Supporting Information

For

Synthesis of the pentacyclic core of citreamicin η

Shawn Blumberg and Stephen F. Martin*

Department of Chemistry
The University of Texas, Austin, Texas 78712

sfmartin@mail.utexas.edu
Experimental Section

GENERAL

Unless otherwise noted, solvents and reagents were used without purification. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were dried by passage through two columns of activated neutral alumina. Methanol (CH₃OH), acetonitrile (CH₃CN), and N,N-dimethylformamide (DMF) were dried by passage through two columns of activated molecular sieves. Toluene was dried by sequential passage through a column of activated neutral alumina followed by a column of Q5 reactant. Methylene chloride (CH₂Cl₂), benzene, triethylamine (Et₃N), diisopropylethylamine (DIPEA) and 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) were distilled from calcium hydride prior to use. Dimethyl sulfoxide (DMSO), and tert-amyl alcohol were stored over 4Å molecular sieves for 48 h prior to use. All solvents were determined to contain less than 50 ppm H₂O by Karl Fischer coulometric moisture analysis. All reactions were performed in flame-dried glassware under argon or nitrogen unless otherwise indicated. Volatile solvents were removed under reduced pressure using a Buchi rotary evaporator. Reaction mixtures were degassed by putting the reaction vessel under vacuum until the solvent effervesced, and backfilling with nitrogen (3 x). Infrared (IR) spectra were obtained using a FT IR 1600 spectrophotometer using sodium chloride plates and reported as wave numbers. Low resolution chemical ionization mass spectra were obtained with a TSQ-70 instrument. High resolution measurements were made with a VG Analytical ZAB2-E instrument. Thin layer chromatography (TLC) was performed on glass-backed precoated silica gel plates (0.25 mm thick with 60 F254) and were visualized using one or both of the following manners: UV light (254 nm) and staining with basic aqueous KMnO₄ or Cerium ammonium molybdate (CAM). Flash chromatography was performed according to Still’s procedure using ICN Silitech 32-67 D 60A silica gel.¹ ¹H nuclear magnetic resonance (NMR) spectra were obtained at either 600, 500, or 400 MHz as indicated as solutions in CDCl₃ with 0.05% v/v tetramethylsilane (TMS) unless indicated otherwise. ¹³C-NMR were obtained at either 125, 100 or 75 MHz as shown in the indicated deuterated solvent. Chemical shifts are reported in parts per million (ppm, δ), and referenced to TMS, and coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; quint, quintuplet; sex, sextet; sept, septuplet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; and app, apparent.
3-Hydroxy-4-((4-methoxybenzyl)oxy) benzaldehyde (S1). Prepared according to a modified procedure used by Plourde et al. via similar procedure A mixture of 4,5-dihydroxybenzaldehyde 13 (10.0 g, 65.6 mmol), NaHCO$_3$ (8.2 g, 98.4 mmol) and sodium iodide (NaI) (3.0 g, 19.6 mmol) in anhydrous DMF (40 mL) was heated at 40 °C for 2 h. p-Methoxybenzyl chloride (PMBCl) (20.6 g, 17.8 mL, 131.2 mmol), prepared according to Sosa’s procedure, was added, and the reaction was stirred at 40 °C for 24 h, whereupon the reaction was cooled to room temperature and H$_2$O (80 mL) was added. The mixture was extracted with EtOAc (3 x 30 mL), and the combined organic extracts were washed with 13% aqueous brine solution (4 x 10 mL) and dried (Na$_2$SO$_4$). Hexanes (50 mL) were added, and the combined organic extracts were filtered through a silica plug and eluted with EtOAc/Hexanes (2:1; 1 x 300 mL), and the combined organic layers were concentrated under reduced pressure. The crude material was crystallized from toluene (40 mL) to yield 13.4g (79%) pure S1 as a white solid: mp 117-120 °C.

