Kedarcidin Chromophore—Synthesis of Its Proposed Structure and Evidence for a Stereochemical Revision
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Supporting Information

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General Experimental Procedures. All reactions were performed in oven- or flame-dried round-bottom or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by alternating freeze (liquid nitrogen)/evacuation/thaw cycles (≥ three iterations). Organic solutions were concentrated by rotary evaporation (house vacuum, ~25 Torr) at 23–30 °C. Flash-column chromatography was performed as described by Still et al.,¹ employing silica gel (60-Å pore size, 230–400 mesh, Merck KGA; or 60-Å pore size, 32–63 μm, standard grade, Sorbent Technologies). Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60-Å pore size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or exposure to ceric ammonium molybdate solution (CAM) or an acidic solution of p-anisaldehyde (anisaldehyde) followed by brief heating on a hot plate (~200 °C, 10–15 s).

Materials. Commercial reagents and solvents were used as received unless mentioned otherwise. Dichloromethane, ether, tetrahydrofuran, N,N-dimethylformamide and toluene were purified by the method of Pangborn et al.² The molarity of solutions of n-butyllithium and t-butyllithium was determined by titration against a standard solution of 2-butanol in tetrahydrofuran using triphenylmethane as an indicator (average of three determinations).³

Instrumentation. Proton nuclear magnetic resonance (¹H NMR) and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded with Varian Unity/Inova 600 (600 MHz), Varian Unity/ Inova 500 (500 MHz/125 MHz), or Varian Mercury 400 (400 MHz/100 MHz) NMR spectrometers. Chemical shifts for protons are reported in parts per million scale (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents (CHCl₃: δ 7.26, C₆D₅H: δ 7.15, CD₂HCN: 1.93). Chemical shifts for carbon are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances

of the solvent (CDCl$_3$: $\delta$ 77.0, C$_6$D$_5$H: $\delta$ 128.0). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant in Hz, and assignment. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. High resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facilities.

**Synthetic Procedures.**

(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the Supporting Information beginning with 17.)

![Chemical Structure](image)

**N-Sulfinyl Imine 19**

Titanium(IV) ethoxide (35.0 mL, 169 mmol, 5.27 equiv) was added to a solution of the aldehyde 17 (6.50 g, 32.0 mmol, 1 equiv) and the (S)-(+)–p-toluenesulfinamide (18) (5.00 g, 32.2 mmol, 1.01 equiv) in dichloromethane (135 mL) at 23 °C, and the resulting solution was stirred for 4 h. Ice (77.0 g) was added and the mixture was allowed to warm to 23 °C. The turbid solution was filtered through a pad of Celite, and the filter cake was washed with dichloromethane (2 × 200 mL). The organic layer was separated and the aqueous layer was further extracted with dichloromethane (2 × 150 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (gradient elution, 10→15→20→30% ethyl acetate in hexanes) to provide a solid that was crystallized from a 1:9 mixture of ethyl acetate and hexanes to afford the enantiopure N-sulfinyl imine 19 (10.3 g, 93%) as a white crystalline solid (mp 102–103 °C).

![Chemical Structure](image)

$R_f = 0.31$ (30% ethyl acetate-hexanes). $^1$H NMR (500 MHz, C$_6$D$_5$H) $\delta$: 9.01 (s, 1H, CHN), 7.62 (d, 2H, $J = 8.5$ Hz, ArH), 7.50 (d, 1H, $J = 8.5$ Hz, H(5')), 6.87 (m, 3H, ArH, H(4')), 4.63 (s, 2H, –OCH$_2$OCH$_3$), 2.97 (s, 3H, –OCH$_2$OCH$_3$), 1.93 (s, 3H, ArCH$_3$). $^{13}$C NMR (126 MHz, C$_6$D$_5$H) $\delta$: 159.5, 151.5, 145.4, 142.7, 141.6, 141.3, 130.0, 124.9, 122.9, 122.6, 94.7, 56.2, 21.1. IR (NaCl, thin film) cm$^{-1}$: 3067 (w), 2995 (m), 2964 (m), 1913 (w), 1600 (s), 1564 (s), 1482 (s), 1451 (s), 1400 (m), 1380 (m), 1320 (s), 1267 (s), 1226 (s), 1164 (s), 1092 (s), 1067 (s), 969 (m), 923 (s), 908 (s), 851 (m), 815 (s), 790 (m), 749 (m), 677 (m), 636 (s). HRMS–ESI (m/z): [M+H]$^+$ calcd for C$_{15}$H$_{16}$ClN$_2$O$_3$S, 339.0570; found, 339.0581. $[\alpha]^{23}_D$ (c 1.7, THF): +117.2°.


