

Supporting Information for Stoltz et al.

An Exceedingly Efficient Synthesis of (±)-Grandifloracin and Acylated Analogues

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Table of Contents:

General information

Materials and Methods SI-2

Experimental Procedures SI-3

¹H NMR and ¹³C NMR Spectra SI-14

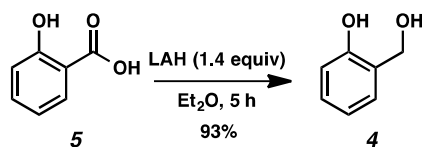
Materials and Methods

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried or oven-dried glassware under argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).¹ Commercially obtained reagents were used as received unless otherwise stated. NEt₃ was distilled from calcium hydride immediately prior to use. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-LCMS. TLC was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. SiliaFlash P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ¹H and ¹³C NMR spectra were recorded on a Varian Inova 500 spectrometer (500 MHz and 126 MHz, respectively) and are reported in terms of chemical shift relative to residual CHCl₃ (δ 7.26 and δ 77.16 ppm, respectively), D₃CS(O)CHD₂ (δ 2.50 and δ 39.52 ppm, respectively). Data for ¹H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for ¹³C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm⁻¹). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: [α]_D^T (concentration in g/100 mL, solvent). Analytical HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak (AD-H) column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Analytical SFC was performed with a Mettler SFC supercritical CO₂ analytical chromatography system utilizing Chiralpak (AD-H) column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High-resolution mass spectra (HRMS) were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in atmospheric pressure chemical ionization (APCI+), electrospray ionization (ESI+), or mixed (MultiMode: ESI-APCI) ionization mode.

List of Abbreviations: ee - enantiomeric excess, dr - diastereomeric ratio, HPLC - high-performance liquid chromatography, UHPLC - Ultra high performance liquid chromatography SFC - supercritical fluid chromatography, TLC - thin-layer chromatography, THF - tetrahydrofuran, IPA - isopropanol, EtOAc - ethyl acetate, LAH - Lithium aluminium hydride, DCM - dichloromethane.

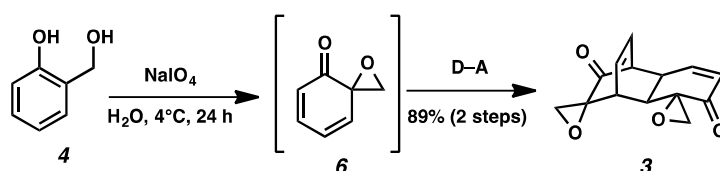
¹ Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518.

Experimental Procedures



Salicylic alcohol (4). Salicylic acid (6.00 g, 43.4 mmol) was dissolved in diethyl ether (40 mL) and added to a solution of LAH (3.30 g, 87 mmol) in diethyl ether (300 mL) at 0 °C. The mixture was warmed to 23°C and stirred for 5 h. The mixture was quenched with 3.3 mL water and 3.3 mL 15% NaOH and 15 mL H₂O. The mixture was stirred for 30 min. A white-gray precipitate formed. The precipitate was filtered off, diluted in water, acidified with 1M HCl and extracted with EtOAc (3x30 mL). The filtrate and the extracted organic fractions were dried with Na₂SO₄, filtered and concentrated under vacuum to give the crude product (7.3 g). The crude product was recrystallized from chloroform to give 2-(hydroxymethyl)phenol (5.01 g, 40.4 mmol, 93% yield).

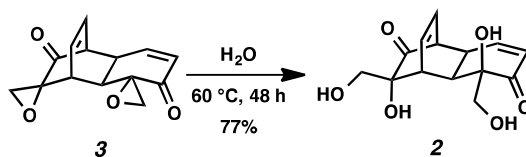
R_f = 0.6 (50% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ ppm 4.88 (s, 2 H), 6.87 (td, J =7.45, 0.98 Hz, 1 H), 6.90 (dd, J =8.18, 0.85 Hz, 1 H), 7.03–7.07 (m, 1 H), 7.23 (td, J =7.69, 1.71 Hz, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 65.0, 116.8, 120.3, 125.0, 128.1, 129.8, 156.4; HRMS (MM: ESI-APCI+) m/z calc'd for C₇H₇O₂ [M-H⁺]=123.0452; found 123.0449.



