SUPPORTING INFORMATION

Synthetic studies on the mycolactone core

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This file contains the experimental procedures for preparation of each intermediate and product.

Abbrevations: CSA = camphorsulfonic acid, DCC = N,N'-dicyclohexylcarbodiimide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DMAP = 4-dimethylaminopyridine, EDAC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HMPA = hexamethylphosphoramide, TBAF = tetra-n-butylammonium fluoride, THF = tetrahydrofuran,
General Experimental Information: Unless otherwise noted, all reagents and chemical compounds were purchased from commercial sources (Alfa Aesar, GFS Chemicals, Strem Chemicals, Sigma-Aldrich and TCI) and used without further purification. High purity anhydrous solvents (tetrahydrofuran, dichloromethane, \(N,N\)-dimethylformamide, diethyl ether, and toluene) were obtained by passing through a solvent column composed of dry activated A–1 alumina. Triethylamine (Et\(_3\)N) and \(N,N\)-diisopropylethylamine (i-Pr\(_2\)NEt) were distilled from ninhydrin, dried (Na\(_2\)SO\(_4\)), and then freshly distilled from sodium. MeOH was distilled from magnesium. Dioxane was distilled from sodium-benzophenone ketyl. All air or moisture sensitive reactions were performed under a positive pressure of dry Ar in oven-dried glassware sealed with a septum. Reactions were magnetically stirred with a Teflon-coated stir bar. Flash chromatography was performed on Silica Gel 60, 230–400 mesh (EM Sciences). TLC analyses were conducted on 250 µm Silica Gel 60 F254 glass plates (EM Sciences). Visualization was achieved with UV light and/or an appropriate stain (I\(_2\) on SiO\(_2\), KMnO\(_4\), bromocresol green, dinitrophenylhydrazine, ninhydrin, and ceric ammonium molybdate). Yields and characterization data correspond to isolated, homogeneous materials. Unless otherwise noted all solvent mixtures are given in v:v ratios. NMR spectra were recorded on a Varian Mercury Plus 400 MHz, Varian Unity 500 MHz, Jeol ECA 500 MHz, Bruker DMX 500 MHz or Varian VX 500 MHz (equipped with XSens cold probe) spectrometer. COSY, NOESY, TOCSY, HMBC and HSQC spectra were collected on a Bruker DMX 500 with 5 mm \(^1\)H (\(^{13}\)C/\(^{15}\)N) triple-resonance indirect XYZ gradient probe. FID files were processed using MestRe-C software version 6.0.2 (MestreLab Research) and were printed from MestraNova. Chemical shifts for \(^1\)H–NMR and \(^{13}\)C–NMR analyses were reported using the signal from residual CHCl\(_3\) (7.26 ppm, \(^1\)H–NMR) or the CDCl\(_3\) signal (77.16 ppm, \(^{13}\)C–NMR). Mass spectra were collected by Dr. Yongxuan Su (UC San Diego). Electrospray (ESI) and atmospheric pressure chemical ionization (APCI) analysis was performed using a Finnigan LCQDECA mass spectrometer, and fast atom bombardment (FAB) analysis was carried out using a ThermoFinnigan MAT900XL mass spectrometer. Spectral data and procedures are provided for all new compounds and copies of select spectra have been provided.

\((2S,3R)-1-(\text{tert-butylidimethylsilyloxy})-2\text{-methylhex-5-en-3-ol (10)}\). A solution of SnCl\(_4\) (2.0 mL, 17.4 mmol) in CH\(_2\)Cl\(_2\) (4 mL) was added to allyltributyltin (5.3 mL, 17.4 mmol) in CH\(_2\)Cl\(_2\) (100 mL) at -78 °C. A solution of \((S)-3-((\text{tert-butylidimethylsilyl})oxy)-2\text{-methylpropanal (S1)}\)\(^1\) (3.2 g, 15.8 mmol) in CH\(_2\)Cl\(_2\) (10 mL) was added. After 4 h at -78 °C, the mixture was diluted with satd. NH\(_4\)Cl (80 mL). The resulting aqueous solution was extracted with CH\(_2\)Cl\(_2\) (200 mL) and the combined organic layers were washed with brine (100 mL), dried
(Na₂SO₄), and the solvent removed by rotary evaporation. Purification by flash chromatography (10:1 to 4:1 hexanes/EtOAc) provided 3.4 g (88%) of compound 10 as a colorless oil: IR (neat) ν 3562, 2926, 1614, 1517, 1248, 1034, 815; ¹H–NMR (400 MHz, CDCl₃) δ ppm 5.94 (m, 1H), 5.12 (m, 1H), 5.09 (m, 1H), 3.78 (m, 2H), 3.60 (m, 2H), 2.20 (m, 1H), 1.74 (hd, J = 4.2, 7.1 Hz, 1H), 0.89 (s, 9H), 0.86 (d, J = 6.8 Hz, 3H), 0.78 (s, 6H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 135.5, 117.1, 75.8, 68.3, 39.7, 39.3, 26.0, 18.3, 13.6, −5.4, −5.5; MS (FAB) m/z 245.04 ([M+H]+, 100%); HRMS (FAB) m/z calcd. for C₁₃H₂₇O₂Si (M-H)⁻ 243.1785, found 243.1781.

(2S,3R)-3-(4-methoxybenzylxylo)-2-methylhex-5-enyloxy)(tert-butyldimethylsilane (11). A solution of p-methoxybenzyltrichloroacetimidate (3.47 g, 12.27 mmol) in CH₂Cl₂ (50 mL) was added drop wise to a solution of alcohol 10 (2.0 g, 8.18 mmol) in CH₂Cl₂ (20 mL) cooled to 0 °C. The mixture was stirred at 0 °C for 10 min. BF₃•Et₂O (8 mL) was added drop wise, and the solution was warmed to rt and stirred for an additional 12 h, during which time a voluminous precipitate formed. The precipitate was removed by filtration, the solvent was concentrated by rotary evaporation, and the residue was dissolved in 1:1 hexanes/EtOAc to induce precipitation. After removal of the insoluble material by filtration, the filtrate was washed with H₂O (40 mL), satd. NH₄Cl (30 mL), H₂O (30 mL), satd. NaHCO₃ (30 mL), H₂O (30 mL), and brine (30 mL), and dried (Na₂SO₄). The solvent was removed by rotary evaporation to afford a yellow oil that was purified by flash chromatography (60:1 to 20:1 hexanes/EtOAc). This purification afforded 0.38 g (19%) of recovered starting material and 2.17 g (73%) of compound 11 as colorless oil: IR (neat) ν 2943, 2862, 1468, 1252, 1109, 839; ¹H–NMR (400 MHz, CDCl₃) δ ppm 7.26 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.90 (ddt, J = 7.0, 10.2, 17.1 Hz, 1H), 5.10 (ddt, J = 1.4, 2.0, 17.0 Hz, 1H), 5.05 (ddt, J = 1.1, 2.1, 10.2 Hz, 1H), 4.48 (d, J = 11.0 Hz, 1H), 4.42 (d, J = 11.0 Hz, 1H), 3.81 (s, 3H), 3.59 (dd, J = 2.5, 5.5 Hz, 1H), 3.46 (td, J = 4.0, 6.8 Hz, 1H), 2.34 (dddt, J = 1.4, 4.0, 6.7, 13.6 Hz, 1H), 2.22 (m, 1H), 1.92 (m, 1H), 0.91 (s, 3H), 0.89 (s, 9H), 0.42 (s, 3H), 0.36 (s, 3H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 159.2, 135.7, 131.3, 129.5, 116.6, 113.6, 79.6, 71.5, 65.1, 55.4, 38.8, 35.1, 26.1, 18.4, 13.0, −5.2, −5.3; MS (FAB) m/z 365.13 ([M+H]+, 100%); HRMS (FAB) m/z calcd. for C₂₁H₃₆O₃Si (M+H)+ 364.2425, found 364.2428.