**β-Amino Ester 20**

*n*-Butyllithium (2.5 M in hexanes, 25.0 mL, 62.5 mmol, 2.17 equiv) was added to a solution of diisopropylamine (8.9 mL, 63.5 mmol, 2.20 equiv) in tetrahydrofuran (180 mL) and hexanes (140 mL) at 0 °C. After stirring for 30 min, the solution was cooled to −78 °C. Methyl acetate (4.7 mL, 59.3 mmol, 2.05 equiv) was added and the resulting colorless solution was stirred at −78 °C for 30 min. Chlorotriisopropoxyltitanium(IV) (1.0 M in hexanes, 125 mL, 125 mmol, 4.33 equiv) was then added via cannula and the resulting bright yellow suspension was stirred at −78 °C for 40 min. The suspension was cooled to −90 °C. A solution of the *N*-sulfinyl imine 19 (9.81 g, 28.9 mmol, 1 equiv) in tetrahydrofuran (100.0 mL) was added slowly via cannula over a period of 20 min at −90 °C and the reaction mixture was stirred for an additional 30 min. Saturated aqueous ammonium chloride solution (600 mL) was added and the suspension was warmed to 23 °C. The mixture was partitioned between ethyl acetate (500 mL) and water (200 mL). The organic layer was separated and washed with saturated aqueous sodium chloride solution (400 mL). The aqueous layers were combined and the combined solution was extracted with ethyl acetate (2 × 300 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (gradient elution, 40→50→60% ethyl acetate in hexanes) to provide the β-amino ester 20 (11.20 g, 94% yield, 91% de) as a colorless oil.

**Rf = 0.40 (50% ethyl acetate-hexanes).**  
$^1$H NMR (500 MHz, CDCl$_3$) δ: 7.60 (d, 2H, $J = 8.5$ Hz, ArH), 7.46 (d, 1H, $J = 8.0$ Hz, H(5’)), 7.35 (d, 1H, $J = 8.5$ Hz, H(4’)), 7.32 (d, 2H, $J = 7.5$ Hz, ArH), 5.43 (d, 1H, $J = 9.0$ Hz, –NH), 5.23 (s, 2H, –OCH$_2$OCH$_3$), 4.71 (ddd, 1H, $J = 9.5, 7.0, 5.5$ Hz, H(7’)), 3.55 (s, 3H, CO$_2$CH$_3$), 3.50 (s, 3H, –OCH$_2$OCH$_3$), 2.90 (dd, 1H, $J = 16.0, 5.5$ Hz, H(8’)), 2.81 (dd, 1H, $J = 16.5$, 7.0 Hz, H(8’)) 2.42 (s, 3H, ArCH$_3$).  
$^{13}$C NMR (126 MHz, CDCl$_3$) δ: 171.2, 152.8, 148.4, 141.4, 141.1, 140.3, 129.5, 125.7, 124.0, 121.7, 95.1, 56.5, 53.0, 51.6, 40.5, 21.3.  
IR (NaCl, thin film) cm$^{-1}$: 3446 (s), 3282 (s), 2954 (s), 2236 (w), 1733 (s), 1646 (m), 1564 (s), 1456 (s), 1441 (s), 1374 (s), 1272 (s), 1205 (s), 1159 (s), 1092 (s), 1072 (s), 989 (m), 923 (s), 862 (s), 815 (s), 733 (s).  
HRMS–ESI (m/z): [M+H]$^+$ calcd for C$_{18}$H$_{22}$ClN$_2$O$_5$S, 413.0938; found, 413.0946.  
$[\alpha]^{23}_D$ (c 1.0, THF): +179.8°.

(6) Titanium enolate additions were most selective; for precedence, see: Ellman, J. A. *Pure Appl. Chem.* 2003, 75, 39.
Ammonium Salt 21

A solution of the β-amino ester 20 (11.2 g, 27.0 mmol, 1 equiv) in methanol (50 mL) was cooled to 0 °C. Acetyl chloride (38.0 mL, 534 mmol, 19.8 equiv) was added slowly via syringe over a period of 10 min at 0 °C. The reaction solution was warmed to 23 °C. After stirring for 12 h, the reaction mixture was concentrated. The resulting white solid was washed with a 1:1 mixture of ethyl acetate and hexanes (2 × 50 mL). The solid was recrystallized from methanol–ethyl acetate (1:10) to afford the ammonium salt 21 (6.69 g, 93%) as a white crystalline solid (mp 198–199 °C).

$\text{N}^\text{HOC(OCH}_3\text{O)NH}_2\text{HCl}$

$\text{R}_f = 0.42$ (20% methanol–dichloromethane). $^1$H NMR (500 MHz, CD$_3$OD) δ: 7.33 (s, 2H, H(4'), H(5')), 4.87 (s, 3H, NH$_3$Cl), 4.74 (dd, 1H, J = 7.0, 6.5 Hz, H(7')), 3.70 (s, 3H, CO$_2$C$_3$H$_7$), 3.05 (dd, 1H, J = 17.0, 6.5 Hz, H(8')), 3.00 (dd, 1H, J = 16.5, 6.5 Hz, H(8')). $^{13}$C NMR (126 MHz, CD$_3$OD) δ: 171.6, 151.9, 145.9, 140.0, 125.7, 123.9, 52.7, 51.9, 38.5. IR (NaCl, thin film) cm$^{-1}$: 3426 (br, s), 3027 (br, s), 1723 (s, C=O), 1600 (w), 1565 (m), 1488 (m), 1436 (m), 1375 (w), 1308 (m), 1221 (s), 1082 (m), 842 (w). HRMS–ESI ($m/z$): [M–Cl]$^+$ calcd for C$_9$H$_{12}$ClN$_2$O$_3$, 231.0536; found, 231.0546. [$\alpha$]$^\text{D}_{23}$ (c 1.1, MeOH): $-9.0^\circ$.

