The Practical Synthesis of a Novel and Highly Potent Analog of Bryostatin

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Supporting Information

General methods. Air- and moisture-sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry nitrogen or argon from a manifold or balloon, unless otherwise indicated. Similarly sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Reactions were stirred using Teflon-coated magnetic stir bars. Elevated temperatures were maintained using Thermowatch-controlled silicone oil baths. Organic solutions were concentrated using a Buchi rotary evaporator with a teflon seal vacuum pump. Tetrahydrofuran, diethyl ether, toluene and dichloromethane were passed through an alumina drying column (*Solv-Tek* Inc.). Analytical TLC was performed with 0.25 mm silica gel 60F plates with 254 nm fluorescent indicator from Merck. Plates were visualized by ultraviolet light and treatment with acidic *p*-anisaldehyde stain followed by gentle heating. Chromatographic purification of products was accomplished by flash chromatography, as described by Still and co-workers.¹ Silica gel 60, 230-400 mesh was purchased from EM.

NMR spectra were measured on a Varian INOVA 500 (¹H at 500 MHz, ¹³C at 125 MHz), Varian XL-400 (¹H at 400 MHz, ¹³C at 100 MHz), Varian Gem-300 (¹H at 300 MHz, ¹³C at 75 MHz), or Varian Gem-200 (¹H at 200 MHz, ¹³C at 50 MHz) magnetic resonance spectrometer. Data for ¹H NMR spectra are reported as follows: chemical shift (□ ppm), integration, multiplicity (s = singlet, brs = broad singlet, d = doublet, brd = broad doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet), coupling constant (Hz). Data for ¹³C are reported in terms of chemical shift relative to residual solvent peak. Infrared spectra were recorded on a Perkin-Elmer 1600 Series Fourier transform spectrometer (FTIR) and are reported in wavenumbers (cm⁻¹). Elemental analyses (%C, %H) were determined by Desert Analytics, Tucson, Arizona. Reported atomic percentages are within error limits of ±0.4%. In instances where purity was not determined by elemental analysis, compounds displayed only one observable spot by TLC at the reported R_f. High-resolution mass spectra (HRMS) were recorded at the NIH regional mass spectrometry facility at the University of California, San Francisco. Reported mass values are with error limits of ±13 millimass units.

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

A 3-neck flask was charged with NaH (16 g, 60 wt% in mineral oil, 0.40 mol). The NaH was washed with Et₂O (3 x 40 mL). THF (800 mL) was added and the mixture stirred. To this suspension was added 2,2-dimethyl-1,3-propanediol (40 g, 0.39 mol) in portions over 10 min. The resulting thick slurry was stirred at rt for 1 h. TBSCl (60.5 g, 0.40 mol) was added in one portion. The slurry thinned and was stirred at rt for 14 h. The reaction was diluted with MTBE (1.0 L) and washed with 10% aq. K₂CO₃ (700 mL, 300 mL) and brine (500 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield a viscous liquid (88.4 g) that was used without further purification.

A solution of this crude liquid (40 g, *ca* 0.18 mol) was stirred in CH₂Cl₂ (900 mL) and cooled in an ice bath to 4°C. To this solution was added NEt₃ (76 mL, 0.54 mol). A slurry of SO₃·pyr (44 g, 0.27 mol) in DMSO (100 mL) was added in two portions 5 min apart to keep the internal temperature lower than 10°C. The reaction was stirred for 2.5 h and the ice bath was removed. Stirring was continued for 6.5 h and another portion of SO₃·pyr (10 g, 63 mmol) was added as a solid. The reaction was stirred for 9 h and diluted with CH₂Cl₂ (1.0 L). The resulting solution was washed with 1 N HCl (2 x 500 mL), saturated NaHCO₃ (500 mL), and brine (500 mL). The resulting organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to **4** (39.8 g) as an orange liquid that was used without further purification.²

A solution of 4-chloro-1-butanol (23 mL, 0.23 mol) in THF (230 mL) was cooled to -78°C. A solution of MeMgCl (77 mL, 3.0 M in THF, 0.23 mol) was added dropwise via addition funnel over 30 min to keep the internal temperature lower than -60°C. The reaction was gradually warmed to -10°C and Mg⁰ (6.04 g, 0.251 mol) was added, followed by BrCH₂CH₂Br (0.1 mL). The reaction was heated to reflux for 14.5 h. The hot bath was removed. THF (220 mL) was added, and the reaction was cooled to -78 °C. A solution of **4** (39 g, *ca* 0.18 mol) in THF (100 mL) was added dropwise via addition funnel over 40 min to keep the internal temperature lower than -60°C. The reaction was stirred for 30 min at -78°C and the cold bath was then removed. MTBE (500 mL) was added when the reaction reached -30°C, followed by aq. citric acid (87 g, 0.41 mol in 500 mL H₂O). The organic layer was collected and the aqueous layer was extracted with MTBE (200 mL). The combined organic layers were washed with brine (2 x 400 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to a light orange oil. The oil was dissolved in EtOAc and filtered through silica. The filtrate was concentrated under reduced pressure to yield a light yellow oil (49.7 g) which was used without further purification.

To a solution of CH₂Cl₂ (800 mL) was added (COCl)₂ (46.9 mL, 0.537 mol) and the resulting solution cooled to -78°C. DMSO (75.8 mL, 1.07 mol) was added dropwise via addition funnel over 15 min to keep the internal temperature lower than -60°C. The resulting solution was stirred for 10 min. A solution of the crude oil from the previous step (49.7 g, *ca* 0.179 mol) in CH₂Cl₂ (150 mL) was added dropwise via addition funnel over 25 min to keep the internal temperature lower than -70°C. The resulting mixture was stirred for 1 h at -78°C and NEt₃ (250

² Richter, F.; Bauer, M.; Perez, C.; Maichle-Mössmer, C.; Maier, M. E. *J. Org. Chem.* **2002**, 67, 2474-2480.

mL, 1.79 mol) was added dropwise via addition funnel over 15 min to keep the internal temperature lower than -60°C . The cold bath was removed and the reaction was allowed to warm to -30°C and then poured into a mixture of H_2O (500 mL) and CH_2Cl_2 (800 mL). The resulting organic layer was collected and washed with H_2O (500 mL), saturated NH_4Cl (2 x 400 mL), saturated NaHCO_3 (500 mL), and brine (500 mL). The organic layer was then dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to a dark oil. Purification by column chromatography (silica gel, 19:1 $\rightarrow$ 9:1 petroleum ether:EtOAc) yielded **i** (27.81 g, 54% based on 2,2-dimethyl-1,3-propanediol) as a straw yellow liquid. **i**: R_f (petroleum ether/EtOAc 9:1) = 0.34; IR (film) 2956, 2931, 2896, 2858, 2715, 1727, 1707, 1472, 1409, 1392, 1363, 1257, 1187, 1094, 1044, 1007 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ = 0.02 (6H, s), 0.86 (9H, s), 1.08 (6H, s), 1.88 (2H, app q, J = 7.0 Hz), 2.45 (2H, td, J = 7.1, 1.5 Hz), 2.58 (2H, t, J = 7.0 Hz), 3.55 (2H, s), 9.75 (1H, s); ^{13}C NMR (75 MHz, CDCl_3) δ = -5.7, 15.9, 18.0, 21.4, 25.7, 36.7, 43.1, 49.3, 70.2, 202.1, 214.0; HRMS Calcd for $\text{C}_{15}\text{H}_{30}\text{O}_3\text{Si}$ ($\text{M}^+ + \text{H}$): 287.2034. Found 287.2040.

