Supporting Information
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Supporting Information

Toward a new palmerolide assembly strategy: synthesis of C16-C24

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General Methods. All non-aqueous reactions were carried out under an inert atmosphere of nitrogen in oven-dried glassware. Air and moisture sensitive liquid reagents were added via a dry syringe or cannula. THF was dried over distilled sodium/benzophenone ketyl. Methylene chloride was distilled from CaH₂. All other solvents and reagents were used as obtained from commercial sources without further purification. Flash column chromatography was performed using EM Science silica gel 60 (43-60 micron mesh). Analytical and preparative thin layer chromatography (TLC) were performed on EM Science silica gel 60 F₂₅₄ plates. ¹H and ¹³C NMR spectral data were recorded in a Bruker 400 or 600 MHz spectrometer using CDCl₃ as a solvent. The chemical shifts are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (0.0 ppm) for ¹H NMR and CDCl₃ (77.0 ppm) for ¹³C NMR. Infrared spectral data were obtained using a Perkin-Elmer Spectrum 100 FT-IR spectrometer with diamond ATR accessory as thin film. All optical rotation data was recorded at 25 °C on a Jasco P-2000 polarimeter with a 100 mm cell (concentration reported as g/100 mL).

Experimental Procedures

![Chemical Structure](image)

Ether 6. THF (8 mL) and iodide 5 (300 mg, 1.06 mmol) were added to flame dried ZnCl₂ (144 mg, 1.06 mmol). The mixture was cooled to -78 °C and stirred for 15 min at -78 °C. tBuLi (1.7 M, 1.6 mL, 2.64 mmol) was added dropwise over 5 min and stirred for an additional 10 min at -78 °C. The yellow solution was then warmed to rt and then added dropwise via
cannula to a flask containing Pd(PPh₃)₄ (61 mg, 52.8 umol) and bromide 4 (411 mg, 1.06 mmol) in THF (2 mL) at rt. The reaction was stirred overnight at rt. Et₂O (10 mL) and H₂O (10 mL) were added to the reaction mixture and the mixture was extracted with Et₂O (3 X 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (10:90 Et₂O/pentanes) to yield olefin 6 as a colorless oil (356 mg, 72%). [α]D²⁵ = 1.44 (c = 0.26, CH₂Cl₂) IR (thin film) 3071, 2931, 2856, 1668, 1589, 1473, 1428, 1111, 1032, 911, 821 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.68-7.70 (m, 8H), 7.35-7.43 (m, 12H), 5.39 (t, J = 6.2 Hz, 2H), 4.54-4.56 (m, 2H), 4.22 (d, J = 6.2 Hz, 4H), 3.83-3.88 (m, 2H), 3.57-3.60 (m, 1H), 3.47-3.51 (m, 3H), 3.20-3.24 (m, 1H), 3.13-3.17 (m, 1H), 2.15-2.20 (m, 1H), 2.08-2.12 (m, 1H), 1.67-1.94 (m, 8H), 1.50-1.62 (m, 9H), 1.43 (s, 6H), 1.04 (s, 18H), 0.89 (d, J = 6.0 Hz, 3H), 0.88 (d, J = 5.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 135.6, 135.5, 135.4, 134.1, 129.5, 127.6, 125.8, 99.1, 98.8, 72.9, 72.8, 62.2, 62.1, 61.1, 44.1, 44.0, 31.5, 31.4, 30.8, 30.7, 19.6, 19.5, 19.2, 17.1, 17.0, 16.2, 16.1. HRMS (ESI): calcd for C₂₉H₄₂O₃SiNa [M+Na+] 489.2800, found 489.2797.

Alcohol 7. Added TsOH (244 mg, 1.286 mmol) to ether 6 (200 mg, 0.429 mmol) in isopropanol (10 mL) at 0 °C. Let stir until all the solids had dissolved and mixture was warmed to rt and stirred for an additional 2 h. Triethylamine (0.5 mL) was added and the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (20:80 Et₂O/pentanes) to yield alcohol 7 as a colorless oil (139 mg, 85%). [α]D²⁵ = 3.77 (c = 0.29, CH₂Cl₂) IR (thin film) 3366 (br), 3071, 2930, 2857, 1667, 1590, 1472, 1428, 1110, 1038,
736, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.67-7.70 (m, 4H), 7.35-7.42 (m, 8H), 5.42 (t, 1H), 4.22 (d, J = 6.2 Hz, 2H), 3.38-3.49 (m, 2H), 2.03-2.11 (m, 1H), 1.74-1.85 (m, 2H), 1.45 (s, 3H), 1.04 (s, 9H), 0.86 (d, J = 6.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 136.1, 135.8, 134.2, 129.7, 127.8, 126.0, 68.5, 61.1, 44.2, 33.8, 27.0, 19.3, 16.8, 16.4. HRMS (ESI): calcd for C₂₄H₃₄O₂SiNa [M+Na⁺] 405.2225, found 405.2216.

