Total Synthesis of (+)-Vigulariol and (−)-Sclerophytin A

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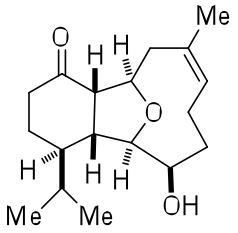
Supporting Information

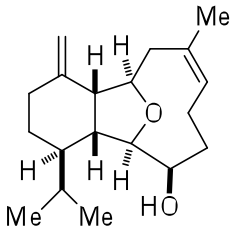
Experimental Procedures

General Materials and Methods. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Nuclear magnetic resonance (^{1}H, ^{13}C) spectra were recorded on Bruker model DRX 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz), Bruker model DRX 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz) and Bruker 600 (^{1}H at 600 MHz; ^{13}C at 150 MHz) instruments. Chemical shifts are reported relative to chloroform (δ 7.26) for ^{1}H NMR spectra and chloroform (δ 77.23) for ^{13}C NMR spectra. ^{1}H NMR multiplicity data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent, and coupling constants are reported in Hertz (Hz). Optical rotations were determined using a Jasco P1010 polarimeter and concentrations are reported in g/100mL. Mass spectra were obtained using a Bruker BioTOF II mass spectrometer with electrospray ionization (ESI). Thin layer chromatography (TLC) was conducted on silica gel F254 TLC plates purchased from EMD Chemicals, Inc. Visualization was accomplished with UV and/or stained using a ceric ammonium molybdate solution followed by heating. Flash column chromatography was carried out using Ultra Pure Silica Gel Silia-P (40 to 63 μm) purchased from SiliCycle Inc. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), and toluene ($PhCH_3$) were dried by passage through a column of neutral alumina under argon immediately prior to use. Pyridine, 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU), and acetonitrile (CH_3CN) were distilled from calcium hydride immediately prior to use. Dess-Martin periodinane was prepared according to literature procedures and stored at –20 °C. All other reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions

were performed in flame-dried flasks under positive flow of argon and conducted under an argon atmosphere. Yield refers to analytically pure material unless otherwise noted. See Supporting Information of reference 19 in the paper for experimental procedures for compounds **4**, **5**, and **10-13**.

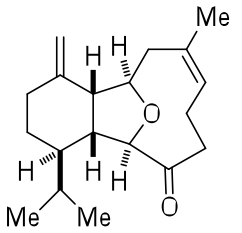


Olefin 14. Into a flask charged with terminal alkene **4** (9.0 mg, 0.031 mmol) dissolved in ethyl acetate (2 mL), was added Pt_2O (1 mg, ~ 0.1 equiv.) and placed under an atmosphere of H_2 using a H_2-filled balloon. The reaction was carefully monitored by TLC until the reaction was complete, approximately 40 minutes. The catalyst was filtered off through a Celite plug and washed with EtOAc (3×). The filtrate was concentrated and the residue purified by flash column chromatography (20% EtOAc/hexane) to yield olefin **14** as a white solid (8.0 mg, 89%): m.p. = 114–115 °C; $[\alpha]^{25}_D$ = +66.3 (c 0.53, $CHCl_3$); IR (film) 3445 (br), 2926, 1707 (str) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.51–1.58 (m, 2H), 1.73–2.02 (m, 9H), 2.30–2.42 (m, 3H), 2.78–2.94 (m, 4H), 3.77 (s, 1H), 4.14 (s, 1H), 4.44 (t, *J* = 2.8 Hz, 1H), 5.73 (dd, *J* = 6.0, 12 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 21.8, 23.4, 25.1, 28.4, 28.8, 31.9, 36.1, 38.2, 41.1, 46.7, 54.0, 73.1, 78.3, 86.7, 129.2, 134.1, 210.8; HRMS (ESI+) calcd for $C_{18}H_{29}O_3$ $[M + H]^+$ 293.2138, found 293.2117.