To a solution of R-BINOL (316 mg, 1.10 mmol) in CH_2Cl_2 (45 mL) was added powdered 4Å MS (4.2 g) followed by $\text{Ti}(\text{O}i\text{Pr})_4$ (0.16 mL, 0.55 mmol). The resulting orange mixture was heated to reflux for 1 h and then cooled in a water bath to rt. A solution of **i** (3.16 g, 11.0 mmol) in CH_2Cl_2 (5 mL) was added, followed by $\text{B}(\text{OMe})_3$ (1.48 mL, 13.2 mmol) and $\text{Bu}_3\text{SnCH}_2\text{CHCH}_2$ (4.1 mL, 13 mmol). The resulting mixture was stirred at rt for 42 h, then filtered through celite into saturated NaHCO_3 (75 mL) and EtOAc (200 mL). The resulting mixture was stirred for 1 h. Petroleum ether (200 mL) was added and the resulting mixture filtered through celite. The organic layer was collected and washed with saturated NaHSO_3 , dried over Na_2SO_4 , and concentrated under reduced pressure to a crude oil. The residue was purified by column chromatography (silica gel, 4:1 petroleum ether/EtOAc) to yield **5** (2.81 g, 77%) as a yellow oil. **5**: R_f (petroleum ether/EtOAc 9:1) = 0.13; IR (film) 3435 (br), 3077, 2955, 2930, 2858, 2743, 2711, 1704, 1642, 1472, 1392, 1362, 1257, 1100, 1006 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 0.02 (6H, s), 0.83 (9H, s), 1.06 (6H, s), 1.36-1.44 (2H, m), 1.55-1.69 (2H, m), 2.07-2.17 (2H, m), 2.25 (1H, app dt, J = 13.8, 5.5 Hz), 2.52 (2H, app td, J = 7.0, 1.1 Hz), 3.53 (2H, s), 3.53-3.60 (1H, m), 5.06-5.11 (2H, m), 5.72-5.86 (1H, m); ^{13}C NMR (75 MHz, CDCl_3) δ = -5.7, 19.3, 21.5, 25.8, 36.3, 37.7, 41.8, 49.3, 70.2, 70.3, 117.9, 134.8, 215.0; Anal. calcd for $\text{C}_{18}\text{H}_{36}\text{O}_3\text{Si}$: C, 65.80; H, 11.04. Found: C, 65.83; H, 11.31.³

To a solution of **5** (28.8 g, 87.6 mmol) in MePh (500 mL) was added bead 4Å MS (50 g) and $p\text{TsOH} \cdot \text{H}_2\text{O}$ (1.66 g, 8.76 mmol). The mixture was stirred at rt for 18 h then filtered through basic alumina (Brockman grade I, basic, 150 mesh) and the alumina washed with petroleum ether. The filtrate was concentrated under reduced pressure to **ii** (23.2 g, 85%) as a clear liquid. **ii**: R_f (petroleum ether) = 0.44; IR (film) 3080, 2953, 2928, 2856, 1669, 1642, 1473, 1434, 1390,

³ A reliable optical rotation for this compound could not be obtained due to its tendency to partially cyclize to the hemiketal.

1359, 1288, 1254, 1215, 1088 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ = 0.01 (6H, s), 0.88 (9H, s), 0.99 (6H, s), 1.40-1.53 (1H, m), 1.72-1.79 (1H, m), 1.91-2.12 (2H, m), 2.24 (1H, app dt, J = 13.8, 6.8 Hz), 2.37 (1H, app dt, J = 14.0, 7.0 Hz), 3.40 (2H, s), 3.70-3.78 (1H, m), 4.52 (1H, app t, J = 3.5 Hz), 5.03-5.11 (2H, m), 5.80-5.94 (1H, m); ^{13}C NMR (75 MHz, CDCl_3) δ = -5.5, 14.1, 19.4, 19.5, 22.6, 25.9, 39.6, 40.6, 41.5, 69.5, 74.4, 93.6, 116.6, 134.9, 158.3; Anal. calcd for $\text{C}_{18}\text{H}_{34}\text{O}_2\text{Si}$: C, 69.62; H, 11.04. Found: C, 69.64; H, 11.16; $[\alpha]_{\text{D}}^{22}$ = +38.6° (c 1.42, CH_2Cl_2).

A mixture of 80% MMPP (8.30 g, 13.4 mmol), CH_2Cl_2 (80 mL), MeOH (40 mL), and NaHCO_3 (2.85 g) was stirred in an ice bath. A solution of **ii** (6.90 g, 22.4 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 10 min. The reaction was stirred for 10 min, and then poured into H_2O (100 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to a thick oil which was purified by column chromatography (silica gel, 19:1 $\rightarrow$ 9:1 petroleum ether/EtOAc) to provide **iiia** (5.19 g, 64%) as a clear oil and **iiib** (1.12 g, 14%) as a clear oil. **iiia**: R_f (petroleum ether/EtOAc 9:1) = 0.40; IR (film) 3585, 3467, 3408, 2935, 2857, 1643, 1472, 1440, 1255, 1091, 1044 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ = 0.09 (6H, s), 0.92 (9H, s), 1.03 (6H, s), 1.20-1.36 (1H, m), 1.56-1.84 (2H, m), 2.16-2.26 (2H, m), 3.25 (1H, d, J = 10.4 Hz), 3.36 (3H, s), 3.35-3.50 (1H, m), 3.59-3.70 (1H, m), 3.82 (1H, d, J = 10.4 Hz), 4.98-5.10 (3H, m), 5.80-5.95 (1H, m); ^{13}C NMR (300 MHz, CDCl_3) δ = -5.61, -5.56, 18.3, 22.4, 22.8, 25.8, 27.5, 30.1, 40.2, 45.2, 51.1, 68.7, 68.9, 70.7, 101.2, 116.6, 135.2; Anal. calcd for $\text{C}_{19}\text{H}_{38}\text{O}_4\text{Si}$: C, 63.64; H, 10.68. Found: C, 63.33; H, 10.62; $[\alpha]_{\text{D}}^{21}$ = +39.44° (c 1.35, CH_2Cl_2). **iiib**: R_f (petroleum ether/EtOAc 9:1) = 0.52; IR (film) 3479, 3368, 3077, 2950, 2390, 1643, 1471, 1254, 1060 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ = 0.09 (6H, s), 0.91 (9H, s), 0.97 (3H, s), 1.04 (3H, s), 1.16-1.35 (1H, m), 1.60-1.95 (3H, m), 2.14-2.36 (2H, m), 3.34 (3H, s), 3.40 (1H, d, J = 10.0 Hz), 3.57 (1H, d, J = 10.1 Hz), 3.59-3.68 (2H, m), 4.97-5.12 (2H, m), 5.20-5.25 (1H, m), 5.80-5.98 (1H, m); ^{13}C NMR (300 MHz, CDCl_3) δ = 3.74, -5.71, 18.3, 21.7, 22.5, 23.6, 25.8, 26.8, 20.8, 46.0, 51.8, 66.1, 69.9, 72.2, 102.2, 116.6, 135.0; HRMS Calcd for $\text{C}_{19}\text{H}_{38}\text{O}_4\text{Si}$ (M^+): 356.2382. Found: 356.2395; $[\alpha]_{\text{D}}^{21}$ = +25.48° (c 2.91, CH_2Cl_2).

To a mixture of 4Å MS (16.6 g) and CH_2Cl_2 was added **iiia** (10.18 g, 28.4 mmol) and NMO (6.65 g, 56.8 mmol). The reaction was stirred in an ice bath and TPAP (1.02 g, 2.84 mmol) was added in portions. Once the addition was complete, the ice bath was removed and the reaction was allowed to stir at rt for 20 h. The resulting mixture was filtered through celite and the filtrate concentrated under reduced pressure. The residue was passed through a silica plug, eluting with CH_2Cl_2 and the filtrate rotovapped to a light colored oil **6** (7.91 g, 78%) **6**: R_f (petroleum ether/EtOAc 9:1) = 0.53; IR (film) 3078, 2955, 2930, 2893, 2858, 1726, 1644, 1472, 1464, 1446, 1406, 1393, 1361, 1302, 1254, 1188, 1117, 1089, 1054, 1006 cm^{-1} ; ^1H NMR (300

MHz, CDCl₃) δ = 0.02 (6H, s), 0.87 (9H, s), 0.93 (3H, s), 1.02 (3H, s), 1.86-2.05 (2H, m), 2.47-2.27 (3H, m), 2.67 (1H, ddd, J = 18.1, 6.4, 4.1 Hz), 3.27 (3H, s), 3.32 (1H, d, J = 10.0 Hz), 3.68 (1H, d, J = 10.0 Hz), 3.89-3.97 (1H, m), 5.09-5.16 (2H, m), 5.84-5.98 (1H, m); ¹³C NMR (75 MHz, CDCl₃) δ = -5.6, -5.5, 18.5, 19.8, 20.1, 25.9, 28.2, 37.6, 40.3, 45.8, 51.8, 68.2, 73.1, 117.7, 134.0; HRMS Calcd for C₁₉H₃₆O₄Si (M⁺): 356.2383. Found: 356.2378. $[\alpha]_D^{24}$ = -5.21° (*c* 1.76, CH₂Cl₂).

