *Chem. Ber.* **1989**, *122*, 1783-9.

(*c*=1.05, $CHCl_3$); $\mathbf{R}_f$ (10% ethyl acetate in hexanes): 0.38; **IR** (neat) 1747, 1112cm^{-1}; **^{1}H** NMR (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.9 Hz, 3H), 1.05 (s, 9H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.66 (d, *J* = 6.1 Hz, 3H), 1.74 (m, 1H), 1.91 (m, 1H), 2.44 (m, 1H), 3.65 (m, 2H), 3.97 (q, *J* = 6.8 Hz, 1H), 4.33 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 5.08 (d/d/d, *J* = 3.1 Hz, 6.1 Hz, 9.3 Hz, 1H), 5.34 (d/d/q, *J* = 1.3 Hz, 7.4 Hz, 15.3 Hz, 1H) 5.43 (d/q, *J* = 6.0 Hz, 15.3 Hz, 1H), 7.32-7.39 (m, 11H), 7.63-7.65 (m, 4H) ppm; **^{13}C** NMR (125 MHz, $CDCl_3$): δ = 15.9, 18.0, 18.8, 19.1, 26.8, 34.1, 40.4, 60.4, 71.8, 74.1, 74.9, 126.1, 127.6, 127.6, 127.7, 127.9, 128.4, 129.6, 132.1, 133.6, 133.8, 135.5, 135.6, 137.7, 172.7 ppm; **MS** (LSIMS) calcd. for $C_{34}H_{45}O_4Si$ (M + H): 545.3087, found 545.3068; **EA** calcd for C:74.96, H:8.14; found C:75.12, H:8.18.

α-Acetoxy ether 11. A sample of 110 mg (0.20 mmol) ester **10** was dissolved in 5 mL dichloromethane and cooled to −78 °C. Then 0.60 mL (0.60 mmol, 3.0 equiv) of a 1.0 M solution of DIBAL-H in hexane were added dropwise and stirring was continued for 45 min. TLC (9:1 hexanes/ethyl acetate) analysis indicated that all starting material **10** was converted at this time. Then 71 mg (72 µl, 4.5 equiv) pyridine, 73 mg (0.6 mmol, 3.0 equiv) DMAP and 184 mg (1.8 mmol, 9.0 equiv) acetic anhydride were added and stirring was continued at −78 °C for 14 h. The solution was allowed to warm to 0 °C and stirred for an additional hour. The reaction was quenched with 5 mL sat. NH_4Cl solution and 5 mL sat. aq. sodium potassium tartrate solution, and the solution was warmed to 23 °C. The mixture was diluted with dichlormethane and stirred vigorously for 1 hour. After extraction with dichlormethane (4 ×), the combined dichlormethane extracts were washed with ice-cooled 1 M potassium bisulfate (2 ×), saturated aq. sodium bicarbonate (3 ×) and brine. After drying (Na_2SO_4) and evaporation we obtained a yellowish oil. After chromatography on silica (10% ethyl acetate in hexanes) we obtained 108 mg (0.18 mmol, 91%) of a colorless oil: $[\alpha]_D$ (T=23°C): +7.6 (*c* = 1.09, $CHCl_3$); $\mathbf{R}_f$ (10% ethyl acetate/hexanes, TLC plate developed twice): 0.36; **IR** (neat) 1111, 1238, 1740 cm^{-1}; **^{1}H** NMR (500 MHz, mixture of diastereomers, $CDCl_3$): δ = 0.94 (d, *J* = 6.9 Hz, 3H, minor diast.), 0.96 (d, *J* = 6.9 Hz, 3H, major diast.), 1.05 (s, 9H), 1.13 (d, *J* = 6.4 Hz, 3H, minor diast.), 1.16 (d, *J* = 6.4 Hz, 3H, major diast.), 1.57-1.81 (m, 5H), 1.88 (s, 3H, major diast.), 2.05 (s, 3H, major diast.), 2.27 (m, 1H, minor diast.), 2.43 (m, 1H, major diast), 3.52 (d/q, *J* = 4.5 Hz, 6.4 Hz, 1H, minor diast.), 3.58 (d/q, *J* = 3.5 Hz, 6.4 Hz, 1H, major diast.), 3.61 (m, 1H, major diast.), 3.66 (m, 1H, minor diast.), 3.75 (m, 2H), 4.52 (d, *J* = 12.0 Hz, 1H, major diast.), 4.57 (s, 2H, minor diast.), 4.63 (d, *J* = 12.0 Hz, 1H, major diast.), 5.39 (m, 2H), 5.94 (d, *J* = 4.5 Hz, 1H, minor diast.), 6.10 (d, *J* = 3.5 Hz, 1H, major diast.), 7.29-7.38 (m, 11H), 7.65-7.67 (m, 4H) ppm; **^{13}C** NMR (125 MHz, mixture of diastereomers, $CDCl_3$): δ = 14.1, 15.0, 15.7, 15.9, 16.0,