**Aldehyde 8.** Added Dess-Martin reagent (1660 mg, 3.92 mmol) to alcohol (750 mg, 1.96 mmol) in CH₂Cl₂ (40 mL) at 0 °C. Let stir until all the solids had dissolved and H₂O (22 uL, 1.25 mmol) was added. The reaction mixture was warmed to rt and stirred for 30 min. The reaction was poured into a column with silica gel and purified by flash chromatography (15:85 ethyl acetate/hexanes) to yield aldehyde 8 as a colorless oil (694 mg, 93%). Aldehyde 8 was immediately used in the next reaction. IR (thin film) 3072, 2960, 2930, 2857, 2711, 1726, 1428, 1111, 1046, 823, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.60 (s, 1H), 7.67-7.70 (m, 4H), 7.35-7.42 (m, 6H), 5.50-5.45 (m, 1H), 4.22 (d, J = 6.2 Hz, 2H), 2.38-2.52 (m, 2H), 1.96 (dd, J = 13.4 Hz, J = 7.8 Hz, 1H), 1.43 (s, 3H), 1.05 (s, 9H), 1.02 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 204.9, 135.7, 134.1, 134.0, 133.6, 129.7, 127.8, 127.2, 61.1, 44.4, 40.6, 26.9, 19.3, 16.3, 13.3. HRMS (ESI): calcd for C₂₄H₃₂O₂SiNa [M+Na⁺] 403.2069, found 403.2075.
**Homopropargyl alcohol 9.** An oven-dried 50 mL round bottom flask cooled under nitrogen was charged with (1R, 2S)-(-)-2-amino-1,2-diphenylethanol (844 mg, 3.94 mmol), indium powder (452 mg, 3.94 mmol) and THF (30 mL). The flask was purged with nitrogen and pyridine (0.28 μL, 3.94 mmol) and propargyl bromide (0.47 μL, 3.94 mmol) were added to the flask. After stirring for 35 minutes at room temperature the flask was cooled to -78 °C and aldehyde 8 (500 mg, 1.31 mmol) was added dropwise. The reaction was allowed to warm to room temperature slowly overnight. After 16-20 h the reaction was quenched with HCl 1M (15 mL) and extracted with hexane/ethyl ether 1:1 (2 x 15 mL). The combined organic layers were washed with HCl 1M, H2O and brine, dried over Na2SO4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (15:85 EtOAc/hexanes) to yield homopropargyl alcohol 9 as a colorless oil in a mixture of diastereomers (96:4 determined by 1H NMR) (553 mg, 93%). (1R, 2S)-(-)-2-amino-1,2-diphenylethanol was recovered by acid/base extraction in 94% yield. [α]D25 = 10.8 (c = 0.14, CH2Cl2) IR (thin film) 3308, 3072, 2960, 2931, 2857, 1472, 1462, 1428, 1383, 1111, 1045, 823, 738, 700 cm⁻¹; 1H NMR (400 MHz, CDCl3) (major diastereomer) δ 7.67-7.71 (m, 4H), 7.35-7.42 (m, 6H), 5.41 (t, J = 6.0 Hz, 1H), 4.23 (d, J = 6.0 Hz, 2H), 3.60-3.67 (m, 1H), 2.32-2.44 (m, 2H), 2.08-2.16 (m, 1H), 2.02-2.04 (m, 1H), 1.81-1.87 (m, 2H), 1.42 (s, 3H), 1.04 (s, 9H), 0.85 (d, J = 5.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 135.9, 135.5, 134.4, 134.3, 129.8, 127.9, 126.7, 81.6, 72.7, 70.8, 61.3, 43.8, 35.1, 27.1, 25.2, 19.5, 16.3, 13.5. HRMS (ESI): calcd for C27H36O2SiNa [M+Na+] 443.2382, found 443.2404.