1,3,4,4a,5,8a-Hexahydro-1,4-ethenonaphthalene-3,5-bis(spirooxirane)2,6-dione (**3**).

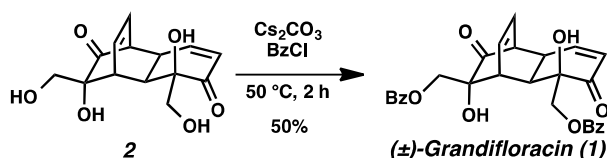
2-(Hydroxymethyl)phenol **4** (1.00 g, 8.06 mmol) was dissolved in water (120 mL). A solution of sodium periodate (1.895 g, 8.86 mmol) in water (40 mL) was added. The mixture was stirred for 10 min and then put in a refrigerator (4 °C) for 24 h. The solid was filtered off and washed with cold water. The filtrate was extracted with EtOAc (3x10 mL). The organic phase was dried with Na₂SO₄ and concentrated. The solids were recrystallized from chloroform to give 1,3,4,4a,5,8a-hexahydro-1,4-ethenonaphthalene-3,5-bis(spirooxirane)2,6-dione (876 mg, 3.59 mmol, 89% yield, dr: >20:1).

R_f = 0.25 (25% EtOAc in hexanes); ^1H NMR (500 MHz, CDCl_3) δ ppm 2.86 (dd, J =9.03, 2.44 Hz, 1 H), 2.88 (d, J =6.59 Hz, 1 H), 2.92–2.95 (m, 2 H), 2.97 (d, J =6.59 Hz, 1 H), 3.18 (d, J =6.10 Hz, 1 H), 3.52 (ddd, J =6.23, 2.32, 1.46 Hz, 1 H), 3.56–3.60 (m, 1 H), 6.14–6.18 (m, 1 H), 6.23 (dd, J =10.25, 1.71 Hz, 1 H), 6.63–6.67 (m, 1 H), 6.69 (dd, J =10.13, 4.27 Hz, 1 H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 38.5, 38.6, 41.5, 52.8, 53.4, 57.3, 57.5, 58.5, 129.0, 131.1, 134.0, 146.6, 192.1, 203.1; HRMS (MM: ESI-APCI+) m/z calc'd for $\text{C}_{14}\text{H}_{11}\text{O}_4$ [$\text{M}-\text{H}^+$]=243.0663; found 243.0662.



(1*S*,4*R*)-5,9-dihydroxy-5,9-bis(hydroxymethyl)-1,4a,5,8a-tetrahydro-1,4-ethanonaphthalene-6,10(4*H*)-dione (2). 1,3,4,4a,5,8a-Hexahydro-1,4-ethanonaphthalene-3,5-bis(spirooxirane)2,6-dione (375 mg, 1.54 mmol) was dissolved in water (10 mL) and stirred at 60 °C for 48h. The crude product was concentrated and purified by column chromatography (20% MeOH in EtOAc) to give (1*S*,4*R*)-5,9-dihydroxy-5,9-bis(hydroxymethyl)-1,4a,5,8a-tetrahydro-1,4-ethanonaphthalene-6,10(4*H*)-dione (333 mg, 1.19 mmol, 77% yield).

R_f = 0.15 (20% MeOH in EtOAc); ^1H NMR (500 MHz, D_2O) δ ppm 2.90–2.96 (m, 1 H), 3.31 (d, J =6.84 Hz, 1 H), 3.38 (d, J =6.35 Hz, 1 H), 3.44 (d, J =12.21 Hz, 2 H), 3.52 (d, J =12.21 Hz, 1 H), 3.56 (d, J =11.96 Hz, 1 H), 3.78 (d, J =11.96 Hz, 1 H), 5.94 (t, J =6.71 Hz, 1 H), 6.11 (dd, J =10.13, 1.34 Hz, 1 H), 6.34 (t, J =7.32 Hz, 1 H), 6.70 (dd, J =10.01, 4.15 Hz, 1 H); ^{13}C NMR (126 MHz, D_2O) δ ppm 37.3, 40.0, 40.9, 52.1, 65.6, 70.7, 76.5, 79.1, 127.8, 128.9, 134.6, 148.7, 202.5, 212.4; HRMS (MM: ESI-APCI+) m/z calc'd for $\text{C}_{14}\text{H}_{16}\text{O}_6\text{Cl}_1$ [$\text{M}+\text{Cl}^-$]=315.0641; found 315.0647.