18.1, 19.1, 21.1, 21.3, 26.8, 34.4, 39.6, 40.3, 43.0, 60.2, 60.9, 63.7, 71.5, 74.9, 75.2, 75.3, 79.1, 80.6, 95.4, 98.0, 124.8, 125.4, 127.4, 127.5, 127.6, 127.7, 128.3, 129.5, 129.6, 129.8, 132.4, 133.2, 133.7, 133.8, 133.9, 134.1, 135.5, 135.6, 138.4, 138.6, 170.6, 171.0 ppm; **MS** (LSIMS) calcd. for $C_{36}H_{48}O_5SiNa$ (M + Na): 611.3169, found 611.3181; **EA** calcd for C:73.43, H:8.22; found C:73.52, H:8.31.

Tetrahydropyran 12. A sample of 2.30 g (3.90 mmol) α-acetoxy ether **11** was dissolved in 20 mL hexanes and cooled to 0 °C. Acetic acid (1.17 g, 19.5 mmol, 1.12 mL, 5 equiv) was added, followed by dropwise addition of 55 mg (48 µl, 0.39 mmol, 0.10 equiv) $BF_3{\cdot}OEt_2$. After 120 min, the reaction was quenched with aq. sat. $NaHCO_3$ and extracted 3 times with hexanes. The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. After 30 min under high vacuum, 2.21 g of an yellow oil were obtained, which were chromatographed on silica, using a 5% ethyl acetate/hexanes. The major product, 1.20 g (2.04 mmol, 52%) of **12** was isolated as a colorless oil and 116 mg of fluoride **13** (0.211 mmol, 5%) also was isolated.

Compound **12**:

$\mathbf{R_f}$ (10% ethyl acetate in hexanes): 0.23; **IR** (neat) 1740, 1240, 1108 cm^{-1}; **^{1}H** NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 9H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.62 (m, 1H), 1.74 (m, 1H), 1.86 (m, 1H), 2.02 (m, 1H), 2.09 (s, 3H), 3.26 (d/d, *J* = 2.3 Hz, 10.3 Hz, 1H), 3.66 (m, 2H), 3.76 (m, 2H), 4.54 (s, 2H), 4.68 (d/d, *J* = 4.8 Hz, 11.0 Hz, 1H), 7.26-7.42 (m, 11H), 7.65-7.67 (m, 4H) ppm; **^{13}C** NMR (125 MHz, $CDCl_3$): δ = 6.4, 13.0, 14.4, 19.2, 21.1, 26.9, 31.8, 35.6, 35.7, 60.8, 70.3, 74.5, 75.0, 78.9, 82.3, 127.3, 127.5, 127.6, 128.2, 129.5, 133.9, 135.5, 138.9, 170.5 ppm; **MS** (LSIMS) calcd. for $C_{36}H_{49}O_5Si$ (M + H): 589.3349, found 589.3349; **EA** calcd for C:73.43, H:8.22; found C:73.49, H:8.12.

Compound **13**:

$\mathbf{R_f}$ (5% ethyl acetate in hexanes): 0.38; **IR** (neat) 1740, 1240, 1109 cm^{-1}; **^{1}H** NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 1.08 (s, 9H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.66 (m, 1H), 1.78 (m, 1H), 1.93 (m, 1H), 2.08 (m, 1H), 3.19 (m, 1H), 3.67 (d/d/d, *J* = 2.4 Hz, 6.5 Hz, 13.0 Hz, 1H), 3.77 (m, 1H), 3.84 (m, 1H), 4.28 (d/d/d, *J* = 5.2 Hz, 10.5 Hz, 49.2 Hz, 1H), 4.55 (d, *J* = 14.7 Hz, 1H), 4.58 (d, *J* = 14.7, 1H), 7.32-7.40 (m, 11H), 7.67-7.70 (m, 4H) ppm; **^{13}C** NMR (125 MHz, $CDCl_3$): δ = 5.9, 12.7, 14.3, 19.2, 21.1, 26.9, 33.1, 35.3, 36.8, 60.7, 70.3, 73.9, 74.8, 81.9, 96.8, 98.3, 127.3, 127.5, 127.6,

128.3, 129.5, 129.6, 133.8, 133.9, 135.5 ppm; **MS** (LSIMS) calcd. for $C_{34}H_{45}O_3SiFNa$ (M + Na): 571.3020, found 571.3020; **EA** calcd for C:74.41, H:8.26; found C:74.60, H:8.12.