To a solution of **6** (1.72 g, 4.82 mmol) in MeOH (50 mL) was added K₂CO₃ (3.66 g, 26.5 mmol) and a solution of methyl glyoxylate (14.2 mL, ~1.7 M, 24 mmol) in THF. The resulting mixture was stirred at rt for 55 min and then poured into a mixture of saturated NH₄Cl (200 mL) and Et₂O (100 mL). The organic layer was collected and the aqueous layer was extracted with Et₂O (100 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to an orange oil which was purified by column chromatography (silica gel, 19:1 petroleum ether/EtOAc) to yield **7** (1.50 g, 72%) as a yellow oil which solidified on standing. **7**: *R_f* (petroleum ether/EtOAc 9:1) = 0.53; IR (film) 3079, 2954, 2930, 2858, 1726, 1709, 1632, 1472, 1435, 1416, 1393, 1357, 1253, 1204, 1179, 1128, 1087, 1061, 1006 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = -0.03 (3H, s), -0.02 (3H, s), 0.83 (9H, s), 0.91 (3H, s), 0.99 (3H, s), 2.44 (2H, app t, J = 6.3 Hz), 2.76 (1H, ddd, J = 17.8, 12.4, 3.2 Hz), 3.27 (3H, s), 3.30 (1H, d, J = 10.0 Hz), 3.46 (1H, d, J = 17.8 Hz), 3.66 (1H, d, J = 10.0 Hz), 3.76 (3H, s), 3.99 (1H, app dtd, J = 11.4, 5.7, 1.7 Hz), 5.13-5.20 (2H, m), 5.86-6.00 (1H, m), 6.65-6.66 (1H, m); ¹³C NMR (75 MHz, CDCl₃) δ = -5.7, -5.6, 18.5, 19.5, 19.9, 25.9, 34.2, 39.8, 46.4, 51.7, 51.9, 68.1, 72.0, 103.9, 118.3, 122.6, 133.3, 147.5, 166.3, 196.1; Anal. Calcd for C₂₂H₃₈O₆Si: C, 61.94; H, 8.98. Found: C, 62.32; H, 8.99; $[\alpha]_D^{22}$ = -72.2° (*c* 1.07, CH₂Cl₂).

To a bright yellow solution of **7** (3.29 g, 7.71 mmol) in MeOH (130 mL) was added CeCl₃·7H₂O (1.44 g, 3.86 mmol). The mixture was stirred until all solids were dissolved and then cooled to -30°C for 15 min. To this solution was added NaBH₄ (0.58 g, 15 mmol) in one portion. The reaction was stirred for 5 min whereupon the color disappeared. The mixture was loaded directly onto a silica column and eluted with 15% EtOAc in petroleum ether. Fractions containing product were washed with H₂O (2x) and brine (3x). The resulting organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to provide crude oil **8**.

Crude **8** was dissolved in CH₂Cl₂ (75 mL). DMAP (1.41 g, 11.5 mmol) and octanoic acid (1.83 mL, 11.5 mmol) were added, followed by DIC (1.81 mL, 11.6 mmol). The resulting mixture was stirred at rt for 20 h. To the reaction was added saturated NaHCO₃ and EtOAc. The resulting mixture was stirred for 5 min and then additional EtOAc and brine were added. The resulting organic layer was collected and the aqueous layer extracted with EtOAc. The combined

organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 5:95 EtOAc/petroleum ether) to yield **9** (3.98 g, 93%) as a pale yellow oil. **9**: R_f (pentane/EtOAc 9:1) = 0.62; IR (film) 2955, 2930, 2857, 1747, 1722, 1667, 1155, 1082 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 0.01 (6H, s), 0.80-0.90 (12H, m), 0.96 (3H, s), 1.00 (3H, s), 1.20-1.38 (10H, m), 1.56-1.72 (1H, m), 2.24-2.46 (4H, m), 3.30 (3H, s), 3.43 (1H, d, *J* = 15.9 Hz), 3.54 (2H, dd, *J* = 18.9, 9.3 Hz), 3.68 (3H, s), 3.87-3.91 (1H, m), 5.09-5.16 (2H, m), 5.53 (1H, s), 5.80-5.98 (1H, m), 5.88 (1H, s); ¹³C NMR (300 MHz, CDCl₃) δ = -5.4, 14.0, 18.4, 20.5, 20.6, 22.6, 24.7, 25.9, 28.9, 29.0, 31.6, 32.1, 34.5, 40.0, 47.0, 51.1, 67.3, 71.0, 72.1, 103.0, 116.6, 117.7, 133.8, 153.1, 166.6, 171.9; HRMS Calcd for C₃₀H₅₄O₇Si (M⁺): 577.3517. Found 577.3537; [α]_D²¹ = -11.3 (*c* 1.56, CH₂Cl₂)

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To a solution of TBS ether **9** (30 mg, 0.054 mmol) in THF (0.55 mL) at rt was added 3HF·Et₃N (90 μ L, 0.54 mmol). The reaction mixture was stirred for 24 h and then diluted with diethyl ether (5 mL). The organic phase was washed with saturated NaHCO₃ (2 x 3 mL) and brine (2 x 3 mL), dried over Na₂SO₄, and flashed through a plug of silica. The residue obtained after evaporation of solvent was carried forward without further purification.

To a solution of the deprotected alcohol in CH₂Cl₂ (1.5 mL) and MeCN (2.1 mL), at rt, was added NaHCO₃ (9.1 mg, 0.11 mmol). The mixture was cooled to 0°C and Dess-Martin Periodinane (52 mg, 0.122 mmol) was added. The reaction mixture was stirred at 0°C for 1 h. The reaction was quenched with 3 mL of a 1:1 solution of saturated NaHCO₃ and saturated Na₂S₂O₃ and was stirred vigorously until the organic layer was no longer cloudy. The quenched reaction mixture was then poured into a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (3 x 3 mL). The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated. Purification via column chromatography (silica gel, 95:5 petroleum ether/EtOAc) revealed pure aldehyde **10** (20 mg, 86% over 2 steps) as a yellow oil. **10**: R_f (hexane/EtOAc 4:1) = 0.49; IR (film) 2930, 2857, 1750, 1723, 1668, 1160, 1048 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 0.86 (3H, t, *J* = 6.3 Hz, octanoate Me), 1.00 (3H, s, C18 Me), 1.16 (3H, s, C18 Me), 1.18-1.31 (10H, m), 1.46-1.60 (2H, m), 2.18 (2H, t, *J* = 7.4 Hz), 2.43 (2H, t, *J* = 6.6 Hz), 3.39 (3H, s), 3.66 (1H, d, *J* = 18.9 Hz), 3.69 (3H, s), 3.74-3.84 (1H, m), 5.13-5.20 (2H, m), 5.85-6.00 (1H, m), 5.96 (1H, s), 9.71 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ = 14.1, 16.3, 19.1, 22.6, 24.3, 28.9, 30.4, 31.6, 38.9, 40.0, 51.2, 51.4, 54.0, 71.5, 71.9, 102.2, 118.2, 119.8, 133.4, 150.3, 166.4, 171.7, 202.4; HRMS Calcd for C₂₄H₃₈O₇ (M⁺): 461.2511. Found: 461.2515; [α]_D^{21.4} = -8.61° (*c* 5.6, CH₂Cl₂).