N-tert-Butoxycarbonyl (Boc) Amine 22

Triethylamine (10.0 mL, 71.75 mmol, 3.18 equiv) was added to a solution of the ammonium salt 21 (6.03 g, 22.54 mmol, 1 equiv) in methanol (55 mL) at 23 °C. Di-tert-butyl dicarbonate (5.42 g, 24.8 mmol, 1.10 equiv) was added and the resulting solution was stirred at 23 °C for 2.5 h. The reaction mixture was partitioned between ethyl acetate (500 mL) and aqueous hydrochloric acid (2 N, 450 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 250 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to afford the N-tert-butoxycarbonyl (Boc) amine 22 (6.28 g, 84%) as a white solid (mp 76–78 °C).
R_f = 0.31 (50% ethyl acetate-hexanes).  

$^1$H NMR (400 MHz, CDCl_3) δ: 7.21 (s, 2H, H(4'), H(5')), 5.71 (d, 1H, $J = 8.5$ Hz, BocNH), 5.08 (m, 1H, H(7')), 3.63 (s, 3H, CO$_2$CH$_3$), 3.00 (dd, 1H, $J = 16.0$, 5.0 Hz, H(8')), 2.83 (dd, 1H, $J = 16.5$, 6.5 Hz, H(8')), 1.44 (s, 9H, OC(C$_3$H$_3$)).  

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 171.6, 155.2, 150.7, 147.5, 137.3, 124.3, 121.9, 51.8, 51.0, 39.4, 28.4.  

IR (NaCl, thin film) cm$^{-1}$: 3331 (m, NH, OH), 2972 (m), 1713 (s, C=O), 1685 (s, C=O).  

HRMS–ESI (m/z): [M+H]$^+$ calcd for C$_{14}$H$_{20}$ClN$_2$O$_5$, 331.1060; found, 331.1064.

**Triethylsilyl (TES) Acetylene 24**

A solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 245 mL, 245 mmol, 1.01 equiv) was added to a solution of the alcohol 23$^7$ (34.0 g, 243 mmol, 1 equiv) in tetrahydrofuran (1.2 L) at −78 °C, and the resulting yellow solution was stirred at −78 °C for 15 min. Chlorotriethylsilane (41.0 mL, 244 mmol, 1.01 equiv) was added and the reaction mixture was allowed to stir at −78 °C for 15 min. A solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 300 mL, 300 mmol, 1.23 equiv) was added to the cold solution and stirring was continued at −78 °C for 15 min, then chlorotriethylsilane (50.0 mL, 297.9 mmol, 1.23 equiv) was added and stirring was continued for 15 min. The cold reaction mixture was partitioned between hexanes (2 L) and saturated aqueous sodium bicarbonate solution (2 L). The organic layer was separated and washed with aqueous hydrochloric acid solution (2 L) and saturated aqueous sodium chloride solution (2 L), in sequence. The aqueous layers were combined and the combined solution was extracted with a 1:1 mixture of ether and hexanes (2 × 1 L). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a colorless oil. Triethylamine trihydrofluoride (79.3 mL, 486 mmol, 2.00 equiv) was added to a solution of the oily concentrate in tetrahydrofuran (1.2 L) at 0 °C and the resulting solution was stirred at 0 °C for 3 h. The cold reaction mixture was partitioned between a 5:1 mixture of ether and hexanes (1.5 L) and saturated aqueous sodium bicarbonate solution (1.2 L). The organic layer was separated and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford the triethylsilyl (TES) acetylene 24 (52.8 g, 90%) as a colorless oil.

$R_f = 0.30$ (20% ethyl acetate-hexanes).  $^1$H NMR (500 MHz, C$_6$D$_6$) δ: 4.57 (d, 1H, $J = 5.5$ Hz, H(3)), 3.93 (m, 1H, H(4)), 3.85 (m, 2H, H(5)), 1.57 (dd, 1H, $J = 8.0$, 6.5 Hz, HO), 1.50 (s, 3H, CH$_3$), 1.16 (s, 3H, CH$_3$), 1.00 (t, 9H, $J = 8.0$ Hz, Si(CH$_2$CH$_3$)$_3$), 0.54 (q, 6H, $J = 8.0$ Hz, Si(CH$_2$CH$_3$)$_3$).  $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ: 110.3, 103.1, 90.2, 78.3, 68.0, 63.2, 27.8, 25.8, 7.6, 4.5.  IR (NaCl, thin film) cm$^{-1}$: 3446 (m, OH), 2954 (s), 2882 (s), 2174 (w, C≡C), 1456 (m), 1380 (m), 1226 (s), 1164 (m), 1067 (s), 1021 (s), 969 (m), 851 (m), 728 (s).  HRMS–ESI (m/z): [M+H]$^+$ calcd for C$_{14}$H$_{27}$O$_3$Si, 271.1729; found, 271.1716.