1-(((2S,3R)-1-iodo-2-methylhex-5-en-3-yloxy)methyl)-4-methoxybenzene (12). A solution of TBAF (5.5 mL, 1 M in THF, 5.5 mmol) was added to compound 11 (1.00 g, 2.74 mmol) dissolved in THF (30 mL). The light yellow solution was stirred for 15 h at rt, diluted with satd. NH₄Cl (50 mL), and the solvent was removed by rotary evaporation. The resulting aqueous solution was extracted with Et₂O (3 x 20 mL) and the combined
organic layers were washed with brine (20 mL), dried (Na₂SO₄), and the solvent removed by rotary evaporation. Purification by flash chromatography (10:1 to 4:1 hexanes/EtOAc) provided 640 mg (93%) of (2S,3R)-3-((4-methoxybenzyl)oxy)-2-methylhex-5-en-1-ol (S2) as a colorless oil: IR (neat) ν 3512, 2934, 1612, 1513, 1247, 1034, 821; ¹H–NMR (400 MHz, CDCl₃) δ ppm 7.26 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.87 (m, 1H), 5.14 (m, 1H), 5.10 (m, 1H), 4.61 (d, J = 11.0 Hz, 1H), 4.38 (d, J = 11.0 Hz, 1H), 3.78 (s, 3H), 3.65 (ddd, J = 3.5, 6.6, 10.4, 1H), 3.55 (ddd, J = 4.0, 6.5, 10.8, 1H), 3.43 (dt, J = 5.0, 7.2, 1H), 2.86 (m, 1H), 2.50 (dddd, J = 1.4, 5.2, 6.6, 14.6 Hz, 1H), 2.33 (m, 1H), 1.88 (hd, J = 3.6, 7.0 Hz, 1H), 0.90 (d, J = 7.0 Hz, 3H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 159.4, 134.2, 130.7, 130.2, 129.6, 117.5, 114.0, 83.3, 71.4, 66.7, 55.4, 38.0, 35.5, 14.2; MS (ESI) m/z 241.21 ([M+H]+, 100%); HRMS (FAB) m/z calcd. for C₁₅H₂₂O₃ (M+H)+ 250.1560, found 250.1563. Imidazole (410 mg, 6.0 mmol), triphenylphosphine (2.0 g, 6.0 mmol), and iodine (1.22 g, 4.8 mmol) were added sequentially to a solution of alcohol S2 (600 mg, 2.39 mmol) in toluene (25 mL) at 0 °C. The heterogeneous yellow mixture was stirred at rt for 3 h. The reaction was quenched by carefully diluting with satd. Na₂S₂O₃ (25 mL) and the layers were separated. The aqueous phase was further extracted with Et₂O (3 x 25 mL) and the combined organic layers were washed with satd. Na₂S₂O₃ (10 mL), H₂O (10 mL), and brine (10 mL), dried (Na₂SO₄), and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to provide 850 mg (98%) of compound 12 as a white solid: ¹H–NMR (400 MHz, CDCl₃) δ ppm 7.29 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.88 (dddd, J = 6.3, 7.9, 10.2, 16.7 Hz, 1H), 5.13 (m, 1H), 5.10 (m, 1H), 4.57 (d, J = 10.6 Hz, 1H), 4.43 (d, J = 10.6 Hz, 1H), 3.78 (s, 3H), 3.47 (dd, J = 5.7, 9.5, 1H), 3.41 (m, 1H), 3.32 (dd, J = 3.6, 9.3, 1H), 2.49 (dddd, J = 1.4, 4.4, 6.0, 13.7 Hz, 1H), 2.25 (m, 1H), 1.88 (m, 1H), 0.99 (d, J = 6.6 Hz, 3H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 159.4, 134.2, 130.7, 129.7, 117.5, 113.9, 81.2, 71.8, 55.4, 37.6, 34.6, 17.3, 15.8; MS (ESI) m/z 360.92 ([M+H]+); HRMS (FAB) m/z calcd. for C₁₅H₂₁IO₂ (M)+ 360.0586, found 360.0586.

1-methoxy-4-(((4R,5S)-5-methyl-7(phenylsulfonyl)oct-1-en-4-yl)oxy)methyl)benzene (13). Ethyl phenyl sulfone (29 mg, 0.17 mmol) was dissolved in THF (1 mL) containing freshly distilled HMPA (29 mL, 0.17 mmol), purged with Ar and cooled to -78 °C. n-BuLi (70 mL, 2.4 M in hexanes, 0.17 mmol) was added and the yellow solution stirred for 1 h at -78 °C. A solution of iodide 12 (30 mg, 0.083 mmol) in THF (0.5 mL) was added drop wise and the reaction incubated at -50 °C for 30 min and -20 °C for 30 min, during which time the yellow color remained. The reaction was quenched with satd. NH₄Cl (2 mL), warmed to 20 °C, and the THF was removed by rotary evaporation. The resulting aqueous solution was extracted with Et₂O (3 x 5 mL) and the
combined organic layers were washed with \( \text{H}_2\text{O} \) (2 mL) and brine (2 mL), dried (\( \text{Na}_2\text{SO}_4 \)), and concentrated by rotary evaporation. The crude product was purified by flash chromatography (3:1 hexanes/EtO) to afford 31 mg of sulfone 13 (95%) as a colorless oil: IR (neat) \( \nu \) 2942, 1512, 1307, 1289, 1151, 527; \(^1\)H–NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 7.86 (m, 1H), 7.77 (m, 1H), 7.58 (m, 3H), 7.25 (m, 1H), 7.17 (m, 1H), 5.81 (ddq, \( J = 6.9, 10.2, 17.2 \) Hz, 1H), 5.07 (m, 1H), 5.04 (m, 1H), 4.48 (dd, \( J = 5.7, 11.0 \) Hz, 1H), 4.34 (d, \( J = 11.0 \) Hz, 1H), 3.81 (s, 3H), 3.26 (m, 0.5H), 3.19 (q, \( J = 4.8 \) Hz, 1H), 3.08 (m, 0.5H), 2.29 (m, 1H), 2.23 (m, 1H), 2.10 (m, 0.5H), 1.89 (dt, \( J = 6.5, 13.2 \) Hz, 0.5H), 1.70 (m, 1.5H), 1.27 (m, 0.5H), 1.21 (d, \( J = 6.8 \) Hz, 3H), 0.92 (d, \( J = 5.4 \) Hz, 1.5H), 0.81 (d, \( J = 6.3 \) Hz, 1.5H); \(^{13}\)C–NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 159.3, 134.9, 134.8, 133.7, 133.5, 130.8, 129.5, 129.4, 129.2, 129.1, 129.1, 117.2, 117.1, 113.9, 82.5, 82.4, 71.6, 71.3, 58.7, 58.5, 55.4, 35.2, 34.7, 33.8, 33.3, 33.2, 31.7, 17.0, 14.9, 14.5, 13.1; MS (FAB) \( m/z \) 425.3 [M+Na]+; HRMS (FAB) \( m/z \) calcd. for C\(_{23}\)H\(_{30}\)O\(_4\)S (M+Na)+ 425.1757, found 425.1759.