The mother liquors were washed with a 5% NaOH solution (3 x 60 mL), and saturated aqueous NH$_4$Cl (ca. 32 mL) was added to the combined aqueous extracts until the pH was 5-7 by pH paper. and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with a saturated aqueous NaHCO$_3$ solution (5 mL), dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The solids were purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 3.4 g (20%) more S1 as an off-white solid (99% total): $^{1}$H-NMR (400 MHz) δ 9.83 (s, 1 H), 7.52 (d, $J = 2.0$ Hz, 1 H), 7.44 (dd, $J = 2.0$, 8.0 Hz, 1 H), 7.36 (d, $J = 8.8$, 2 H), 7.05 (d, $J = 8.0$ Hz, 1 H), 6.95 (d, $J = 8.8$ Hz, 2 H), 5.10 (s, 2 H), 3.84 (s, 3 H); $^{13}$C-NMR (100 MHz) δ 191.0, 160.0, 151.1, 146.3, 130.7, 129.8, 127.2, 124.3, 114.3, 114.2, 111.5, 71.1, 55.3; IR (film) 3213, 1668, 1612, 1504, 1274, 1128 cm$^{-1}$; HRMS (ESI) $m/z$ calc for C$_{15}$H$_{14}$O$_4^-$, 257.0819; found, 257.0826.
2-Bromo-3-hydroxy-4-((4-methoxybenzyl)oxy) benzaldehyde (14). A suspension of aldehyde S1 (3.73 g, 14.44 mmol) in CH$_2$Cl$_2$ (144 mL) was cooled to –78 °C. In a separate flask, TMG (3.32 g, 3.62 mL, 28.88 mmol) was added to a slurry of NBS (2.57 g, 14.44 mmol) in CH$_2$Cl$_2$ (43 mL) at 0 °C. The mixture was stirred until it became homogenous (~5 min), whereupon it was added in one portion to the slurry of S1 at –78 °C. The reaction mixture was stirred for 30 min at –78 °C, whereupon AcOH (0.87 g, 0.83 mL, 28.88 mmol) was added, and the reaction was warmed to room temperature. The mixture was filtered through a silica plug (300 mL) eluting with EtOAc/Hexane (1:1, 1 x 1.5 L). The eluent was concentrated under reduced pressure to provide 4.05 g (83%) 14 as a pale yellow solid: mp 154-156 °C (IPA). The crude material can be purified by flash chromatography eluting with a gradient of acetone/hexanes with 1% Et$_3$N (7:13 → 7:3), but the material was sufficiently pure for use in the next step; $^1$H-NMR (400 MHz) δ 10.26 (s, 1 H), 7.55 (d, $J = 8.2$ Hz, 1 H), 7.35 (d, $J = 8.8$ Hz, 2 H), 6.99 (d, $J = 8.2$ Hz, 1 H), 6.95 (d, $J = 8.8$ Hz, 2 H), 6.13 (s, 1 H), 5.17 (s, 2 H), 3.84 (s, 3 H); $^{13}$C-NMR (100 MHz) δ 190.9, 160.1, 143.5, 137.9, 129.8, 127.3, 126.8, 122.5, 114.3, 113.0, 110.6, 71.5, 55.4; IR (film) 3388, 2927, 1680, 1588, 1516, 1487, 1464, 1282, 1251, 1176, 1130 cm$^{-1}$; HRMS (ESI) m/z calc for NaC$_{15}$H$_{13}$BrO$_4$ (+M+Na), 358.9889; found, 358.9010.