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(Z)-1-bromo-2-ethoxyethylene (690 μ L, 6.5 mmol) was added to an oven-dried flask containing diethyl ether (22 mL). The solution was cooled to -78°C , and *t*-BuLi (7.6 mL, 13 mmol, 1.7 M in pentane) was added, dropwise. The reaction was stirred, at -78°C , for 30 min. Me_2Zn (3.4 mL, 6.7 mmol, 2.0 M in toluene) was added, dropwise, and the reaction was stirred, at -78°C , for 30 min. A 0.0001 M solution of aldehyde **10** (0.95 g, 2.2 mmol dissolved in 22 mL Et_2O) was added dropwise, via syringe, and the reaction was stirred for 2 h at -78°C . The reaction was quenched with a 1.0 M solution of HCl (40 mL) and allowed to warm to rt. The mixture was stirred vigorously for 19 h and was quenched with saturated NaHCO_3 (60 mL), diluted with EtOAc (35 mL) and H_2O (35 mL). The separated aqueous phase was extracted with EtOAc (3 x 60 mL) and the combined organic phases were washed with brine (1 x 85 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification via column chromatography (silica gel, petroleum ether $\rightarrow$ 7% $\rightarrow$ 10% EtOAc:petroleum ether) revealed pure enal **11** (905 mg, 90%) as a nearly colorless oil. **11**: R_f (hexane/EtOAc 4:1) = 0.46; IR (film) 2930, 2360, 2343, 1746, 1721, 1689, 1436, 1382, 1259, 1225, 1156, 1104, 1044 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ = 0.86 (3H, t, J = 6.3 Hz, octanoate Me), 1.13 (3H, s, C18 Me), 1.17 (3H, s, C18 Me), 1.23-1.31 (10H, m), 1.40 (t), 2.00-2.20 (2H, m), 2.24-2.36 (m), 2.43 (2H, t), 3.34 (3H, s), 3.49-3.55 (1H, dd, J = 15.6 Hz, 1.8 Hz), 3.68 (3H, s), 3.81-3.86 (1H, m), 5.13 (1H, m), 5.20 (1H, m), 5.37 (1H, s), 5.87 (1H, s), 5.87-5.95 (1H, dd, J = 7.8 Hz, 16.1 Hz), 7.32 (1H, d, J = 16.2 Hz), 9.53 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ = 13.96, 21.62, 22.46, 23.75, 24.46, 28.80, 28.84, 31.36, 31.51, 34.34, 39.92, 47.37, 51.18, 51.30, 71.36, 71.86, 97.85, 102.57, 117.97, 118.25, 126.75, 133.46, 151.56, 166.50, 167.19, 194.80; Anal. Calcd for $\text{C}_{26}\text{H}_{40}\text{O}_7$: C, 67.22; H, 8.68. Found: C, 67.34; H, 8.48; $[\alpha]_{\text{D}}^{24.2} = -31.79^{\circ}$ (*c* 0.47, CH_2Cl_2).

14

Preparation of stock solution: $\text{K}_2\text{OsO}_2(\text{OH})_4$ (2.0 mg, 0.005 mmol), $(\text{DHQD})_2\text{PYR}$ (12.0 mg, 0.014 mmol), $\text{K}_3\text{Fe}(\text{CN})_6$ (1.34 g, 4.07 mmol), and K_2CO_3 (563 mg, 4.07 mmol) were combined in a round-bottom flask, to which was added H_2O (6.75 mL) and *t*BuOH (6.75 mL). The two-phase system was vigorously stirred at rt for 2 h. Enal **11** (300 mg, 0.65 mmol) was cooled to 0°C , and an aliquot (6.4 mL) of the stock solution was added. The yellow-orange

colored reaction mixture was stirred at 0–4°C for 60 h (in cold room). After diluting with water (50 mL) the aqueous phase was extracted with ethyl acetate (3 x 250 mL). The combined organic phases were dried over MgSO₄, and then filtered. The solvents were removed *in vacuo*. Purification via column chromatography (silica gel, 1:9 hexane:ethyl acetate) yielded diol **12** (233 mg, 72%) as a 2.5:1 α : β inseparable mixture of diastereomers.

Diol **12** (10 mg, 0.020 mmol) was taken up in a solution of MeCN:H₂O (960 μ L, 240 μ L), and transferred to an oven-dried flask. *p*TsOH·H₂O (38 mg, 0.200 mmol) was added as 0.22M solution in MeCN:H₂O (730 μ L, 180 μ L). The reaction was stirred overnight, at rt, and then quenched with saturated NaHCO₃ (6 mL). The aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Crude product **13** was carried forward without further purification.

A 0.5 M stock solution of 1:3 TBSCl:imidazole was prepared by dissolving TBSCl (754 mg, 5.0 mmol) and imidazole (1.02 g, 15.0 mmol) in CH₂Cl₂ (10.0 mL). A total of 9 eq. of this stock solution were added to a solution of **13** in CH₂Cl₂ (2.0 mL), over the course of 6 h (added in 3 eq. aliquots, 2 h apart). Reaction was quenched with saturated NH₄Cl (2 mL) and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification via column chromatography (silica gel, 3:1 Hexanes/EtOAc) revealed pure **14** (5.6 mg, 47% over 2 steps). **14**: *R*_f (EtOAc/pentane 4:6) = 0.38; IR (film) 3421, 2930, 2857, 1723, 1691, 1257, 1156, 1110 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ = 0.10 (6H, s), 0.87 (3H, t, *J* = 6.8 Hz), 0.92 (9H, s), 1.14 (3H, s), 1.15 (3H, s), 1.18–1.32 (10H, m), 1.49 (1H, t, *J* = 7.2 Hz), 1.66–1.74 (1H, m), 1.84–2.00 (1H, m), 1.98–2.15 (3H, m), 3.49 (1H, dd, *J* = 10.0, 6.0 Hz), 3.66–3.76 (1H, m), 3.70 (3H, s), 3.82–4.00 (2H, m), 4.07 (1H, t, *J* = 6.6 Hz), 4.20 (1H, t, *J* = 10.8 Hz), 5.13 (1H, s), 5.96 (1H, dd, *J* = 16.0, 7.7 Hz), 6.03 (1H, s), 7.35 (1H, d, *J* = 16.0 Hz), 9.57 (1H, d, *J* = 7.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ = -5.3, 14.0, 18.4, 20.0, 22.5, 23.1, 24.4, 25.9, 28.9, 28.9, 31.1, 31.6, 34.5, 39.0, 45.7, 51.3, 67.1, 67.2, 67.9, 72.6, 99.7, 120.7, 127.6, 150.1, 166.1, 171.7, 194.5; HRMS Calcd for C₃₁H₅₄O₉Si (M⁺): 621.3445, Found: 621.3435; $[\alpha]_D^{26.6}$ = -27.24° (c 1.04, CH₂Cl₂).

To a flask was added 1,6-heptadiene-4-ol (4.183 g, 37.3 mmol, Aldrich) and anhydrous MeOH (180 mL, JT Baker). The reaction flask was cooled to -78°C and ozone was bubbled through the solution for 35 min until a deep blue color persisted. N₂ was bubbled through the solution for 20 min to purge excess ozone. To the stirring solution at -78°C was added NaBH₄ (11.3 g, 299 mmol). The mixture was allowed to stir for 12 h while it warmed to rt in the thawing bath. The reaction was acidified to pH 3 with conc. HCl until a white precipitate formed. The solution was filtered to remove the precipitate and the filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (200 mL) and concentrated *in vacuo*. This MeOH evaporation was repeated one additional time to ensure the removal of residual boron as B(OMe)₃. The resulting orange residue was vacuum distilled to give **iv** (4.02 g, 94%). **iv**: *R*_f (EtOH (200 prf.)/EtOAc 1:4) = 0.4; IR (film) 3338, 2944, 2888, 1421, 1061 cm⁻¹; ¹H NMR (500 MHz, D₂O) δ = 1.66 (4H, m), 3.64 (4H, t, *J* = 6.5 Hz), 3.82 (1H, m, *J* = 4 Hz); ¹³C NMR (500 MHz, CD₃OD) δ = 41.06, 60.12, 67.41; Anal. calcd for C₅H₁₂O₃: C, 49.98; H, 10.07. Found: C, 50.05; H, 10.29.