**Mosher ester analysis of homopropargyl alcohol 9**
**S- and R-MTPA-esters from Mosher’s acid.** To a stirred solution of alcohol 9 (10 mg, 0.022 mmol), \( S(-)-\alpha\)-methoxy-\( \alpha\)-trifluoromethylphenylacetic acid (\( S(-)-\text{MTPA-OH} \)) (26 mg, 0.11 mmol), and \( N,N\)-dicyclohexylcarbodiimide (23 mg, 0.11 mmol) in \( \text{CH}_2\text{Cl}_2 \) (1mL), was added \( N,N\)-dimethylaminopyridine (13.5 mg, 0.11 mmol). The reaction was stirred at room temperature until consumption of the alcohol was observed by TLC analysis (20 h). The reaction was then filtered through Celite™ to remove most of the \( N,N\)-dicyclohexylurea. The crude oil containing \( S1 \) was passed through a plug of silica gel and used without further purification for NMR analysis. The same protocol was used to prepare the \( R\)-MTPA-ester of 9 with \( R(+)-\text{MTPA-OH} \) to give \( S2 \).

Stereochemistry assignment was confirmed based in Mosher, H. S. model.\(^1\)

Alcohol 12. To a solution of \([\text{Cp}_2\text{ZrCl}_2]\) (152 mg, 0.52 mmol) and trimethylaluminum 2M solution in hexanes (0.79 mL, 1.57 mmol) in CH\(_2\text{Cl}_2\) was added water dropwise (9 μL, 0.52 mmol) carefully at -23°C. After 10 minutes, alcohol 9 (100 mg, 0.26 mmol) was slowly added to the mixture. After stirring for 35 minutes at -23°C the reaction was quenched with water (0.5 mL). At this point K\(_2\text{CO}_3\) saturated solution was added (3.3 mL) and the mixture was allowed to warm to room temperature. The solution was extracted with CH\(_2\text{Cl}_2\) (3x) and the solvent
evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (15:85 EtOAc/hexanes) to yield alcohol 12 as a colorless oil (19 mg, 36%). $\left[\alpha\right]_D^{25} = -28.6$ (c = 0.82, CH$_2$Cl$_2$) IR (thin film) 3288 (br), 2928, 2872, 1494, 1451, 1374, 1275, 1028, 968, 745 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26-7.30 (m, 2H), 7.16-7.19 (m, 3H), 5.35-5.40 (m, 1H), 3.40-3.52 (m, 2H), 3.37 (d, $J = 7.3$ Hz, 2H), 2.10-2.16 (m, 1H), 1.84-1.88 (m, 2H), 1.72 (s, 3H), 0.88 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.8, 135.0, 128.6, 128.5, 126.0, 125.1, 68.6, 44.4, 34.5, 33.9, 16.9, 16.3. HRMS (EI): calcd for C$_{14}$H$_{20}$O [M+Na$^+$] 204.1514, found 204.1505.

Diol 13. To a solution of homopropargyl alcohol 9 (400 mg, 0.95 mmol) in 40 mL of THF was added dropwise tetrabutylammonium fluoride 1.0 M solution in THF (1.9 mL, 1.9 mmol) at room temperature. After 2 hours, the reaction was quenched with water. The solution was extracted with CH$_2$Cl$_2$ (3x) and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30:70 EtOAc/hexanes) to yield diol 13 as a colorless oil (173 mg, 100%). $\left[\alpha\right]_D^{25} = 13.2$ (c = 1.04, CH$_2$Cl$_2$) IR (thin film) 3303, 2965, 2918, 2118, 1667, 1430, 1381, 1266, 984 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 5.45 (t, $J = 6.5$ Hz, 1H), 4.12-4.20 (m, 2H), 3.65-3.70 (m, 1H), 2.33-2.44 (m, 2H), 2.11 (m, 1 H), 2.05 (t, $J = 2.6$ Hz, 1H), 1.87-1.93 (m, 2H), 1.66 (s, 3H), 0.87 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 137.5, 125.6, 81.3, 72.1, 70.5, 59.2, 43.5, 34.6, 24.9, 15.9, 13.2. HRMS (ESI): calcd for C$_{11}$H$_{18}$O$_2$Na [M+Na$^+$] 205.1204, found 205.1198.
Vinyl iodide 14. Trimethylaluminum 2M solution in hexanes (1.65 mL, 3.31 mmol) was added water dropwise to a solution of \([\text{Cp}_2\text{ZrCl}_2]\) (321 mg, 1.10 mmol) in 5 mL of \(\text{CH}_2\text{Cl}_2\) at room temperature. After stirring for 15 minutes, a solution of homopropargyl alcohol 13 (100 mg, 0.55 mmol) in 0.5 mL of \(\text{CH}_2\text{Cl}_2\) was added dropwise to the reaction mixture. The reaction was left stirring for 2 days at room temperature when iodine (280 mg, 1.10 mmol) in 5 mL of THF was added to the reaction mixture at -30°C. After 10 minutes, the reaction was allowed to warm to room temperature and let stirring for 1 hour. Then, a saturated solution of potassium sodium tartrate (400 mL) and 2 mL of MeOH were added to the yellow solution. After 2 hours stirring at room temperature, the solution was extracted with ethyl acetate (6x). The organic phase was washed with brine, dried using MgSO\(_4\) and evaporated under reduced pressure to give a mixture of vinyl iodides 14/15 in 8:2 ratio. The residue was purified by flash column chromatography on silica gel (30:70 EtOAc/hexanes) to yield vinyl iodide 14 as a colorless oil (107 mg, 60%).