2-Bromo-4-((4-methoxybenzyl)oxy)-3-(methoxymethoxy) benzaldehyde (S2). A solution of the crude aldehyde 14 (6.76 g, 20.05 mmol) and diisopropylethylamine (DIPEA) (3.89 g, 5.25 mL, 30.07 mmol) in CH$_2$Cl$_2$ (140 mL) was cooled to 0 °C. Chloromethyl methyl ether (MOMCl) (1.18 M, 25.5 mL, 30.07 mmol), prepared according to Chong’s procedure, was added, and the cooling bath was removed. The solution was stirred at room temperature for 3 h, whereupon a solution of saturated
aqueous NaHCO₃ (20 mL) was added. The mixture was extracted with CH₂Cl₂ (3 x 20 mL), and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced pressure to provide crude S2 as a white solid: mp 88-90 °C. The crude material can be purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:3), but the material was sufficiently pure for use in the next step; ¹H-NMR (400 MHz) δ 10.27 (s, 1 H), 7.72 (d, J = 8.6 Hz, 1 H), 7.34 (d, J = 8.6 Hz, 2 H), 7.02 (d, J = 8.6 Hz, 1 H), 6.92 (d, J = 8.6 Hz, 2 H), 5.19 (s, 2 H), 5.11 (s, 2 H), 3.82 (s, 3 H), 3.58 (s, 3 H); ¹³C-NMR (100 MHz) δ 191.0, 159.8, 157.4, 143.6, 129.4, 127.5, 127.2, 126.4, 123.2, 114.1, 112.2, 98.8, 71.0, 58.1, 55.3; IR (film) 2968, 1674, 1515, 1382, 1250, 931 cm⁻¹; HRMS (ESI) m/z calc for NaC₁₇H₁₅BrO₅⁺ (M+Na), 403.0152; found, 403.0147.

2-Bromo-4-[(4-methoxybenzyl)oxy]-3-(methoxymethoxy)-1-vinylbenzene (12).