Deprotection of Tetrahydropyran 12. A sample of 1.13 g (1.92 mmol) *O*-benzyl ether **12** was dissolved in 25 mL ethyl acetate. The flask was flushed with argon several times. To this flask was added 0.12 g $Pd(OH)_2$ (20% on C), and the flask was flushed with hydrogen gas and the pressure of 1 atm was maintained via a ballon filled with hydrogen gas. After 7 h the flask was flushed with argon and the black suspension was filtered. The solvent was removed under reduced pressure. Traces of toluene were removed by concentrating 3 times with methanol and then 3 times with chloroform. Chloroform traces was removed under high vacuum to give 0.96 g (1.13 mmol, quant. yield) of alcohol: $[\alpha]_D$ (T=23°C): +32.0° (*c*=0.86, $CHCl_3$); $\mathbf{R}_f$ (33% ethyl acetate/hexanes): 0.48; **IR** (neat) 3474, 1727, 1236 cm^{-1}; **^{1}H** NMR (500 MHz, $CDCl_3$): δ 0.80 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 1.05 (s, 9H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.65 (m, 2H), 1.80 (m, 1H), 2.04 (m, 1H), 2.09 (s, 3H), 2.21 (d (br.), *J* = 9.3 Hz, 1H), 3.18 (d/d, *J* = 2.9 Hz, 10.5 Hz, 1H), 3.70 (m, 3H), 3.85 (m, 1H), 4.67 (d/d, *J* = 4.8 Hz, 11.0 Hz, 1H), 7.37-7.43 (m, 6H), 7.64-7.66 (m, 4H) ppm; **^{13}C** NMR (125 MHz,$CDCl_3$): δ 6.3, 12.1, 16.2, 19.1, 21.1, 26.8, 31.5, 35.6, 36.0, 60.6, 67.2, 74.7, 78.5, 83.6, 127.6, 127.7, 129.6, 133.6, 135.5, 170.5 ppm; **MS** (LSIMS) calcd. for $C_{29}H_{43}O_5Si$ (M + H): 499.2879, found 499.2878; **EA** calcd for C:69.84, H:8.49; found C:69.77, H:8.28.

Ketone 14. A sample of 0.11 mL oxalylchloride (1.28 mmol, 1.1 equiv) was dissolved in 10 mL dichlormethane and the solution was cooled to −78 °C. 0.18 mL (0.20g, 2.55 mmol, 2.20 equiv) DMSO, diluted in 10 mL dichloromethane, were slowly added to the solution. After 5 min, 0.58 g (1.16 mmol) alcohol **39**, diluted in 8 mL dichloromethane were added slowly, and stirring was continued for an additional 15 min. Triethylamine (0.81 mL, 5.80 mmol, 5.0 equiv) was added and the solution was warmed to 23 °C. The aqueous layer was extracted with additional dichloromethane. The organic layers were combined, washed with saturated sodium chloride solution and dried with anhydrous magnesium sulfate. The filtered solution was concentrated under reduced pressure. The residue was purified by chromatography on silica using a mixture of 10% ethyl acetate/hexanes to give 0.58 g (1.16 mmol, 100%) of the ketone **14** as white crystals. A sample was recrystallized from hexanes for melting point determination and x-ray analysis: **MP**: 88°C; $[\alpha]_D$ (T=23°C): +77.2° (*c*=0.93, $CHCl_3$); $\mathbf{R}_f$ (10% ethyl acetate /hexanes): 0.26; **IR** ($CHCl_3$) 1722, 1216cm^{-1}; **^{1}H** NMR (500 MHz, C_6D_6): δ = 0.91 (m, 6H), 1.28 (s, 9H), 1.58 (m, 1H), 1.73 (s, 3H), 1.93 (s, 3H), 2.04 (d/d/q, *J* = 1.9Hz, 4.7Hz, 6.8Hz, 1H), 3.29 (d, *J* = 10.7Hz, 1H), 3.55 (d/d/d, *J* =