**Vinyl iodide 14**: \([\alpha]_D^{25} = 17.8\) (c = 3.15, CH\(_2\)Cl\(_2\)) IR (thin film) 3350 (br), 2930, 1725, 1440, 1375, 1270, 1244, 1046, 981, 731 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.26-7.30 (m, 2H), 7.16-7.19 (m, 3H), 5.35-5.40 (m, 1H), 3.40-3.52 (m, 2H), 3.37 (d, \(J = 7.3\) Hz, 2H), 2.10-2.16 (m, 1H), 1.84-1.88 (m, 2H), 1.72 (s, 3H), 0.88 (d, \(J = 6.4\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 145.2, 137.5, 125.5, 70.9, 59.1, 44.7, 43.5, 35.3, 24.0, 16.0, 13.2. HRMS (EI): calcd for C\(_{12}\)H\(_{21}\)O\(_2\)I [M+] 324.0587, found 324.0578.
Vinyl iodide 15: $[\alpha]_D^{25} = 19.9$ (c = 0.16, CH$_2$Cl$_2$) IR (thin film) 3455 (br), 2960, 2929, 1456, 1377, 1271, 1143, 1048, 979, 760, 671 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26-7.30 (m, 2H), 7.16-7.19 (m, 3H), 5.35-5.40 (m, 1H), 3.40-3.52 (m, 2H), 3.37 (d, $J$ = 7.3 Hz, 2H), 2.10-2.16 (m, 1H), 1.84-1.88 (m, 2H), 1.72 (s, 3H), 0.88 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 145.4, 132.5, 128.7, 71.2, 44.8, 43.7, 35.5, 24.0, 21.2, 15.6, 14.3, 13.3. HRMS (EI): calcd for C$_{13}$H$_{23}$O$I$ [M+] 322.0800, found 322.0794.

Vinyl iodide 2. To a solution of vinyl iodide 14 (20 mg, 0.062 mmol) in 3 mL of CH$_2$Cl$_2$ was added imidazole (8 mg, 0.124 mmol) and TBSCl (11 mg, 0.074 mmol) at room temperature. The reaction mixture was stirred overnight and quenched with NH$_4$Cl. The solution was extracted with CH$_2$Cl$_2$ (3x) and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5:95 EtOAc/hexanes) to yield vinyl iodide 2 as a colorless oil (23 mg, 85%). $[\alpha]_D^{25} = 15.9$ (c = 5.32, CH$_2$Cl$_2$) IR (thin film) 3467 (br), 2954, 2928, 2856, 1462, 1379, 1252, 1050, 832, 773, 666 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.00 (d, $J$ = 7.3 Hz, 1H), 5.32-5.36 (m, 1H), 4.19 (d, $J$ = 6.2 Hz, 2H), 3.62-3.68 (m, 1H), 2.28-2.40 (m, 2H), 2.12-2.20 (m, 1H), 1.86 (d, $J$ = 0.9 Hz, 3H), 1.68-1.78 (m, 2H), 1.60 (s, 3H), 1.47 (d, $J$ = 4.1 Hz, 2H), 0.89 (s, 9H), 0.84 (d, $J$ = 6.8 Hz, 3H), 0.06 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 145.4, 132.5, 128.7, 71.2, 44.8, 43.7, 35.5, 24.0, 21.2, 15.6, 14.3, 13.3. HRMS (EI): calcd for C$_{13}$H$_{23}$O$I$ [M+] 322.0800, found 322.0794.
MHz, CDCl₃) δ 145.3, 135.1, 126.6, 71.3, 60.1, 44.7, 43.5, 35.5, 25.9, 24.0, 18.4, 16.1, 13.3, -