(2S,3R,5R)-3,5-bis(tert-butyldimethylsilyloxy)-2-methylhexanal (14). (5R,7R)-5-((R)-but-3-en-2-yl)-2,2,3,3,7,9,9,10,10-nonamethyl-4,8-dioxo-3,9-disilaundecane \( \text{S3} \) (0.1 g, 0.27 mmol) was dissolved in 3:1 CH\(_2\text{Cl}_2/\text{MeOH} \) (8 mL) and cooled to -78 °C. Ozone was bubbled through the solution until a grayish-blue color persisted. The ozone was then flushed from the solution with stream of nitrogen. Still cooled at -78 °C, dimethylsulfide (122 µL, 1.66 mmol) was added and the resulting mixture was warmed to rt and stirred for an additional 8 h. The solvent was removed by rotary evaporation and the residue was purified by flash chromatography (9:1 hexanes/EtOAc; \( R_f = 0.31 \)) to afford 100 mg (92%) of colorless oil 14:

\[ \begin{align*}
\text{H}–\text{NMR (400 MHz, CDCl}_3\text{)} & \quad \delta \text{ ppm 9.74 (s, 1H), 4.36 (ddd,} \quad \text{J} = 2.8, 6.0, 8.6 \text{ Hz, 1H), 3.83 (m, 1H), 2.48 (qd,} \quad \text{J} = 3.6, 6.9 \text{ Hz, 1H),} \\
\text{13C–NMR (100 MHz, CDCl}_3\text{)} & \quad \delta \text{ ppm 205.2, 68.8, 65.8, 50.7, 50.6, 44.4, 26.0,} \\
& \quad 25.9, 25.8, 24.1, 18.1, 18.1, 7.1, -4.0, -4.0, -4.5, -4.6; \quad \text{HRMS (FAB) m/z calcd. for C}_{19}\text{H}_{41}\text{O}_{3}\text{Si}_2 \text{(M-H)}^+ \quad 373.2593, \text{ found 373.2589.}
\end{align*} \]

(2R,4R,5R,9S,10R)-10-(4-methoxybenzylxylo)-2,4-bis(tert-butyldimethylsilyloxy)-5,7,9-trimethyl-7-(phenylsulfonyl)tridec-12-en-6-yl benzoate (15). A solution of sulfone 13 (30.0 mg, 0.075 mmol) in anhydrous THF (2 mL) at -78 °C was treated with \( n-\text{BuLi} \) in hexanes (1.4 M, 64 µL, 0.05 mmol). After stirring for 30 min, a solution of aldehyde 14 (19 mg, 0.05 mmol) in THF (2 mL) was added drop wise and the yellow solution was stirred at -78 °C for 1 h. Benzoyl chloride (14.0 µL, 0.118 mmol) was added at -78 °C. The cooling bath was removed and the reaction mixture was stirred for 1 h as it warmed to rt. The reaction was...
quenched by addition of 1:1 MeOH/Et,N (0.5 mL). The mixture was diluted with Et₂O (30 mL) and washed with H₂O (10 mL). The combined organic layers were washed sequentially with 10% HCl (10 mL), 5% NaHCO₃ (10 mL) and brine (10 mL) and then treated to flash chromatography (20:1 hexanes/EtOAc) to afford 37.4 (57%) of adducts 15 as a colorless oil that contained a 12:6:1:1 (w:w:w:w) mixture of diastereomers: IR (neat) ν 2955, 2929, 2856, 1721, 1514, 1302, 1249, 1070, 835; ¹H–NMR (400 MHz, CDCl₃) δ ppm 8.02-7.86 (m, 6H), 7.62-7.10 (m, 12H), 7.21-7.16 (m, 3H), 6.84 (m, 4H). 5.92–5.66 (m, 4H), 5.12–5.01 (m, 2H), 4.92 (m, 2H), 4.56–4.30 (m, 4H), 3.96–3.88 (m, 2H), 3.81 (m, 6H), 3.52 (m, 1H), 3.28 (m, 1H), 3.14 (m, 1H), 2.82 (m, 1H), 2.58 (m, 1H), 2.30–2.18 (m, 4H), 1.84 (m, 1H), 1.70 (m, 2H), 1.50 (m, 3H), 1.14 (m, 6H), 1.04 (m, 4H), 0.88–0.78 (m, 30H), 0.10–0.08 (m, 18H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 164.9, 159.2, 159.1, 138.6, 138.3, 136.3, 136.4, 136.1, 135.4, 133.7, 133.6, 133.4, 133.1, 131.4, 131.2, 131.1, 131.0, 130.7, 130.6, 130.0, 129.8, 129.5, 129.4, 128.9, 128.8, 128.5116.8, 116.3, 113.8, 113.8, 83.2, 82.8, 82.6, 75.6, 73.7, 73.2, 71.4, 71.2, 70.9, 70.6, 70.5, 69.9, 66.2, 66.1, 65.6, 55.4, 44.6, 43.9, 43.9, 40.7, 39.6, 37.9, 37.3, 36.6, 34.8, 34.5, 33.9, 33.8, 31.7, 30.7, 30.326.3, 26.2, 26.1, 26.0, 25.4, 24.0, 23.8, 22.8, 20.0, 18.2, 18.2, 18.0, 17.4, 17.2, 16.1, 14.3, 12.1, 11.8, 9.6, –3.6 (3), –4.0 (4), –4.52; MS (FAB) m/z 903.15 ([M+Na]⁺, 100%); HRMS (FAB) m/z calcd. for C₄₉H₇₆O₇Si₂ (M⁺) 880.4799, found 880.4794.