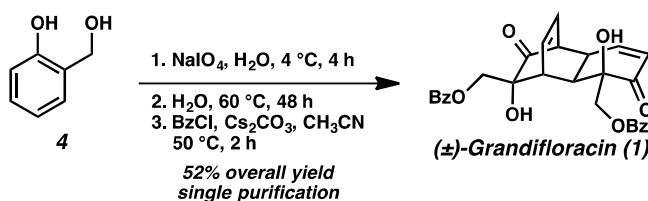
(±)-Grandifloracin (1). To a solution of (1*S*,4*R*)-5,9-dihydroxy-5,9-bis(hydroxymethyl)-1,4a,5,8a-tetrahydro-1,4-ethanonaphthalene-6,10(4*H*)-dione (2, 105 mg, 0.375 mmol) and cesium carbonate (366 mg, 1.12 mmol) in acetonitrile (2 mL), was added benzoyl chloride (0.087 mL, 0.75 mmol) and the mixture was stirred at 50 °C for

2 h. The mixture was concentrated and dissolved in 1:1 H₂O:EtOAc (8 mL). The organic phase was collected and the water phase was extracted with EtOAc (2x5 mL). The combined organic phases were concentrated onto silica and purified by column chromatography (25% EtOAc in hexanes) to give (±)-grandifloracin (92 mg, 0.19 mmol, 50% yield).

R_f = 0.3 (33% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ ppm 3.34 (br. s., 1 H), 3.36–3.40 (m, 2 H), 3.46 (ddt, J =8.45, 4.24, 1.83, 1.83 Hz, 1 H), 3.69 (dt, J =6.65, 1.80 Hz, 1 H), 4.24 (d, J =11.96 Hz, 1 H), 4.35 (s, 1 H), 4.36–4.43 (m, 2 H), 4.47 (d, J =11.72 Hz, 1 H), 6.02 (ddd, J =7.93, 6.23, 1.47 Hz, 1 H), 6.20–6.24 (m, 1 H), 6.44 (ddd, J =8.12, 6.78, 1.22 Hz, 1 H), 6.60 (dd, J =10.13, 4.27 Hz, 1 H), 7.41–7.45 (m, 2 H), 7.45–7.49 (m, 2 H), 7.54–7.58 (m, 1 H), 7.58–7.62 (m, 1 H), 7.92–7.94 (m, 1 H), 7.94–7.95 (m, 1 H), 8.05–8.06 (m, 1 H), 8.06–8.08 (m, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 37.4, 40.0, 41.1, 52.2, 68.2, 71.8, 74.4, 75.4, 128.1, 128.4 (s, 2 C) 128.4 (s, 2 C) 128.5 (s, 2 C) 129.4, 129.7 (s, 2 C) 129.8 (s, 2 C) 133.3, 133.4, 135.2, 146.6, 165.8, 166.7, 198.0, 208.0; HRMS (MM: ESI-APCI+) m/z calc'd for C₂₈H₂₄O₈Cl₁ [$M+Cl$]=523.1165; found 523.1168.

Chiral separation of Grandifloracin enantiomers:

27 mg (±)-Grandifloracin was dissolved in 1 mL of acetone, diluted with 1 mL IPA and concentrated to 1 mL. The solution was injected onto a Chiralpak (AD-H) column (19 mm x 25 cm) chiral Prep-HPLC column to give (+)-grandifloracin (10 mg, 0.020 mmol, 38.6%, >99.5% ee, [α]_D²⁵+7.81 (c 0.45, CHCl₃)) and (–)-grandifloracin (9 mg, 0.018 mmol, 34.8%, 96% ee, [α]_D²⁵–3.72 (c 0.45, CHCl₃)).

