Supporting Information

Structure Determination of Mycolactone C via Total Synthesis

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**General Procedures and Methods**

Except as otherwise indicated, reactions were carried out under an nitrogen atmosphere in flame- or oven-dried glassware. Reagents and solvents are commercial grade and were used as supplied, with the following exceptions: THF was distilled from sodium/benzophenone; toluene, diethyl ether and dichloromethane were purified by passing through two alumina (A-2) columns using the J. C. Myer (Glass Contour) system; benzene was distilled from calcium hydride and stored over 3Å MS; and triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Reactions were monitored by thin layer chromatography (TLC) with 0.25-mm E. Merck pre-coated silica gel plates. Silica gel 60 for flash chromatography (particle size 0.040-0.063 mm) was supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Inova 600 MHz, Varian Inova 500 MHz or Varian Mercury 400 MHz spectrometer. Chemical shifts are reported as $\delta$ values (ppm) relative to internal chloroform ($\delta$ 7.26), benzene ($\delta$ 7.15), methanol ($\delta$ 3.34), or acetone ($\delta$ 2.04) for $^1$H spectra and either chloroform ($\delta$ 77.0), benzene ($\delta$ 128.0), methanol ($\delta$ 49.0), or acetone ($\delta$ 29.8) for $^{13}$C spectra. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Low- and high-resolution mass spectra were measured at the Harvard University Chemistry and Chemical Biology Mass Spectrometry Facility.

To a solution of (+)-Ipc$_2$BOMe (516 mg, 1.63 mmol) in Et$_2$O (24 mL) at -78 °C was added allyl magnesium bromide (1.63 mL, 1.63 mmol, 1M in Et$_2$O) by dropwise addition. After stirring 10 min, the resulting solution was allowed to come to ambient temperature for 1h and recooled to -78 °C. The known aldehyde 4 (300 mg, 1.48 mmol; Paterson, I.; Craw, P. A. Tetrahedron Lett. 1989, 30, 5799) in Et$_2$O was added in dropwise fashion and the reaction was allowed to stir for 1h at -78 °C. After warming to 0 °C, the reaction was quenched by careful addition of aqueous 3N NaOH (1.1 mL) and
30% H₂O₂ (0.44 mL) and stirred 12 hrs at ambient temperature and diluted with H₂O. The layers were separated, and the aqueous layer was extracted 3 x Et₂O. The combined organic layers were washed 1 x H₂O, 1 x brine, and dried over MgSO₄. Concentration in vacuo and purification by flash chromatography (9:1 Hex/EtOAc) afforded the corresponding allylic alcohol (243 mg, 67% yield) as a single diastereomer. (Note- in the case of the anti-1,3 diols used to prepare 11c and 11d, the diastereoselectivity was ca. 8:1 in favor of the desired product. The minor diastereomer was seperated following DiBAI-H reduction at a later stage vide supra).

A solution of the allylic alcohol described above, TBSCl, and imidazole in DMF (800 μL) was stirred for 2.5h at ambient temperature. The reaction was quenched by dilution with Et₂O and H₂O. The layers were separated, and the aqueous layer was extracted 2 X Et₂O. The combined organic layers were washed 2 x H₂O, 1 x brine, and dried over MgSO₄. Concentration in vacuo and purification by flash chromatography (20:1 Hex/EtOAc) afforded the corresponding bis TBS-protected diol as a colorless oil (346 mg, 97% yield). [α]²³₀ = -2.4 (c 1.4, MeOH) ¹H NMR (400 MHz, CDCl₃) δ 5.85 (m, 1H), 5.05 (m, 1H), 5.01 (m, 1H), 3.90 (m, 1H), 3.79 (m, 1H), 2.26 (m, 1H), 2.16 (m, 1H), 1.67 (ddd, J= 13.6, 6.4, 6.4 Hz, 1H), 1.51 (ddd, J=13.6, 6.4, 6.4 Hz, 1H), 1.13 (d, J= 6.4 Hz, 3H), 0.88 (s, 18H), 0.05 (s, 6H), 0.04 (s, 6H);¹³C NMR (CDCl₃, 100 MHz) δ 135.1, 116.8, 69.3, 65.8, 47.1, 41.8, 25.9 (x3), 25.8 (x3), 23.9, -4.3, -4.3, -4.6, -4.8; HRMS (ES+) 359.2804, calcd 359.2801.