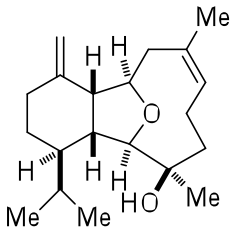
Diene 15. To a flask charged with methyltriphenylphosphonium bromide (1.85 g, 5.2 mmol) in anhydrous THF (10 mL) under argon, was added KO^{t}Bu (0.47 g, 4.16 mmol). The resulting yellow solution was stirred for 30 minutes at rt. Olefin **14** (303 mg, 1.04 mmol), dissolved in anhydrous THF (10 mL), was added dropwise to the ylide and the reaction was stirred an additional 3 hours. Upon completion, the reaction was quenched by addition of saturated aqueous NH_4Cl and diluted with Et_2O. The two layers were separated and the aqueous layer extracted with Et_2O (3×), the combined organic layers dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (15% EtOAc/hexane) to obtain the desired diene **15** as a white solid (297 mg, 99%): m.p. = 51–52 °C; $[\alpha]^{25}_D$ = +76.3 (c 0.27, $CHCl_3$); IR (film) 3453 (br), 2929, 1646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 1.04 (ddd, *J* = 3.3, 13.0, 25 Hz, 1H), 1.35 (tt, *J* = 2.5, 12.2 Hz, 1H), 1.68–1.77 (m, 2H), 1.87 (s, 3H), 1.90–2.05 (m, 4H), 2.12 (t, *J* = 16 Hz, 1H), 2.24–2.31 (m, 2H), 2.78– 2.93 (m, 3H), 3.11–3.24 (m, 1H), 3.59 (dd, *J* = 3.6, 10.5 Hz, 1H), 4.10–4.18 (m, 2H), 4.71 (s, 1H) 4.77 (s, 1H), 5.892 (dd, *J* = 3.9, 10.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 22.0, 25.6, 26.9, 29.1, 29.2, 31.6, 31.9, 34.8,

42.4, 47.2, 48.5, 74.2, 79.8, 87.8, 110.5, 129.3, 135.6, 146.9; HRMS (ESI+) calcd for $C_{19}H_{31}O_2$ $[M + H]^+$ 291.2346, found 291.2324.



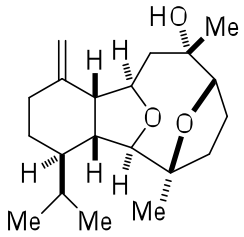
Ketone 3. To a flask charged with diene **15** (39 mg, 0.13 mmol), dissolved in anhydrous CH_2Cl_2 (4 mL) under argon and cooled to 0 °C, was added pyridine (53 μL, 0.65 mmol) and Dess-Martin periodinane (120 mg, 0.28 mmol). The ice-bath was removed and the reaction allowed to come to rt and stirred for 1 hour. The reaction was quenched by addition of a saturated solution of 5:1 $Na_2S_2O_3$:$NaHCO_3$ and the two layers were stirred until the CH_2Cl_2 layer was clear. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×), the combined organic layers washed with saturated aqueous $NaHCO_3$ (1×), brine (1×), dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (8% EtOAc/hexane) to obtain ketone **3** as white crystals (37 mg, 97%): m.p. = 64–65 °C; $[\alpha]^{25}_D$ = +1.5 (c 0.55, $CHCl_3$); IR (film) 2931, 1708 (str), 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.07 (ddd, *J* = 3.2, 13.0, 25 Hz, 1H), 1.36 (tt, *J* = 2.5, 12 Hz, 1H), 1.63–1.72 (m, 1H), 1.74–1.82 (m, 4H), 1.85 (dd, *J* = 3.6, 14.9 Hz, 1H), 2.11 (br t, *J* = 12.1 Hz, 2H), 2.27 (dt, *J* = 10.6, 13.6 Hz, 1H), 2.38–2.46 (m, 1H), 2.55 (app t, *J* = 9.2 Hz, 1H), 2.65 (dd, *J* = 6.6, 11.9 Hz, 1H), 2.83–2.90 (m, 2H), 3.32–3.42 (m, 1H), 4.18 (s, 1H), 4.26–4.29 (m, 1H), 4.73 (s, 1H), 4.79

(s, 1H), 5.54 (d, *J* = 5.7, 11.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 21.8, 25.6, 26.7, 28.1, 28.9, 31.7, 34.5, 41.1, 42.8, 45.5, 46.8, 82.9, 89.2, 111.0, 127.3, 133.6, 146.1, 213.5; HRMS (ESI+) calcd for $C_{19}H_{29}O_2$ $[M + H]^+$ 289.2189, found 289.2168.