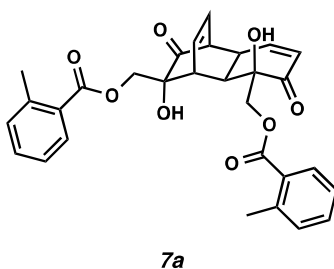


Condensed synthesis of (±)-Grandifloracin (1). 2-(hydroxymethyl)phenol (200 mg, 1.61 mmol) was dissolved in water (24 mL). A solution of sodium periodate (379 mg, 1.77 mmol) in water (8 mL) was added. The mixture was stirred for 10 min at 23 °C and then put in a refrigerator (4 °C) for 4h. A slightly yellow solid was filtered off and the filtrate was extracted with EtOAc (10 mL) and DCM (2x10 mL). The combined organic phases were concentrated until solid. The solid was dissolved in water (8 mL) and stirred at 60 °C for 48h. The crude product was concentrated to dryness under high-vacuum. The crude material was dissolved in acetonitrile (10 mL).

Cesium carbonate (2.1 g, 6.4 mmol) followed by benzoyl chloride (0.561 mL, 4.83 mmol) were added and the mixture was stirred at 50 °C for 2h. The mixture was concentrated, dissolved in DCM (5 mL) washed with H₂O (2x5 mL). The organic phase is dried over Mg₂SO₄ and purified by column chromatography (33% EtOAc in hexanes) to afford (±)-grandifloracin (204 mg, 0.418 mmol, 52% yield).

General procedure A for grandifloracin analogues.

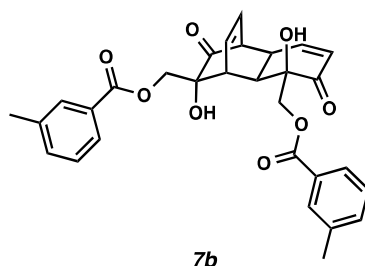
To a solution of (1S,4R)-5,9-dihydroxy-5,9-bis(hydroxymethyl)-1,4a,5,8a-tetrahydro-1,4-ethanonaphthalene-6,10(4H)-dione (**2**, 1 equiv) and cesium carbonate (4 equiv) in acetonitrile (1 mL), was added acid chloride (3 equiv) and the mixture was stirred at 50 °C for 2h. The mixture was concentrated and dissolved in 1:1 H₂O: EtOAc (8 mL). The organic phase was collected and the water phase was extracted with EtOAc (2x5 mL). The combined organic phases were concentrated onto silica and purified by column chromatography.



((1S,4R,4aR,8aS)-5,9-dihydroxy-6,10-dioxo-1,4,4a,5,6,8a-hexahydro-1,4-ethanonaphthalene-5,9-diyl)bis(methylene) bis(2-methylbenzoate) (**7a**).

The product was synthesized according to general procedure A using 2-methylbenzoyl chloride (49.6 mg, 0.321 mmol), yield: 26.7 mg, 0.052 mmol, 48%.

