DYKAT of Vinyl Aziridines: Total Synthesis of (+)-Pseudodistomin D

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Supporting Information Part A: Experimental Procedures

General

Flash chromatography was performed on silica gel (EM Science, Kieselgel 60, 230-400mesh, ASTM) or neutral alumina (Fluka, Aluminum Oxide, type 507, Brockmann grade III, 6% hydrate) using compressed air. TLC was performed using glass-backed plates coated with 0.2mm silica (Merck, DC-Platten, Kieselgel; 60 F₂₅₄) or plastic backed plates coated with 0.2mm neutral alumina (EM, 60 F₂₅₄, Type E). Chiral HPLC analysis was performed on Daicel Chiralpack columns, eluting with a heptane and isopropanol mixture, using a Thermo Separation Products Spectra SERIES P100 or P200 instruments. NMR spectra were carried out on a Varian Gemini 300 (300 MHz), Mercury 400 (400 MHz), or Unity 500 (500 MHz) instruments and are calibrated to TMS or residual solvent peaks: proton (CDCl₃ 7.26ppm, MeOH 4.87ppm) and carbon (CDCl₃ 77ppm, MeOH 49.15ppm). Optical rotation was measured on a Jasco DIP-1000 digital polarimeter in 5 cm cells at room temperature. (–)-C₃H₅PdCl₂,¹ Trost ligand (S,S) L_N,² alkyne **8**³ and vinyl iodide **9**⁴ were prepared according to literature procedures. All compounds are >95% pure by proton NMR unless otherwise noted. All reagents were used as purchased unless otherwise noted.

Experimental Procedures

1-(2,4-Dimethoxybenzyl)-aziridine-2-carboxylic acid ethyl ester

2,4 Dimethoxybenzylamine (5.0 mL, 5.7 g, 33 mmol) followed by Et₃N (67 mmol, 6.7 g, 9.3 mL) were added to a solution of ethyl 2,3-dibromopropanoate **5** (4.8 mL, 8.7 g, 33 mmol) in anhydrous ethanol (300 mL) at 0°C under nitrogen. The reaction was allowed to warm to room temperature and stirred at 50°C in a sealed flask of nitrogen for 20 h. The resulting yellow solution was concentrated *in vacuo* to an oily solid. The oily solid was suspended in ether (300 mL) and vigorously stirred for _ h. The solids were removed by filtration and rinsed thoroughly with ether. The filtrate was

¹ *Inorganic Syntheses* **1991**, 28, 342-343.

² Trost, B.M.; Bunt, R.C.; Lemoine, R.C.; Calkins, T.L. *J. Am. Chem. Soc.* **2000**, 122, 5968-5976.

³ a) Ma, D.; Lu, X. *Tetrahedron* **1990**, 46, 6319-6330. b) Huang, H.; Forsyth, C.J. *J. Org. Chem.* **1997**, 62, 8595-8599.

⁴ Chen, M.-J.; Narkunan, K.; Liu, R.-S. *J. Org. Chem.* **1999**, 64, 8311-8318.

concentrated *in vacuo* to afford the intended aziridine as a yellow oil (8.5 g, 96%). This material was used in the next step without further purification. $^1\text{H NMR}$ (CDCl_3 300 MHz) δ 7.32 (d, $J=8.1$ Hz, 1H), 6.47 (dd, $J=8.4$, 2.1 Hz, 1H), 6.43 (d, $J=2.4$ Hz, 1H), 4.12-4.25 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.55 (d, $J=14$ Hz, 1H), 3.47 (d, $J=14$ Hz, 1H), 2.19-2.20 (m, 2H), 1.76 (dd, $J=4.4$, 3.2 Hz, 1H), 1.27 (t, $J=7.2$ Hz, 3H). $^{13}\text{C NMR}$ (CDCl_3 100 MHz) δ 171.03, 160.06, 157.98, 130.03, 118.54, 103.82, 98.11, 60.89, 57.44, 55.24, 55.11, 37.35, 34.21, 14.10. **IR** (KBr –Neat) 2979, 2837, 1742, 1614, 1589, 1509, 1465, 1415, 1385, 1289, 1209, 1187, 1157, 1121, 1083, 1038, 834 cm^{-1} . **EI-HRMS** calculated for $\text{C}_{14}\text{H}_{19}\text{NO}_4$ 265.1314 found 265.1311.

1-(2,4-Dimethoxybenzyl)-aziridine-2-carbaldehyde

DIBAL-H (1M in Hexanes, 63 mL, 63 mmol) was slowly added over 20 minutes to an anhydrous solution of 1-(2,4-dimethoxybenzyl)-aziridine-2-carboxylic acid ethyl ester (7.95 g, 30.0 mmol) in methylene chloride (125 mL) at -78°C under nitrogen. The solution was stirred for 1.5h at -78°C . The reaction was carefully quenched with a saturated aqueous solution of NaF (38 mL) at -78°C . The resulting mixture was vigorously stirred for 50 min while allowing the reaction to warm to room temperature. The mixture was poured into methylene chloride (750 mL), dried with Na_2SO_4 , filtered, and concentrated *in vacuo* to provide the intended aldehyde as a cloudy orange oil. The aldehyde was isolated in >95% purity by $^1\text{H NMR}$ and used in the next reaction without further purification (6.4 g, 97%) $^1\text{H NMR}$ (CDCl_3 300 MHz) δ 8.90 (d, $J=6.6$ Hz, 1H), 7.23 (d, $J=8.1$ Hz, 1H), 6.45-6.49 (m, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 3.52 (s, 2H), 2.18-2.26 (m, 2H), 1.96 (d, $J=6.6$ Hz, 1H). $^{13}\text{C NMR}$ (CDCl_3 75 MHz) δ 200.35, 160.38, 158.16, 130.35, 118.29, 104.02, 98.39, 57.15, 55.29, 55.25, 44.59, 32.52. **IR** (KBr –Neat) 2939, 2837, 1719, 1614, 1589, 1509, 1464, 1290, 1266, 1209, 1158, 1122, 1035, 834 cm^{-1} . **EI-HRMS** calculated for $\text{C}_{12}\text{H}_{15}\text{NO}_3$ 221.1052 found 221.1049.