Tertiary alcohol 16. To a flask charged with ketone **3** (93 mg, 0.32 mmol) in anhydrous THF (5 mL) cooled to 0 °C under argon, was added methylmagnesium bromide (0.9 mL, 3.0 M in THF, 2.6 mmol) dropwise. The reaction was stirred at 0 °C for 3.5 hours. Upon completion, the reaction was quenched by addition of saturated aqueous NH_4Cl and diluted with Et_2O. The two layers were separated and the aqueous layer extracted with Et_2O (2×). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography (7% EtOAc/hexane) to obtain tertiary alcohol **16** as a white solid (92 mg, 98%): m.p. = 91–92 °C; $[\alpha]^{25}_D$ = +82.2 (c 0.27, $CHCl_3$); IR (film) 3521, 2929, 1645 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.8 Hz, 3H), 0.93–1.09 (m, 7H), 1.31 (t, *J* = 12.1 Hz, 1H), 1.69–1.83 (m, 3H), 1.86–2.03 (m, 6H), 2.11 (br t, *J* = 13.5 Hz, 1H), 2.23 (dd, *J* = 6.8, 12 Hz, 1H), 2.28 (dt, *J* = 2.8, 13.6 Hz, 1H), 2.81–2.92 (m, 2H), 3.17–3.33 (m, 2H), 3.90 (s, 1H), 4.12 (dt, *J* = 2.9, 9.9 Hz, 1H), 4.69 (s, 1H), 4.76 (s, 1H), 5.88 (dd, J = 5.7, 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 22.0, 25.3, 27.7, 28.5, 28.7,

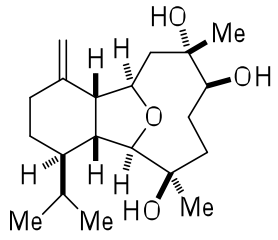
29.1, 31.6, 34.5, 38.9, 42.5, 47.1, 48.2, 75.4, 80.4, 91.4, 110.6, 128.7, 136.5, 146.9; HRMS (ESI+) calcd for $C_{20}H_{33}O_2$ $[M + H]^+$ 305.2502, found 305.2481.



(+)-Vigulariol (1). To a flask charged with tertiary alcohol **16** (9.0 mg, 0.03 mmol) in anhydrous CH_2Cl_2 (1 mL), cooled to 0 °C under Ar, was added *m*-CPBA (6 mg, 0.033 mmol). The reaction was stirred at 0 °C for one hour. Upon completion, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×), the combined organic layers washed with brine (1×), dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (30% EtOAc/hexane) to obtain vigulariol (**1**) as a white crystalline solid (4.0 mg, 57% brsm): m.p. = 138–139 °C; $[\alpha]^{25}_D$ = +3.1 (c 0.24, $CHCl_3$); $[\alpha]^{27}_{D\ lit.}$ = +3.6 (c 0.24, $CHCl_3$)[1]; IR (film) 3427, 2958, 2932, 1645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.9 Hz, 3H), 0.95–1.06 (m, 4H), 1.19 (s, 3H), 1.26 (app t, J = 10.3 Hz, 1H), 1.55, (s, 3H), 1.66–1.75 (m, 3H), 1.80 (app q, *J* = 9.9, 20 Hz, 1H), 1.87 (dd, *J* = 2.7, 15.1 Hz, 1H), 1.98–2.11 (m, 2H), 2.15–2.23 (m, 2H), 2.24–2.32 (m, 2H), 2.40–2.49 (m, 1H), 3.67 (s, 1H), 3.70 (t, *J* = 8.0 Hz, 1H), 4.05–4.13 (m, 2H), 4.72 (s, 1H), 4.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.4, 21.9, 23.9, 24.8, 27.9, 29.0, 31.2, 31.8, 38.4, 42.1, 42.9, 45.8, 47.5, 74.4,

[1] Su, J.-H.; Huang, H.-C.; Chao, C.-H.; Yan, L.-Y.; Wu, Y.-C.; Wu, C.-C.; Sheu, J.-H. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 877-879.