16_R

16_S

To an oven dried, argon purged 1L round bottom flask, charged with a magnetic stir bar, was added **iv** (8.40 g, 70 mmol) at rt. To this was added (-)-menthone (27.9 mL, 161 mmol, ~5% isomenthone, Aldrich), *p*TsOH•H₂O (658 mg, 3.5 mmol, Aldrich), followed by diethyl ether (232 mL). Triethyl orthoformate (26 mL, 154 mmol, Aldrich) was then added followed by additional diethyl ether (232 mL). The reaction was stirred for 48 h at rt and then a mixture of 1 N NaOH (155 mL) and EtOH (50 mL, 200 proof) was added. The mixture was allowed to stir for an additional 24 h. The reaction was extracted with CH₂Cl₂ (3 x 100 mL) and the organic layers were combined, dried over MgSO₄ and concentrated. Purification by column chromatography (silica gel, 20:80 EtOAc/hexanes) gave a mixture of alcohols (12.77 g, 71%) as a yellow oil, which was taken directly into the next step.

A solution of DMSO (3.41 mL, 48.25 mmol) in CH₂Cl₂ (12 mL) at -78°C was cannulated dropwise into a solution of oxalyl chloride (3.35 mL, 38.6 mmol) in CH₂Cl₂ (77 mL) at -78°C under N₂ and stirred for 20 min. Crude alcohol (4.94 g, 19.3 mmol) in CH₂Cl₂ (39 mL) at -78°C was then slowly cannulated into the reaction mixture at -78°C over 30 min. The reaction was maintained at -78°C with stirring for 2 h then Et₃N (18.83 mL, 135.1 mmol) was added dropwise via syringe over 5 min. The reaction was transferred to a 0°C ice bath and allowed to warm to rt over 2 h. The reaction was diluted with 4:1 petroleum ether/Et₂O (500 mL) and extracted with saturated NH₄Cl (3 x 50 mL) followed by brine (1 x 100 mL). The organic phase was dried over MgSO₄, filtered and concentrated. Purification by flash chromatography (silica gel, 4:1 hexanes/Et₂O) gave a 1.6 **16_R**: 1 **16_S** mixture (4.25 g, 87%) as a yellow oil. Alternatively, **16_R** and **16_S** could be separated by flash chromatography (silica gel, 4:1 hexanes/Et₂O). For operational simplicity, the mixture of diastereomers can be taken directly into the next reaction if desired. **16_R**: *R_f* (Et₂O/hexanes 2:8) = 0.33; IR (film) 2952, 2869, 1728, 1456, 1383, 1308, 1265 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 0.72 (1H, t, *J* = 13.2 Hz), 0.85 (3H, d, *J* = 7.0 Hz), 0.87 (3H, d, *J* = 7.0 Hz), 0.90 (3H, d, *J* = 6.3 Hz), 1.17 (1H, ddd, *J* = 1.9, 4.1, 12.4 Hz), 1.54-1.76 (3H, m), 1.29-1.53 (4H, m), 2.39 (1H, dsept, *J* = 1.6, 7.1 Hz), 2.44 (1H, ddd, *J* = 1.8, 4.3, 16.1 Hz), 2.56 (1H, ddd, *J* = 2.5, 8.2, 16.1 Hz), 2.72 (1H, ddd, *J* = 1.9, 3.1, 13.5 Hz), 3.83 (1H, ddd, *J* = 1.3, 5.2, 11.7 Hz), 4.13 (1H, ddd, *J* = 2.7, 11.7, 11.9 Hz), 4.36 (1H, dddd, *J* = 2.9, 4.3, 7.4, 8.2 Hz), 9.80 (1H, dd, *J* = 1.8, 2.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ = 18.8, 21.7, 22.2, 23.7, 24.2, 28.9, 31.1, 34.8, 37.2, 49.9, 51.1, 58.7, 63.8, 100.9, 201.4; HRMS Calcd for C₁₅H₂₆O₃: 254.1882. Found: 254.1877; [α]_D²⁰ = -11.2° (*c* 1.28, CHCl₃). **16_S**: *R_f* (Et₂O/hexanes 2:8) = 0.41; IR (film) 2952, 2869, 2725, 1728, 1456, 1379, 1308, 1245, 1160, 1115, 1008 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 0.71 (1H, t, *J* = 13.0 Hz), 0.86 (3H, d, *J* = 6.9 Hz), 0.87 (3H, d, *J* = 6.9 Hz), 0.89 (3H, d, *J* = 6.0 Hz), 1.17 (1H, ddd, *J* = 2.4, 3.9, 12.6 Hz), 1.25-1.74 (7H, m), 2.33 (1H, dsept, *J* = 2.4, 6.9 Hz), 2.47 (1H, ddd, *J* = 1.8, 5.1, 16.2 Hz), 2.57 (1H, ddd, *J* = 2.4, 6.9, 16.2 Hz), 2.72 (1H, ddd, *J* = 1.5, 3.3, 13.6 Hz), 3.78 (1H, ddd, *J* = 1.5, 5.4, 11.7 Hz), 3.90 (1H, ddd, *J* = 2.7, 12.0, 12.0 Hz), 4.53 (1H, m), 9.79 (1H, dd, *J* = 1.8, 2.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ = 18.9, 22.2, 22.3, 23.8, 24.5, 29.0, 31.1, 34.8, 37.3, 50.0, 51.0, 58.4, 63.7, 100.9, 201.5; HRMS Calcd for C₁₅H₂₆O₃: 254.1882. Found: 254.1871; [α]_D²⁰ = -50.5° (*c* 0.19, CHCl₃).