1-(2,4-Dimethoxybenzyl)-2-vinylaziridine (4)

KHMDS (0.47 M in THF, 86 mL, 40 mmol) was slowly added over 20 minutes to an anhydrous suspension of methyltriphenylphosphonium bromide (16 g, 45 mmol) in THF (150 mL) at -15°C under nitrogen. The resulting heterogeneous yellow mixture was stirred at -15°C for 15 min and at 0°C for 1h. An anhydrous solution of 1-(2,4-dimethoxybenzyl)-aziridine-2-carbaldehyde (6.4 g, 29 mmol) in THF (70 mL) was added to the above mixture over 10 min at -15°C . The yellow mixture was stirred at -15°C for 15 min, warmed to ambient temperature, and stirred at for 45 min. The yellow mixture was

poured into a mixture of brine (100 mL) and ether (100 mL). The layers were separated, and the aqueous portion was extracted with 3x100 mL of ether. The combined organic extracts were dried with Na₂SO₄, filtered, and concentrated *in vacuo* to yield a cloudy, thick, and orange oil. The intended vinyl aziridine **4** was isolated in >95% purity as a clear and slightly yellow oil (4.8 g, 76%) after purification by silica gel chromatography (50% Et₂O in petroleum ether). ¹H NMR (CDCl₃ 400 MHz) δ 7.33 (d, *J*=8.3 Hz, 1H), 6.47 (dd, *J*=8.3, 2.4 Hz, 1H), 6.44 (d, *J*=2.4 Hz, 1H), 5.59 (ddd, *J*=17.2, 10.3, 8.0 Hz, 1H), 5.30 (ddd, *J*=17.2, 1.6, 0.6 Hz, 1H), 5.11 (ddd, *J*=10.3, 1.6, 0.5 Hz, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 3.51 (d, *J*=14 Hz, 1H), 3.37 (d, *J*=14 Hz, 1H), 2.01 (ddd, *J*=7.9, 6.5, 3.5 Hz, 1H), 1.83 (d, *J*=3.4 Hz, 1H), 1.65 (d, *J*=6.5 Hz, 1H). ¹³C NMR (CDCl₃ 100 MHz) δ 159.81, 157.83, 138.71, 129.50, 119.96, 115.97, 103.76, 98.15, 58.25, 55.28, 55.19, 41.36, 35.28. IR (KBr –Neat) 2958, 2836, 1614, 1590, 1508, 1464, 1438, 1418, 1288, 1258, 1209, 1156, 1121, 1038, 918, 833, 733 cm⁻¹. EI-HRMS calculated for C₁₃H₁₇NO₂ 219.1259 found 219.1260.

2,4 Dimethoxybenzyl isocyanate

2,4-Dimethoxybenzyl isocyanate was prepared by a modification of the procedure published by Hirota *et. al.*⁵ An anhydrous solution of 2,4-dimethoxybenzylamine (1.97 mL, 2.20 g, 13 mmol) and Et₃N (3.66 mL, 2.66 g, 26.3 mmol) in ether (100 mL) was carefully added through an addition funnel to an anhydrous solution of triphosgene (1.30 g, 4.4 mmol) in ether (50 mL) at -78°C under nitrogen. After stirring for 10 min, the heterogeneous solution was allowed to warm to ambient temperature over 1 h. The mixture was then diluted with ether (100 mL), and the solids were removed by filtration. The filtrate was concentrated *in vacuo* to a yellow oil. The crude oil was distilled to afford the intended isocyanate as a cloudy colorless oil (1.86 g, 74%). ¹H NMR (CDCl₃ 400 MHz) δ 7.15 (d, *J*=7.6 Hz, 1H), 6.40-6.50 (m, 2H), 4.33 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H). ¹³C NMR (CDCl₃ 100 MHz) δ 160.96, 158.09, 129.46, 124.56, 117.93, 103.89, 98.58, 55.38, 55.31, 42.25. IR (KBr –Neat) 3005, 2941, 2838, 2251 (s), 1614, 1590, 1509, 1465, 1439, 1419, 1294, 1267, 1210, 1158, 1131, 1036, 921, 828, 781 cm⁻¹. EI-HRMS calculated for C₁₀H₁₁NO₃ 193.0793 found 193.0732.

(R)-(+)-1,3-Bis-(2,4-dimethoxybenzyl)-4-vinyl-imidazolidin-2-one (**3**)

⁵ Hirota, K.; Kazaoka, K.; Niimoto, I.; Sajiki, H. *Org. Biomol. Chem.* **2003**, *1*, 1354-1365.

