Supporting Information

Synthesis and Biological Activity of Novel Epothilone Aziridines

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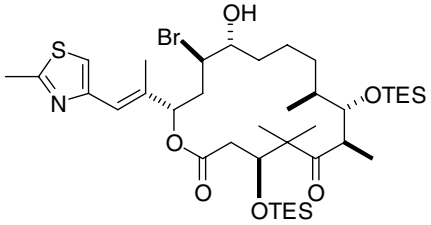
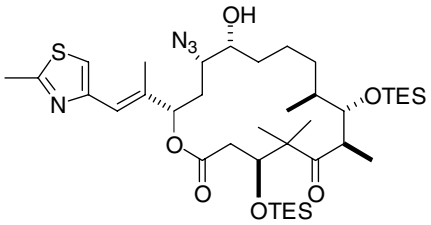
[4S-[4R*,7S*,8R*,9R*,13S*,14S*,16R*(E)]]-14-Bromo-4,8-bistriethylsilyloxy-13-hydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxacyclohexadecane-2,6-dione (8).



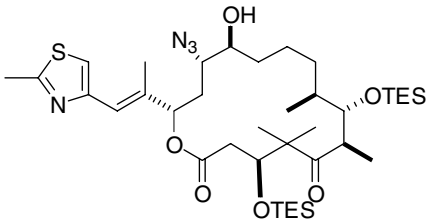
Et_3SiCl (25 mL, 149 mmol) was added to epothilone A (10.39 g, 21 mmol), *N,N*-diisopropylethylamine (55 mL**,** 315 mmol), and imidazole (7.15 g, 105 mmol) in DMF (75 mL) at 25 °C. The reaction mixture was heated at 55 °C for 6.5 h and concentrated *in vacuo*. The residue was then diluted with CH_2Cl_2 (100 mL) and the organic extracts were washed with aqueous $NaHCO_3$ (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 5.0 x 30 cm, hexanes to 15% EtOAc/hexanes gradient elution) to afford bis-TES-epothilone A as a white solid (15.1 g, >95%). MS (ESI^+): $(M+H)^+$ 722. To a solution of bis-TES-epothilone A (2.0 g, 2.8 mmol) in CH_2Cl_2 (30 mL) at –20 °C under Ar was added $MgBr_2 \bullet OEt_2$ (3 x 1.1 g, 12 mmol total) in three portions every two hours while maintaining an internal temperature between –15 and –5 °C. After 7 h, the reaction mixture was quenched with pH 7 aqueous phosphate buffer (40 mL) and brine (40 mL), carefully extracted with EtOAc (3 x 100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 4.5 x 25 cm, 10-20 % EtOAc/hexanes gradient elution) to afford **8** as a white solid [1.0 g, 45 % (67 % based on 0.6 g of recovered starting material; <2 % of the other C13-Br/C14-OH regioisomer was detected]. ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1 H), 6.55 (s, 1 H), 5.48-5.46 (m, 1 H), 4.39-4.38 (m, 1 H), 3.69-3.66 (m, 1 H), 3.01-2.99 (m, 1 H), 2.76-2.74 (m, 1 H), 2.73 (s, 3 H), 2.71-2.56 (m, 3 H), 2.49-2.47 (m, 1 H), 2.13 (s, 3 H), 1.63-1.61 (m, 4 H), 1.30-1.28 (m, 2 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 0.99-0.93 (m, 26 H), 0.72-0.63 (m, 12 H). MS (ESI^+): $(M+H)^+$ 802.

[4S-[4R*,7S*,8R*,9R*,13S*,14R*,16R*(E)]]-14-Azido-4,8-bistriethylsilyloxy-13-hydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxacyclohexadecane-2,6-dione (9).