17_R

17_S

Tridentate Cr^{III} Catalyst

To an oven dried argon purged flask was added activated powdered 4 Å MS (182 mg), which were cooled to rt under a stream of argon. This was transferred to a solution of **16** (232 mg, 0.912 mmol) dissolved in acetone (182 μ L, freshly distilled from CaCO₃ under N₂) in a 5 mL oven dried, argon purged flask. To this was added the tridentate Cr^{III} catalyst (47 mg, 0.093 mmol) and the mixture was allowed to stir for 3 h at rt. At this time Danishefsky's Diene (90%, 252 μ L, 1.11 mmol, Aldrich) was added and the reaction was stirred for 22 h at rt. To this was added TBME (1 mL, HPLC grade, J. T. Baker) and the reaction was cooled to -78°C followed by the dropwise addition of TFA (100 μ L). The reaction was stirred at -78°C for 13 min then quenched with saturated NaHCO₃ (5 mL). The entire mixture was filtered through Celite 521, eluted with Et₂O and dried over MgSO₄. Upon filtration and evaporation the residue was passed through a plug of silica gel, eluting with 30% EtOAc/hexanes to yield a crude mixture of **17_R** and **17_S**. The diastereomeric ratio of **17_R** to **17_S** was determined to be 33 **17_R**: 1 **17_S** using a HP 6890 Series GC. The column used to facilitate separation was a HP-5 column and the following method was used for elution: 50°C for 0.00 min, ramping to 200°C at $10^{\circ}\text{C}/\text{min}$. The oven was kept at 200°C for 0.00 min and then ramped to 230°C at $1^{\circ}\text{C}/\text{min}$ where it was kept for 10 min. The retention time for **17_R** was 23.56 min and the retention time for **17_S** was 22.76 min. The crude mixture was then purified by column chromatography, (silica gel, 2:8 EtOAc/hexanes). **17_R** (260 mg, 88%) was isolated as a colorless solid. **17_R** was crystallized by evaporation of a solution in EtOAc/hexanes to yield colorless crystals. **17_S** was crystallized by evaporation of a solution in EtOAc/hexanes to yield colorless crystals. **17_R**: R_f (EtOAc/petroleum ether 15:85) = 0.25; ^1H NMR (300 MHz, CDCl₃) δ = 0.70 (1H, t, J = 12.6 Hz), 0.83 (3H, d, J = 6.9 Hz), 0.87 (3H, d, J = 7.1 Hz), 0.88 (3H, d, J = 6.6 Hz), 1.18 (1H, ddd, J = 1.9, 3.9, 12.5 Hz), 1.28-1.75 (8H, m), 1.91 (1H, ddd, J = 2.3, 9.6, 14.3 Hz), 2.38 (1H, dsept, J = 1.6, 6.9 Hz), 2.42-2.56 (2H, m), 2.70 (1H, ddd, J = 1.9, 2.8, 13.5 Hz), 3.81 (1H, ddd, J = 1.2, 5.2, 11.6 Hz), 4.03-4.15 (2H, m), 4.67 (1H, dddd, J = 3.0, 5.8, 9.6, 11.8 Hz), 5.40 (1H, d, J = 6.0 Hz), 7.31 (1H, d, J = 6.0 Hz); ^{13}C NMR (75 MHz, CDCl₃) δ = 18.9, 21.9, 22.2, 23.6, 24.2, 29.0, 31.7, 34.8, 37.3, 41.7, 42.5, 51.1, 58.9, 63.3, 75.7, 100.7, 107.3, 162.9, 192.7; Anal. Calcd for C₁₉H₃₀O₄: C, 70.77; H, 9.38. Found: C, 70.91; H, 9.58; $[\alpha]_D^{20}$ = $+42.5^{\circ}$ (c 1.59, CH₂Cl₂). **17_S**: R_f (EtOAc/hexanes 15:85) = 0.15; IR (film) 2952, 2869, 1682, 1597, 1456, 1405, 1269 cm⁻¹; ^1H NMR (300 MHz, CDCl₃) δ = 0.70 (1H, t, J = 13.5 Hz), 0.86 (3H, d, J = 6.9 Hz), 0.87 (3H, d, J = 6.9 Hz), 0.89 (3H, d, J = 6.7 Hz), 1.17 (1H, ddd, J = 1.9, 3.8, 12.6 Hz), 1.20-1.75 (7H, m), 1.79 (1H, ddd, J = 4.2, 6.9, 14.0 Hz), 2.02 (1H, ddd, J = 5.6, 8.3, 14.0 Hz), 2.39 (1H, dsept, J = 1.6, 6.9 Hz), 2.47 (1H, ddd, J = 0.9, 4.0, 16.8 Hz), 2.63 (1H, dd, J = 13.3, 16.8 Hz), 2.67 (1H, ddd, J = 1.9, 3.2, 13.5 Hz), 3.81 (1H, ddd, J = 1.4, 5.4, 11.6 Hz), 4.00 (1H, dddd, J = 1.0, 4.2, 8.3, 15.5 Hz), 4.09 (1H, ddd, J = 2.8, 11.6, 12.0 Hz), 4.61 (1H, dddd, J = 2.8, 11.6, 12.0 Hz), 5.40 (1H, dd, J = 0.9, 6.0 Hz), 7.33 (1H, d, J = 6.0 Hz); ^{13}C NMR (75 MHz, CDCl₃) δ = 18.8, 21.8, 22.2, 23.7, 24.2, 29.3, 31.4, 34.7, 37.3,

40.9, 41.6, 51.1, 58.8, 63.9, 76.4, 100.7, 107.1, 163.3, 192.6; HRMS Calcd for C₁₉H₃₀O₄: 322.2144. Found: 322.2146;; [α]_D²⁰ = -57.8° (c 1.5, CH₂Cl₂).

17a

17b

In an oven dried argon purged 250 mL round bottom flask, charged with a magnetic spin vane was added a solution of **17a** (1.9 g, 5.90 mmol) dissolved in anhydrous MeOH (130 mL, HPLC grade, JT Baker). To this solution was added CeCl₃•7H₂O (1.32 g, 3.54 mmol) and the reaction was allowed to stir at rt for 10 min. It was then cooled to -50°C and NaBH₄ (480 mg, 12.69 mmol) was added in one portion. The reaction was allowed to stir for 30 min at -50°C and then warmed to rt, at which temperature it was allowed to react for an additional 10 min. The reaction was then quenched with brine (50 mL). The aqueous layer was extracted with EtOAc (3 x 75 mL) and the combined organic washes were dried over MgSO₄. After filtration and evaporation the crude material was purified by column chromatography (silica gel, 2:8 EtOAc/hexanes). Single diastereomer **v** (1.76 g, 92%) was isolated as a colorless oil. **v**: R_f (EtOAc/hexanes 2:8) = 0.19; IR (film) 3386, 2951, 2869, 1643, 1456, 1380, 1307, 1268, 1231 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 0.69 (1H, t, *J* = 12.7 Hz), 0.88 (6H, d, *J* = 6.9 Hz), 0.90 (3H, d, *J* = 6.2 Hz), 1.17 (1H, ddd, *J* = 1.9, 4.4, 12.3 Hz), 1.33-1.74 (9H, m), 1.90 (1H, ddd, *J* = 6.6, 7.7, 14.0 Hz), 2.18 (1H, dddd, *J* = 1.7, 1.9, 6.4, 13.0 Hz), 2.39 (1H, dsept, *J* = 1.7, 6.9 Hz), 2.69 (1H, br d, *J* = 13.5 Hz), 3.81 (1H, ddd, *J* = 1.5, 5.2, 11.5 Hz), 3.98 (1H, dddd, *J* = 2.7, 5.2, 7.9, 10.9 Hz), 4.08 (1H, ddd, *J* = 2.7, 12.4, 12.4 Hz), 4.08-4.17 (1H, m), 4.36-4.46 (1H, m), 4.75 (1H, ddd, *J* = 1.9, 1.9, 6.1 Hz), 6.35 (1H, br d, *J* = 5.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ = 18.8, 21.8, 22.2, 23.7, 24.2, 29.2, 31.3, 34.9, 37.4, 37.7, 41.5, 51.2, 58.9, 63.0, 64.3, 71.4, 100.6, 105.5, 145.3; [α]_D²⁰ = +2.0° (c 0.59, CHCl₃).⁴

⁴ Compound's instability prevented the acquisition of reliable HRMS and elemental analysis data.

18

In an oven dried argon purged 100 mL round bottom flask charged with a magnetic stir bar was added a solution of **v** (482 mg, 1.49 mmol) in isobutylvinyl ether (31 mL, 238 mmol). $\text{Hg}(\text{OAc})_2$ (237 mg, 0.744 mmol) was added and the reaction was run at rt for 48 h. The reaction was diluted with EtOAc (30 mL) and the organic layer was washed with saturated NaHCO_3 (3 x 30 mL), followed by brine (1 x 30 mL). The organic layer was dried over MgSO_4 , filtered and concentrated. Rapid column chromatography (silica gel, 15:85 EtOAc/hexanes + 1% by volume Et_3N) gave the crude enol ether. This was carried on immediately to the next reaction.