Anti-1,3 bis TBS-protected diol for the preparation of 11c and 11d:
¹H NMR (400 MHz, CDCl₃) δ 5.85 (m, 1H), 5.05 (d, J=3.6 Hz, 1H), 5.02 (s, 1H), 3.89 (m, 1H), 3.82 (m, 1H), 2.22 (m, 2H), 1.64 (ddd, J= 7.2, 14.0, 5.2 Hz, 1H), 1.47 (ddd, J=6.8, 14.0, 5.2 Hz, 1H), 1.15 (d, J= 6.0 Hz, 3H), 0.88 (s, 18H), 0.06 (s, 12H).

Ozone was passed through a solution of bis TBS-protected diol (346 mg, 0.965 mmol) described above in CH₂Cl₂ (50 mL) at -78 °C until a blue solution was observed. Oxygen followed by nitrogen gas was bubbled through the solution followed by addition of triphenylphosphine (313 mg, 1.29 mmol). After stirring at room temperature for 3h, the solution was concentrated in vacuo and purified by flash chromatography (20:1 Hex/EtOAc) to furnish the corresponding aldehyde (337 mg, 97% yield).¹H NMR (400 MHz, CDCl₃) δ 9.79 (dd, J= 2.0, 3.2 Hz, 1H), 4.32 (m, 1H), 3.86 (m, 1H), 2.56 (ddd, J=
4.4, 15.2, 1.6 Hz, 1H), 2.49 (ddd, J= 7.2, 16.0, 3.6 Hz, 1H), 1.78 (ddd, J= 13.6, 8.0, 5.6 Hz, 1H), 1.56 (ddd, J= 13.6, 8.0, 4.8 Hz, 1H), 1.15 (d, J= 6.0, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.07 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H).

To a solution of the above aldehyde (337 mg, 0.934 mmol) in toluene (10 mL) was added carbethoxyethylidene triphenylphosphorane (792 mg, 2.19 mmol). The reaction was heated to 110 °C for 12h, cooled to room temperature, and then concentrated in vacuo. Flash chromatography (20:1 Hex/E$_2$O) gave ester 5 (357 mg, 86% yield) as a colorless oil. [α]$^2_3^2$D = +9.4 (c 1.0, MeOH) $^1$H NMR (400 MHz, CDCl$_3$) δ 6.83 (ddd, J= 1.2, 7.6, 76 Hz 1 H), 4.20 (q, J= 7.2 Hz, 2H), 3.89 (m, 2H), 2.35 (m, 1H), 2.30 (m, 1H), 1.82 (s, 3H), 1.70 (m, 1H), 1.49 (m, 1H), 1.27 (t, J= 7.2 Hz, 3H), 1.13 (d, J=5.6 Hz, 3H), 0.87 (s, 18 H), 0.04 (s, 6H), 0.03 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.0, 138.7, 128.9, 68.8, 65.7, 60.3, 47.7, 36.5, 25.8 (x 3), 25.8 (x 3), 23.9, 18.0, 17.9, 14.2, 12.6, -4.3, -4.6, -4.6, -4.8; HRMS (ES+) 445.3163, calcd 445.3169.

To a solution of ester 5 (357 mg, 0.803 mmol) in CH$_2$Cl$_2$ (10 mL) at -78 °C was slowly added DiBAl-H (2.0 ml, 2.0 mmol, 1M in hexanes). The resulting solution was stirred at -78 °C for 1.5h and quenched with saturated aqueous potassium sodium tartrate (25 mL). The mixture was stirred vigorously for 6h while warming to ambient temperature and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted 2 X EtOAc. The combined organic layers were washed 1 x H$_2$O, 1 x brine, and dried over MgSO$_4$. Concentration in vacuo and purification by flash chromatography (10:1 Hex/EtOAc) afforded the corresponding alcohol. [α]$^2_3^2$D = -8.6 (c 1.2, MeOH) $^1$H NMR (400 MHz, CDCl$_3$) δ 5.43 (ddd, J= 1.2, 7.2, 7.2 Hz 1 H), 3.99 (s, 2H), 3.90 (m, 1H), 3.77 (m, 1H), 2.19 (m, 2H), 1.65 (s, 3H), 1.63 (m, 1H), 1.49 (m, 1H), 1.12 (d, J= 6.4 Hz, 3H), 0.86 (s, 18 H), 0.03 (s, 3H), 0.03 (s, 3 H), 0.02 (s, 6 H); $^{13}$C NMR (CDCl$_3$, 100
organic layers were separated, and the aqueous layer was extracted 2 x Et₂O. The combined organic layers were washed 1 x 50% saturated aqueous NaHCO₃, 1 x H₂O, 1 x brine, and dried over MgSO₄. Concentration in vacuo and purification by flash chromatography (20:1 Hex/Et₂O) afforded aldehyde 6 (43 mg, 96% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 9.41 (s, 1H), 6.59 (t, J = 7.6 Hz, 1H), 3.99 (m, 1H), 3.88 (m, 1H), 2.52 (m, 2H), 1.74 (s, 3H), 1.72 (m, 1H), 1.50 (ddd, J = 12.8, 7.2, 5.2 Hz, 1H), 1.15 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H).