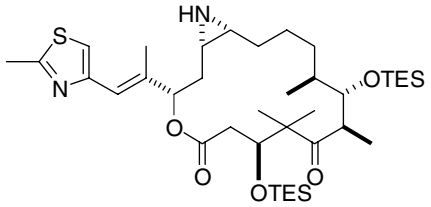
To a solution of **8** (0.17 g, 0.21 mmol) in DMF (2 mL) under Ar was added sodium azide (0.14 g, 2.1 mmol) and the resulting suspension was warmed to 43 °C. After 36 h, the solvent was removed *in vacuo* and the residue was directly purified by flash chromatography (SiO_2, 2.5 x 15 cm, 10-20 % EtOAc/hexanes gradient elution) to give **9** (0.14 g, 88 %) as a white foam. ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1 H), 6.51 (s, 1 H), 5.26-5.23 (m, 1 H), 3.99-3.92 (m, 1 H), 3.90-3.86 (m, 1 H), 3.81-3.72 (m, 1 H), 3.41-3.37 (m, 1 H), 2.92-2.89 (m, 1 H), 2.82-2.74 (m, 1 H), 2.64 (s, 3 H), 2.57-2.52 (m, 1 H), 2.21-2.18 (m, 1 H), 2.03 (s, 3 H), 1.81-1.42 (m, 5 H), 1.37-0.96 (m, 10 H), 0.92-0.75 (m, 24 H), 0.67-0.51 (m, 12 H). MS (ESI^+): $(M+H)^+$ 765.

[4S-[4R*,7S*,8R*,9R*,13R*,14R*,16R*(E)]]-14-Azido-4,8-bistriethylsilyloxy-13-hydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-oxacyclohexadecane-2,6-dione (10).



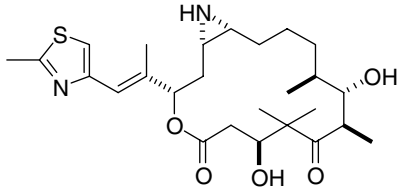
To a solution of **9** (0.10 g, 0.13 mmol) in THF under Ar was sequentially added 4-nitrobenzoic acid (55 mg, 0.33 mmol), triphenylphosphine (86 mg, 0.33 mmol), and diethyl azodicarboxylate (**52** µL**,** 0.33 mmol). The reaction mixture was stirred at 25 °C for 1.5 h, concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, 2.5 x 10 cm, 10-20 % EtOAc/hexanes gradient elution) to afford the corresponding p-nitrobenzoate (0.10 g, 86 %) as a white foam. MS (ESI^+): 914.6 $(M+H)^+$. This intermediate (0.10 g, 0.11 mmol) was then treated with 2.0 M ammonia in methanol (1 mL) at 25 °C under Ar for 4 h. The solvent was removed *in vacuo* and the residue was directly purified by flash chromatography (SiO_2, 1.5 x 10 cm, 10-30% EtOAc/hexanes gradient elution) to afford **10** (71 mg, 85%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1 H), 6.59 (s, 1 H), 5.55-5.52 (m, 1 H), 4.42-4.39 (m, 1 H), 3.96-3.94 (m, 1 H), 3.61-3.56 (m, 1 H), 3.05- 3.01 (m, 1 H), 2.75-2.74 (m, 1 H), 2.70 (s, 3 H), 2.61-2.56 (m, 1 H), 2.13 (s, 3 H), 2.04-2.02 (m, 1 H), 1.84-1.50 (m, 3 H), 1.18 (s, 3 H), 1.14-1.10 (m, 6 H), 1.07-0.93 (m, 24 H), 0.68-0.57 (m, 12 H). MS (ESI^+): 765.5 $(M+H)^+$; MS (ESI^-): 763.3 $(M-H)^-$.

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Bistriethylsilyloxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (11).



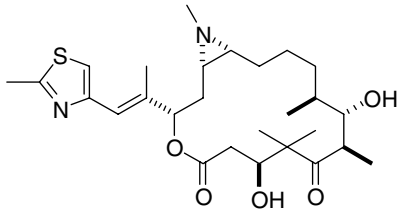
To a solution of **10** (56.5 mg, 67 µmol) in THF- H_2O (12:1, 1.2 mL) under Ar was added trimethylphosphine (134 µL, 1.0 M in THF). The reaction mixture was warmed to 45 °C for 10 h, and the solvent was removed under a constant flow of nitrogen. The residue was purified by flash chromatography (SiO_2, 1 x 5 cm, 0-5 % MeOH/$CHCl_3$ gradient elution) to afford **11** (41 mg, 85 %) as a film. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 1 H), 6.52 (s, 1 H), 5.20-5.18 (m, 1 H), 4.02-4.00 (m, 1 H), 3.91-3.89 (m, 1 H), 2.99-2.96 (m, 1 H), 2.72-2.70 (m, 2 H), 2.66 (s, 3 H), 2.17-2.14 (m, 1 H), 2.10-2.09 (m, 1 H), 2.06 (s, 3 H), 1.95-1.91 (m, 1 H), 1.69-1.27 (m, 5 H), 1.14 (s, 3 H), 1.11 (s, 3 H), 0.98-0.87 (m, 24 H), 0.66-0.54 (m, 12 H). MS (ESI^+): 537.3 $(M+H)^+$.