Degassed and anhydrous methylene chloride (90 mL) was added to a flame dried 250 mL round bottom flask charged with (η^5 -C₃H₅PdCl)₂ (85.3 mg, 235 μ mol) and (S,S)-L_N (560 mg, 0.71 mmol) under nitrogen. The solution was stirred for 15 min to afford a deep red homogeneous solution to which was added acetic acid (67 μ L, 71 mg, 1.18 mmol). After stirring for another 10 min, aziridine **4** (2.58 g, 11.8 mmol) and 2,4-dimethoxybenzyl isocyanate (2.38 g, 12.3 mmol) were added in sequence to the above catalyst solution in a room temperature water bath, to control the exothermic additions. The resulting yellow homogeneous solution was stirred under nitrogen for 18 h to afford a deep red orange solution. At which point, all aziridine was absent by TLC. The reaction was concentrated *in vacuo* to provide a red oil. The oil was purified by silica gel chromatography (45% ethyl acetate in petroleum ether) to afford the intended imidazolidinone **3** as a tan viscous oil (4.28 g, 88%). $[\alpha]_D^{22.2} = +15.6^\circ$ (c=1.19 in CHCl₃ at 94% ee) Chiralpak OJ **HPLC** (10% isopropanol in Heptane, 1 mL/min, 230 nm) shows 94% ee favoring 23.718 over 20.423 min compared to a racemic sample⁶ that shows enantiomers at 19.248 and 22.875 min. **¹H NMR** (CDCl₃ 300 MHz) δ 7.20 (d, *J*= 7.8 Hz, 1H), 7.19 (d, *J*= 8.1 Hz, 1H), 6.40-6.46 (m, 4H), 5.65 (ddd, *J*=17.1, 10.1, 8.5 Hz, 1H), 5.14 (d, *J*=8.4 Hz, 1H), 5.10 (d, *J*=16.5 Hz, 1H), 4.59 (d, *J*=15.3 Hz, 1H), 4.41 (d, *J*=14.7 Hz, 1H), 4.31 (d, *J*=15.0 Hz, 1H), 4.08 (d, *J*=15.0 Hz, 1H), 3.70-3.82 (m, 13H), 3.31 (t, *J*=8.7 Hz, 1H), 2.86 (dd, *J*=9.0, 7.5 Hz, 1H). **¹³C NMR** (CDCl₃ 75 MHz) δ 160.78, 160.14, 160.00, 158.55, 158.39, 136.91, 130.73, 130.54, 118.30, 118.29, 117.94, 104.11, 103.92, 98.20, 98.08, 56.20, 55.25, 55.05, 48.63, 41.91, 39.57. **IR** (KBr–Neat) 2937, 2837, 1694 (s), 1612, 1589, 1508, 1453, 1421, 1294, 1240, 1210, 1157, 1121, 1037, 920, 834, 732 cm⁻¹. **EI-HRMS** calculated for C₂₃H₂₈N₂O₅ 412.1998 found 412.2019.

(R)-(-)-1,3-Bis-(2,4-dimethoxybenzyl)-4-vinyl-imidazolidine

Solid LiAlH_4 (737 mg, 19.4 mmol) was added in small portions to an anhydrous solution of imidazolidinone **3** (2.0 g, 4.85 mmol) in ether (200 mL). The gray suspension was stirred at reflux for 13h at which point starting imidazolidinone **3** was still present by TLC. An additional 250mg of LiAlH_4 were added to the above reaction, and the suspension was stirred at reflux for another 6h at which point all starting imidazolidinone was absent by TLC. The reaction was carefully quenched at 0°C by the consecutive addition of water (1 mL), 4M NaOH (1 mL), and water (2.2 mL). After stirring the resulting mixture for _ h at 0°C and _ h at ambient temperature, the mixture was diluted with methylene chloride (150 mL), dried with Na_2SO_4 , filtered, and concentrated to provide the intended imidazolidine as a yellow oil (1.92 g) in 90-95% purity by ^1H NMR.

⁶ Racemic imidazolidinone **3** was prepared by the same procedure as that for chiral **3** but 12% triphenylphosphine was employed as the ligand.

This material was used in the next step without further purification. $[\alpha]_D^{24.1} = -59.0^\circ$ ($c=1.32$ in CHCl_3 at 94% ee) $^1\text{H NMR}$ (CDCl_3 400 MHz) δ 7.28 (d, $J=8.4$ Hz, 1H), 7.22 (d, $J=8.5$ Hz, 1H), 6.40-6.46 (m, 4H), 5.81 (ddd, $J=17.2, 10.1, 7.9$ Hz, 1H), 5.22 (dd, $J=17.1, 1.9, 0.8$ Hz, 1H), 5.09 (ddd, $J=10.1, 1.9, 0.6$ Hz, 1H), 3.75-3.84 (m, 13H), 3.73 (d, $J=5.9$ Hz, 1H), 3.66 (s, 2H), 3.47 (d, $J=13.9$ Hz, 1H), 3.34 (d, $J=5.9$ Hz, 1H), 3.27 (quartet, $J=7.9$ Hz, 1H), 3.07 (dd, $J=9.6, 7.3$ Hz, 1H), 2.64 (dd, $J=9.6, 8.2$ Hz, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 159.73, 159.64, 158.32, 158.30, 139.40, 130.61, 130.51, 120.09, 119.85, 116.41, 103.77, 103.75, 98.27, 98.20, 76.30, 66.80, 58.79, 55.30, 55.27, 55.24, 53.06, 49.88. **IR** (KBr –Neat) 2937, 2834, 1614, 1589, 1507, 1485, 1438, 1419, 1290, 1265, 1208, 1156, 1132, 1039, 920, 833, 733 cm^{-1} . **EI-HRMS** calculated for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_4$ 398.2206 found 398.2184.