Dibromoolefin 25

Methyl sulfoxide (35.5 mL, 503 mmol, 4.00 equiv) was added dropwise to a solution of oxalyl chloride (22.0 mL, 252 mmol, 2.00 equiv) in dichloromethane (700 mL) at $-78 \degree C$, and the resulting solution was stirred at $-78 \degree C$ for 30 min. A solution of the triethylsilyl (TES) acetylene 24 (34.0 g, 126 mmol, 1 equiv) in dichloromethane (350 mL) was added to the cold reaction mixture. The resulting suspension was stirred at $-78 \degree C$ for 45 min. Triethylamine (88.0 mL, 631 mmol, 5.01 equiv) was then added dropwise over 30 min to the reaction mixture and stirring was continued for an additional 15 min at $-78 \degree C$. The reaction mixture was warmed to 0 $\degree C$ over a period of 15 min. After stirring at 0 $\degree C$ for 15 min, the product mixture was partitioned between a 1:1 mixture of ether and hexanes (2 L) and aqueous hydrochloric acid solution (1.0 M, 1 L). The organic layer was separated and washed with saturated aqueous sodium chloride solution (1 L). The washed solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide a pale yellow oil. Triphenylphosphine (133 g, 507 mmol, 4.03 equiv) was added to a solution of carbon tetrabromide (79.1 g, 254 mmol, 2.02 equiv) in dichloromethane (2.0 L) at 0 $\degree C$ and the resulting yellow solution was stirred for 15 min. Triethylamine (177 mL, 1.27 mol, 10.1 equiv) was added and stirring was continued at 0 $\degree C$ for 10 min. A solution of the crude oily concentrate in dichloromethane (600 mL) was added via cannula over 30 min at 0 $\degree C$, and the resulting red solution was stirred for an additional 20 min. The cold reaction mixture was poured into pentane (4.0 L). The solids were removed by filtration through anhydrous sodium sulfate. After washing with pentane (1 L), the solids were dissolved in the minimum amount of dichloromethane (300 mL) and were reprecipitated by addition of pentane (2 L). The resulting solid was removed by filtration through sodium sulfate. The filtrates were combined and the combined solution was concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to provide the dibromoolefin 25 (46.0 g, 87%) as a colorless oil.

$R_f = 0.53$ (5% ethyl acetate-hexanes).  $^1$H NMR (500 MHz, C$_6$D$_6$) δ: 6.89 (d, 1H, $J = 8.0$ Hz, H(2)), 4.67 (d, 1H, $J = 6.0$ Hz, H(4)), 4.63 (dd, 1H, $J = 8.0$, 6.0 Hz, H(3)), 1.49 (s, 3H, CH$_3$), 1.14 (s, 3H, CH$_3$), 1.05 (t, 9H, $J = 8.0$ Hz, Si(CH$_2$CH$_3$)$_3$), 0.59 (q, 6H, $J = 8.0$ Hz, Si(CH$_2$CH$_3$)$_3$).  $^{13}$C
NMR (126 MHz, C₆D₆) δ: 136.2, 111.0, 102.6, 93.5, 91.0, 78.8, 68.9, 27.8, 26.0, 7.7, 4.5. IR (NaCl, thin film) cm⁻¹: 2985 (m), 2954 (s), 2872 (s), 2174 (w, C≡C), 1615 (w, C=CBr₂), 1456 (m), 1380 (m), 1226 (s), 1159 (m), 1056 (s), 1015 (m), 867 (s), 723 (s). HRMS–CI (m/z): [M+NH₄]⁺ calcd for C₁₅H₂₈Br₂NO₂Si, 440.0256; found, 440.0273.

HF, CH₃CN, H₂O
98%

**Diol 26**

A solution of the dibromoolefin 26 (45.6 g, 108 mmol, 1 equiv) and hydrofluoric acid (48 wt % in water, 100 mL, 2.75 mol, 25.5 equiv) in acetonitrile (1.0 L) was stirred at 23 °C for 4 h. Saturated aqueous sodium bicarbonate solution (4 L) was added slowly to the reaction mixture. A 1:1 mixture of ethyl acetate and hexanes (5.0 L) was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 1 L). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to provide the diol 26 (40.4 g, 98%) as a colorless oil that crystallized slowly over several days.