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (7).



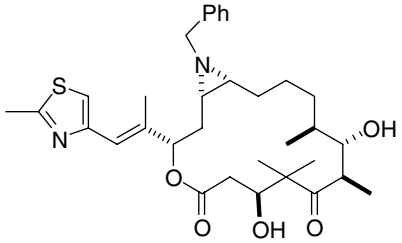
Compound **11** (17.2 mg, 24 µmol) was treated with 20 % trifluoroacetic acid in methylene chloride (0.5 mL) at 0 °C under Ar for 10 min. The reaction mixture was concentrated under a constant stream of nitrogen at 0 °C and the residue was purified by radial chromatography (1 mm SiO_2 GF rotor, 2-10 % MeOH-$CHCl_3$ gradient elution) to afford **7** (10.6 mg, 86 %) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1 H), 6.52 (s, 1 H), 5.46-5.44 (m, 1 H), 4.08- 4.04 (m, 1 H), 3.69-3.68 (m, 1 H), 3.20-3.17 (m, 1 H), 2.57 (s, 3 H), 2.44-2.38 (m, 1 H), 2.34-2.30 (m, 1 H), 1.95-1.93 (br s, 4 H), 1.82-1.78 (m, 2 H), 1.71-1.53 (m, 2 H), 1.46-1.31 (m, 4 H), 1.27 (s, 3 H), 1.23-1.01 (m, 2 H), 0.99 (d, 3 H, J = 6.9 Hz), 0.91 (s, 3 H), 0.81 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 220.3, 171.2, 165.1, 152.4, 136.8, 119.2, 115.9, 76.5, 66.1, 75.4, 52.5, 45.0. 38.1, 34.6, 34.2, 30.1, 29.9, 26.1, 24.9, 22.9, 19.3, 17.6, 16.4, 15.4, 14.3. MS (ESI^+): 493.2 $(M+H)^+$.

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-Methyl-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (12a).



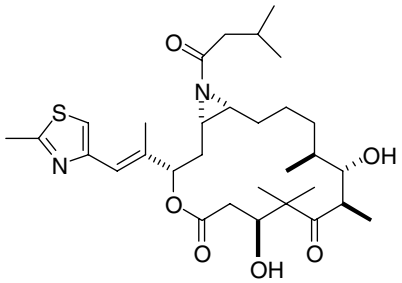
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1 H), 6.66 (s, 1 H), 5.72-5.61 (m, 1 H), 4.35-4.15 (m, 1 H), 3.84-3.83 (m, 1 H), 3.34-3.33 (m, 1 H), 2.72 (s, 3 H), 2.57-2.47 (m, 2 H), 2.39 (s, 3 H), 2.08 (s, 3 H), 1.96-1.85 (m, 2 H), 1.72-1.45 (m, 5 H), 1.42 (s, 3 H), 1.37-1.20 (m, 2 H), 1.18-1.16 (m, 2 H), 1.12 (d, 3 H, *J* = 6.9 Hz), 1.03 (s, 3 H), 0.93 (d, 3 H, *J* = 6.8 Hz). MS (ESI^+): 507.3 $(M + H)^+$.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-Benzyl-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (12b).**



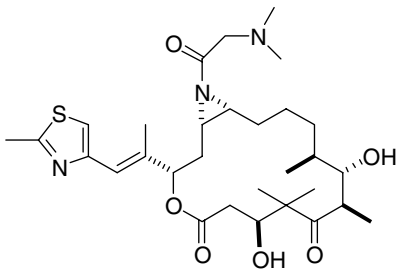
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 5 H), 6.99 (s, 1 H), 6.67 (s, 1 H), 5.50-5.47 (m, 1 H), 4.09-4.00 (m, 1 H), 3.78-3.73 (m, 2 H), 3.37-3.33 (m, 1 H), 3.20-3.17 (m, 1 H), 2.73 (s, 3 H), 2.54 (dd, 1 H, *J* = 13.8, 10.2 Hz), 2.46 (dd, 1 H, *J* = 13.8, 3.0 Hz), 2.08 (s, 3 H), 1.98-1.84 (m, 4 H), 1.58-1.48 (m, 3 H), 1.42-1.37 (m, 4 H), 1.36 (s, 3 H), 1.28-1.22 (m, 2 H), 1.16 (d, 3 H, *J* = 6.8 Hz), 1.11 (s, 3 H), 0.95 (d, 3 H, *J* = 6.9 Hz); LRMS (ESI^+): 583.4 $(M + H)^+$.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-*N*-[2-Methylpropyl]amido-9-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (13a).**