A slurry of methyltriphenylphosphonium bromide (Ph₃PMeBr) (14.12 g, 40.10 mmol) in THF (35 mL) was cooled to 0 °C and degassed. A solution of n-BuLi in hexanes (1.61 M, 25 mL, 40.10 mmol) was slowly added over 10 min. The mixture was stirred for an additional 5 min, whereupon DMSO (70 mL) was added followed by a solution of crude S2 in THF (35 mL). The reaction was stirred for 10 min, whereupon a solution of saturated aqueous NaHCO₃ (50 mL) and water (100 mL) was added. The mixture was extracted with EtOAc (3 x 100 mL), and the combined extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:4) to provide 6.51 g (86% from 14) of 12 as a white waxy solid: mp 41-43 °C; ¹H-NMR (400 MHz) δ 7.34 (d, J = 8.8 Hz, 2 H), 7.26 (d, J = 8.8 Hz, 1 H), 7.02 (dd, J = 11.2, 17.2 Hz, 1 H), 6.90 (comp, 3 H), 5.56 (dd, J = 1.2, 17.2 Hz, 1 H), 5.25 (dd, J = 1.2, 11.2 Hz, 1 H), 5.17 (s, 2 H), 5.03 (s, 2 H) 3.82 (s, 3 H), 3.59 (s, 3 H); ¹³C-NMR (100 MHz) δ 159.8, 151.8, 143.7, 135.7, 131.7, 129.3, 128.3, 121.9, 119.6, 115.2, 114.0, 113.2, 98.7, 71.0, 58.1, 55.3; IR (film) 2934, 2835, 1614, 1587, 1515, 1484, 1465, 1382, 1287, 1251, 1214, 1174, 1159, 1033, 985 cm⁻¹; HRMS (Cl) m/z calc for C₁₉H₁₉BrO₄⁺, 377.0388; found, 377.0391.
4,4-Dimethoxy-3-(3-((4-methoxybenzyl)oxy)-2-(methoxymethoxy)-6-vinylphenyl)-2-vinylcyclobut-2-en-1-one (15). Compound 12 (500 mg, 1.32 mmol) was dried by dissolving in toluene (2 mL) and concentrating under reduced pressure (2 x), whereupon it was stored under vacuum for 2 h. 3,4,4-Trimethoxy-2-vinylcyclobut-2-en-1-one (11), prepared according to Moore’s procedure, was freshly purified via flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2), and the solid thus obtained was stored under vacuum for 2 h. Toluene (9 mL), Et₂O (44 mL) and NaH (60 % dispersion in mineral oil, 16 mg, 0.26 mmol) were added to the flask containing 12, and the mixture was stirred for 10 min before cooling to –78 °C. This mixture was degassed, and a solution of tert-BuLi in pentanes (1.85 M, 1.64 mL, 3.03 mmol) was added dropwise at –78 °C. Stirring was continued for an additional 5 min, whereupon a solution of 11 in Et₂O (2 mL) that had been slurried over NaH (60 % dispersion in mineral oil, 8 mg, 0.13 mmol) for at least 5 min was added. The reaction mixture was warmed to –20 °C and stirring continued for 15 min, whereupon a solution of saturated aqueous NaHCO₃ (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:4) to provide 364 mg (61%) of 15 as a yellow oil that slowly turns solid upon standing: mp 75-77 °C; ¹H-NMR (600 MHz) δ 7.37 (d, J = 8.6 Hz, 1 H), 7.34 (d, J = 8.8 Hz, 2 H), 7.02 (d, J = 8.6 Hz, 1 H), 6.90 (d, J = 8.8 Hz, 2 H), 6.77 (dd, J = 10.8, 17.6 Hz, 1 H), 6.16 (dd, J = 2.8, 17.6 Hz, 1 H), 6.08 (dd, J = 10.4, 18.0 Hz, 1 H) 5.60 (dd, J = 1.2, 17.6 Hz, 1 H), 5.56 (dd, J = 2.8, 10.4 Hz, 1 H), 5.18 (dd, J = 1.2, 10.8 Hz, 1 H), 5.06 (s, 2 H), 5.04 (s, 2 H) 3.81 (s, 3 H), 3.47 (s, 6 H), 3.38 (s, 3 H); ¹³C-NMR (150 MHz) δ 191.1, 170.9, 159.6, 152.8, 151.1, 142.5, 134.2, 129.3, 129.3, 128.4, 126.0, 125.8, 124.1, 121.3, 116.7, 115.1, 114.5, 114.0, 99.0, 70.7, 57.3, 55.3, 52.7; IR (film) 2945, 1765, 1515, 1465, 1251, 1028, 992 cm⁻¹; HRMS (CI) m/z calc for C₂₆H₂₈O₇⁺ (M⁺), 452.1835; found, 452.1837.
1,1-Dimethoxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)cyclobuta[a]naphthalen-2(1H)-one (10). A solution of 15 (1.14 g, 2.513 mmol), Grubbs II (149 mg, 0.176 mmol) and butylated hydroxytoluene (BHT) (111 mg, 0.502 mmol) in dichloroethylene (DCE) was degassed and then heated under reflux for 8 h. The reaction mixture was cooled to room temperature, DMSO (0.564 g, 0.62 mL, 8.795 mmol) was added, and the mixture was stirred for 16 h at room temperature. The solvent was removed under reduced pressure, and the crude material was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:10 → 1:2) to provide 836 mg (78%) of 10 as a brownish green solid: mp 83-85 °C and 214 mg (13%) 15 (91% brsm); ¹H-NMR (500 MHz) δ 7.90 (d, J = 8.4 Hz, 1 H), 7.70 (d, J = 8.8 Hz, 1 H), 7.51 (d, J = 8.8 Hz, 1 H), 7.41 (d, J = 8.8 Hz, 2 H), 7.36 (d, J = 8.4 Hz, 1 H), 6.92 (d, J = 8.8 Hz, 2 H), 5.35 (s, 2 H), 5.20 (s, 2 H), 3.82 (s, 3 H), 3.57 (comp, 9 H); ¹³C-NMR (125 MHz) δ 193.2, 160.3, 159.6, 150.4, 147.5, 140.6, 133.8, 132.7, 129.4, 128.4, 125.8, 125.2, 120.1, 118.2, 114.7, 114.0, 99.6, 71.7, 57.7, 55.3, 53.7; IR (film) 2942, 2836, 1760, 1614, 1584, 1515, 1462, 1334, 1251, 1174, 1108, 1033, 937 cm⁻¹; HRMS (CI) m/z calc for C₂₄H₂₅O₇⁺ (M⁺), 425.1600; found, 425.1596.