1.9Hz, 3.6Hz, 9.0Hz, 1H), 3.77 (m, 2H), 4.75 (d/d, *J* = 4.7Hz, 11.0Hz, 1H), 7.36-7.40 (m, 6H), 7.87-7.89 (m, 4H) ppm; **^{13}C** NMR (125 MHz,$CDCl_3$): δ = 6.4, 12.6, 19.1, 21.0, 25.7, 26.8, 31.1, 35.5, 35.7, 60.2, 74.5, 78.2, 86.9, 127.6, 129.6, 133.7, 135.5, 170.4, 206.6 ppm; **MS** (LSIMS/MNBA) calcd. for $C_{29}H_{41}O_5Si$ (M + H): 497.2723, found 497.2711; **EA** calcd for C:70.12, H:8.12; found C:70.29, H:7.88.

Horner-Emmons reaction with ketone 14. A sample of 72 mg (0.362 mmol, 1.8 equiv) potassium bis(trimethylsilyl)amide (Acros) was dissolved in 4 mL THF and cooled to 0 °C. To this solution was added 80 µl (90 mg, 0.403 mmol, 2.0 equiv) triethyl phosphonoacetate and stirring was continued for 55 minsutes. Then 100 mg (0.201 mmol) ketone **14** was added and the ice-bath was removed. After 20 h the mixture was diluted with diethyl ether and shaken with brine. The organic layer was separated and the aqueous layer was washed 3 times with diethyl ether. The combined organic layers were dried (Na_2SO_4) concentrated under reduced pressure, and the residue purified by chromatographie (silica, 10%ethyl acetate in hexanes) to give 83 mg (73%) of ester **15** as a 3.9:1 (*E/Z*)[2] mixture of diastereomers: $\mathbf{R_f}$ (10% ethyl acetate/hexanes, twofold developement): 0.46; **IR** (neat) 1718, 1653 cm^{-1}; **^{1}H** NMR (500 MHz, mixture of stereoisomers, $CDCl_3$): δ = 0.75 (d, *J* = 6.5Hz, 3H, major st.), 0.80 (d, *J* = 6.6Hz, 3H, minor st.), 0.92 (m, 3H), 1.01 (m, 9H), 1.24 (tr, *J* = 7.2Hz, 3H), 1.31 (tr, *J* = 7.1Hz, 3H, major st.), 1.64 (m, 1H), 1.80 (m, 1H), 1.90 (m, 2H), 2.09 (s, 3H, minor st.), 2.10 (s, 3H, major st.), 2.17 (s, 3H), 3.42 (d, *J* = 10.2Hz, 1H, major st.), 3.70 (m, 1H), 3.77 (m, 2H), 4.11 (q, *J* = 7.1Hz, 2H, minor st.). 4.19 (m, 2H, major st.), 4.74 (d/d, *J* = 4.8Hz, 11.0Hz, 1H, major st.), 4.85 (d/d, *J* = 4.8Hz, 10.0Hz, 1H, minor st.), 5.32 (d, *J* = 10.4Hz, 1H, minor st.), 5.79 (s, 1H, major st.), 5.82 (s, 1H, minor st.), 7.44-7.35 (m, 6H), 7.65-7.67 (m, 4H) ppm; **^{13}C** NMR (125 MHz, mixture of stereoisomers, $CDCl_3$): δ = 6.4, 12.2, 13.1, 14.0, 14.2, 18.8, 19.1, 21.0, 26.8, 32.0, 32.3, 35.4, 35.8, 59.7, 59.9, 60.2, 60.4, 74.5, 77.8, 78.4, 78.8, 87.8, 118.9, 119.2, 127.3, 127.6, 127.7, 129.4, 129.5, 129.6, 133.7, 133.8, 135.5, 154.9, 155.2, 165.4, 166.3, 170.2, 170.3 ppm; **MS** (LSIMS) calcd. for $C_{33}H_{47}O_6Si$ (M + H): 567.3144, found 567.3129. ; **EA** calcd for C:69.91, H:8.28; found C:69.93, H:8.18.

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[2] The *E/Z* assignment was based upon precedent and ^{1}H NMR spectra comparison to a similar Horner-Emmons reaction with methyl ketone **9** to give a 6:1 ratio of *E* to *Z* products **26** and **27** as reported in the following reference: Chen, K.-M.; Semple, J. E.; Joullie, M. M. *J. Org. Chem.* **1985**, *50*, 3997-4005. Or a related example, see White, J. D.; Jeffrey, S. C. *J. Org. Chem.* **1996**, *61*, 2600-2601.