Rᵢ = 0.29 (20% ethyl acetate-hexanes). ¹H NMR (500 MHz, C₆D₆) δ: 6.55 (d, 1 H, J = 8.5 Hz, H(2)), 4.20 (ddd, 1 H, J = 8.5, 6.0, 4.0 Hz, H(3)), 4.12 (dd, 1 H, J = 6.0, 3.5 Hz, H(4)), 1.68 (d, 1 H, J = 5.5 Hz, HO(C4)), 1.62 (d, 1 H, J = 6.0 Hz, HO(C3)), 1.04 (t, 9H, J = 8.0 Hz, Si(CH₂CH₃)₃), 0.58 (q, 6H, J = 8.0 Hz, Si(CH₂CH₃)₃). ¹³C NMR (126 MHz, C₆D₆) δ: 136.6, 103.9, 93.7, 89.7, 75.0, 64.9, 7.7, 4.6. IR (NaCl, thin film) cm⁻¹: 3385 (s, OH), 2954 (s), 2872 (s), 2174 (w, C≡C), 1621 (m, C=CBr₂), 1456 (m), 1415 (m), 1380 (m), 1231 (m), 1067 (s), 1005 (s), 887 (m), 784 (m), 728 (s). HRMS–CI (m/z): [M+NH₄]⁺ calcd for C₁₂H₂₄Br₂NO₂Si, 399.9943; found, 399.9949.

SO₂Cl₂, Et₃N, DMAP
CH₂Cl₂, –78 °C
63%

**Cyclic Sulfate 27**

4-(Dimethylamino)pyridine (768 mg, 6.29 mmol, 0.40 equiv) was added to a solution of the diol 26 (6.05 g, 15.8 mmol, 1 equiv) in dichloromethane (350 mL), and the resulting solution was cooled to –78 °C. Triethylamine (8.76 mL, 62.8 mmol, 3.97 equiv) was added to the cold solution and stirring was continued for 10 min. A solution of freshly distilled sulfuryl chloride (2.40 mL, 29.9 mmol, 1.89 equiv) in dichloromethane (350 mL) was added to the cold reaction mixture via cannula over 3.5 h. After stirring at –78 °C for 30 min, the cold reaction mixture was partitioned between hexanes (600 mL) and saturated aqueous sodium bicarbonate solution (250 mL). The organic layer was separated and washed with saturated aqueous sodium chloride
solution (250 mL). The individual aqueous layers were separately extracted with hexanes (2 × 200 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to provide the cyclic sulfate 27 (4.39 g, 63%) as a white solid.

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\text{Rf} = 0.22 \text{ (5% ethyl acetate-hexanes).} \]

\(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\): 6.62 (d, 1H, \(J = 8.5\) Hz, H(2)), 4.80 (dd, 1H, \(J = 8.5, 6.0\) Hz, H(3)), 4.59 (d, 1H, \(J = 6.5\) Hz, H(4)), 0.94 (t, 9H, \(J = 8.0\) Hz, Si(CH\(_2\)CH\(_3\))\(_3\)), 0.48 (q, 6H, \(J = 8.0\) Hz, Si(CH\(_2\)CH\(_3\))\(_3\)). \(^{13}\)C NMR (126 MHz, C\(_6\)D\(_6\)) \(\delta\): 129.7, 100.5, 99.2, 94.4, 82.3, 73.2, 7.5, 4.0. IR (NaCl, thin film) cm\(^{-1}\): 3046 (w), 2954 (s), 2872 (s), 1621 (m, C=CBr\(_2\)), 1456 (m), 1400 (s), 1328 (w), 1236 (m), 1210 (s), 1128 (m), 1077 (m), 964 (s), 877 (m), 846 (s), 794 (m), 728 (s).

**Alcohol 28**

Potassium hexamethyldisilazide (0.5 M in toluene, 68.0 mL, 39.0 mmol, 1.37 equiv) was added dropwise over 20 min to a solution of the \(N\)-tert-butoxycarbonyl (Boc) amine 22 (11.8 g, 35.7 mmol, 1.25 equiv) in acetonitrile (300 mL) at \(-40^\circ\)C. The resulting solution was stirred at \(-40^\circ\)C for 30 min. A solution of the cyclic sulfate 27 (12.7 g, 28.5 mmol, 1 equiv) in acetonitrile (170 mL) was added via cannula over 1.5 h to the cold reaction mixture. The resulting solution was stirred at \(-40^\circ\)C for 1 h, then was warmed to 23 \(^\circ\)C. The mixture was concentrated and dried under high vacuum for 2 h to afford a tan-colored foam. The crude residue was dissolved in tetrahydrofuran (240 mL) at 23 \(^\circ\)C. Water (6.0 mL, 333 mmol, 11.7 equiv) and concentrated sulfuric acid (1.0 mL, 18.0 mmol, 0.63 equiv) were added sequentially. After stirring for 1 h, solid sodium bicarbonate (22.0 g) was added to the reaction mixture. (Caution: gas evolution!). The resulting suspension was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford the alcohol 28 (18.5 g, 93%, containing ~10% of the regioisomeric product of sulfate opening) as a white foam.