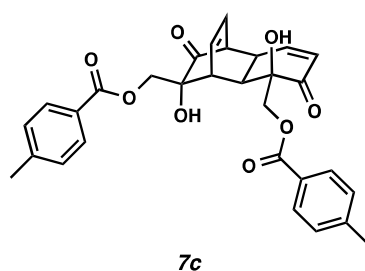
R_f = 0.3 (2:1Hexane: EtOAc); ¹H NMR (500 MHz, CDCl₃) δ ppm 2.54 (s, 3 H), 2.60 (s, 3 H), 3.33–3.42 (m, 3 H), 3.45 (ddd, J =6.23, 4.15, 2.08 Hz, 1 H), 3.68 (d, J =6.59 Hz, 1 H), 4.19 (d, J =11.96 Hz, 1 H), 4.33 (br. s., 1 H), 4.35 (d, J =11.23 Hz, 1 H), 4.39–4.44 (m, 1 H), 4.47 (d, J =11.96 Hz, 1 H), 6.00–6.05 (m, 1 H), 6.21 (dd, J =10.13, 1.34 Hz, 1 H), 6.43 (t, J =7.20 Hz, 1 H), 6.59 (dd, J =10.13, 4.27 Hz, 1 H), 7.20–7.25 (m, 2 H), 7.25–7.29 (m, 2 H), 7.37–7.46 (m, 2 H), 7.80 (d, J =7.81 Hz, 1 H), 7.95 (d, J =7.81 Hz, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ ppm 21.7, 37.4, 40.0, 41.2, 52.3, 68.0, 71.7, 74.5, 75.5, 125.8, 125.8, 128.1, 128.5, 128.7, 128.8, 130.7, 130.8, 131.7, 131.7, 132.3, 132.4, 135.2, 140.5, 140.6, 146.5, 166.7, 167.5, 198.2, 208.1; IR (Neat Film NaCl) 3456, 2968, 1723, 1602, 1457, 1383, 1292, 1251, 1142, 1077, 738 cm⁻¹; HRMS (MM: ESI-APCI+) m/z calc'd for C₃₀H₂₉O₈ [M+H⁺]=517.1857; found 517.1831.



((1S,4R,4aR,8aS)-5,9-dihydroxy-6,10-dioxo-1,4,4a,5,6,8a-hexahydro-1,4-ethanonaphthalene-5,9-diyl)bis(methylene) bis(3-methylbenzoate) (7b).

The product was synthesized according to general procedure A using 3-methylbenzoyl chloride (49.6 mg, 0.321 mmol), yield: 28.1 mg, 0.054 mmol, 51%.

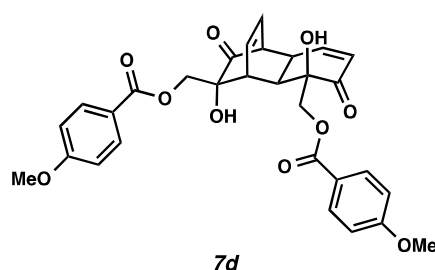
R_f = 0.3 (2:1Hexane: EtOAc); ^1H NMR (500 MHz, CDCl_3) δ ppm 2.39 (s, 3 H), 2.42 (s, 3 H), 3.34–3.43 (m, 3 H), 3.45 (ddd, J =6.29, 4.21, 1.95 Hz, 1 H), 3.68 (d, J =6.59 Hz, 1 H), 4.23 (d, J =11.96 Hz, 1 H), 4.34 (d, J =3.42 Hz, 1 H), 4.36 (s, 1 H), 4.39–4.44 (m, 1 H), 4.46 (d, J =11.96 Hz, 1 H), 5.99–6.04 (m, 1 H), 6.21 (dd, J =10.13, 1.34 Hz, 1 H), 6.44 (t, J =7.32 Hz, 1 H), 6.59 (dd, J =10.13, 4.27 Hz, 1 H), 7.28–7.33 (m, 1 H), 7.34–7.38 (m, 2 H), 7.38–7.42 (m, 1 H), 7.72 (d, J =7.81 Hz, 1 H), 7.75 (s, 1 H), 7.84–7.88 (m, 2 H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 21.2, 37.5, 40.0, 41.2, 52.3, 68.2, 71.8, 74.5, 75.4, 126.8, 127.0, 128.1, 128.3, 128.4, 129.3, 130.2, 130.4, 134.1, 134.2, 135.2, 138.3, 138.3, 146.5, 166.0, 166.9, 198.1, 208.0; IR (Neat Film NaCl) 3454, 2922, 1722, 1589, 1450, 1382, 1276, 1198, 1102, 1082, 743 cm^{-1} ; HRMS (MM: ESI-APCI+) m/z calc'd for $\text{C}_{30}\text{H}_{29}\text{O}_8$ $[\text{M}+\text{H}^+]$ =517.1857; found 517.1836.



((1S,4R,4aR,8aS)-5,9-dihydroxy-6,10-dioxo-1,4,4a,5,6,8a-hexahydro-1,4-ethanonaphthalene-5,9-diyl)bis(methylene) bis(4-methylbenzoate) (7c).