(R)-(-)- N^1,N^2 -Bis-(2,4-dimethoxybenzyl)-but-3-ene-1,2-diamine

$\text{H}_2\text{NOH}\cdot\text{HCl}$ (1.69 g, 24.3 mmol) was added as a solid to a suspension of (R)-(-)-1,3-bis-(2,4-dimethoxybenzyl)-4-vinylimidazolidine (all material from above) in aqueous 0.01% HCl (125 mL). The suspension was stirred at 60°C for 1 h to afford a homogeneous colorless solution with no starting material present by TLC. After cooling the reaction to room temperature, the solution was diluted with 0.5M HCl aq. (100 mL) and washed with 2x75 mL CH_2Cl_2 . The aqueous portion was basified by the careful addition of solid Na_2CO_3 and 1M NaOH (50 mL). The resulting aqueous suspension was extracted with 4x75 mL of CH_2Cl_2 . The final basic organic extracts were dried with Na_2SO_4 , filtered, and concentrated to the intended diamine (1.72 g, 92% for two steps) in approximately 95% purity by $^1\text{H NMR}$ analysis. This material was used in the next step without further purification. $[\alpha]_D^{25.7} = -19.0^\circ$ ($c=2.20$ in CHCl_3 at 94% ee) $^1\text{H NMR}$ (CDCl_3 300 MHz) δ 7.11 (d, $J=8.1$ Hz, 1H), 7.08 (d, $J=7.8$ Hz, 1H), 6.38-6.42 (m, 4H), 5.66 (ddd, $J=17.7, 10.2, 7.8$ Hz, 1H), 5.19 (d, $J=16.2$ Hz, 1H), 5.15 (d, $J=10.2$ Hz, 1H), 3.50-3.86 (m, 16H), 3.17 (quartet, $J=7.5$ Hz, 1H), 2.52-2.66 (m, 2H), 1.50-2.10 (s, 2H). $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 159.84, 158.62, 158.48, 140.23, 130.35, 130.14, 121.17, 121.05, 116.62, 103.49, 98.42, 98.37, 60.09, 55.29, 55.14, 53.20, 48.28, 46.18. **IR** (KBr –Neat) 3314, 3000, 2936, 2835, 1613, 1588, 1507, 1464, 1418, 1289, 1260, 1208, 1156, 1133, 1038, 921, 833, 755 cm^{-1} . **EI-HRMS** calculated for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_4$ 386.2206 found 386.2219.

(R)-(+)-1,2 Bis-(tert-butoxycarbonylamino)-3-butene (6)

A mixture of (R)-(-)-*N*¹,*N*²-Bis-(2,4-dimethoxybenzyl)-but-3-ene-1,2-diamine (1.77 g, 4.59 mmol) and TsOH-H₂O (6.98 g, 36.7 mmol) in toluene (13 mL) was stirred at 110°C in a sealed tube under argon for 7 h to afford a biphasic deep purple mixture. The mixture was cooled to room temperature and diluted with methanol (63 mL) and Et₃N (7 mL). Di-tert-butyl-dicarbonate (5.0 g, 23 mmol) was added to the resulting tan mixture. The mixture was stirred at ambient temperature for 45 min and at 60°C for 2.5 h. The mixture was cooled to room temperature, and approximately 90% of the solvent was removed *in vacuo*. The brown concentrate was suspended in ethyl acetate (170 mL) and washed with 3x50 mL 0.5M pH=5 phosphate buffer, 2x50 mL aqueous and saturated NaHCO₃, 1x50 mL brine, dried with Na₂SO₄, filtered, and concentrated to a tan solid. Purification by silica gel chromatography (30% ethyl acetate in petroleum ether) and recrystallization from hot heptane afforded diamine **6** as thin white needles (730 mg, 56%). **Mp** = 116-118°C. $[\alpha]_D^{24.9} = +26.2^\circ$ (c=1.09 in CDCl₃). ¹H NMR (DMSO-d₆, 80°C, 300 MHz) δ 6.40 (bs, 2H), 5.74 (ddd, *J*=17.1, 10.5, 6.0 Hz, 1H), 5.11 (dt, *J*=17.1, 1.8 Hz, 1H), 5.05 (dt, *J*=10.5, 1.2 Hz, 1H), 4.05 (q, *J*=6.6 Hz, 1H), 3.00-3.06 (m, 2H), 1.40 (s, 9H), 1.39 (s, 9H). ¹³C NMR (DMSO-d₆, 80°C, 75 MHz) δ 155.29, 154.63, 137.09, 114.56, 77.39, 52.66, 43.60, 27.83. **IR** (KBr-neat) 3362, 2986, 2937, 1686 (s), 1531 (s), 1447, 1390, 1367, 1310, 1274, 1251, 1225, 1170, 1041, 1016, 994, 920, 882 cm⁻¹. **EA** calculated for C₁₄H₂₆N₂O₄ C: 58.72, H: 9.15 found C: 58.80, H: 9.30.

Diastereoselective Epoxidation of Olefin 6:

A mixture of olefin **6** (1.63 g, 5.70 mmol), purified mCPBA⁷ (4.92 g, 28.5 mmol) and NaHCO₃ (2.40 g, 28.5 mmol) in anhydrous CH₂Cl₂ (100 mL) was stirred at reflux for 5 h at which point all starting material was consumed by TLC. The reaction was cooled to room temperature and diluted with a solution of 1M Na₂SO₃ (40 mL) and saturated NaHCO₃ (40 mL). After stirring the bubbling mixture room temperature for 1/2 h, it was extracted with 1x100 mL CH₂Cl₂. The organic extract was washed with 1x100 mL (50 mL 1M Na₂SO₃, 50 mL saturated NaHCO₃), 1x100 mL (75 mL saturated NaHCO₃, 25 mL brine), 1x100 mL brine, dried with Na₂SO₄, filtered, and concentrated to a white solid. Crude ¹H NMR analysis (CDCl₃, 55°C) showed a 4:1 diastereomeric ratio in favor diastereomer **7**. Purification by silica gel chromatography (30% ethyl acetate in petroleum ether) provided the diastereomeric epoxides in a combined 84% yield.

⁷ Perrin, D.D.; Armarego, L.F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Elmsford, NY, 1988, pg 123.