(2R,4R,5R,9S,10R)-2,4-bis((tert-butyldimethylsilyloxy)-10-((5S,6S)-5-(tert-butyldimethylsilyloxy)-6β-dimethylnon-8-enoyloxy)-5,7,9-trimethyl-7-(phenylsulfonyl)tridec-12-en-6-yl benzoate (17). DDQ (8.5 mg, 0.037 mmol) was added a solution of compound 15 (30.0 mg, 0.034 mmol) in CH₂Cl₂ (2 mL) and H₂O (2 mL). The resulting mixture was stirred 2 h at rt. The mixture was filtered with CH₂Cl₂ (10 mL). The resulting solution washed with satd. NaHCO₃ (5 mL) and brine (5 mL), dried (Na₂SO₄) and concentrated by rotary evaporation. Purification by flash chromatography (2:1 hexanes/EtOAc) yielded 24.7 mg (95%) of (2R,4R,5R,9S,10R)-2,4-bis((tert-butyldimethylsilyl)oxy)-10-hydroxy-5,7,9-trimethyl-7-(phenylsulfonyl)tridec-12-en-6-yl benzoate (16), as a colorless oil: IR (neat) ν 3421, 2927, 1256, 835; ¹H–NMR (400 MHz, CDCl₃) δ ppm 8.04-7.32 (m, 10H), 5.96–5.62 (m, 2H), 5.18–5.08 (m, 2H), 3.96–3.84 (m, 1H), 3.74 (m, 1H), 3.54 (m, 1H), 2.84–2.64 (m, 1H), 2.94–2.82 (m, 1H), 2.46–2.10 (m, 3H), 2.01 (m, 2H), 1.78–1.70 (m, 2H), 1.62–1.44 (m, 5H), 1.14–0.96 (m, 7H), 0.90–0.72 (m, 21H), 0.01 (12H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 171.3, 165.5, 165.3, 138.4, 138.0, 136.5, 135.6, 135.4, 135.0, 134.8, 133.7, 133.6, 133.5, 133.2, 133.1, 131.0, 130.6, 130.5, 130.4, 130.3, 130.0 (3), 129.8, 129.6, 129.0, 128.8, 128.7, 128.5, 118.7, 118.2, 118.1, 117.9, 100.3, 75.4, 75.3, 75.3, 75.1, 74.2, 73.6, 73.4, 73.1, 72.2, 71.5, 70.4, 70.2, 66.1, 66.1, 65.6, 60.5, 44.7, 44.1, 43.6, 40.7, 39.6, 38.7, 38.4, 37.8, 37.7,
37.4, 35.9, 38.4, 34.3, 33.9, 32.4, 26.3, 26.2, 26.1(3), 23.9, 23.8, 21.1, 19.8, 19.2(2), 18.2, 18.0, 17.6, 14.3, 12.1, 11.8, 9.9, –3.7 (3), –4.0 (4), –4.4(2), –4.5; MS (ESI) m/z 783.14 ([M+Na]^+, 100%); HRMS (FAB) m/z calcd. for C_{41}H_{69}O_7SSi_2 (M+H)^+ 761.4295, found 761.4297.

DMAP (4.0 mg), CSA (7.2 mg, 0.031 mmol) and DCC (11.4 mg, 0.053 mmol) were added sequentially to a solution of alcohol 16 (25.0 mg, 0.033 mmol) and acid 17 (11.4 mg, 0.036 mmol) in CH2Cl2 (2 mL) at 0 °C. The resulting mixture was stirred at rt. After 8 h, the starting material was no longer detectable by TLC (4:1 hexanes/EtOAc). The reaction was diluted with hexanes (20 mL) and EtOAc (40 mL). The mixture was filtered and washed with 5% aqueous citric acid (10 mL), satd. NaHCO3 (10 mL) and brine (10 mL), dried (Na2SO4) and concentrated by rotary evaporation. Purification by flash chromatography (2:1 hexanes/EtOAc) yielded 33.0 (96%) of ester 18 as a white solid: IR (neat) ν 2893, 1236, 1084, 917, 825; 1H–NMR (400 MHz, CDCl3) δ ppm 8.04–7.36 (m, 10H), 5.78–5.48 (m, 2H), 5.08–4.94 (m, 2H), 4.80 (m, 1H), 4.76–4.62 (m, 2H), 4.16–4.06 (m, 1H), 3.96–3.78 (m, 2H), 3.50 (m, 1.5H), 3.16 (m, 0.5H), 2.84–2.64 (m, 1H), 2.46–2.10 (m, 6H), 2.01 (m, 2H), 1.78–1.70 (m, 2H), 1.68–1.57 (m, 6H), 1.54–1.44 (m, 3H), 1.44–1.26 (m, 4H), 1.18–1.04 (m, 4H), 102–0.94 (m, 3H), 0.90–0.72 (m, 21H), 0.01 (12H); 13C–NMR (100 MHz, CDCl3) δ ppm 173.5, 173.1, 172.9, 165.3, 164.8, 144.9, 144.8, 138.4, 138.2, 136.5, 134.4, 134.2, 133.7, 133.6, 133.5, 133.1, 133.1, 131.2, 131.0, 130.7, 130.5, 130.4, 130.1, 130.0, 129.9, 128.9, 128.8, 128.6, 128.5, 128.5, 128.4, 117.2, 117.6, 111.5, 111.5, 77.3, 76.9, 76.0, 75.6, 74.8, 74.8, 73.2, 73.2, 72.2, 71.3, 71.2, 69.9, 66.1, 66.0, 65.6, 55.9, 45.0, 44.0, 43.9 40.7, 40.7, 40.5, 39.8, 37.5, 35.9, 35.7, 35.6, 35.6, 35.2, 35.0, 34.8, 34.7, 34.5, 32.8, 32.7, 32.6, 32.4, 32.1, 31.9, 31.8, 26.9, 26.2, 26.0, 25.5, 24.8, 24.2, 23.8, 22.4, 21.8, 21.720.0, 18.9, 18.8, 18.2, 18.0, 17.8, 17.4, 14.2, 14.1, 14.1, 12.1, 11.36, 8.9, –3.6, –3.8 (4), –4.0, –4.1, –4.2, –4.3 (3), –4.4, –4.5; MS (ESI) m/z 1079.46 ([M+Na]^+,100%). HRMS (FAB) m/z calcd. for C_{58}H_{100}O_{9}S_{1}Si_{3} (M)^+ 1056.6636, found 1056.6637.

**Preparation of phenylsulfone lactone (19).** Grubbs second-generation catalyst (1.0 mg, 0.001 mmol) was added to a solution of diene 18 (24.3 mg, 0.023 mmol) in refluxing CH2Cl2 (1 mL). The solution was refluxed for 72 h until TLC indicated complete conversion. The solvent was removed by rotary evaporation. The residue was diluted with hexanes (10 mL) and filtered through a short pad of silica gel in order to remove the catalyst. The crude product was purified by flash chromatography (100:1 toluene/Et2O) to provide 22.2 mg (64%) of macrolide 19 as a colorless oil. IR (neat) ν 2929, 2856, 1726, 1251, 1070, 836; 1H–NMR (400 MHz, CDCl3) δ ppm 8.04–7.22 (m, 20H), 5.70 (m, 0.6H), 5.48 (m, 0.4H), 5.41–4.84 (m, 2H), 4.82–4.64 (m, 1H), 4.16–4.04 (m, 2H), 3.96–3.78 (m, 3H), 3.52 (m, 0.5H), 3.39–3.28 (m, 2H), 3.20 (m, 0.5H), 2.87–2.75 (m, 1H), 2.58–2.10 (m,
6H), 2.05 (m, 2H), 1.78–1.80 (m, 8H), 1.68–1.32 (m, 30H), 1126 (m, 8H), 1.18–0.80 (m, 56H), 0.01 (m, 36H); \(^{13}\)C–NMR (100 MHz, CDCl\(_3\)) δ ppm 173.9, 173.6, 173.5, 165.4, 164.8, 138.4, 138.2, 137.7, 137.6, 136.6, 133.7, 133.6, 133.5, 133.0, 131.2, 131.0, 130.8, 130.4, 130.0 (2), 129.9, 128.9 (2), 128.6, 128.5, 128.5, 121.2, 121.1, 77.7, 77.5, 76.5, 76.3, 76.2, 75.9, 74.7, 74.4, 73.2, 73.2, 72.2, 71.3, 71.2, 70.1, 66.1, 66.0, 65.6, 60.5, 45.5, 45.3, 44.0, 43.9, 40.7, 39.7, 37.4, 36.3, 36.2, 36.1, 35.8, 35.3, 33.6, 33.5, 33.4, 33.3, 33.0 (2), 31.9, 30.9, 30.4, 30.1, 26.3, 26.2, 26.0, 24.3, 23.8, 23.8, 21.9, 20.1, 19.5, 18.6, 18.6, 18.3, 18.2, 18.1, 18.0, 17.2, 15.8, 15.6, 14.4, 12.1, 11.7, 8.7, –3.6, –3.7, –3.8, –3.9 (2), –4.0, –4.1, –4.2, –4.3, –4.4 (2), –4.5, –4.6 (2); MS (ESI) m/z 1051.28 ([M+Na]^+, 100%); HRMS (FAB) m/z calcd. for C\(_{56}\)H\(_{97}\)O\(_9\)S\(_1\)Si\(_3\) (M)\(^+\) 1028.6776, found 1028.6775.