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\text{Rf} = 0.30 \text{ (30% ethyl acetate-hexanes).} \]

\(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\): 6.86 (d, 1H, \(J = 8.5\) Hz, H(5')), 6.72 (d, 1H, \(J = 8.5\) Hz, H(4')), 6.25 (d, 1H, \(J = 9.0\) Hz, H(12)), 5.65 (d, 1H, \(J = 9.0\) Hz,
NH), 5.33 (m, 1H, H(7’)), 4.62 (dd, 1H, J = 8.5, 7.0 Hz, H(11)), 4.32 (dd, 1H, J = 6.0, 6.0 Hz, H(10)), 3.18 (s, 3H, OCH3), 2.88 (dd, 1H, J = 16.0, 5.0 Hz, H(8’)), 2.67 (dd, 1H, J = 16.0, 7.0 Hz, H(8’)), 2.10 (d, 1H, J = 5.5 Hz, OH), 1.43 (s, 9H, OC(CH3)3), 1.05 (t, 9H, J = 8.0 Hz, Si(CH2CH3)3). 13C NMR (126 MHz, C6D6) δ: 171.4, 155.3, 153.8, 148.9, 141.1, 133.9, 124.0, 121.8, 103.3, 96.7, 89.8, 82.8, 79.4, 64.6, 51.4, 51.3, 39.1, 28.4, 7.7, 4.5. IR (NaCl, thin film) cm–1: 3424 (br, m), 2952 (s), 2870 (m), 2275 (w), 2173 (w), 1712 (s), 1692 (s), 1625 (w), 1563 (m), 1502 (s), 1451 (s), 1389 (m), 1369 (s), 1286 (s), 1240 (s), 1169 (s), 1086 (s), 1056 (m), 1020 (m), 979 (m), 912 (w), 851 (m), 794 (m), 738 (s), 676 (w).

HRMS–ESI (m/z): [M+H]+ calcd for C26H38Br2ClN2O6Si, 695.0554; found, 695.0520.

TBSCl, Im, DMF, 23 °C
88%

**tert-Butyldimethylsilyl (TBS) Ether 3**

tert-Butyldimethylsilyl chloride (6.52 g, 43.3 mmol, 1.53 equiv) was added to a solution of the alcohol 28 (19.6 g, 28.2 mmol, regioisomeric mixture, ~9:1, 1 equiv) and imidazole (8.30 g, 122 mmol, 4.32 equiv) in DMF (180 mL). The resulting solution was stirred at 23 °C for 65 min. The reaction mixture was partitioned between a 1:1 mixture of ethyl acetate and hexanes (1 L) and saturated aqueous bicarbonate solution (500 mL). The aqueous layer was separated and extracted with a 1:1 mixture of ethyl acetate and hexanes (2 × 300 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (gradient elution, 5→10→15% ethyl acetate in hexanes) to provide the tert-butyldimethylsilyl (TBS) ether 3 (20.1 g, 88%, regioisomeric mixture, ~23:1 (NMR)) as a white foam.

Rf = 0.42 (20% ethyl acetate-hexanes). 1H NMR (500 MHz, C6D6) δ: 6.86 (d, 1H, J = 8.5 Hz, H(5’)), 6.81 (d, 1H, J = 8.5 Hz, H(4’)), 6.29 (d, 1H, J = 9.0 Hz, H(12)), 5.64 (d, 1H, J = 8.5 Hz, NH), 5.33 (dd, 1H, J = 14.0, 6.0 Hz, H(7’)), 4.81 (dd, 1H, J = 8.5, 7.5 Hz, H(11)), 4.60 (d, 1H, J = 7.0 Hz, H(10)), 3.19 (s, 3H, OCH3), 2.87 (dd, 1H, J = 16.0, 5.0 Hz, H(8’)), 2.65 (dd, 1H, J = 16.0, 7.0 Hz, H(8’)), 1.42 (s, 9H, OC(CH3)3), 1.09 (t, 9H, J = 8.0 Hz, Si(CH2CH3)3), 0.97 (s, 9H, SiC(CH3)3), 0.64 (q, 6H, J = 8.0 Hz, Si(CH2CH3)3), 0.25 (s, 3H, t-BuSi(CH3)2), 0.14 (s, 3H, t-BuSi(CH3)2). 13C NMR (126 MHz, C6D6) δ: 171.3, 155.1, 152.5, 148.9, 140.7, 133.9, 122.9, 121.7, 103.8, 96.8, 90.0, 82.0, 79.2, 65.7, 51.3, 51.1, 39.2, 28.4, 25.8, 18.4, 7.7, 4.5, –4.6, –4.7. IR (NaCl, thin film) cm–1: 3438 (br, w), 3341 (br, w), 2953 (s), 2928 (m), 2177 (w), 1733 (s), 1710 (s), 1625 (w), 1560 (m), 1496 (m), 1453 (s), 1388 (w), 1366 (m), 1286 (s), 1248 (s), 1167
(s), 1102 (s), 1086 (s), 779 (m), 725 (m), 671 (w). HRMS–ESI (m/z): [M+H]⁺ calcd for C₃₂H₅₂Br₂ClN₂O₆Si₂, 809.1419; found, 809.1382.