(2S,3R)-(+)-1,2-Bis-(tert-Butoxycarbonylamino)-3,4-epoxy-but-3 ene (threo epoxide) (7) White powder (1.15 g, 67%). **Mp** = 135-140°C. $[\alpha]_D^{23.2} = +16.6^\circ$ ($c=0.82$ in CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 55°C, 500 MHz) δ 4.81 (s, 1H), 4.62 (s, 1H), 3.96 (m, 1H), 3.30-3.41 (m, 2H), 3.06 (dt, $J=4.0, 2.6$ Hz, 1H), 2.72 (dd, $J=4.8, 4.0$ Hz, 1H), 2.59 (dd, $J=4.8, 2.7$ Hz, 1H), 1.45 (s, 9H), 1.43 (s, 9H). $^{13}\text{C NMR}$ (CDCl_3 , 50°C, 75 MHz) δ 156.20, 155.84, 79.87, 79.65, 51.80, 50.01, 43.66, 43.42, 28.37, 28.33. **IR** (KBr-neat) 3356, 2987, 2940, 1685 (s), 1528, 1459, 1392, 1369, 1318, 1276, 1249, 1223, 1161, 1018, 872 cm^{-1} . **EI-HRMS** $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_5$ (M^+), calculated for ($\text{M}-\text{C}_4\text{H}_9$) $^+$ 245.1137 found 245.1165, calculated for ($\text{M}-\text{C}_4\text{H}_9\text{O}$) $^+$ 229.1188 found 229.1188. **ESI-MS** calculated for $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_5$ 302.2 found ($\text{M}+\text{Na}$) $^+$ 325.2. **EA** calculated for $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_5$: C: 55.61 and H: 8.67 found C: 55.49 and H: 8.45.

(2S,3S)-(+)-1,2-Bis-(tert-Butoxycarbonylamino)-3,4-epoxy-but-3 ene (erythro epoxide) (8) White solid (295 mg, 17%). **Mp** = 99-102°C. $[\alpha]_D^{22.7} = +10.8^\circ$ ($c=0.622$ in CHCl_3). $^1\text{H NMR}$ ($\text{DMSO}-d_6$, 80°C, 500 MHz) δ 6.44 (bs, 1H), 6.35 (bs, 1H), 3.35-3.41 (m, 1H), 3.07-3.18 (m, 2H), 2.86 (dt, $J=6.2, 3.3$ Hz, 1H), 2.64 (t, $J=4.6$ Hz, 1H), 2.59 (dd, $J=5.2, 2.6$ Hz, 1H), 1.40 (s, 9H), 1.39 (s, 9H). $^{13}\text{C NMR}$ ($\text{DMSO}-d_6$, 80°C, 125 MHz) δ 155.35, 154.82, 77.63, 77.49, 51.83, 51.25, 43.94, 41.40, 27.81, 27.78. **IR** (KBr-neat) 3366, 2983, 2937, 1689 (s), 1532, 1459, 1392, 1369, 1345, 1316, 1252, 1164, 1043, 868 cm^{-1} . **EI-HRMS** $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_5$ (M^+), calculated for ($\text{M}-\text{C}_4\text{H}_9\text{O}$) $^+$ 229.1188 found 229.1191. **ESI-MS** calculated for $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_5$ 302.2 found ($\text{M}+\text{H}$) $^+$ 303.1 and ($\text{M}+\text{Na}$) $^+$ 325.2. **EA** calculated for $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_5$: C: 55.61 and H: 8.67 found C: 55.80 and H: 8.53.

Trideca-6,8-dien-1-ol (10)

This cross coupling was performed by a modified procedure published by Negishi *et. al.*⁸ A suspension of $\text{Cp}_2\text{ZrHCl}^9$ (24 g, 94 mmol) and alkyne **8** (18.1 g, 92.3 mmol) in anhydrous THF (450 mL) was stirred under N_2 shielded from light for 1h to afford a deep green solution. To a separate suspension of $\text{PdCl}_2(\text{PhCN})_2$ (1.06 g, 2.77 mmol) and 1,1'-bis-(diphenylphosphino) ferrocene (3.07 g, 5.54 mmol) in anhydrous THF (50 mL) was added DIBAL-H (1M in hexanes, 5.5 mL, 5.5 mmol) under N_2 to afford a deep brown-red solution. After stirring the catalyst solution for 15 minutes, vinyl iodide **9** (20.4 g, 97 mmol) was added to the above catalyst solution. The vinyl iodide and catalyst solution was cannulated to the above hydrozirconated solution. The reaction was stirred under N_2 shielded from light for 22h. The reaction solution was diluted with petroleum ether (200 mL) and passed through a neutral alumina plug (eluting with a further 600 mL of 20% Et_2O in petroleum ether). The filtrate was concentrated to an oily brown solid. The solid was suspended in 300mL of 10% Et_2O in petroleum ether, filtered through celite, and

⁸ Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D.E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393-2401.

⁹ The Schwartz's reagent was purchased from Aldrich and used without further purification.

concentrated to the THP adduct of alcohol **10** as a red oil. A solution of the above red oil and TsOH-H₂O (880 mg, 4.6 mmol) in methanol (300 mL) was stirred at room temperature for 1.25 h at which point only trace THP protected alcohol remained by TLC. The reaction was quenched with Et₃N (1.3 mL) and concentrated to a brown oil. The brown oil was purified by silica gel chromatography (30% Et₂O in petroleum ether) to afford the intended alcohol **10** as a clear and slightly yellow oil (14.7 g, 82%). ¹H NMR (CDCl₃ 500 MHz) δ 5.92-6.02 (m, 2H), 5.48-5.60 (m, 2H), 3.64 (dd, *J*=10.5, 6 Hz, 2H), 2.04 (quintet, *J*=7.5 Hz, 4H), 1.50-1.60 (m, 3H), 1.20-1.42 (m, 8H), 0.89 (t, *J*=7.0 Hz, 3H). ¹³C NMR (CDCl₃ 100 MHz) δ 132.57, 131.92, 130.54, 130.19, 62.92, 32.60, 32.49, 32.24, 31.53, 29.16, 25.26, 22.21, 13.91. IR (KBr –Neat) 3346, 3014, 2956, 2928, 1461, 1378, 1054, 986, 729 cm⁻¹. EA calculated for C₁₃H₂₄O: C: 79.53; H: 12.32 found C: 79.70; H: 12.46.