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1 H), 6.57 (s, 1 H), 5.38-5.35 (m, 1 H), 4.15- 4.11 (m, 1 H), 3.84-3.80 (m, 2 H), 3.18-3.15 (m, 1 H), 2.70 (s, 3 H), 2.66-2.53 (m, 2 H), 2.52-2.49 (m, 2 H), 2.45-2.11 (m, 6 H), 2.09 (s, 3 H), 1.84-1.72 (m, 3 H), 1.55-1.40 (m, 4 H), 1.36 (s, 3 H), 1.19 (s, 3 H, *J* = 6.8 Hz), 1.14 (s, 3 H), 1.02 (d, 3 H, *J* = 6.9 Hz), 0.95-0.93 (m, 6 H). MS (ESI^+): 577.3 $(M + H)^+$.

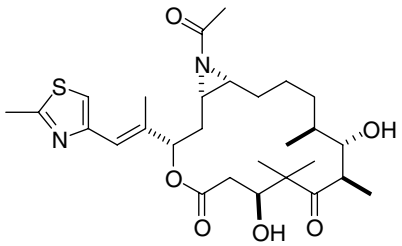
[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-*N*-[(*N*,*N*-dimethylamino)methyl]amido-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (13b).**



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1 H), 6.57 (s, 1 H), 5.37-5.35 (m, 1 H), 4.15-4.12 (m, 1 H), 3.83-3.81 (m, 1 H), 3.26 (br s, 2 H),3.19-3.16 (m, 1 H), 2.70 (s, 3 H), 2.58-2.41 (m, 3 H), 2.37 (s, 6 H), 2.32-2.28 (m, 1 H), 2.09 (s, 3 H),

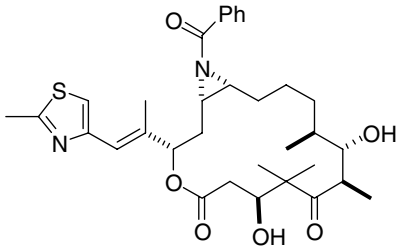
2.07-1.80 (m, 4 H), 1.79-1.41 (m, 3 H), 1.19 (s, 3 H, *J* = 6.8 Hz), 1.14 (s, 3 H), 1.02 (d, 3 H, *J* = 7.0 Hz). MS (ESI^+): 578.3 $(M + H)^+$.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17- *N*-Methylamido -7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (13c).**



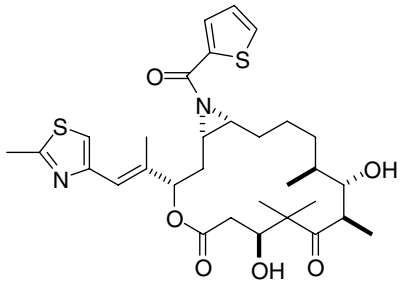
^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1 H), 6.58 (s, 1 H), 5.39-5.37 (m, 1 H), 3.86-3.83 (m, 1 H), 3.75-3.73 (m, 1 H), 3.20-3.18 (m, 1 H), 2.71 (s, 3 H), 2.57-2.46 (m, 3 H), 2.42-2.38 (m, 1 H), 2.29-2.25 (m, 1 H), 2.14 (s, 3 H) 2.11 (s, 3 H), 1.87-1.74 (m, 4 H), 1.56-1.41 (m, 4 H), 1.37 (s, 3 H), 1.20 (d, 3 H, *J* = 6.8 Hz), 1.16 (s, 3 H), 1.03 (d, 3 H, *J* = 6.9 Hz). MS (ESI^+): 535.3 $(M + H)^+$.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-*N*-Phenylamido-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (13d).**