80.6, 85.7, 87.0, 90.0, 109.9, 147.9; HRMS (ESI+) calcd for $C_{20}H_{33}O_2$ $[M + H]^+$ 321.2451, found 321.2430.



(–)-Sclerophytin A (2). (Step 1) To a vial containing ketone **3** (11.0 mg, 0.038 mmol) in $CHCl_3$ (3.7 mL) at –12 °C, a precooled (0 °C) solution of *m*-chloroperoxybenzoic acid (75%, 24.0 mg, 0.080 mmol) was added dropwise via syringe. The mixture was stirred at –12 °C for 24 h. The reaction was quenched by the addition of dimethylsulfide (0.025 mL, 0.34 mmol) at –12 °C and stirred for 30 min at –12 °C. The mixture was diluted with $CHCl_3$ (1 mL) and quickly washed with saturated $NaHCO_3$ (3 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude mixture was passed through a short silica plug (5% EtOAc/hexanes → 10% EtOAc/hexanes) to provide 6.5 mg of a mixture of α- and β-expoxides **17**. **(Step 2)** To a vial containing α- and β-**17** (6.5 mg, 0.0213 mmol) in 1, 4-dioxane (0.5 mL), was added LiOH (20.2 mg, 0.482 mmol) and H_2O (0.5 mL). After disappearance of the α-epoxide as monitored by TLC, potassium hydrogensulfate (153 mg, 1.13 mmol) in water (0.5 mL) was added and the mixture was stirred for 15 min. Then scandium trifluoromethanesulfonate (12.2 mg, 0.0247 mmol) in acetonitrile (1.2 mL) was added and the mixture was stirred at rt for 4 h. The mixture was diluted water (2 mL) and $NaHCO_3$ (1 mL) and extracted with $CHCl_3$ (3 × 4 mL). The combined organic layers were dried over

$NaSO_4$, filtered, and concentrated. The crude mixture was passed through a short silica plug (25% EtOAc/hexanes → 50% EtOAc/hexanes) to provide 4.2 mg white solid hemiketal **18**. **(Step 3)** To a vial containing hemiketal **18** (4.2 mg, 0.0129 mmol) was added MeMgBr (3M in THF, 2.0 mL, 6.0 mmol). The mixture was warmed to 52 °C for 24 h, then cooled to 0 °C and treated with wet THF (prepared by washing THF with saturated NH_4Cl; 2 mL), and then saturated NH_4Cl (3 mL). The resulting solids were dissolved with water and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic layers were dried over $NaSO_4$, filtered, and concentrated. Purification via flash column chromatography (50% EtOAc/hexanes → 75% EtOAc/hexanes) afforded sclerophytin A **(2)** as a white solid (2.0 mg, 15% over 3 steps): $[\alpha]^{20}_D$ = – 3.0 (c 0.10, $CHCl_3$); $[\alpha]^{20}_{D\ lit.}$ = – 6.9 (c 0.087, $CHCl_3$)[2]; IR (film) 3386 (br), 1646 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.06 (ddd, *J* = 2.7, 12.3, 25.4 Hz, 1H), 1.16 (s, 3H), 1.20 (s, 3H), 1.24–1.31 (m, 1H), 1.67–2.07 (m, 8H), 2.16 (dd, *J* = 7.9, 10.0 Hz, 1H), 2.22–2.29 (m, 2H), 2.97 (t, *J* = 7.0 Hz, 1H), 3.63 (s, 1H), 4.10–4.15 (m, 1H), 4.57 (br s, 1H), 4.64 (s, 1H), 4.67 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.2, 22.3, 25.1, 29.3, 29.5, 30.5, 31.8, 40.2, 43.9, 45.4, 45.5, 53.2, 75.1, 78.3, 80.4, 90.7, 109.4, 148.1; HRMS (ESI+) calcd for $C_{20}H_{34}O_4$ [M + Cs]$^+$ 471.1511, found 471.1466.

[2] Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J. *Org. Lett.* **2001**, *3*, 135-137.