2,2-Di-tert-butyl-4-ethynyl-6,7-dimethoxy-4H-benzo[cd][1,3,2]dioxasiline (9). A solution of aldehyde 17 (1.56 mg, 8.57 mmol), prepared according to literature procedures,⁷ in THF (16 mL) was cooled to –78 °C, and the reaction vessel was degassed. A solution of ethynyl magnesium bromide (0.5 M, 42.8 mL, 21.41 mmol) was then added at –78 °C. The cooling bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h, whereupon a solution of dilute NH₄Cl (10 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The crude oil was purified by silica plug
eluting with 1:1 mixture acetone/hexanes (500 mL) to provide 1.44 g of the acetylide adduct as a brown solid that used directly in the next step.

A solution the acetylide adduct (1.44 g, 6.92 mmol) and 2,6-lutidine (1.85 g, 2.0 mL, 17.3 mmol) in CH$_2$Cl$_2$ (18 mL) was cooled to – 40 °C, (tert-Bu)$_2$Si(OTf)$_2$ (3.65 g, 2.7 mL, 8.30 mmol) was added, and the reaction mixture was warmed to 0 °C by replacing the cooling bath with an ice/water bath. The mixture was stirred for 4 h, whereupon a solution of saturated aqueous NaHCO$_3$ (5 mL) was added, and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:20 → 1:10) to provide 1.98 g (82%) of 9 as a waxy white solid: mp 78-80 °C; $^1$H-NMR (500 MHz) δ 6.82 (s, 1 H), 6.49 (s, 1 H), 5.84 (dd, $J$ = 0.7, 2.3 Hz, 1 H), 3.85 (s, 1 H), 3.83 (s, 3 H), 2.66 (d, $J$ = 2.3 Hz, 1 H), 1.06 (s, 9 H), 1.03 (s, 9 H); $^{13}$C-NMR (125 MHz) δ 149.8, 147.1, 143.2, 116.5, 109.8, 103.6, 83.1, 74.1, 64.5, 56.4, 55.9, 26.9, 26.9, 21.5, 20.9; IR (film) 3287, 2936, 2896, 2860, 2120, 1616, 1512, 1471, 1471, 1450, 1405, 1364, 1326, 1291, 1264, 1218, 1200, 1195, 1175, 1126, 1084, 1012, 940 cm$^{-1}$; HRMS (ESI) m/z calc for NaC$_{19}$H$_{28}$O$_4$Si$^+$ (M+Na), 371.1649; found, 371.1652.