In an oven dried argon purged 250 mL round bottom flask charged with a magnetic stir bar was added a solution of the enol ether (480 mg, 1.37 mmol) dissolved in anhydrous decane (26 mL, 99%+, Aldrich). Previous to its use, the decane was degassed by purging it with argon for 1 h in an oven dried and argon purged 150 mL round bottom flask. The reaction vessel was lowered into a preheated 155°C oil bath and heated for 3 h at this temperature under an argon atmosphere. It was then removed from the oil bath and cooled to rt. The whole reaction was loaded onto a column using hexanes to assist in the transfer, and purification via column chromatography (silica gel, 1:9 EtOAc/hexanes) yielded **18** (431 mg, 83% from **v**) as a colorless oil. **18**: R_f (EtOAc/hexanes 1:9) = 0.38; IR (film) 2950, 2869, 1728, 1646, 1456, 1373, 1307, 1267 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ = 0.68 (1H, t, J = 12.9 Hz), 0.88 (6H, d, J = 7.1 Hz), 0.89 (3H, d, J = 6.6 Hz), 1.12-2.14 (12H, m), 2.40 (1H, dsept, J = 1.6, 6.9 Hz), 2.55 (2H, dd, J = 2.4, 6.2 Hz), 2.69 (1H, ddd, J = 1.9, 3.0, 13.4 Hz), 3.66-3.82 (2H, m), 3.90-4.01 (1H, m), 4.08 (1H, ddd, J = 2.7, 12.1, 12.1 Hz), 4.57-4.66 (1H, m), 5.64 (1H, dddd, J = 1.3, 1.3, 2.5, 10.0 Hz), 5.89 (1H, dddd, J = 2.0, 2.0, 4.7, 10.0 Hz), 9.78 (1H, t, J = 2.4 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ = 18.9, 21.9, 22.2, 23.7, 24.3, 29.1, 30.7, 31.5, 34.9, 37.4, 42.5, 48.5, 51.2, 59.1, 64.4, 70.5, 70.6, 100.5, 126.3, 128.5, 201.7; HRMS Calcd for $\text{C}_{21}\text{H}_{34}\text{O}_4$: 350.2457. Found: 350.2466; $[\alpha]_D^{27} = 0^\circ$ (c 1, CH_2Cl_2).

19

In an oven dried, argon purged 200 mL round bottom flask, charged with a magnetic spin vane was added a solution of **18** (269 mg, 0.77 mmol) in EtOAc (77 mL, HPLC grade, JT Baker). Pearlman's catalyst (89 mg, $\text{Pd}(\text{OH})_2/\text{C}$ 20wt%, $\text{H}_2\text{O} \leq 50\%$) was added and the flask was evacuated under vacuum, then filled with H_2 from a balloon. This procedure was repeated three times. The reaction was allowed to stir under H_2 (1 atm) for 30 min. The reaction was filtered through Celite 521, eluting with EtOAc. The filtrate was evaporated and purified by column chromatography (silica gel, 2:8 EtOAc/hexanes) to yield the saturated aldehyde (229 mg, 85%) as a colorless oil which was carried on crude into the next reaction. R_f (EtOAc/hexanes 2:8) = 0.24.

A stock solution of $\text{Ipc}_2\text{B}(\text{allyl})$ was prepared by dissolving (-)- Ipc_2BOMe (5.37 g, 17.0 mmol), weighed into a 100 mL round bottom oven dried flask in a glove box, in Et_2O (43 mL).

This solution was cooled to -78°C and a 1.0 M solution of allyl magnesium bromide in Et_2O (13.9 mL, 13.9 mmol) was added dropwise. The mixture was warmed to rt and stirred for 1 h. This was then allowed to stand without stirring for 15 min. In a separate oven dried, argon purged 250 mL round bottom flask was added a solution of the saturated aldehyde (815 mg, 2.31 mmol) in Et_2O (91 mL). To this solution was added an aliquot (15 mL) of the stock solution of $\text{Ipc}_2\text{B(allyl)}$, dropwise, at -78°C . After stirring at -78°C for 2 h, the reaction was treated with 30% H_2O_2 (2.13 mL) and 3 N NaOH (5.13 mL) and allowed to warm to rt. After stirring at rt for 2 h, the reaction was diluted with EtOAc (75 mL) and the organic phase was extracted with brine (1 x 100 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were dried over MgSO_4 . After filtration and evaporation the crude material was cleaned by column chromatography (silica gel, 2:98 EtOAc /hexanes) to yield an inseparable mixture of the homoallylic alcohol and pinan-3-ol. To a solution of this mixture dissolved in CH_2Cl_2 (92 mL) was added TBSCl (3.48 g, 23.1 mmol), and imidazole (3.145 g, 46.2 mmol) at rt. The reaction was allowed to stir for 16 h. It was quenched by the addition of saturated NaHCO_3 (60 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried over MgSO_4 , filtered and concentrated. The crude material was purified by column chromatography (silica gel, 2:98 EtOAc /hexanes) to yield the homoallylic TBS ether (812 mg, 69% over two steps) as a colorless oil. R_f (EtOAc /hexanes 2:98) = 0.27.

In an oven dried argon purged 100 mL round bottom flask charged with a magnetic spin vane was added NaIO_4 (1.00 g, 4.69 mmol) followed by a pH 7 phosphate buffer (54 mL). To this solution was added KMnO_4 (93 mg, 0.586 mmol) in one portion. This was allowed to stir for 10 min under an argon atmosphere. This solution was then added to a solution of the homoallylic TBS ether (298 mg, 0.586 mmol) dissolved in *tert*-butanol (54 mL). The reaction was allowed to stir for 90 min at rt under an argon atmosphere, maintaining its purple color. The reaction was quenched by the addition of $\text{Na}_2\text{S}_2\text{O}_3$ (400 mg, 1.6 mmol) in one portion. The aqueous reaction was extracted with EtOAc (3 x 60 mL) and the organic layers were dried over MgSO_4 . After filtration and evaporation the crude reaction was purified by column chromatography (silica gel, 2:8 EtOAc /hexanes, +1% glacial acetic acid) to yield **19** (258 mg, 84%) as a colorless oil. Glacial acetic acid was removed by azeotroping with heptane. **19**: R_f (EtOAc /hexanes 1:4, +1% glacial acetic acid) = 0.49; IR (film) 2933, 1712, 1457, 1255, 1114 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 0.11 (s, 3 H), 0.12 (s, 3 H), 0.88 (br s, 18 H), 1.85-1.15 (m, 21 H), 2.40 (quint, J = 6.8 Hz, 1 H), 2.48 (dd, J = 15.2, 5.2 Hz, 1 H), 2.62 (dd, J = 15.2, 5.2 Hz, 1 H), 2.69 (d, J = 13.2 Hz, 1 H), 3.44 (m, 2 H), 3.81 (m, 1 H), 3.93 (m, 1 H), 4.08 (m, 1 H), 4.32 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ = -4.77, 17.92, 19.15, 21.89, 22.25, 23.52, 23.77, 24.31, 25.74, 29.23, 30.93, 31.89, 32.13, 37.43, 42.48, 43.25, 43.89, 43.97, 51.24, 59.14, 64.26, 66.15, 73.52, 73.88, 100.44, 173.48; HRMS Calcd for $\text{C}_{29}\text{H}_{54}\text{O}_6\text{Si}$: 526.3689. Found: 526.3687; $[\alpha]_D^{25}$ = +22.6 $^{\circ}$ (c 0.58, CH_2Cl_2).