Each diastereomer of the polyunsaturated carboxylic acid was prepared analogous to our previously reported conditions, see: Song, F.; Fidanze, S.; Benowitz; Kishi, Y. Org. Lett. 2002, 4, 647.

To a stirred solution of aldehyde 6 (32 mg, 79.0 μmol) and phosphonate 7 (50 mg, 158 μmol; Gurjar, M. K.; Cherian, J; Heterocycles 2001, 55, 1095) in THF (0.6 mL) at -78 °C was added dropwise freshly prepared LDA (0.3 mL, 150 μmol, 0.5M in THF). The resulting dark red solution was stirred at -78 °C for 10 min, then allowed to warm to 0 °C over 1h. After stirring for an additional 1h at ambient temperature, the reaction was quenched by addition of saturated aqueous NH₄Cl followed by dilution with EtOAc. The layers were separated, and the aqueous layer was extracted 3 x EtOAc. The combined organic layers were washed 1 x H₂O, 1 x brine, and dried over Na₂SO₄. Concentration in
vacuo and purification by flash chromatography (20:1 Hex/EtOAC) furnished the corresponding ester (50 mg, 96%) as a yellow oil. This ester exists as a 1:1 mixture of 4′Z:4′E isomers.

To a stirred solution of the above ester (25 mg, 44.4 µmol) in 4:1:1 THF/MeOH/H$_2$O (1.4 mL) was added LiOH (430 µl, 0.43 mmol, 1.0M in H$_2$O). The resulting solution was protected from light and stirred for 18h at ambient temperature. The reaction was quenched by addition of saturated aqueous NH$_4$Cl followed by dilution with EtOAc. The layers were separated, and the aqueous layer was extracted 3 x EtOAc. The combined organic layers were washed 1 x H$_2$O, 1 x brine, and dried over Na$_2$SO$_4$. Concentration in vacuo and purification by flash chromatography (4:1 Hex/EtOAC) furnished the acid 8 (23 mg, 96%) as a yellow oil. This acid exists as a ca. 1:1 mixture of 4′Z:4′E isomers. [α]$^{23}_{D}$ = +12.3 (c 0.76, MeOH); $^1$H NMR (400 MHz, CD$_3$COCD$_3$, 4′Z isomer) δ 7.95 (d, J= 16.0 Hz, 1H), 6.54 (dd, J= 14.8, 10.8 Hz, 1H), 6.44 (s, 1H), 6.37 (d, J = 10.4 Hz, 1H), 6.17 (d, J= 11.2 Hz, 1 H), 5.89 (d, J= 15.6, 1 H), 5.71 (dd, J= 8.0, 16.0 Hz, 1H), 3.93 (m, 2H), 2.37 (m, 2H), 2.01 (s, 3H), 1.96 (s, 3H), 1.84 (s, 3H), 1.71 (m, 1H), 1.51 (m, 1H), 1.14 (d, J= 6.0 Hz, 3 H), 0.89 (s, 9H), 0.08 (s, 6H). $^1$H NMR (400 MHz, CD$_3$COCD$_3$, 4′E isomer) δ 7.36 (d, J= 15.6 Hz, 1H), 6.56 (dd, J= 14.8, 10.8 Hz, 1H), 6.48 (d, J= 14.8, 1H), 6.44 (s, 1H), 6.33 (d, J = 8.0 Hz, 1H), 5.87 (d, J= 16.0 Hz, 1 H), 5.71 (dd, J= 8.0, 16.0 Hz, 1H), 3.98 (m, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 1.84 (s, 3H), 1.68 (m, 1H), 1.54 (m, 1H), 1.15 (d, J= 5.6 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H). $^{13}$C NMR (100 MHz, CD$_3$COCD$_3$, 4′Z and 4′E isomers); MS (ES+) 549.3800 (M+H), calcd. 549.3795.