2-((2,2-Di-tert-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)ethynyl)-1,1-dimethoxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)-1,2-dihydrocyclobuta[a]naphthalen-2-ol (8). A solution of 9 (1 g, 2.36 mmol) in toluene (5 mL) was concentrated under reduced pressure (1 X), put under vacuum for 2 h, and dissolved in THF (5 mL). A separate round bottomed flask containing 10 (1.64 mg, 4.72 mmol) was dissolved in toluene (5 mL), concentrated under reduced pressure (1 X), and put under vacuum for 2 h. 4-(Phenylazo)diphenylamine (PDA) (4.118) (32 mg, 0.12 mmol), THF (24 mL) and a solution of CeCl$_3$·2LiCl in THF (0.33 M, 17.8 mL, 5.89 mmol)$^8$ was added to the flask containing 9 and the mixture was cooled to – 78 °C and the reaction vessel was degassed. A solution of n-BuLi in hexanes was added until the reaction mixture turned a persistent purple color. After the purple endpoint had been seen, an additional amount of n-BuLi in hexanes (2.47 M, 1.91 mL, 4.72 mmol) was
added, the cooling bath was removed, and the reaction mixture was warmed to 0 °C. The solution of 10 in THF was slurried over NaH (60 % dispersion in mineral oil, ca. 60 mg, 1.5 mmol) before adding to the reaction mixture containing 9, and stirring continued for an additional 1 h. AcOH (7.07 mL, 1.36 g, 23.6 mmol) and de-ionized H₂O (50 mL) were then added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:4 → 1:2) to provide 1.64 g (90%) of 8 as a golden foam; ¹H-NMR (600 MHz) δ 7.81 (d, J = 8.3 Hz, 2 H), 7.60 (d, J = 8.9 Hz, 2 H), 7.41 (d, J = 8.3 Hz, 1 H), 7.40 (d, J = 8.3 Hz, 1 H), 7.39 (d, J = 8.8 Hz, 4 H), 7.31 (d, J = 9.0 Hz, 2 H), 6.90 (d, J = 9.7 Hz, 4 H), 6.78 (s, 1 H), 6.69 (s, 1 H), 6.44 (s, 1 H), 6.43 (s, 1 H), 5.89 (d, J = 6.4 Hz, 2 H), 5.31 (dd, J = 5.3, 6.8 Hz, 2 H), 5.18 (dq, J = 2.4, 11.4 Hz, 4 H), 5.10 (dd, J = 5.3, 8.3 Hz, 2 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 3.67 (s, 3 H), 3.66 (s, 3 H), 3.65 (s, 3 H), 3.61 (s, 3 H), 3.56 (s, 3 H), 3.53 (s, 3 H), 3.52 (s, 3 H), 3.51 (s, 3 H), 3.50 (s, 3 H), 3.50 (s, 3 H), 1.51 (s, 9 H), 1.03 (s, 9 H), 0.96 (s, 9 H), 0.90 (s, 9 H); ¹³C-NMR (150 MHz) δ 159.5, 150.1, 150.0, 149.5, 149.4, 147.0, 146.3, 143.0, 143.0, 142.9, 138.7, 136.8, 136.7, 132.5, 131.0, 129.4, 128.8, 128.7, 126.3, 126.2, 117.1, 117.0, 116.6, 113.9, 109.9, 109.8, 107.6, 107.5, 103.4, 99.8, 86.7, 83.8, 77.5, 71.6, 64.8, 57.6, 56.1, 55.9, 55.3, 53.2, 51.9, 51.8, 26.9, 21.5, 21.0, 20.8; IR (film) 3498, 2937, 2860, 2353, 1732, 1615, 1594, 1513, 1464, 1405, 1337, 1252, 1200, 1175, 1121, 1080, 1035, 1012, 938 cm⁻¹; HRMS (ESI) m/z calc for NaC₁₉H₂₈O₄Si⁺ (M+Na), 795.3171; found, 795.3163.