1. LiOH, H₂O₂, H₂O, THF
2. FmOH, DMAP, MNBA

CH₂Cl₂, 23 °C

93% Br

9-Fluorenymethyl (Fm) Ester 29

Lithium hydroxide (2.92 g, 69.6 mmol, 2.68 equiv) was added to a solution of the tert-butyldimethylsilyl (TBS) ether 3 (21.0 g, 26.0 mmol, 1 equiv) in tetrahydrofuran (270 mL) containing 30% aqueous hydrogen peroxide (90 mL). The resulting solution was stirred at 23 °C for 22 h. The reaction mixture was cooled to 0 °C and aqueous sodium sulfite solution (1 M, 1L) was added slowly. The cooling bath was removed and the solution was allowed to warm to 23 °C over 10 min. The mixture was partitioned between ethyl acetate (1.5 L) and aqueous hydrochloric acid solution (1 N, 1 L). The organic layer was separated and washed with saturated aqueous sodium chloride solution (400 mL). The individual aqueous fractions were separately extracted with ethyl acetate (3 × 300 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford the carboxylic acid as a colorless oil.

2-Methyl-6-nitrobenzoic anhydride (MNBA, 9.82 g, 28.5 mmol, 1.10 equiv) was added to a solution of the carboxylic acid (unpurified) (26.0 mmol, 1 equiv), 9-fluorenemethanol (6.06 g, 30.9 mmol, 1.19 equiv), and 4-dimethylaminopyridine (10.4 g, 85.1 mmol, 3.27 equiv) in dichloromethane (300 mL). The resulting solution was stirred at 23 °C for 15 min. The reaction mixture was then partitioned between ethyl acetate (1 L) and aqueous hydrochloric acid (1 N, 200 mL). The organic layer was further washed with saturated aqueous sodium chloride solution (200 mL). The individual aqueous layers were separately extracted with ethyl acetate (3 × 200 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (gradient elution, 6→8→10→12→14% ethyl acetate in hexanes) to provide the 9-fluorenymethyl ester 29 (23.6 g, 93%) as a white foam.

Rᵣ = 0.47 (20% ethyl acetate-hexanes). ¹H NMR (500 MHz, C₆D₆), δ: 7.55 (d, 2H, J = 7.5 Hz, ArH), 7.36 (m, 2H, ArH), 7.22 (dd, 2H, J = 7.5, 7.0 Hz, ArH), 7.16 (m, 2H, ArH), 6.87 (d, 1H, J = 8.0 Hz, H(5'))), 6.81 (d, 1H, J = 8.5 Hz, H(4'))), 6.26 (d, 1H, J = 9.0 Hz, H(12)), 5.65 (d, 1H, J = 9.5 Hz, NH), 5.36 (m, 1H, H(7')), 4.80 (dd, 1H, J = 8.0, 7.5 Hz, H(11)), 4.59 (d, 1H, J = 7.5 Hz, H(10)), 4.16–4.07 (m, 2H, Ar₂CHCH₂), 3.90 (t, 1H, J = 7.0 Hz, Ar₂CHCH₂), 2.95 (dd, 1H, J =
16.0, 5.0 Hz, H(8')), 2.67 (dd, 1H, J = 16.5, 7.0 Hz, H(8')), 1.43 (s, 9H, OC(CH3)3), 1.08 (t, 9H, J = 8.0 Hz, SiC(CH2CH3)3), 0.96 (s, 9H, SiC(CH3)3), 0.63 (q, 6H, J = 8.0 Hz, SiC(CH2CH3)3), 0.24 (s, 3H, t-BuSi(CH3)2), 0.13 (s, 3H, t-BuSi(CH3)2). 13C NMR (126 MHz, C6D6) δ: 170.9, 155.2, 152.5, 148.9, 144.3, 144.2, 141.6, 140.7, 133.9, 127.3, 125.5, 125.4, 122.9, 121.7, 120.2, 103.8, 96.8, 90.0, 82.0, 79.3, 66.5, 65.7, 51.4, 47.0, 39.2, 28.4, 25.8, 18.4, 7.7, 4.5, –4.6, –4.7. IR (NaCl, thin film), cm⁻¹: 3428 (br, w), 3341 (br, w), 2953 (s), 2921 (s), 2878 (s), 2274 (w), 2177 (w), 1733 (s), 1717 (s), 1701 (s), 1625 (s), 1570 (m), 1496 (m), 1490 (s), 1447 (s), 1388 (m), 1366 (m), 1286 (s), 1248 (s), 1167 (s), 1102 (s), 1086 (s), 1000 (m), 838 (m), 779 (m), 757 (m), 741 (s), 671 (w).