Trideca-6,8-dienal

Anhydrous DMSO (9.15 mL, 129 mmol) was added dropwise to a anhydrous solution of methylene chloride (300 mL) and oxalyl chloride (6.35 mL, 73 mmol) under nitrogen at -78°C. After stirring the solution for 15min, alcohol **10** (11.0 g, 56.0 mmol) dissolved in anhydrous methylene chloride (200 mL) was cannulated to the above solution at -78°C. The solution was stirred at -78°C for 30min. At which point, Et₃N (39 mL, 280 mmol) was added dropwise to the above mixture at -78°C. The resulting white mixture was stirred for 2h allowing the reaction to warm to room temperature. The resulting yellow-white mixture was diluted with ether (500 mL), washed with 2x250 mL 0.5M pH = 5 phosphate buffer, 2x200 mL saturated NaHCO₃, 1x150 mL brine, dried with Na₂SO₄, filtered, and concentrated *in vacuo* to a yellow-brown oil. The product aldehyde was isolated as a yellow oil (9.75 g, 89%) after silica gel chromatography (7.5% Et₂O in petroleum ether). ¹H NMR (CDCl₃ 400 MHz) δ 9.76 (t, *J*=1.6 Hz, 1H), 5.95-6.02 (m, 2H), 5.48-5.60 (m, 2H), 2.43 (dt, *J*=7.6, 2.0 Hz, 2H), 2.02-2.12 (m, 4H), 1.58-1.68 (m, 2H), 1.26-1.46 (m, 6H), 0.89 (t, *J*=7.2 Hz, 3H). ¹³C NMR (CDCl₃ 100 MHz) δ 202.55, 132.79, 131.11, 130.90, 130.04, 43.67, 32.19, 32.16, 31.46, 28.77, 22.16, 21.49, 13.87. IR (KBr –Neat) 3014, 2957, 2928, 2858, 2717, 1727 (s), 1460, 988 cm⁻¹. EI- HRMS calculated for C₁₃H₂₂O 194.1671 found 194.1668.

Tetradeca-7,9-dien-1-yne (**11**)

The Ohira-Bestmann reagent¹⁰ (3.71 g, 19.3 mmol) was slowly added to an anhydrous mixture of trideca-6,8-dienal (1.50 g, 7.73 mmol) and K₂CO₃ (3.20 g, 23.2 mmol) in methanol (100 mL) at 0°C under nitrogen. The mixture was stirred under nitrogen for 2 h allowing the reaction to warm to room temperature. At 2 h, all aldehyde was consumed by TLC. The mixture was diluted with ether (500 mL), washed with 1x200 mL water, 1x100 mL brine, dried with MgSO₄, filtered, and concentrated to an orange heterogeneous oil. The intended alkyne **11** was isolated as a clear colorless oil (1.43g, 97%) in >98% purity after silica gel chromatography (100% pentane). ¹H NMR (CDCl₃ 400 MHz) δ 5.94-6.05 (m, 2H), 5.49-5.62 (m, 2H), 2.19 (dt, *J*=7.2, 1.2 Hz, 2H),

¹⁰ a) Muller, S.; Liepold, B.; Roth, B.; Bestmann, H.J. *Synlett*. **1996**, 521-522. b) Xu, Z.; Peng, Y.; Ye, T. *Org. Lett.* **2003**, 5(16), 2821-2824.

CC(C)(C)OC(=O)N[C@H](C[C@@H](O)C#CCCCC/C=C/C/C=C\CCCC)C(=O)NOC(C)(C)C

n-Butyllithium (2.48M in hexanes, 1.04 mL, 2.58 mmol) was added dropwise to an anhydrous solution of alkyne **11** (492 mg, 2.6 mmol) in toluene (35 mL) under nitrogen at -25°C. The solution was stirred at -20°C for 20min. The solution was allowed to warm to 0°C and stirred at 0°C for an additional 5min. At which point, Me₂AlCl (1M in hexanes, 2.6 mL, 2.6 mmol) was added to the above thick solution at 0°C. The resulting white cloudy solution was stirred at 0°C for 1 h. This solution at 0°C was cannulated to an anhydrous solution of epoxide **7** (252 mg, 0.834 mmol) in toluene (35 mL) cooled to 0°C under nitrogen. The cloudy white solution was then stirred at 0°C for 2.75 h. A saturated aqueous solution of NaF (4.0 mL) was added to the above reaction at 0°C, and the resulting mixture was stirred for _ h allowing the mixture to warm to room temperature. The mixture was diluted with methylene chloride (100 mL), dried with Na₂SO₄, filtered, and concentrated to approximately 1/2 of the volume of the original toluene solution. This solution was directly subjected to silica gel chromatography (20% ethyl acetate in petroleum ether until the toluene solvent eluted than 25% ethyl acetate in petroleum ether) to isolate the intended alcohol **12** as a yellow oil (375 mg, 91%). [α]_D^{23.1} = +1.1 (c=0.90 in CHCl₃). ¹H NMR (CDCl₃ 500 MHz) _ 5.96-6.03 (m, 2H), 5.51-5.60 (m, 2H), 4.91 (s, 1H), 4.85 (s, 1H), 3.76-3.82 (m, 1H), 3.65-3.70 (m, 1H), 3.34 (dt, J=14.8, 7.5 Hz, 1H), 3.30 (s, 1H), 3.17-3.23 (m, 1H), 2.42 (ddt, J=16.4, 7.4, 2.3 Hz, 1H), 2.35 (ddt, J=16.6, 6.2, 2.3 Hz, 1H), 2.13-2.17 (m, 2H), 2.02-2.09 (m, 4H), 1.43-1.50 (m, 22H), 1.24-1.37 (m, 4H), 0.89 (t, J=7.1 Hz, 3H). ¹³C NMR (CDCl₃ 125 MHz) _ 157.15, 156.19, 132.42, 131.56, 130.75, 130.31, 82.56, 79.79, 79.47, 76.09, 69.39, 53.48, 42.29, 32.12, 31.94, 31.54, 28.58, 28.41, 28.34, 24.23, 22.13, 18.60, 13.75. IR (KBr –Neat) 3361, 2978, 2931, 1692 (s), 1514, 1454, 1392, 1367, 1311, 1251, 1169, 1055, 988, 758 cm⁻¹. EI-HRMS calculated for C₂₈H₄₈N₂O₅ 492.3563 found 492.3540. EA calculated for C₂₈H₄₈N₂O₅: C: 68.26; H: 9.82 found C: 67.90; H: 9.93.