The product was synthesized according to general procedure A using 3-methylbenzoyl chloride (49.6 mg, 0.321 mmol), yield: 30.6 mg, 0.059 mmol, 55%.

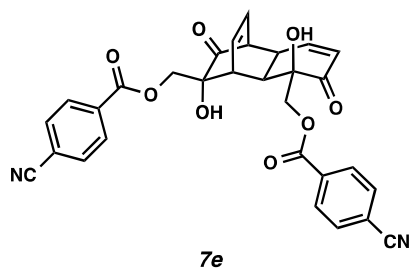
R_f = 0.3 (2:1Hexane: EtOAc); ^1H NMR (500 MHz, CDCl_3) δ ppm 2.40 (s, 3 H), 2.42 (s, 3 H), 3.34–3.40 (m, 2 H), 3.40–3.49 (m, 2 H), 3.68 (d, J =6.59 Hz, 1 H), 4.22 (d, J =11.96 Hz, 1 H), 4.33–4.41 (m, 3 H), 4.45 (d, J =11.96 Hz, 1 H), 6.01 (t, J =6.59 Hz, 1 H), 6.20 (dd, J =10.13, 1.34 Hz, 1 H), 6.43 (t, J =7.32 Hz, 1 H), 6.58 (dd, J =10.13, 4.27 Hz, 1 H), 7.21 (d, J =8.06 Hz, 2 H), 7.25 (d, J =8.06 Hz, 2 H), 7.82 (d, J =8.06 Hz, 2 H), 7.94 (d, J =8.30 Hz, 2 H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 21.6, 21.6, 37.5, 40.0, 41.2, 52.3, 68.1, 71.7, 74.5, 75.5, 126.7, 128.1, 128.4, 129.2, 129.2, 129.7, 129.9, 135.2, 144.0, 144.2, 146.6, 165.9, 166.8, 198.1, 208.0; IR (Neat Film NaCl) 3452, 2923, 1721, 1611, 1449, 1408, 1380, 1271, 1179, 1098, 1020, 751 cm^{-1} ; HRMS (MM: ESI-APCI+) m/z calc'd for $\text{C}_{30}\text{H}_{29}\text{O}_8$ $[\text{M}+\text{H}^+]$ =517.1857; found 517.1838.



((1S,4R,4aR,8aS)-5,9-dihydroxy-6,10-dioxo-1,4,4a,5,6,8a-hexahydro-1,4-ethanonaphthalene-5,9-diyl)bis(methylene) bis(4-methoxybenzoate) (7d).

The product was synthesized according to general procedure A using 4-methoxybenzoyl chloride (54.8 mg, 0.321 mmol), yield: 40.7 mg, 0.074 mmol, 69%.

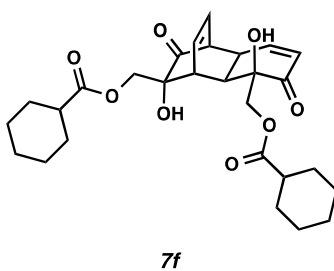
R_f = 0.2 (2:1Hexane: EtOAc); ^1H NMR (500 MHz, CDCl_3) δ ppm 3.34–3.39 (m, 2 H), 3.44 (ddt, J =8.39, 4.18, 1.89, 1.89 Hz, 2 H), 3.67 (dt, J =6.59, 1.71 Hz, 1 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 4.20 (d, J =11.96 Hz, 1 H), 4.31–4.39 (m, 3 H), 4.43 (d, J =11.96 Hz, 1 H), 6.00 (ddd, J =7.93, 6.23, 1.46 Hz, 1 H), 6.20 (dd, J =10.13, 1.59 Hz, 1 H), 6.43 (ddd, J =8.06, 6.84, 1.22 Hz, 1 H), 6.58 (dd, J =10.13, 4.27 Hz, 1 H), 6.88–6.91 (m, 2 H), 6.91–6.94 (m, 2 H), 7.86–7.90 (m, 2 H), 7.99–8.02 (m, 2 H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 37.5, 40.0, 41.2, 52.3, 55.4, 55.5, 68.0, 71.6, 74.5, 75.5, 110.0, 113.8, 113.8, 121.8, 128.1, 128.4, 131.8, 132.0, 135.3, 146.6, 163.7, 163.8, 165.5, 166.4, 198.2, 208.0; IR (Neat Film NaCl) 3450, 2937, 1712, 1605, 1512, 1459, 1420, 1359, 1317, 1258, 1099, 1027, 847, 767 cm^{-1} ; HRMS (MM: ESI-APCI+) m/z calc'd for $\text{C}_{30}\text{H}_{29}\text{O}_{10}$ $[\text{M}+\text{H}^+]$ =549.1755; found 549.1735.