Anti-1,3 bis TBS-protected diol carboxylic acid for the preparation of 11c and 11d: $^1$H NMR (400 MHz, CD$_3$COCD$_3$, 4′Z isomer) δ 7.95 (d, J= 15.6 Hz, 1H), 6.54 (dd, J= 14.8, 10.8 Hz, 1H), 6.44 (d, J= 15.2 Hz, 1H), 6.39 (d, J = 11.6 Hz, 1H), 6.19 (d, J= 10.4 Hz, 1H), 5.94 (d, J= 16.0, 1 H), 5.70 (dd, J= 8.0, 16.0 Hz, 1H), 3.99 (m, 2H), 2.39 (m, 2H), 2.01 (s, 3H), 1.96 (s, 3H), 1.84 (s, 3H), 1.62 (m, 1H), 1.52 (m, 1H), 1.14 (d, J= 6.0 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H). $^1$H NMR (400 MHz, CD$_3$COCD$_3$, 4′E isomer) δ 7.36 (d, J= 15.6 Hz, 1H), 6.56 (dd, J= 14.8, 10.8 Hz, 1H), 6.48 (d, J= 14.4 Hz, 1H), 6.46 (s, 1H), 6.34 (s, 1H), 5.88 (d, J= 15.6 Hz, 1 H), 5.70 (dd, J= 8.0, 16.0 Hz, 1H), 3.98
(m, 2H), 2.40 (m, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 1.84 (s, 3H), 1.62 (m, 1H), 1.52 (m, 1H), 1.15 (d, J = 6.0 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H).

To a stirred solution of acid 8 (19 mg, 34.6 µmol) in benzene (1.4 mL) was added i-Pr2NEt (16 µL, 92.4 µmol) Cl3C6H2COCl (6.8 µL, 43.8 µmol) and DMAP (11.3 mg, 92.4 µmol). After 20 min, alcohol 9 (15 mg, 23.1 µmol) was added as a solution in benzene (1.6 mL). The reaction was protected from light and stirred 24 h. The reaction was quenched by addition of saturated aqueous NaHCO3 and diluted with EtOAC. The layers were separated, and the aqueous layer was extracted 3 x EtOAc. The combined organic layers were washed 1 x H2O, 1 x brine, and dried over Na2SO4. Concentration in vacuo and purification by flash chromatography (20:1 Hex/EtOAC) gave the corresponding ester (25 mg, 91% yield) as a yellow oil. This ester exists as a ca. 1:1 mixture of 4’Z:4’E isomers.

To a stirred solution of the above ester 10 (25 mg, 21.1 µmol) in THF (2.3 mL) was added TBAF (190 µL, 190 µmol, 1M in THF). The reaction was protected from light and stirred 18 h. The reaction was quenched by addition of saturated aqueous NH4Cl and diluted with EtOAC. The layers were separated, and the aqueous layer was extracted 3 x EtOAc. The combined organic layers were washed 1 x H2O, 1 x brine, and dried over
Na₂SO₄. Concentration *in vacuo* and purification by flash chromatography (100:1 EtOAc/MeOH) gave the corresponding synthetic mycolactone 11 as a yellow oil (12.8 mg, 84% yield). The synthetic mycolactones exist as a ca. 1:1 mixture of 4′Z:4′E isomers. [α]²³°D = -15.5 (c 0.48, MeOH) ¹H NMR (500 MHz, CD₃COCD₃, 4′Z isomer) δ 7.93 (d, J = 16.0 Hz, 1H), 6.51 (dd, J= 11.0, 15.5 Hz, 1H), 6.45 (d, J = 15.5 Hz, 1H), 6.32 (s, 1H), 6.15 (d, J=11.0 Hz, 1H), 5.93 (d, J= 16.0 Hz, 1 H), 5.72 (dd, J= 7.5, 15.5 Hz, 1H), 5.12 (m, 1H), 5.04 (d, J= 10.0 Hz, 1H), 4.88 (m, 1H), 4.70 (m, 1H), 4.23 (dd, J= 3.5, 3.5 Hz, 1H), 4.19 (d, J= 3.5 Hz, 1H), 3.50 (m, 1H), 2.49 (m, 1H), 2.38 (m, 2H), 2.34 (m, 2H), 2.07-1.85 (m, 8H), 2.01 (s, 3H), 1.99 (s, 3H), 1.84 (s, 3H), 1.69 (s, 3H), 1.64 (s, 3H), 1.83 (m, 1H), 1.70 (m, 1H), 1.66 (m, 1H), 1.55-1.60 (m, 4H), 1.48 (m, 1H), 1.38 (m, 1H), 1.13 (d, J= 5.5 Hz, 3H), 1.11 (d, J= 6.0 Hz, 3H), 0.97 (d, J= 7.0 Hz, 3H), 0.90 (d, J= 6.5 Hz, 1H), 0.88 (d, J= 7.0 Hz, 3H).