**Preparation of macrolide (20a).** To a stirred suspension of 6% (m/m) Na/Hg in 3 mL of MeOH at -20 °C was added lactone 19 (20.0 mg, 0.019 mmol). The resulting mixture was stirred at 0 °C until TLC indicated complete conversion of the substrate (~ 8 h). The reaction was quenched by the addition of satd. NH\(_4\)Cl (1 mL) and warmed to rt. The mixture was extracted with Et\(_2\)O (2 x 20 mL), and the combined organic layers washed sequentially with 5% NaHCO\(_3\) (10 mL), H\(_2\)O (10 mL), and brine (10 mL), dried over Na\(_2\)SO\(_4\), and concentrated by rotary evaporation. Purification by flash chromatography (2:1 hexanes/EtOAc) yielded 13.0 (90%) of a 2:1 mixture 19, as a colorless oil: \(^1\)H–NMR (500 MHz, CDCl\(_3\)) δ ppm 5.50 (d, J = 10.0 Hz, 0.3 H), 5.45 (d, J = 9.2 Hz, 0.7 H), 4.98 (m, 1H), 4.84 (m, 1H), 3.88 (m, 1H), 3.58 (m, 1H), 3.36 (m, 1H), 2.54–2.36 (m, 4H), 2.38 (m, 1H), 2.04–1.92 (m, 3H), 1.88–1.78 (m, 4H), 1.78–1.54 (m, 15H), 1.42 (m, 3H), 1.26 (m, 3H), 1.02 (m, 4H), 0.98–0.82 (m, 40H), 0.04 (m, 18H); \(^{13}\)C–NMR (100 MHz, CDCl\(_3\)) δ ppm 173.7, 137.6, 137.4, 131.8, 131.7, 131.4, 130.5, 121.6, 75.9, 75.5, 73.5, 73.3, 66.3, 66.1, 46.3, 45.5, 45.2, 43.2, 38.2, 37.8, 36.1, 35.4, 35.2, 33.5, 30.3, 29.9, 26.2, 26.1, 26.0 (2), 24.1, 24.0, 23.6, 21.9, 18.7, 18.3, 16.1, 15.9, 15.8 (2), 15.3, –3.8, –3.9, –4.1, –4.2, –4.4, –4.5, –4.6; HRMS (FAB) m/z calcd. for C\(_{43}\)H\(_{86}\)O\(_5\)Si\(_3\) (M)\(^+\) 766.5774, found 766.5778.

**(2R,3S)-1-(((S)-4-benzyl-2-thioxothiazolidin-3-yl)-7-((tert-butyl diphenylsilyl)oxy)-3-((4-methoxy benzyl)oxy)-2-methyl heptan-1-one (23)** A solution of TiCl\(_4\) (7.7 mL, 39.2 mmol) in dry CH\(_2\)Cl\(_2\) (45 mL) under an Ar atmosphere was added drop wise to a solution of auxiliary 21 (5.2 g, 19.6 mmol) in dry CH\(_2\)Cl\(_2\) (150 mL) at -78 °C. i-Pr\(_2\)NEt (3.76 mL, 21.6 mmol) was added, and the resulting solution was stirred for 1 h at -78 °C and 15 min at 0 °C. The mixture was recooled to -78 °C, and a solution of aldehyde 22 (7.3 g, 21.6 mmol) was added. The reaction was stirred for 2 h at -78 °C, warmed from -78 °C to 0 °C over 15 min and then maintained at 0 °C for an additional 30 min. The reaction mixture was quenched with a 1:1 mixture of H\(_2\)O and satd. NH\(_4\)Cl (60 mL), and the layers were separated. The organic layer was dried (Na\(_2\)SO\(_4\)), filtered, and
concentrated. Purification by flash chromatography (9:1 to 4:1 hexanes-EtOAc) yielded 11.3 g (95%) of adduct 23 as a colorless oil: 1H–NMR (500 MHz, CDCl$_3$) δ ppm 7.72 (dd, $J = 1.5$, 7.3 Hz, 4H), 7.38 (m, 11H), 5.40 (ddd, $J = 4.2$, 7.0, 10.8 Hz, 1H), 4.73 (qd, $J = 2.1$, 6.9 Hz, 1H), 4.06 (m, 1H), 3.72 (t, $J = 6.0$ Hz, 2H), 3.37 (dd, $J = 4.2$, 7.0, 10.8 Hz, 1H), 4.73 (qd, $J = 2.1$, 6.9 Hz, 1H), 4.06 (m, 1H), 3.72 (t, $J = 6.0$ Hz, 2H), 3.07 (dd, $J = 10.4$, 13.2 Hz, 1H), 2.89 (d, $J = 11.6$ Hz, 1H), 2.81 (d, $J = 2.8$ Hz, 1H), 1.61 (m, 4H), 1.46 (m, 2H), 1.22 (d, $J = 7.1$, 3H), 1.10 (s, 9H); 13C–NMR (100 MHz, CDCl$_3$) δ ppm 201.7, 178.5, 136.7, 135.8, 134.3, 129.8, 129.7, 127.9, 127.5, 71.2, 69.1, 64.0, 42.9, 37.3, 33.7, 32.7, 32.1, 27.2, 22.6, 19.5, 10.7; HRMS (FAB) m/z calcd. for C$_{34}$H$_{43}$NO$_3$S$_2$SiNa (M+Na)$^+$ 628.2346, found 628.2348. 