2-((2,2-Di-tert-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)ethynyl)-2-hydroxy-7-((4-methoxybenzyl)oxy)-8-(methoxymethoxy)cyclobuta[a]naphthalen-1(2H)-one (S5). H₃PO₄ (85%, 7 mg, 4 µL, 0.0697 mmol) and H₂O (28 mg, 28 µL, 1.2546 mmol) was added to a slurry of silica (280 mg) in CH₂Cl₂ (2.1 mL). The mixture was stirred vigorously for 1 h, whereupon 8 (54 mg, 0.0697 mmol) and CH₂Cl₂ (1 mL) were added, and the mixture was stirred for 1 h. Et₃N (35 mg, 49 µL, 0.3485 mmol) was then added, and the mixture was filtered through a silica plug (~10 mL). The plug was eluted with EtOAc/hexanes (1:1, 1 x 100 mL) and the eluant was concentrated under reduced pressure (bath
temp 30 °C) to provide 48 mg (95%) of S5 as an orange oil. The material was unstable, so it was used directly in the next step without further purification; ¹H-NMR (600 MHz) δ 8.04 (d, J = 8.3 Hz, 1 H), 8.03 (d, J = 8.5 Hz, 1 H), 7.66 (d, J = 9.0 Hz, 1 H), 7.65 (d, J = 9.0 Hz, 1 H), 7.63 (d, J = 8.2 Hz, 1 H), 7.61 (d, J = 8.2 Hz, 1 H), 7.41-7.37 (comp, 6 H), 6.91 (d, J = 8.7 Hz, 4 H), 6.72 (s, 1 H), 6.68 (s, 1 H), 6.46 (s, 1 H), 6.44 (s, 1 H), 5.90 (d, J = 0.7 Hz, 1 H), 5.87 (d, J = 0.7 Hz, 1 H), 5.40-5.36 (m, 4 H), 5.20 (d, J = 3.2 Hz, 4 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 6 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.54 (s, 3 H), 3.52 (s, 3 H), 1.04 (s, 9 H), 1.03 (s, 9 H), 0.99 (s, 9 H), 0.97 (s, 9 H); ¹³C-NMR (150 MHz) δ 182.9, 160.4, 160.3, 159.6, 151.6, 149.8, 149.7, 147.0, 146.9, 143.2, 142.1, 140.4, 138.6, 130.9, 129.3, 128.3, 126.1, 124.1, 118.1, 116.6, 116.4, 116.3, 114.0, 109.5, 103.6, 103.5, 99.6, 99.5, 90.0, 89.9, 85.5, 82.2, 82.1, 71.5, 64.7, 57.7, 56.3, 56.2, 56.0, 55.9, 55.3, 27.0, 26.9, 26.8, 21.5, 20.8; IR (neat) 3435, 2935, 2860, 1765, 1615, 1587, 1512, 1465, 1406, 1336, 1251, 1216, 1200, 1175, 1120, 1080, 1034, 941 cm⁻¹; HRMS (ESI) m/z calc for NaC₄H₄O₁₀Si⁺ (M+Na), 749.2752; found, 749.2739.