O-(tert-Butyl-dimethylsilyl)-Pseudodistomin D (13)

2: 3-(tert-Butyl-dimethylsilyloxy)-octadeca-11,13-dien-5-yn-1,2-diamine: An anhydrous solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (77 μ L, 89 mg, 34 μ mol) and 2,6-lutidine (42 μ L, 39 mg, 36 μ mol) in anhydrous methylene chloride

(2 mL) was cannulated to an anhydrous solution of protected diamine **12** (22 mg, 45 μ mol) in methylene chloride (2 mL) under nitrogen. The homogenous and colorless solution was stirred in a sealed tube for 2 h at 40°C. The reaction was cooled to room temperature, and the solvent was removed *in vacuo*. The oily mixture was taken up in a solution of methanol (3 mL), THF (1 mL), H₂O (0.5 mL) and acetic acid (60 μ L). The solution was stirred in a sealed tube for 2 h at 50°C. The reaction was concentrated *in vacuo* to an oily solid. The material was suspended in 1M NaOH (15 mL) and brine (15 mL). This suspension was extracted with 3x15 mL methylene chloride. The organic portion was dried with Na₂SO₄, filtered, concentrated *in vacuo*, and further dried under high vacuum (0.5 torr) overnight to afford the protected diamine **2** as a slightly green oil. The material was isolated in approximately 95% purity by ¹H NMR analysis and used in the next step without further purification. ¹H NMR (CDCl₃ 500 MHz) δ 5.95-6.04 (m, 2H), 5.50-5.62 (m, 2H), 3.69-3.73 (m, 1H), 2.78-2.83 (m, 1H), 2.68 (dd, *J*=12.4, 4.3 Hz, 1H), 2.58 (dd, *J*=12.4, 8.8 Hz, 1H), 2.45 (ddt, *J*=16.3, 8.7, 2.2 Hz, 1H), 2.29 (ddt, *J*=16.5, 4.6, 2.1 Hz, 1H), 2.11-2.15 (m, 2H), 2.03-2.08 (m, 4H), 1.20-1.50 (m, 12H), 0.87-0.91 (m, 12H), 0.09 (s, 3H), 0.06 (s, 3H). ¹³C NMR (CDCl₃ 125 MHz) δ 132.62, 131.67, 130.61, 130.16, 82.32, 76.32, 72.56, 56.44, 46.35, 32.22, 31.99, 31.51, 28.55, 28.35, 25.76, 24.67, 22.20, 18.60, 17.96, 13.90, -4.28, -4.89.

An anhydrous suspension of diamine **2** (all material from above) and AgOTs (1.3 mg, 4.7 μ mol) in acetonitrile (2 mL) was stirred at 40°C under nitrogen in a sealed tube for 2 h. The resulting yellow homogenous solution was cooled to room temperature and diluted with a solution of methanol (2 mL), water (0.5 mL), THF (1 mL) and acetic acid (7 μ L, 7.3 mg, 0.12 mmol). After stirring for 10min, the above solution was treated with a solution of NaBH₃CN (80 mg, 1.3 mmol) in methanol (1 mL) to afford a deep tan heterogeneous mixture that was stirred at room temperature for 18 h. The mixture was concentrated *in vacuo* to a black oily residue. The residue was suspended in 1M NaOH (15 mL) and methylene chloride (5 mL). The mixture was vigorously stirred for $_\$ h, saturated with solid NaCl, diluted with brine (10 mL) and extracted with 3x20 mL methylene chloride. The organic extract was dried with Na₂SO₄, filtered, and concentrated *in vacuo* to a black oily residue. Purification by silica gel chromatography (4% NH₄OH aq. (30% NH₃ in water), 4% methanol in ethyl acetate) and high vacuum drying (0.5 torr) for 18h afforded protected piperidine **13** as a slightly yellow viscous oil (9.6 mg, 52% for two steps from **12**). [α]_D²⁵ = +15 (*c*=0.52 in CHCl₃). ¹H NMR (CD₃OD 500 MHz) δ 5.93-6.01 (m, 2H), 5.48-5.57 (m, 2H), 3.35 (ddd, *J*=10.9, 9.0, 4.7 Hz, 1H),

3.04 (dd, $J=12.2, 4.5$ Hz, 1H), 2.50-2.57 (m, 2H), 2.35 (dd, $J=12.1, 11.1$ Hz, 1H), 2.01-2.08 (m, 4H), 1.90 (ddd, $J=12.6, 4.6, 2.5$ Hz, 1H), 1.25-1.50 (m, 15H), 1.11 (quartet, $J=11.3$ Hz, 1H), 0.89-0.93 (m, 12H), 0.12 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (CD_3OD 125 MHz) δ 133.20, 133.01, 132.13, 131.99, 77.16, 56.80, 56.62, 51.35, 42.03, 37.18, 33.67, 33.47, 33.01, 30.60, 30.42, 27.05, 26.46, 23.43, 18.98, 14.43, -3.69, -4.33. **IR** (KBr –Neat) 2927, 2856, 1462, 1252, 1089, 986, 836, 775 cm^{-1} . **EI-HRMS** calculated for $\text{C}_{24}\text{H}_{48}\text{N}_2\text{OSi}$ 408.3536 found 408.3542.