(2R,3S)-7-((tert-butyldiphenylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2-methylheptanal (24). Adduct 23 (10.2 g, 16.9 mmol) was dissolved in dry CH$_2$Cl$_2$ (200 mL). After cooling to 0 °C, N,O-dimethylhydroxylamine hydrochloride (3.29 g, 33.8 mmol) and imidazole (5.7 g, 84.5 mmol) were added. The reaction was maintained at 0 °C for 30 min and then warmed to rt. After 14 h at rt, the solution was quenched by the addition of satd. aqueous NH$_4$Cl (100 mL) and extracted with CH$_2$Cl$_2$ (3 x 200 mL). The dried (MgSO$_4$) extracted was concentrated via rotary evaporation and purified by chromatography over a short plug of silica gel, eluting with 1:3 hexanes/EtOAc to afford (2R,3S)-7-((tert-butyldiphenylsilyl)oxy)-3-hydroxy-N-methoxy-N,2-dimethylheptanamide (S4) (5.8 g, 12.7 mmol, 75%) as a pale yellow solid. Sodium hydride (0.36 g, 15.0 mmol) was slowly added into a solution of amide S4 (5.7 g, 12.5 mmol) in DMF (100 mL) at rt. p-Methoxybenzylchloride (1.95 mL, 15.0 mmol) was added to the solution. The mixture was stirred at rt for 4 h under Ar, diluted with EtOAc (200 mL), washed with H$_2$O (3 x 80 mL), and aqueous satd. NaHCO$_3$ (80 mL). The solution was dried over magnesium sulfate. The solvent was removed by rotary evaporation. The product was purified by flash chromatography (7:3 EtOAc/hexane) to afford 6.5 g (90%) of (2R,3S)-7-((tert-butyldiphenylsilyl)oxy)-N-methoxy-3-((4-methoxybenzyl)oxy)-N,2-dimethylheptanamide (S5) as a solid. A solution of amide S5 in dry toluene (120 mL) under Ar was cooled to -78 °C. DIBAL–H (17 mL of 1.0 M in toluene, 17 mmol) was added drop wise. The mixture was stirred at -78 °C for 30 min and quenched with a solution of potassium sodium- (+)-tartrate tetrahydrate (10 g). The mixture was stirred vigorously for 12 h. The organic layer was collected and the aqueous layer was further extracted with CH$_2$Cl$_2$ (200 mL). The organic layers were combined, dried (Na$_2$SO$_4$) and concentrated by rotary evaporation. The residue was purified by flash chromatography (10:1 hexanes/EtOAc) to afford 5.7 mg (97%) of aldehyde 24 as a colorless oil: 1H–NMR (500 MHz, CDCl$_3$) δ ppm 9.78 (s, 1H), 7.68 (dd, $J = 1.6$, 7.6 Hz, 4H), 7.43 (m, 6H), 7.26 (d, $J = 8.5$ Hz, 2H),
6.90 (d, J = 8.5, 2H), 4.48 (td, J = 2.8, 11.8 Hz, 2H), 3.84 (s, 3H), 3.73 (t, J = 6.1 Hz, 2H), 2.53 (m, 1H), 1.56 (m, 6H), 1.17 (d, J = 7.0 Hz, 3H), 1.12 (s, 9H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 204.9, 159.5, 135.8, 134.3, 130.6, 129.9, 129.7, 129.6, 129.6, 127.9, 114.1, 78.4, 71.7, 63.9, 49.9, 32.9, 31.8, 27.2, 22.6, 19.5, 8.4; HRMS (FAB) m/z calcd. for C\(_{32}\)H\(_{42}\)O\(_4\)SiNa(M+Na)\(^+\) 541.2745, found 541.2746.

\((4R,5S)-9-((\text{tert-butyldiphenylsilyl})oxy)-5-((4-methoxybenzyl)oxy)-2,4-dimethylnon-1-en-3-yl acetate\) (25) Magnesium turnings (0.73 g, 31.0 mmol), a crystal of I\(_2\) (50 mg), and THF (10 mL) were added to a flame dried flask purged with Ar. A solution of 2-bromoprop-1-ene (3.6 mL, 30.0 mmol) in THF (30 mL) was added slowly via cannula. The mixture was stirred vigorously and after 20 min the magnesium had dissolved. The solution was stirred for 1 h at rt before it was cooled to 0 °C and a solution of aldehyde 24 (5.2 g, 10.0 mmol) in THF (100 mL) was added via cannula. The reaction mixture was stirred for 1 h at rt, quenched with satd. NH\(_4\)Cl (100 mL), and extracted with CH\(_2\)Cl\(_2\) (200 mL). The combined organic layers were washed with satd. NaHCO\(_3\) (100 mL), H\(_2\)O (50 mL), and brine (100 mL), dried over Na\(_2\)SO\(_4\) and concentrated via rotary evaporation. The resulting oil was dissolved in pyridine (100 mL) and treated with acetic anhydride (80 mL). After stirring for 1 h, the volume was reduced to about 15 mL by rotary evaporation. The crude oil was diluted with 1:1 hexanes/EtOAc (200 mL) and washed with Cu\(_2\)SO\(_4\) (100 mL), H\(_2\)O (100 mL), NaHCO\(_3\) (100 mL), H\(_2\)O (100 mL), and brine (100 mL). The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated via rotary evaporation. The crude product was purified by flash chromatography (1:1 hexanes/CHCl\(_3\)) to yield 5.3 g (87%) of a diastereomeric mixture of allyl acetates 25: \(^1\)H–NMR (500 MHz, CDCl\(_3\)) \(\delta\) ppm 7.68 (m, 4H), 7.41 (m, 6H), 7.26 (m, 2H), 6.87 (m, 2H), 5.30 (d, J = 6.6 Hz, 1H), 5.19 (d, J = 10.1 Hz, 1H), 4.94 (m, 2H), 3.80 (s, 3H), 3.68 (t, J = 6.5 Hz, 2H), 3.29 (dt, J = 4.0, 6.2 Hz, 1H), 2.05 (s, 1.8H), 1.96 (s, 1.2H), 1.56 (m, 8H), 1.07 (s, 3.5 H), 1.05 (s, 5.5H), 0.96 (d, J = 6.8 Hz, 1.8H), 0.79 (J = 7.0 Hz, 1.2H); \(^{13}\)C–NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 170.4, 159.2, 142.4, 135.8, 134.3, 131.3, 129.8, 129.6, 129.2, 127.8, 116.1, 114.3, 114.0, 113.9, 79.7, 79.6, 78.8, 77.2, 72.1, 71.7, 71.5, 64.0, 55.5, 37.8, 37.3, 33.0, 32.9, 31.8, 30.9, 30.3, 27.1, 22.7, 22.3, 21.5, 21.4, 19.5, 18.6, 17.6, 9.8, 9.5; HRMS (FAB) m/z calcd. for C\(_{37}\)H\(_{49}\)O\(_5\)SiNa(M+Na)\(^+\) 625.3462, found 625.3465.

tert-butyl((5S,6S)-5-((4-methoxybenzyl)oxy)-6,8-dimethylnon-8-en-1-yl)oxy)diphenylsilane (26) Dioxane (2.5mL) was added to a mixture of NH\(_4\)HCO\(_2\) (97 mg, 16.2 mmol) and Pd(PPh\(_3\))\(_4\) (93.6 mg, 0.08 mmol) in a dry flask under Ar. PBu\(_3\) (0.16 mL, 0.81 mmol) was added and the mixture heated at reflux. The evolution of gas was observed prior to reaching reflux. A solution of allyl acetates 25 (4.9 g, 8.1 mmol) in dioxane (150 mL) was added via cannula to the heated reaction mixture. The reaction was stirred at reflux for 3 h, cooled to rt, diluted...
with hexanes (200mL), washed with H₂O (100 mL), satd. NaHCO₃ (100 mL), brine (100 mL), and dried over Na₂SO₄, and concentrated by rotary evaporation. Purification by flash chromatography (20:1 to 1:1 hexanes/CHCl₃) yielded 4.73 g (87%) of alkene 26 as a colorless oil: ¹H–NMR (400 MHz, CDCl₃) δ ppm 7.66 (dd, J = 1.6, 7.8 Hz, 4H), 7.39 (m, 6H), 7.24 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 6.7, 2H), 4.74 (s, 1H), 4.65 (s, 1H), 4.43 (s, 2H), 3.77 (s, 3H), 3.65 (t, J = 6.2 Hz, 2H), 3.22 (m, 1H), 2.22 (dd, J = 4.2, 13.2 Hz, 1H), 1.90 (ddd, J = 5.4, 10.1, 14.5 Hz, 1H), 1.81 (dd, J = 9.7, 13.0 Hz, 1H), 1.55-1.26 (m, 7H), 1.04 (s, 9H), 0.83 (d, J = 6.7 Hz, 2H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 159.2, 144.9, 135.8, 134.3, 131.6, 129.7, 129.4, 127.8, 113.9, 111.7, 82.6, 71.7, 64.1, 55.5, 41.2, 33.5, 33.0, 30.7, 27.1, 22.7, 22.4, 19.5, 14.8; HRMS (FAB) m/z calcd. for C₃₅H₄₇O₃SiNa (M+Na)⁺ 567.3451, found 567.3453.

