Total Synthesis of the Supposed Structure of (–)-Sclerophytin A and an Improved Route to (–)-7-Deacetoxyalcyonin Acetate

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Supporting Information

Experimental procedures and characterization data for the preparation of compounds 15, 16, 19, 25, and 2[1]

(1*R*,3*R*,3a*S*,7*R*,7a*R*)-7-Isopropyl-4-methyl-1-*Z*-[1-methyl-4-(triisopropylsiloxy)but-1-enyl]-3-[3-(trimethylsilyl)-prop-2-ynyl]-1,6,7,7a-tetrahydroisobenzofuran-3a-carbaldehyde (16). *p*-Toluenesulfonic acid monohydrate (0.057 g, 0.30 mmol) was added to a stirring mixture of diol **14** (0.91 g, 3.0 mmol), enal **13** (0.98 g, 3.6 mmol), $MgSO_4$ (0.40 g, 3.3 mmol), and CH_2Cl_2 (6.0 mL) at –78 °C. After 30 min, the mixture was warmed to –20 °C and stirred for 2 h before being quenched with saturated aqueous $NaHCO_3$ (20 mL) and warmed to room temperature. The aqueous layer was diluted with saturated aqueous $NaHCO_3$ (20 mL) and washed with CH_2Cl_2 (3 × 40 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (98:2 hexane-ethyl acetate) to afford 1.2 g (75%) of **15** (a mixture of 4 diastereomers) as a clear colorless oil:

[1] General experimental details have been described: Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210–9216.

diagnostic signals, ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.8, 98.9, 99.3, 100.0; HRMS (ES) *m/z* 581.3829 (M+Na, 581.3822 calcd for $C_{33}H_{58}NaO_3Si_2$).

A mixture of acetal **15** (1.2 g, 2.1 mmol), $MeNO_2$ (11 mL), and CH_2Cl_2 (11 mL) at –50 °C was treated dropwise with $SnCl_4$ (25 μL, 0.21 mmol). The resulting solution was stirred at –50 °C for 1.5 h before being quenched with saturated aqueous $NaHCO_3$ (20 mL) and warmed to room temperature. The aqueous layer was diluted with saturated aqueous $NaHCO_3$ (20 mL) and washed with CH_2Cl_2 (5 × 40 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by medium pressure liquid chromatography (Lobar pre-packed column, LiChroprep™ Si 60 silica gel; 98:2 hexane-ethyl acetate) to afford 1.0 g (88%) of **16** as a clear colorless oil: $[\alpha]^{23}_D$ +42.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1 H), 5.72 (br s, 1 H), 5.54 (t, *J* = 7.2 Hz, 1 H), 4.52 (d, *J* = 10.0 Hz, 1 H), 4.07 (t, *J* = 6.5 Hz, 1 H), 3.66 (t, *J* = 7.1 Hz, 2 H), 2.82 (dd, *J* = 10.0, 3.7 Hz, 1 H), 2.70 (d, *J* = 6.4 Hz, 2 H), 2.38–2.42 (m, 1 H), 2.26–2.30 (m, 1 H), 2.01 (br s, 2 H), 1.95 (s, 3 H), 1.77 (s, 3 H), 1.34–1.39 (m, 1 H), 1.02–1.12 (m, 22 H), 0.81 (t, *J* = 6.8 Hz, 6 H), 0.12 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 133.5, 130.8, 128.3, 125.6, 102.7, 88.4, 83.0, 79.3, 63.3, 61.6, 45.3, 38.1, 31.6, 27.8, 23.7, 23.5, 21.1, 20.6, 20.4, 18.0, 17.7, 11.9, –0.2; IR (film) 2957, 2865, 2726, 2179, 1716, 1463 cm^{-1}; HRMS (FAB) *m/z* 559.4001 (M+H, 559.4003 calcd for $C_{33}H_{59}O_3Si_2$). Anal. Calcd for $C_{33}H_{58}O_3Si_2$: C, 70.91; H, 10.46. Found: C, 70.91; H, 10.55.

(1*R*,3*R*,3a*R*,7*R*,7a*R*)-2(*R*)-[3(*R*)-(7-Isopropyl-4-methyl-3-prop-2-ynyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-1-yl)-3-methyloxiranyl]ethanol (19). A mixture of alcohol **18** (110 mg, 0.38 mmol), aluminum (III) *tert*-butoxide (140 mg, 0.57 mmol), 4 Å powdered molecular sieves (190 mg), and toluene (3.8 mL) was cooled to –20 °C and treated dropwise with *tert*-