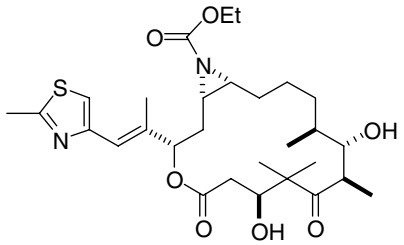
^1H NMR (400 MHz, $CDCl_3$) δ 7.96-7.93 (m, 2 H), 7.60-7.56 (m, 1 H), 7.49-7.45 (m, 2 H), 7.00 (s, 1 H), 6.59 (s, 1 H), 5.37 (d, 1 H, *J* = 8.1 Hz), 3.85-3.83 (m, 1 H), 3.72 (br s, 1 H), 3.21-3.18 (m, 1 H), 2.72 (s, 3 H), 2.69-2.43 (m, 6 H), 2.06 (s, 3 H), 2.06-1.93 (m, 4 H), 1.79-1.71 (m, 2 H), 1.64-1.45 (m, 3 H), 1.39 (s, 3 H), 1.21 (d, 3 H, *J* = 6.8 Hz), 1.17 (s, 3 H), 1.05 (d, 3 H, *J* = 6.9 Hz). MS (ESI^+) 597.3 ($M^+ + H$).

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17- *N*-(2-Thiophenyl)carbamoyl -7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (13e).



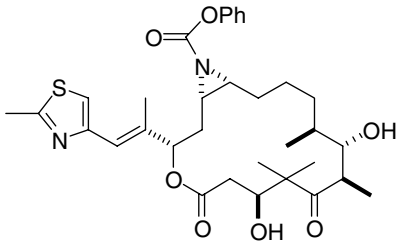
^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, 1 H, *J* = 3.9 Hz), 7.58 (d, 1 H, *J* = 4.6 Hz), 7.14 (dd, 1 H, *J* = 4.3, 3.9 Hz), 7.00 (s, 1 H), 6.59 (s, 1 H), 5.40-5.37 (m, 1 H), 3.85-3.84 (m, 1 H), 3.73-3.70 (m, 1 H), 3.21-3.18 (m, 1 H), 2.77-2.76 (m, 1 H), 2.72 (s, 3 H), 2.60-2.41 (m, 4 H), 2.13 (s, 3 H), 2.03-1.99 (m, 1 H), 1.76-1.74 (m, 1 H), 1.57-1.43 (m, 6 H), 1.38 (s, 3 H), 1.21 (d, 3 H, *J* = 6.8 Hz), 1.17 (s, 3 H), 1.05 (d, 3 H, *J* = 6.9 Hz). MS (ESI^+): 603.3 $(M + H)^+$.

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-*N*-Ethylcarbamoyl-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (14a).



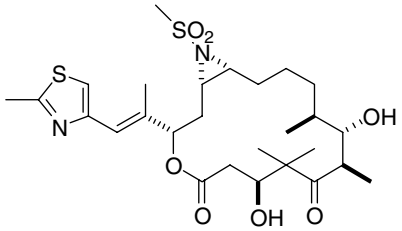
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1 H), 6.63 (s, 1 H), 5.44-5.32 (m, 1 H), 4.19-4.11 (m, 3 H), 3.91 (br s, 1 H), 3.86 (br s, 1 H), 3.22-3.18 (m, 1 H), 2.71 (s, 3 H), 2.58-2.39 (m, 4 H), 2.24-2.20 (m, 1 H), 2.11 (s, 3 H), 1.90-1.76 (m, 3 H), 1.55-1.41 (m, 3 H), 1.37 (s, 3 H), 1.30-1.27 (m, 3 H), 1.18 (d, 3 H, *J* = 6.8 Hz), 1.13 (s, 3 H), 1.01 (d, 3H, *J* = 6.9 Hz). MS (ESI$^+$): 565.3 (M + H)$^+$.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-*N*-Phenylcarbamoyl-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (14b).**