(5S,6S)-5-((4-methoxybenzyl)oxy)-6,8-dimethylnon-8-en-1-ol (27) A solution of alkene 26 (4.5 g, 8.3 mmol) in THF (150 mL) was added drop wise to a 1 M solution of TBAF (12.5 mL, 12.5 mmol) in THF at 0 °C. The cooling bath was removed and the reaction mixture stirred for 1 h at rt, at which point it was then diluted with EtOAc (200 mL). The mixture was washed with satd. aqueous NaHCO₃ (2 x 60 mL), H₂O (3 x 60 mL), and brine (600 mL) and then dried over magnesium sulfate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated by rotary evaporation to give a crude product which was purified by column chromatography to obtain compound 27 (2.5 g, 8.2 mmol, 98%) as an oil: ¹H–NMR (400 MHz, CDCl₃) δ ppm 7.27 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.75 (s, 1H), 4.66 (s, 1H), 4.45 (q, J = 11.1 Hz, 2H), 3.80 (s, 3H), 3.63 (t, J = 6.4 Hz, 2H), 3.26 (dt, J = 3.9, 7.5 Hz, 1H), 2.24 (dd, J = 4.39, 13.3 Hz, 1H), 1.93 (tdd, J = 5.5, 8.8, 10.9 Hz, 1H), 1.82 (dd, J = 9.7, 13.2 Hz, 1H), 1.69 (s, 3H), 1.47 (m, 6H), 0.85 (d, J = 6.7 Hz, 3H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 159.3, 144.9, 135.8, 134.3, 131.6, 129.7, 129.4, 127.8, 113.9, 111.7, 82.6, 71.7, 64.1, 55.5, 41.1, 33.5, 33.1, 30.5, 22.6, 22.4, 14.9; HRMS (FAB) m/z calcd. for C₁₉H₂₉O₃Na (M+Na)⁺ 329.2237, found 329.2235.

(5S,6S)-5-((4-methoxybenzyl)oxy)-6,8-dimethylnon-8-enoic acid (28) Oxalyl chloride (0.75 mL, 8.6 mmol) and CH₂Cl₂ (5 mL) were added to a flame dried flask purged with Ar. After cooling to -78 °C, a solution of DMSO (1.3 mL, 18.7 mmol) in CH₂Cl₂ (5 mL) was added drop wise over 5 min. After 10 min at -78 °C, a solution of alcohol 27 (2.4 g, 7.8 mmol) in CH₂Cl₂ (50 mL) was added drop wise over 5 min, during which time a white precipitate formed. The reaction was stirred for 15 min at -78 °C before Et₃N (5.4 mL, 39.0 mmol) was added and the bath was removed. The solution was warmed to rt over 30 min. After stirring at rt for 5 min, H₂O (30 mL). After an additional 10 min, the layers were separated, the aqueous phase was extracted with CH₂Cl₂.
(100 mL) and the combined organic layers were washed with 1% HCl (50 mL), H₂O (50 mL), satd. NaHCO₃ (50 mL) and brine (50 mL), dried over Na₂SO₄. The mixture was concentrated on a rotary evaporator affording 2.3 g (97%) of (5S,6S)-5-((4-methoxybenzyl)oxy)-6,8-dimethylnon-8-enal (S6), which was used further without purification. A buffered oxidant solution was prepared by combining NaClO₂ (0.92 g) and NaH₂PO₄ (0.59 g) in H₂O (5 mL). t-BuOH (30 mL) and 2-methyl-2-butene (15 mL, 2 M in THF) were added to the oxidant with stirring vigorously. After 10 min, the resulting solution was transferred to a flask containing aldehyde S6 (2.3 g, 7.6 mmol). The reaction was stirred vigorously at rt for 1 h. Water (100 mL) was added and the solution was extracted with EtOAc (200 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), concentrated by rotary evaporation. Purification by flash chromatography (4:1 hexanes/EtOAc) to yielded 2.2 g (88%) of acid 28 as a colorless oil: ¹H–NMR (400 MHz, CDCl₃) δ ppm 7.27 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.76 (s, 1H), 4.67 (s, 1H), 4.46 (q, J = 11.1 Hz, 2H), 3.80 (s, 3H), 3.26 (m, 1H), 2.37 (m, 2H), 2.24 (dd, J = 3.9, 13.3 Hz, 1H), 1.94 (m, 1H), 1.81 (dd, J = 10.1, 13.1 Hz, 1H), 1.70 (s, 3H), 1.78-1.42 (m, 4H), 0.86 (d, J = 6.7 Hz, 2H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 179.9, 159.3, 144.7, 131.3, 129.5, 114.0, 111.9, 82.2, 71.7, 55.5, 40.9, 34.3, 33.4, 30.1, 22.4, 21.6, 14.9; HRMS (FAB) m/z calcd. for C₉H₁₈O₄ (M⁺) 320.2762, found 320.2763.

(5S,6S)-(2S,3R)-1-((tert-butyldimethylsilyl)oxy)-2-methylhex-5-en-3-yl 5-((4-methoxybenzyl)oxy)-6,8-dimethylnon-8-enoate (29) Alcohol 10 (1.1 g, 4.8 mmol) and acid 28 (1.5 g, 4.8 mmol) were dissolved in CH₂Cl₂ (30 mL) and cooled to 0 °C. DMAP (0.7 g), and DCC (1.2 g), and pyridine (3 mL) were added sequentially to this solution. The reaction was for 8 h at which point the starting material had been consumed. The reaction was diluted with hexanes (100 mL), filtered, and concentrated. Purification by flash chromatography (20:1 hexanes/EtOAc) yielded 2.5 g (95%) of ester 29 as a colorless oil: ¹H–NMR (400 MHz, CDCl₃) δ ppm 7.26 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.73 (m, 1H), 5.06 (m, 1H), 5.01 (m, 1H), 4.86 (dt, J = 5.0, 7.5 Hz, 2H), 4.74 (s, 1H), 4.66 (s, 1H), 4.44 (dd, J = 11.6, 14.2 Hz, 2H), 3.79 (s, 3H), 3.67 (m, 1H), 3.60 (m, 1H), 3.26 (m, 1H), 3.19 (m, 1H), 2.24 (m, 3H), 1.81 (m, 4H), 1.68 (s, 3H), 1.54 (m, 2H), 1.29 (m, 3H), 0.90 (d, J = 7.0 Hz, 3H), 0.85 (s, 9H), 0.84 (d, J = 6.8 Hz, 3H), 0.04 (s, 6H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 173.4, 159.3, 144.7, 134.5, 131.4, 129.4, 117.6, 113.9, 111.8, 82.3, 76.9, 71.7, 61.3, 56.0, 55.5, 41.0, 35.8, 35.1, 35.0, 34.9, 33.4, 32.9, 30.3, 26.2, 25.7, 22.4, 22.0, 15.8, 14.9, -5.1, -5.1; HRMS (FAB) m/z calcd. for C₃₂H₅₄O₅Si (M⁺) 546.4281 found 546.4283.