¹H NMR (500 MHz, CD₃COCD₃, 4′E isomer) δ 7.37 (d, J = 15.5 Hz, 1H), 6.52 (dd, J= 10.5, 15.0 Hz), 6.45 (s, 1 H), 6.42 (d, J= 15.5 Hz, 1H), 6.34 (d, J= 12.0 Hz, 1H), 5.88 (d, J= 16.0 Hz, 1H), 5.72 (dd, J= 7.5, 15.5 Hz, 1H), 5.12 (m, 1H), 5.04 (d, J= 10.0 Hz, 1H), 4.88 (m, 1H), 4.70 (m, 1H), 4.22 (d, J= 3.5 Hz, 1H), 4.09 (dd, J= 3.0, 5.5 Hz, 1H), 3.50 (m, 1H), 2.49 (m, 1H), 2.38 (m, 2H), 2.34 (m, 2H), 2.07-1.85 (m, 8H), 2.07 (s, 3H), 1.96 (s, 3H), 1.83 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.83 (m, 1H), 1.70 (m, 1H), 1.66 (m, 1H), 1.55-1.60 (m, 4H), 1.48 (m, 1H), 1.38 (m, 1H), 1.13 (d, J= 5.5 Hz, 3H), 1.11 (d, J= 6.0 Hz, 3H), 0.97 (d, J= 7.0 Hz, 3H), 0.90 (d, J= 6.5 Hz, 1H), 0.87 (d, J= 6.5 Hz, 3H). ¹³C NMR (100 MHz, CD₃COCD₃, 4′E and 4′Z isomer) δ 173.2 (x 2), 166.9 (x 2), 151.2, 144.5, 143.2, 141.9, 141.0, 140.6, 137.3 (x 2), 136.6, 136.4 (x 2), 135.3, 134.4, 133.9, 133.4 (x 2), 132.1, 131.9, 131.8, 131.2 (x 3), 123.8 (x 4), 123.4 (x 2), 119.4, 117.1, 79.2 (x 3), 76.9 (x 2), 76.2, 76.2, 72.2 (x 3), 69.0 (x 2), 68.2 (x 2), 64.6 (x 2), 46.4 (x 2), 45.8 (x 2), 44.3 (x 2), 43.8, 40.5 (x 2), 38.0, 36.0 (x 2), 35.9, 35.3 (x 2), 32.8, 32.7, 31.5, 31.3, 24.6 (x 2), 24.4 (x 2), 20.9, 20.7, 20.6 (x 2), 20.5, 17.5, 17.1 (x 2), 17.0, 16.2, 15.9, 14.9 (x 2), 14.3(x 2), 12.7 (x 2). HRMS (ES+) 727.5143 (M+H), calcd 727.5149. UV (MeOH) λ_max 365 nm (log ε 4.69).

¹H NMR spectrum for each of the four diastereomers 11a, 11b, 11c, and 11d, are included.
$^{1}H$ NMR, 500 MHz, acetone-$d_{6}$
11a (H NMR, 500 MHz, acetone-d6)
11b (H NMR, 500 MHz, acetone-d6)
$^1$H NMR, 600 MHz, acetone-\(d_6\)

IIa. Synthetie Mycoelasticone C