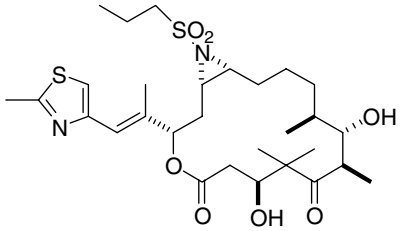
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.34 (m, 2 H), 7.24-7.20 (m, 1 H), 7.11-7.08 (m, 2 H), 6.93 (s, 1 H), 6.61 (s, 1 H), 5.44 (d, 1 H, *J* = 8.6 Hz), 4.19-4.12 (m, 1 H), 3.87-3.83 (m, 2 H), 3.21-3.18 (m, 1 H), 2.75-2.62 (m, 1 H), 2.67 (s, 3 H), 2.62-2.56 (m, 1 H), 2.55 (dd, 1 H, *J* = 14.4, 10.2 Hz), 2.47 (dd, 1 H, *J* = 14.4, 3.3 Hz), 2.32-2.27 (m, 1 H), 2.04 (s, 3 H), 1.92-1.84 (m, 4 H), 1.81-1.44 (m, 5 H), 1.37 (s, 3 H), 1.17 (d, 3 H, *J* = 6.8 Hz), 1.13 (s, 3 H), 1.01 (d, 3 H, *J* = 6.9 Hz); HRMS (ESI$^+$) *m/z* (M$^+$ + H) calcd for $C_{33}H_{44}N_2O_7S$: 613.2948, found: 613.2958.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-*N*-Methylsulfonyl-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (15a).**



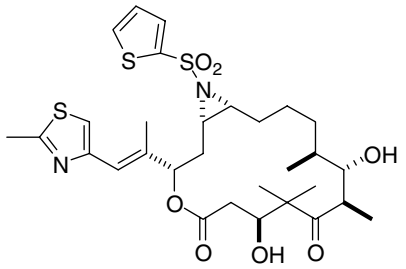
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1 H), 6.57 (s, 1 H), 5.34 (d, 1 H, *J* = 8.0 Hz), 4.15-4.12 (m, 1 H), 3.84-3.81 (m, 1 H), 3.78-3.75 (m, 1 H), 3.18-3.10 (m, 1 H), 3.04 (s, 3 H), 2.87-2.83 (m, 1 H), 2.75-2.71 (m, 1 H), 2.70 (s, 3 H), 2.62-2.55 (m, 1 H), 2.52 (dd, 1 H, *J* = 14.7, 10.2 Hz), 2.43 (dd, 1 H, *J* = 14.7, 3.0 Hz), 2.32-2.27 (m, 1 H), 2.05 (s, 3 H), 1.93-1.70 (m, 3 H), 1.58-1.42 (m, 5 H), 1.36 (s, 3 H), 1.18 (d, 3 H, *J* = 6.8 Hz), 1.15 (s, 3 H), 1.01 (d, 3 H, *J* = 6.9 Hz). HRMS (ESI$^+$) *m/z* (M$^+$ + H) calcd for $C_{27}H_{42}N_2O_7S_2$: 571.2512, found: 571.2525.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-*N*-*n*-Propylsulfonyl-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (15b).**



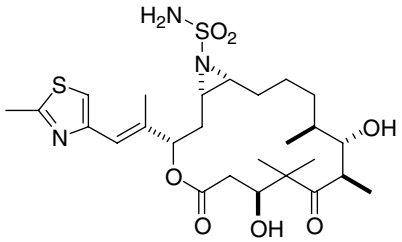
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1 H), 6.57 (s, 1 H), 5.34 (d, 1 H, *J* = 8.0 Hz), 3.83-3.82 (m, 1 H), 3.63-3.62 (m, 1 H), 3.18-3.15 (m, 1 H), 3.11- 3.07 (m, 2 H), 2.70 (s, 3 H), 2.67-2.51 (m, 1 H), 2.47- 2.43 (m, 1 H), 2.29- 2.25 (m, 1 H), 2.32-2.27 (m, 1 H), 2.10 (s, 3 H), 2.02-1.70 (m, 5 H), 1.55-1.46 (m, 3 H), 1.37 (s, 3 H), 1.21- 1.08 (m, 12 H), 1.03 (d, 3 H, *J* = 6.9 Hz). MS (ESI$^+$) 599.3 (M$^+$ + H).

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-17-(2-thiophenyl)sulfonyl-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (15c).