3-(2,2-Di-tert-butyl-6,7-dimethoxy-4H-benzo[d][1,3,2]dioxasilin-4-yl)-6-((4-methoxybenzyl)oxy)-5-(methoxymethoxy)phenanthrene-1,4-dione (7). A solution of crude S5 (50 mg, 0.0647 mmol) in MTBE (4 mL) was heated to 60 °C for 1 h. The reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the crude oil was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:10 → 3:10) to provide 23 mg (49%) of 7 as a red solid and 9 mg (19%) of 21 as a mixture (1.2:1) of E- and Z-isomers: ¹H-NMR (600 MHz) δ 8.00 (d, J = 8.5 Hz, 1 H), 7.97 (d, J = 8.5 Hz, 1 H), 7.63 (d, J = 8.9 Hz, 1 H), 7.48 (d, J = 8.9 Hz, 1 H), 7.40 (d, J = 8.7 Hz, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 6.73 (s, 1 H), 6.56 (s, 1 H), 6.47 (s, 1 H), 6.37 (s, 1 H), 5.29-5.16 (comp, 4 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.66 (s, 3 H), 3.31 (s, 3 H), 1.09 (s, 9 H), 1.02 (s, 9 H); ¹³C-NMR (150 MHz) δ 186.9, 185.4, 159.6, 154.8, 150.9, 149.8, 148.3, 143.3, 142.8, 133.6, 133.1,
3-(Hydroxy(2-hydroxy-4,5-dimethoxyphenyl)methyl)-6-((4-methoxybenzyl)oxy)-5-(methoxymethoxy)phenanthrene-1,4-dione (20). One drop of HF•Pyridine was added to a solution of 7 (41 mg, 0.0565 mmol) and pyridine (49 mg, 50 µL, 0.621 mmol) in THF (2 mL), and the reaction was stirred for 30 min at room temperature. The mixture was diluted with EtOAc (5 mL), and the solution was washed with NH₄Cl (1 x 2 mL) and de-ionized H₂O (1 x 2 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure, and the crude oil was purified by flash chromatography eluting with a gradient of EtOAc/hexanes (1:2 → 3:4) to provide 24 mg (72%) of 20 as a red solid: ¹H-NMR (600 MHz) δ 7.97 (d, J = 8.5 Hz, 1 H), 7.90 (d, J = 8.5 Hz, 1 H), 7.68 (bs, 1 H), 7.63 (d, J = 8.9 Hz, 1 H), 7.47 (d, J = 8.9 Hz, 1 H), 7.39 (d, J = 8.7 Hz, 2 H), 6.93 (d, J = 8.7 Hz, 2 H), 6.67 (s, 1 H), 6.55 (s, 1 H), 6.47 (d, J = 1.6 Hz, 1 H), 6.17 (bs, 1 H), 5.19 (s, 2 H), 5.13 (d, J = 4.8 Hz, 1 H), 5.19 (d, J = 4.8 Hz, 1 H), 4.40 (bs, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.82 (s, 3 H), 3.19 (s, 3 H); ¹³C-NMR (150 MHz) δ 188.8, 185.0, 159.7, 152.7, 150.9, 150.3, 150.0, 143.0, 141.4, 133.8, 133.2, 132.9, 132.7, 130.0, 129.4, 128.3, 125.3, 125.1, 119.6, 114.1, 114.0, 113.6, 111.2, 102.4, 98.2, 71.7, 70.3, 57.6, 56.6, 56.0, 55.3;  IR (film) 3431, 2933, 2837, 1659, 1614, 1588, 1514, 1449, 1335, 1302, 1250, 1197, 1137, 1112, 1055, 1035, 916 cm⁻¹; HRMS (ESI) m/z calc for NaC₃₃H₃₉O₈⁺ (M+Na), 609.1731; found, 609.1722.
10,11-Dimethoxy-2-((4-methoxybenzyl)oxy)-1-(methoxymethoxy)-13H-naphtho[1,2-b]xanthene-7,13,14-trione (6). Activated manganese dioxide (MnO₂) (667 mg, 7.67 mmol) was added to a solution of 20 (30 mg, 0.051 mmol) in CH₂Cl₂ (6.1 mL) and pyridine (0.3 mL) at room temperature and stirred for 4 h. The mixture was then filtered through a silica plug, eluting with a mixture (1:1) of acetone/hexanes (20 mL) and the combined filtrates were concentrated under reduced pressure. The crude material was then purified by flash chromatography eluting with a gradient of acetone/hexanes (7:20 → 1:2) to provide 13 mg (44%) of 6 as an orange solid:¹H-NMR (500 MHz) δ 8.04 (d, J = 8.5 Hz, 1 H), 7.99 (d, J = 8.5 Hz, 1 H), 7.65 (s, 1 H), 7.61 (d, J = 9.1 Hz, 1 H), 7.50 (d, J = 9.0 Hz, 1 H), 7.42 (d, J = 8.8 Hz, 2 H), 7.15 (s, 1 H), 6.92 (d, J = 8.8 Hz, 2 H), 5.26 (s, 2 H), 5.23 (s, 2 H), 4.03 (s, 3 H), 4.01 (s, 3 H), 3.82 (s, 3 H), 3.44 (s, 3 H); ¹³C-NMR (125 MHz) δ 182.1, 179.1, 172.6, 159.6, 155.6, 153.8, 151.2, 150.6, 148.8, 143.7, 135.2, 133.7, 133.3, 130.4, 129.4, 128.5, 125.2, 124.7, 121.6, 121.0, 119.8, 119.1, 114.0, 105.1, 100.6, 99.2, 77.1, 57.8, 56.8, 56.5, 55.3; IR (film) 2928, 1688, 1641, 1620, 1600, 1512, 1467, 1450, 1428, 1402, 1334, 1272, 1249, 1175, 1126, 1081, 1048, 992 cm⁻¹; HRMS (ESI) m/z calc for NaC₃₅H₂₆O₁₀ + (M+Na), 605.1418; found, 605.1410.