((1S,4R,4aR,8aS)-5,9-dihydroxy-6,10-dioxo-1,4,4a,5,6,8a-hexahydro-1,4-ethanonaphthalene-5,9-diyl)bis(methylene) bis(4-cyanobenzoate) (7e**).**

The product was synthesized according to general procedure A using 4-cyanobenzoyl chloride (53.2 mg, 0.321 mmol), yield: 14.2 mg, 0.026 mmol, 25%.

R_f = 0.25 (2:1Hexane: EtOAc); ^1H NMR (500 MHz, CDCl_3) δ ppm 3.20 (br. s., 1 H), 3.35 (d, J =8.30 Hz, 1 H), 3.42 (d, J =5.86 Hz, 1 H), 3.44–3.49 (m, 1 H), 3.67 (d, J =6.59 Hz, 1 H), 4.26 (d, J =11.96 Hz, 1 H), 4.34 (br. s., 1 H), 4.42 (s, 2 H), 4.50 (d, J =11.96 Hz, 1 H), 6.06 (t, J =6.84 Hz, 1 H), 6.23 (d, J =10.01 Hz, 1 H), 6.44 (t, J =7.32 Hz, 1 H), 6.63 (dd, J =10.25, 4.15 Hz, 1 H), 7.73 (m, J =8.30 Hz, 2 H), 7.77 (d, J =8.30 Hz, 2 H), 8.03 (d, J =8.30 Hz, 2 H), 8.16 (m, J =8.30 Hz, 2 H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 37.1, 39.9, 40.8, 52.0, 68.8, 72.2, 74.2, 75.3, 116.8, 116.9, 117.8, 127.9, 128.7, 130.2, 130.3, 132.3, 132.3, 133.0, 133.1, 134.8, 146.8, 164.1, 165.0, 197.7, 208.0; IR (Neat Film NaCl) 3450, 2923, 2853, 2231, 1727, 1450, 1377, 1271, 1178, 1099, 1019, 861, 804, 764 cm^{-1} ; HRMS (MM: ESI-APCI+) m/z calc'd for $\text{C}_{30}\text{H}_{23}\text{N}_2\text{O}_8$ $[\text{M}+\text{H}^+]$ = 501.2483; found 501.2464.

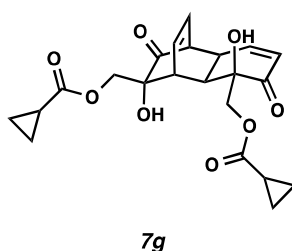


((1S,4R,4aR,8aS)-5,9-dihydroxy-6,10-dioxo-1,4,4a,5,6,8a-hexahydro-1,4-ethanonaphthalene-5,9-diyl)bis(methylene) dicyclohexanecarboxylate (7f**).**

The product was synthesized according to general procedure A using cyclohexane carbonyl chloride (34.5 mg, 0.235 mmol), yield: 31.3 mg, 0.063 mmol, 58%.