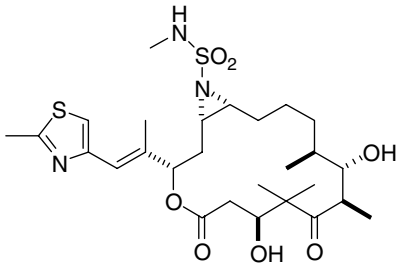
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 2 H), 7.15 (dd, 1 H, *J* = 4.3, 3.9 Hz), 6.99 (s, 1 H), 6.58 (s, 1 H), 5.36-5.34 (m, 1 H), 3.83-3.80 (m, 1 H), 3.70-3.69 (m, 1 H), 3.18-3.16 (m, 1 H), 2.88-2.83 (m, 1 H), 2.76-2.73 (m, 1 H), 2.71 (s, 3 H), 2.59- 2.53 (m, 2 H), 2.46-2.41 (m, 1 H), 2.19-2.07 (m, 1 H), 2.06 (s, 3 H), 1.92-1.89 (m, 1 H), 1.87-1.70 (m, 3 H), 1.49-1.29 (m, 3 H), 1.27 (s, 3 H), 1.18 (d, 3 H, *J* = 6.8 Hz), 1.16 (s, 3 H), 1.00 (d, 3 H, *J* = 6.9 Hz). MS (ESI$^+$): 639.2 (M + H)$^+$.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-Sulfonylurea-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (16a).**



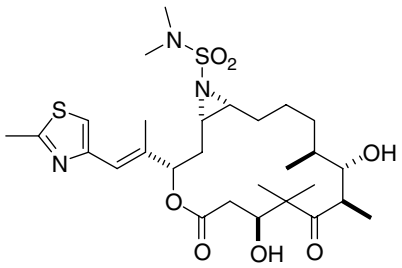
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1 H), 6.64 (s, 1 H), 5.39 (dd, 1 H, *J* = 6.9, 2.3 Hz), 5.20 (br s, 2 H, NH_2), 4.15-4.09 (m, 1 H), 3.82-3.77 (m, 2 H), 3.18-3.10 (m, 1 H), 2.65-2.62 (m, 1 H), 2.62 (s, 3 H), 2.51 (dd, 1 H, *J* = 14.6, 10.4 Hz), 2.48-2.43 (m, 1 H), 2.40 (dd, 1 H, *J* = 14.6, 3.1 Hz), 2.34-2.29 (m, 1 H), 2.06-2.03 (m, 1 H), 1.95 (s, 3 H), 1.93-1.86 (m, 2 H), 1.74-1.64 (m, 1 H), 1.63-1.34 (m, 5 H), 1.33 (s, 3 H), 1.08 (d, 3 H, *J* = 6.9 Hz), 1.03 (s, 3 H), 0.91 (d, 3 H, *J* = 7.0 Hz); LRMS (ESI$^+$): 572.4 (M + H)$^+$.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-*N*-Methylsulfonylurea-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (16b).**



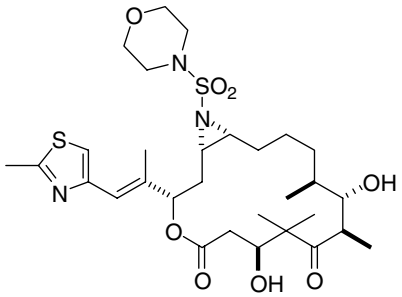
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1 H), 6.61 (s, 1 H), 5.37 (dd, 1 H, *J* = 9.5, 2.3 Hz), 4.65 (dd, 1 H, *J* = 10.3, 5.0 Hz), 4.16-4.11 (m, 1 H), 3.83 (dd, 1 H, *J* = 8.7, 4.4 Hz), 3.75 (d, 1 H, *J* = 6.5 Hz), 3.20-3.18 (m, 1 H), 2.89 (d, 3 H, *J* = 5.2 Hz), 2.74-2.70 (m, 1 H), 2.71 (s, 3 H), 2.64-2.55 (m, 1 H), 2.56 (dd, 1 H, *J* = 14.8, 10.2 Hz), 2.46 (dd, 1 H, *J* = 14.8, 3.2 Hz), 2.29-2.18 (m, 1 H), 2.08 (s, 3 H), 1.92-1.84 (m, 1 H), 1.83-1.75 (m, 2 H), 1.57-1.39 (m, 6 H), 1.38 (s, 3 H), 1.19 (d, 3 H, *J* = 6.7 Hz), 1.15 (s, 3 H), 1.02 (d, 3 H, *J* = 7.0 Hz); HRMS (ESI$^+$) *m/z* (M$^+$ + H) calcd for $C_{27}H_{43}N_3O_7S_2$: 586.2621, found: 586.2635.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-*N*,*N*-Dimethylsulfonylurea-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (16c).**