To a solution of acid **19** (28 mg, 0.05 mmol) in toluene (1.1 mL) was added NEt_3 (14 μL , 0.1 mmol) and 2,4,6-trichlorobenzoyl chloride (8 μL , 0.05 mmol) at rt and the mixture was stirred for 1 h. To this reaction mixture was added a solution of alcohol **14** (15 mg, 0.025 mmol) and DMAP (15 mg, 0.125 mmol) in toluene (1.1 mL) at rt. The reaction mixture was stirred for 1 h and then directly poured onto a column (silica gel, 85:15 hexane:ethyl acetate) and eluted with this solvent system to afford ester **vi** (24 mg, 87%) as a colorless oil. **vi**: R_f (hexane/ethyl acetate 85:15) = 0.29; IR (film) 3492, 2930, 2859, 1725, 1691, 1155, 1112, 837, 777 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ = 0.04 (3H, s), 0.05 (3H, s), 0.07 (6H, s), 0.68 (1H, t, J = 13.2 Hz), 0.60-0.92 (30H, m), 1.10-1.30 (18H, m), 1.34-1.84 (18H, m), 1.85-2.14 (3H, m), 2.34-2.52 (3H, m), 2.68 (1H, d, J = 12.3 Hz), 3.13 (1H, s), 3.34-3.46 (2H, m), 3.60-3.70 (3H, m), 3.68 (3H, s), 3.76-3.86 (2H, m), 3.86-3.96 (1H, m), 4.06 (1H, dt, J = 11.9, 2.1 Hz), 4.24-4.34 (1H, m), 5.11 (1H, s), 5.20-5.32 (1H, m), 5.96 (1H, dd, J = 16.1, 7.8 Hz), 6.00 (1H, s), 7.42 (1H, d, J = 16.1 Hz), 9.58 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ = -5.3, -5.3, -4.7, -4.6, 14.0, 18.0, 18.3, 19.2, 20.1, 21.9, 22.3, 22.5, 22.9, 23.6, 23.7, 23.8, 24.3, 24.5, 25.8, 28.9, 28.9, 29.2, 30.9, 31.0, 31.6, 31.8, 31.9, 32.0, 34.5, 35.0, 37.4, 37.4, 43.5, 43.8, 44.7, 45.6, 51.2, 51.3, 59.2, 64.4, 64.9, 65.7, 66.3, 71.1, 72.7, 73.4, 73.8, 99.5, 100.4, 120.5, 127.5, 150.5, 166.4, 166.5, 171.7, 172.1, 194.6; HRMS Calcd for $\text{C}_{60}\text{H}_{106}\text{O}_{14}\text{Si}_2$ (M^+): 1129.7037, Found: 1129.7019; $[\alpha]_{\text{D}}^{24.4}$ = -27.42° (c 0.87, CH_2Cl_2).

To a solution of ester **vi** (20 mg, 0.02 mmol) in THF (5 mL) at rt in a plastic vial was added 70% HF·pyridine (970 μ L, 0.05 mmol) dropwise and the yellow reaction mixture was stirred for 1.5h. The reaction was quenched by addition of saturated NaHCO₃ solution (12.5 mL) and H₂O (7.5 mL). The biphasic mixture was extracted with EtOAc (4 x 12 mL). The combined organic phases were dried over Na₂SO₄. After filtration and evacuation of solvents the residue was purified by column chromatography (silica gel, 1:4 hexane:EtOAc) to picolog **1** (11 mg, 82%) as a white solid. **1**: R_f (hexane/ethyl acetate 1:4) = 0.29; IR (film) 3454, 3332, 2932, 2858, 1723, 1663, 1138, 976, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ = 0.86 (3H, t, *J* = 6.7 Hz), 1.01 (3H, s), 1.17 (3H, s), 1.18-1.38 (12H, m), 1.40-1.66 (7H, m), 1.72-1.88 (3H, m), 1.94-2.14 (3H, m), 2.29 (1H, dt, *J* = 7.5/ 1.7 Hz), 2.52 (1H, d, *J* = 7.2 Hz), 3.45 (1H, t, *J* = 11.2 Hz), 3.53 (1H, t, *J* = 10.6 Hz), 3.61- 3.72 (4H, m), 3.68 (3H, s), 3.88 (3H, t, *J* = 12.4 Hz), 4.02-4.09 (2H, m), 4.10-4.19 (1H, m), 4.48 (1H, d, *J* = 11.6 Hz), 5.02 (1H, d, *J* = 7.6 Hz), 5.10 (1H, s), 5.13 (1H, s), 5.34-5.39 (1H, m), 5.40 (1H, dd, *J* = 15.0/ 7.6 Hz), 5.97 (1H, d, *J* = 15 Hz), 5.99 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ = 14.1, 19.3, 22.5, 23.0, 24.4, 24.7, 28.9, 29.0, 31.0, 31.3, 31.4, 31.6, 32.4, 34.6, 35.9, 39.9, 42.5, 42.9, 45.1, 51.1, 64.5, 65.8, 66.3, 68.6, 71.6, 74.1, 75.8, 76.0, 78.7, 98.9, 102.4, 119.9, 125.7, 142.6, 151.7, 167.0, 172.1, 172.6; HRMS Calcd for C₃₈H₆₀O₁₃ (M⁺): 747.3891, Found: 747.3932; [α]_D^{24.0} = -20.02° (c 0.70, CH₂Cl₂).

PKC Binding Assay Protocol

Filters (Whatman GF-B, 21 mm dia.) are soaked for 1 hour in a solution containing deionized water (97 mL), and 10% polyethylenamine (3 mL). An assay buffer solution is prepared by the addition of TRIS (1M, pH 7.4, 1 mL), KCl (1M, 2 mL), CaCl₂ (0.1M, 30 μ L), bovine serum albumin (40 mg), diluted to 20 mL with deionized water and stored on ice. Phosphatidyl serine vesicles are prepared by the addition of phosphatidyl serine (10 mg/mL in chloroform, 0.4 mL) to a glass test tube followed by removal of the chloroform under a stream of nitrogen (5 min). To this viscous liquid is added a portion of the prepared assay buffer (4 mL) and the resulting mixture is then transferred to a plastic tube with washing. This tube is then sonicated (Branson Sonifier 250, power = 6, 40% duty cycle) four times for 30 sec. with a 30 sec. rest in-between sonications. The resulting solution is stored over ice. PKC is prepared by the addition of cooled assay buffer (10 mL) to PKC (25 μ L) purified from the rat brain by the method of Mochly-Rosen⁵ and then stored on ice. Stock solutions of compounds are diluted with absolute ethanol in glass in serial fashion.

Each plastic assay incubation tube is made to contain prepared phosphatidyl serine vesicles (60 μ L), prepared PKC solution (200 μ L) and analogue (0-20 μ L plus EtOH (20-0 μ L) for a total volume of 20 μ L). Lastly, tritiated PDBu (30 nM, 20 μ L) is added to each tube. The assay is carried out using 7-10 analogue concentrations, each in triplicate. Non-specific binding is measured in 1-3 tubes by the substitution of phorbol myristate acetate (PMA) (1 mM, 5 μ L) and EtOH (15 μ L) for the analogue / EtOH combination. The tubes are incubated at 37°C for 30 min. and then put on ice for 5 min. Each tube is then filtered separately through a pre-soaked filter disc. The filter is subsequently rinsed with cold 20 mM TRIS buffer (5 mL) dropwise. The filters are then put in separate scintillation vials and Universol[®] scintillation fluid is added (3 mL). The filters are immediately counted in a scintillation counter (Beckman LS 6000SC). Counts per minute are averaged among three trials at each concentration.

The data is then plotted using a least square fit algorithm with the Macintosh version of Kaleidagraph[®] (Abelbeck Software) and an IC₅₀ (defined as the concentration of analogue required to displace half of the specific PDBu binding to PKC) is calculated. The IC₅₀ then

⁵ Mochly-Rosen, D.; Koshland, Jr., D. E. *J. Biol. Chem.* **1987**, 262, 2291-2297.

allows determination of the K_i for the analogue from the equation: $K_i = IC_{50} / (1 + [PDBu]) / K_d$ of PDBu). The K_d of [3H]-PDBu is determined under identical conditions to be 1.17 nM.

Cell Line: ⁶	log (GI ₅₀) values (in M)		
	<u>1</u>	<u>Bryo 1</u>	<u>2</u>
Leukemia			
MOLT-4	<-8.0	-5.50	-6.91
K-562	-7.5	-5.40	-7.34
NSC Lung			
NCI-H460	<-8	-5.60	-7.47
A549/ATCC	-6.62	-5.20	-6.49
Colon			
COLO 205	-7.08	-5.40	-6.7
HCC-2998	-7.54	-5.30	-3.5
CNS			
SF-295	-6.05	-5.20	-6.56
Melanoma			
SK-MEL-5	-6.43	-5.70	-5.05
Ovarian			
OVCAR-5	-5.28	>-5	>-4
Renal			
TK-10	-7.03	>-5	-7.22
A498	-6.38	>-5	-5.7
Prostate			
PC-3	-5.6	-5.30	-5.55
Breast			
MDA-MB-435	-7.66	-5.10	-7.26
MDA-MB-231/ATCC	-5.69	-5.20	-5.01

⁶ Assays performed by NCI.