butylhydroperoxide (0.23 mL of a 5–6 M solution in decane, 1 mmol, pre-dried with 4 Å molecular sieves). The mixture was stirred at –20 °C for 24 h before being warmed to room temperature, and quenched with saturated aqueous Rochelle's salt (5 mL). After stirring vigorously for 1 h, saturated aqueous Rochelle's salt (15 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (2:1 hexane–ethyl acetate) to afford 13 mg (10%) of **20** and 79 mg (66%) of **19** both as a clear pale yellow oils. Major isomer **19**: $[\alpha]^{23}_{D}$ +10.7 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (br s, 1 H), 3.81–3.89 (m, 3 H), 3.67 (d, *J* = 8.9 Hz, 1 H), 2.98 (dd, *J* = 9.3, 3.2 Hz, 1 H), 2.50–2.66 (m, 3 H), 2.42 (ddd, *J* = 8.5, 8.5, 4.3 Hz, 1 H), 1.97–2.09 (m, 5 H), 1.74 (m, 1 H), 1.66 (s, 3 H), 1.59–1.66 (m, 1 H), 1.34 (s, 3 H), 1.24–1.29 (m, 1 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 0.86 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 120.8, 81.7, 81.0, 80.0, 70.1, 62.1, 60.8, 60.7, 45.4, 42.4, 37.2, 31.5, 28.9, 25.9, 23.8, 21.8, 21.2, 20.2, 18.1; IR (film) 3444, 3310, 2959, 2733, 2120, 1463 cm^{-1}; HRMS (FAB) *m/z* 319.2270 (M+H, 319.2273 calcd for $C_{20}H_{31}O_3$).

(4*R*,4a*R*,5*R*,6*R*,9*S*,10*R*,12*R*,12a*R*)-Tetradecahydro-4-isopropyl-6,10-dimethyl-1-methyl-5,12:6,10-diepoxybenzocyclodec-1-en-9-ol (25). Mercury (II) acetate (11 mg, 0.036 mmol) was added to a solution of diol **24** (8.5 mg, 0.027 mmol) and THF (0.7 mL) and the mixture was stirred at room temperature. After 30 min, a mixture of sodium borohydride (6 mg, 0.16 mmol) and sodium hydroxide (0.5 mL of a 1.0 M aqueous solution) was added and the mixture was stirred for 1 h before being quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was diluted with saturated aqueous NH_4Cl (5 mL) and washed with ethyl acetate (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The

residue was purified by silica gel chromatography (1:1 hexane–ethyl acetate) to afford 2.5 mg (29%) of recovered **24** and 4.0 mg (47%) of **25** both as colorless oils. Tetracycle **25**: $[\alpha]^{23}_{D}$ +5.9 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (app d, *J* = 2.8 Hz, 1 H), 4.08 (td, *J* = 4.9, 1.6 Hz, 1 H), 3.84 (s, 1 H), 3.28–3.30 (m, 1 H), 2.97–3.00 (m, 1 H), 2.71 (tdd, *J* = 13.6, 5.7, 2.3 Hz, 1 H), 2.34 (dd, *J* = 11.9, 8.1 Hz, 1 H), 2.15 (dd, *J* = 14.7, 4.8 Hz, 1 H), 1.77–1.92 (m, 5 H), 1.69–1.73 (m, 3 H), 1.67 (s, 3 H), 1.34 (s, 3 H), 1.25–1.30 (m, 1 H), 1.14 (s, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.78 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.2, 121.3, 91.8, 81.6, 76.5, 76.2, 71.7, 47.6, 46.4, 41.9, 38.8, 30.9, 29.0, 28.3, 28.0, 24.6, 22.4, 22.1, 21.8, 15.4; IR (film) 3346, 2957, 1446 cm^{-1}; HRMS (FAB) *m/z* 320.2351 (M+, 320.2351 calcd for $C_{20}H_{32}O_3$).

(4*R*,4a*R*,5*R*,6*R*,9*S*,10*R*,12*R*,12a*R*)-Tetradecahydro-4-isopropyl-6,10-dimethyl-1-methylene-5,12:6,10-diepoxybenzocyclodecen-9-ol (2). A mixture of tetracycle **25** (4.0 mg, 0.012 mmol), glacial acetic acid (71 μL, 1.2 mmol), *p*-xylene (15 μL, 0.12 mmol), and degassed 2-propanol (1.2 mL) in a quartz reaction vessel was irradiated at room temperature with a Canrad-Hanovia 450 W medium pressure Hg lamp fitted with a Vycor filter ($h\upsilon$ > 240 nm) for 3 h. The reaction mixture was neutralized by addition to saturated aqueous $NaHCO_3$ (5 mL) and stirred for 30 min. The aqueous layer was diluted with saturated aqueous $NaHCO_3$ (5 mL) and washed with ethyl acetate (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel chromatography (4:1 hexane-ethyl acetate) to afford 3.2 mg (80%) of a 4:1 mixture of **2** and **25**. Spectral data for **2** were identical to those reported by Paquette and co-workers.[2]

[2] Paquette, L. A.; Moradei, O. M.; Bernardelli, P.; Lange, T. *Org. Lett.* **2000**, *2*, *ASAP* article.