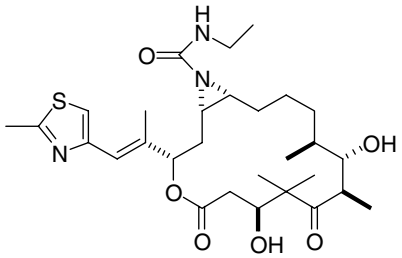
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1 H), 6.57 (s, 1 H), 5.32 (dd, 1 H, *J* = 10.2, 2.1 Hz), 4.15-4.12 (m, 1 H), 3.83-3.81 (m, 1 H), 3.65-3.62 (m, 1 H), 3.19-3.16 (m, 1 H), 2.88 (s, 6 H), 2.73-2.69 (m, 1 H), 2.71 (s, 3 H), 2.62-2.55 (m, 1 H), 2.54-2.50 (m, 1 H), 2.52 (dd, 1 H, *J* = 15.0, 10.0 Hz), 2.45 (dd, 1 H, *J* = 15.0, 3.0 Hz), 2.29-2.25 (m, 1 H), 2.07 (s, 3 H), 1.86-1.79 (m, 2 H), 1.79-1.75 (m, 1 H), 1.56-1.40 (m, 5 H), 1.37 (s, 3 H), 1.21 (d, 3 H, *J* = 6.9 Hz), 1.17 (s, 3 H), 1.03 (d, 3 H, *J* = 6.9 Hz); HRMS (ESI$^+$) *m/z* (M^+ + H) calcd for $C_{28}H_{45}N_3O_7S_2$: 600.2777, found: 600.2761.

[1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-*N*-Morpholinosulfonylurea-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (16d).**



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1 H), 6.50 (s, 1 H), 5.23 (d, 1 H, *J* = 9.3 Hz), 4.06-4.04 (m, 1 H), 3.73-3.72 (m, 1 H), 3.70-3.58 (m, 4 H), 3.20-3.17 (m, 4 H), 3.10-3.08 (m, 1 H), 2.66-2.63 (m, 1 H), 2.64 (s, 3 H), 2.64-2.62 (m, 1 H), 2.61-2.57 (m, 1 H), 2.56 (dd, 1 H, *J* = 14.8, 10.2 Hz), 2.46 (dd, 1 H, *J* = 14.8, 3.2 Hz), 2.19-2.14 (m, 1 H), 2.02 (s, 3 H), 1.80-1.72 (m, 1 H), 1.72-1.32 (m, 8 H), 1.29 (s, 3 H), 1.12 (d, 3 H, *J* = 6.7 Hz), 1.08 (s, 3 H), 0.95 (d, 3 H, *J* = 6.9 Hz); LRMS (ESI$^+$): 642.4 $(M + H)^+$.

1*S*-[1*R,3*R**(*E*),7*R**,10*S*,11*R**,12*R**,16*S**]]-17-*N*-Ethylurido-7,11-dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-oxa-17-azabicyclo[14.1.0]heptadecane-5,9-dione (17).**



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1 H), 6.60 (s, 1 H), 5.62-5.59 (m, 2 H), 4.51 (br s, 1 H, OH), 4.23-4.18 (m, 1 H), 3.86-3.83 (m, 1 H), 3.23-3.20 (m, 3 H), 2.70 (s, 3 H), 2.53-2.42 (m, 2 H), 2.40-2.36 (m, 2 H), 2.09 (s, 3 H), 1.98-1.92 (m, 2 H), 1.82-1.77 (m, 1 H), 1.61-1.36 (m, 7 H), 1.35 (s, 3 H), 1.15 (d, 3 H, *J* = 7.0 Hz), 1.11 (t, 3 H, *J* = 7.4 Hz), 1.08 (s, 3 H), 0.97 (d, 3 H, *J* = 6.9 Hz); HRMS (ESI$^+$) *m/z* (M^+ + H) calcd for $C_{29}H_{45}N_3O_6S$: 564.3107, found: 564.3367.