Pseudodistomin D (1)

A solution of TBS protected alcohol **13** (9.2 mg, 23 μmol) and TBAF (1M in THF, 90 μL , 90 μmol) in THF (5 mL) was stirred for 20h at room temperature. The reaction was directly chromatographed through silica gel (10% NH_4OH (30% NH_3 in H_2O), 10% methanol in ethyl acetate) and concentrated overnight under high vacuum (0.5 torr) to afford pseudodistomin D **1** as a white gum (7 mg, 100%). $[\alpha]_{\text{D}}^{25} = +6$ ($c=0.2$ in MeOH) literature¹¹ ($[\alpha]_{\text{D}}^{25} = +5$ ($c=0.26$ in MeOH)). ^1H NMR (CD_3OD 500 MHz) δ 5.93-6.01 (m, 2H), 5.47-5.56 (m, 2H), 3.24 (ddd, $J=11.2, 9.3, 4.6$ Hz, 1H), 3.07 (dd, $J=12.2, 4.5$ Hz, 1H), 2.52-2.58 (m, 2H), 2.35 (dd, $J=12.1, 11.1$ Hz, 1H), 2.02-2.08 (m, 4H), 1.98 (ddd, $J=12.7, 4.7, 2.5$ Hz, 1H), 1.27-1.47 (m, 12H), 1.09 (ddd, $J=11.4, 11.4, 11.4$ Hz, 1H), 0.90 (t, $J=7.1$ Hz, 3H). ^{13}C NMR (CD_3OD 125 MHz) δ 133.21, 132.99, 132.12, 131.97, 74.99, 56.80, 56.32, 51.39, 41.20, 37.15, 33.66, 33.47, 33.00, 30.61, 30.44, 27.02, 23.42, 14.42. **IR** (KBr – neat) 3282, 3013, 2925, 2853, 1560-1598, 1465, 984 cm^{-1} . ^1H , ^{13}C NMR, and IR data correlates with the listed chemical shifts and coupling constants reported for the isolated material.¹¹

Table SI 1: ^1H NMR correlation between the synthetic and natural Pseudodistomin D

carbon	Isolated			Synthetic ^b			Difference in shift ^c
	Lit. ^a	Mult.	coupling		Mult.	coupling	
2	2.5	m		2.52	m		-0.02
3	1.96	ddd	4.6,4.6,12.1	1.98		2.5,4.7,12.7	-0.02
	1.07	ddd	11.1,11.3,12.1	1.09		11.4,11.4,11.4	-0.02
4	3.2	ddd	4.6,9.5,11.1	3.24		4.6,9.3,11.2	-0.04
5	2.5	m		2.52	m		-0.02
6	3.04	ddd	4.5,12.1	3.07		4.5,12.2	-0.03
	2.31	ddd	10.9,12.1	2.35		11.1,12.1	-0.04
1'	1.35	m		1.35			0
2'	1.35	m		1.35			0
3'	1.35	m		1.35			0
4'	1.35	m		1.35			0
5'	2.04	dt	7.0, 7.1	2.02	m		0.02
6'	5.53	dm	14.4	5.49	m		0.04
7'	5.96	dm	14.4	5.94	m		0.02
8'	5.96	dm	14.4	5.94	m		0.02

¹¹ Freyer, A.J.; Patil, A.D.; Killmer, L.; Troupe, N.; Mentzer, M.; Carte, B.; Faucette, L.; Johnson, R.K. *J. Nat. Prod.* **1997**, *60*, 986-990.

9'	5.53	dm	14.4	5.49	m	0.04
10'	2.04	dt	7.0,7.1	2.02	m	0.02
11'	1.35	m		1.35		0
12'	1.35	m		1.35		0
13'	0.9	t	7.1	0.9	t	7.1

^a Proton NMR chemical analysis of the isolated Pseudodistomin D as reported by Freyer *et. al.* at 400 Mhz in CD₃OD.¹¹ ^b 500 Mhz in CD₃OD. ^c Difference in chemical shift between the isolated and synthetic pseudodistomin D.

Table SI 2: ¹³ C NMR correlation between the synthetic and natural Pseudodistomin D

carbon	Isolated ^a	Synthetic ^b	Difference ^c
2	56.7	56.8	-0.1
3	41.2	41.2	0
4	75.5	75	0.5
5	56.4	56.3	0.1
6	51.9	51.4	0.5
1'	37.2	37.2	0
10'	33.5	33.6	-0.1
11'	32.8	33	-0.2
12'	23.3	23.4	-0.1
13'	14.3	14.4	-0.1
2'	26.9	27	-0.1
3'	30.3	30.4	-0.1
4'	30.5	30.6	-0.1
5'	33.3	33.5	-0.2
6'	132.9	133	-0.1
7'	132	132.1	-0.1
8'	131.8	132	-0.2
9'	133.1	133.2	-0.1

^a Proton NMR chemical analysis of the isolated Pseudodistomin D as reported by Freyer *et. al.* in CD₃OD at 100 Mhz.¹¹ ^b 125 Mhz in CD₃OD. ^c Difference in chemical shift between the isolated and synthetic pseudodistomin D.