R_f = 0.3 (4:1Hexane: EtOAc); ^1H NMR (500 MHz, CDCl_3) δ ppm 1.21–1.29 (m, 5 H), 1.30–1.40 (m, 3 H), 1.40–1.49 (m, 2 H), 1.60–1.68 (m, 2 H), 1.70–1.86 (m, 7 H), 1.89–1.97 (m, 2 H), 2.25 (tt, J =11.20, 3.57 Hz, 1 H), 2.37 (tt, J =11.32, 3.57 Hz, 1 H), 3.22 (dd, J =8.30, 1.71 Hz, 1 H), 3.29–3.34 (m, 1 H), 3.37 (ddd, J =6.23, 4.15, 2.08

Hz, 1 H), 3.51 (d, $J=6.59$ Hz, 1 H), 3.92 (d, $J=11.96$ Hz, 1 H), 4.09 (d, $J=11.23$ Hz, 1 H), 4.17–4.22 (m, 2 H), 4.25 (d, $J=11.96$ Hz, 1 H), 5.93–5.99 (m, 1 H), 6.15 (dd, $J=10.13$, 1.59 Hz, 1 H), 6.31–6.37 (m, 1 H), 6.54 (dd, $J=10.13$, 4.27 Hz, 1 H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 25.3, 25.3, 25.4 (s, 2 C) 25.7 (s, 2 C) 28.8, 28.9, 29.0 (s, 2 C) 37.3, 40.0, 41.1, 42.9, 43.1, 52.3, 67.5, 70.9, 74.4, 75.5, 128.1, 128.4, 135.1, 146.3, 175.3, 176.2, 198.0, 207.9; IR (Neat Film NaCl) 3447, 2932, 2855, 2361, 1734, 1456, 1387, 1313, 1246, 1166, 1131, 1038, 754 cm^{-1} ; HRMS (MM: ESI-APCI+) m/z calc'd for $\text{C}_{28}\text{H}_{37}\text{O}_8$ $[\text{M}+\text{H}^+]=501.2483$; found 501.2464.



((1S,4R,4aR,8aS)-5,9-dihydroxy-6,10-dioxo-1,4,4a,5,6,8a-hexahydro-1,4-ethanonaphthalene-5,9-diyl)bis(methylene) dicyclopropanecarboxylate (7g).

The product was synthesized according to general procedure A using cyclopropanecarbonyl chloride (33.6 mg, 0.321 mmol), yield: 24.5 mg, 0.059 mmol, 55.0%.

$R_f=0.25$ (4:1Hexane: EtOAc); ^1H NMR (500 MHz, CDCl_3) δ ppm 0.84–0.88 (m, 2 H), 0.92–0.98 (m, 4 H), 1.01–1.06 (m, 2 H), 1.56 (tt, $J=8.06$, 4.64 Hz, 1 H), 1.68 (tt, $J=8.06$, 4.64 Hz, 1 H), 3.21 (br. s., 1 H), 3.24 (dd, $J=8.42$, 2.08 Hz, 1 H), 3.30–3.34 (m, 1 H), 3.35–3.40 (m, 1 H), 3.55 (dt, $J=6.59$, 1.71 Hz, 1 H), 3.94 (d, $J=11.96$ Hz, 1 H), 4.12 (d, $J=11.23$ Hz, 1 H), 4.19 (d, $J=11.23$ Hz, 1 H), 4.22 (s, 1 H), 4.26 (d, $J=11.96$ Hz, 1 H), 5.96 (ddd, $J=7.93$, 6.23, 1.46 Hz, 1 H), 6.17 (dd, $J=10.01$, 1.71 Hz, 1 H), 6.36 (ddd, $J=8.00$, 6.65, 1.22 Hz, 1 H), 6.55 (dd, $J=10.13$, 4.27 Hz, 1 H); ^{13}C NMR (126 MHz, CDCl_3) δ ppm 8.7, 8.7, 8.9, 9.0, 12.7, 12.8, 37.3, 40.0, 41.1, 52.3, 67.8, 71.3, 74.4, 75.4, 128.1, 128.4, 135.2, 146.4, 174.2, 175.2, 198.0, 207.8; IR (Neat Film NaCl) 3447, 3014, 2917, 1730, 1457, 1399, 1267, 1169, 1098, 1077, 1034, 752 cm^{-1} ; HRMS (MM: ESI-APCI+) m/z calc'd for $\text{C}_{22}\text{H}_{25}\text{O}_8$ $[\text{M}+\text{H}^+]=417.1544$; found 417.1540.

1 Grandifloracin