(6S,7S,12R,E)-12-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-6-((4-methoxybenzyl)oxy)-7,9-
**dimethyloxacyclododec-9-en-2-one (30).** Grubbs second-generation catalyst (36 mg, 0.04 mmol) was dissolved in CH₂Cl₂ (50 mL) under an Ar atmosphere. The flask was fitted with a condenser and heated at reflux. A solution of diene 29 (2.3 g, 4.2 mmol) in CH₂Cl₂ (200 mL) was added via syringe. After 24 h, TLC analysis indicated the starting material had been consumed. The reaction mixture was flushed through a plug of silica gel with CH₂Cl₂ and concentrated to give a colorless oil. Purification by flash chromatography (20:1 hexanes/EtOAc) yielded 1.3 g (60%) of macrolide 30 as colorless oil: ¹H–NMR (400 MHz, CDCl₃) δ ppm 7.24 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.96 (d, J = 10.0 Hz, 1H), 4.91 (ddd, J = 2.9, 5.6, 11.6 Hz, 1H), 4.46 (d, J = 11.0 Hz, 1H), 4.28 (d, J = 11.0 Hz, 1H), 3.78 (s, 3H), 3.64 (m, 2H), 3.10 (m, 1H), 2.38 (m, 2H), 2.04 (m, 2H), 1.89-1.57 (m, 5H), 1.62 (s, 3H), 1.40 (m, 1H), 1.28 (m, 2H), 1.00 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 173.9, 159.3, 137.4, 131.3, 129.6, 122.1, 113.9, 83.4, 76.2, 71.1, 61.5, 55.5, 46.0, 36.2, 35.7, 34.4, 32.9, 30.6, 29.2, 26.2, 20.8, 19.5, 18.9, 15.7, -5.0, -5.1; HRMS (FAB) m/z calcd. for C₃₀H₅₀O₅Si (M)⁺ 518.3801, found 518.3802.

**(6S,7S,12R,E)-12-((R)-1-iodopropan-2-yl)-6-((4-methoxybenzyl)oxy)-7,9-dimethyloxacyclododec-9-en-2-one (8).** A solution of lactone 30 (1.2 g, 2.3 mmol) was dissolved in dry THF (20 mL) under Ar and cooled to 0 °C. A solution of TBAF (3.4 mL, 3.5 mmol, 1 M in THF) was added drop wise. The cooling bath was removed and the reaction mixture stirred for 1 h at rt and then diluted with EtOAc (50 mL). The mixture was washed with satd. aqueous NaHCO₃ (20 mL), H₂O (20 mL), and brine (30 mL) and then dried over magnesium sulfate. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated by rotary evaporation. The crude product was purified by flash chromatography to obtain 864 mg (93%) of (6S,7S,12R,E)-12-((S)-1-hydroxypropan-2-yl)-6-((4-methoxybenzyl)oxy)-7,9-dimethyloxacyclododec-9-en-2-one (S7) as an oil: ¹H–NMR (400 MHz, CDCl₃) δ ppm 7.26 (d, J = 3.2 Hz, 2H), 6.87 (dd, J = 8.4, 3.2 Hz, 2H), 4.98 (m, 2H), 4.50 (d, J = 10.8 Hz, 1 H), 4.32 (d, J = 10.8 Hz, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.63 (m, 1H), 3.10 (m, 1H), 2.49 (m, 2H), 2.06 (m, 2H), 1.88 (m, 2H), 1.79 (m, 2H), 1.27 (m, 2H), 1.64 (s, 3H), 1.58 (m, 1H), 1.44 (m, 1H), 1.37 (m, 3H), 0.95 (m, 3H); ¹³C–NMR (100 MHz, CDCl₃) δ ppm 174.1, 159.3, 137.6,131.3, 129.6, 121.9, 113.9, 83.3, 76.1, 71.1, 60.9, 55.5, 45.9, 36.2, 35.5, 34.4, 32.9, 30.6, 29.2, 20.8, 19.5, 15.9, 15.6; HRMS (FAB) m/z calcd. for C₂₄H₃₆O₅ (M)⁺ 404.2762, found 404.2763.

Imidazole (390 mg, 5.8 mmol), triphenylphosphine (750 mg, 2.9 mmol), and iodine (722 g, 2.9 mmol) were added sequentially to a solution of alcohol S7 (774 mg, 1.92 mmol) in toluene (25 mL) at 0 °C. The heterogeneous yellow mixture was stirred at rt for 1 h. The reaction was quenched by diluting with satd.
Na$_2$S$_2$O$_3$ (25 mL) and the layers were separated. The aqueous layer was further extracted with Et$_2$O (3 x 25 mL) and the combined organic layers were washed with satd. Na$_2$S$_2$O$_3$, H$_2$O, and brine, dried (Na$_2$SO$_4$), and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to provide 968 mg (98%) of 8 as a colorless oil: $^1$H–NMR (400 MHz, CDCl$_3$) δ ppm 7.29 (m, 2H), 6.89 (m, 2H), 4.96 (m, 2H), 4.52 (d, $J =$ 11.0 Hz, 1H), 4.33 (d, $J =$ 11.0 Hz, 1H), 3.82 (s, 3H), 3.33 (m, 1H), 3.34 (dd, $J =$ 3.8, 10.0 Hz, 1H), 3.13 (m, 1H), 2.49 (m, 1H), 2.46 (m, 1H), 2.07 (m, 2H), 1.88-1.32 (m, 8H), 1.64 (s, 3H), 1.05 (d, $J =$ 6.9 Hz, 3H), 0.95 (d, $J =$ 7.1 Hz, 3H); $^{13}$C–NMR (100 MHz, CDCl$_3$) δ ppm 173.9, 159.3, 137.8, 131.3, 129.6, 121.6, 113.9, 83.3, 75.4, 71.1, 55.5, 45.9, 38.7, 36.6, 36.2, 32.9, 31.1, 29.2, 20.8, 19.5, 16.0, 14.9, 4.5; HRMS (FAB) m/z calcd. for C$_{24}$H$_{35}$IO$_4$ (M)$^+$ 514.2676, found 514.2679.

References


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SUPPORTING INFORMATION

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$^1$H-NMR (400 MHz) and $^{13}$C-NMR (100 MHz) spectra of S2 in CDCl$_3$
$^{1}$H-NMR (400 MHz) and $^{13}$C-NMR (100 MHz) spectra of S5 in CDCl$_3$
$^1$H-NMR (400 MHz) and $^{13}$C-NMR (100 MHz) spectra of S7 in CDCl$_3$