HRMS–ESI (m/z): [M+H]+ calcd for C45H60Br2ClN2O6Si2, 973.2045; found, 973.2060.

Naphthoic Amide 5

Trimethylsilyl trifluoromethanesulfonate (18.0 mL, 99.5 mmol, 5.29 equiv) was added to a solution of the 9-fluorenemethyl ester 29 (18.3 g, 18.8 mmol, 1 equiv) and 2,6-lutidine (23.0 mL, 198 mmol, 10.5 equiv) in dichloromethane (250 mL). The reaction mixture was stirred at 23 °C for 4.5 h. Saturated aqueous sodium bicarbonate solution (1.5 L) was added. At this point a solution of the activated ester 4 (~1.10 equiv) in dichloromethane (50 mL) [prepared by treatment of the corresponding naphthoic acid (7.73 g, 19.8 mmol, 1.10 equiv) with EDC•HCl (12.5 g, 65.2 mmol, 3.47 equiv) and 1-hydroxybenzotriazole hydrate (HOBT, 2.90 g, 21.5 mmol, 1.14 equiv) in dichloromethane (50 mL)] was added to the biphasic mixture. The resulting suspension was stirred at 23 °C for 16 h. The organic layer was separated and washed with aqueous hydrochloric acid solution (2 N, 1 L). The individual aqueous layers were separately extracted with dichloromethane (2 × 500 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (gradient elution, 1→2→4→6→8→10% ethyl acetate in dichloromethane) to provide the naphthoic amide 5 (22.7 g, 97%) as a white foam.
R_f = 0.44 (20% ethyl acetate-hexanes).  

1H NMR (500 MHz, C_6D_6), δ: 8.84 (s, 1H, ArH), 7.54 (d, 2H, J = 7.5 Hz, ArH), 7.43 (m, 2H, ArH), 7.39 (d, 1H, J = 6.0 Hz, NH), 7.38 (s, 1H, ArH), 7.22–7.14 (m, 5H, ArH), 6.94 (d, 1H, J = 9.0 Hz, H(4')), 6.63 (s, 1H, ArH), 6.31 (d, 1H, J = 8.5 Hz, H(12)), 5.88 (m, 1H, J(7')), 4.86 (dd, 1H, J = 8.5, 6.5 Hz, H(11)), 4.63 (d, 1H, J = 7.0 Hz, H(10')), 4.29–4.17 (m, 3H, H(10''), Ar_2CHCH_2), 3.98 (t, 1H, J = 7.0 Hz, Ar_2CHCH_2), 3.76 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.17 (dd, 1H, J = 16.0, 5.0 Hz, H(8')), 2.84 (dd, 1H, J = 16.0, 5.0 Hz, H(8')), 1.47 (s, 9H, OCH(CH_3)_3), 1.15 (d, 6H, J = 6.5 Hz, H(11''), H(12'')), 1.09 (t, 9H, J = 8.0 Hz, SiC(CH_2CH_3)_3), 0.97 (s, 9H, SiC(CH_3)_3), 0.64 (q, 6H, J = 8.0 Hz, SiC(CH_2CH_3)_3), 0.25 (s, 3H, t-BuSi(CH_3)_2), 0.15 (s, 3H, t-BuSi(CH_3)_2).  

13C NMR (126 MHz, C_6D_6), δ: 176.9, 171.2, 165.6, 153.8, 152.1, 149.4, 149.1, 147.0, 144.3, 144.2, 141.6, 140.6, 133.8, 132.8, 127.9, 127.4, 127.3, 126.0, 125.5, 125.4, 124.7, 123.3, 122.6, 122.2, 120.2, 119.4, 104.0, 103.8, 96.9, 90.0, 82.0, 70.6, 66.7, 65.7, 50.3, 47.0, 39.3, 38.6, 27.4, 25.9, 18.4, 17.7, 4.5, –4.6, –4.7.  

IR (NaCl, thin film) cm⁻¹: 3417 (br, w), 3061 (w), 2953 (s), 2921 (s), 2878 (s), 2274 (w), 2177 (w), 1749 (s), 1744 (s), 1668 (s), 1663 (s), 1625 (m), 1620 (m), 1550 (s), 1490 (m), 1458 (s), 1453 (s), 1416 (s), 1393 (s), 1263 (s), 1242 (s), 1172 (m), 1113 (s), 1021 (m), 1005 (m), 838 (m), 779 (w), 735 (m), 671 (w).  

MS–ESI (m/z): [M+H]^+ calcd for C_61H_76Br_2ClN_2O_10Si_2, 1245.3; found, 1245.4.

Bromoenetriyne 7

Triethylamine (0.91 mL, 6.53 mmol, 2.50 equiv) was added to a solution of the naphthoic amide 5 (3.25 g, 2.61 mmol, 1 equiv) and the terminal alkyne 6 (1.45 g, 2.62 mmol, 1.00 equiv) in ether (140 mL) at 23 °C. The resulting solution was cooled to −78 °C and was degassed at this temperature. The degassed solution was then warmed to 23 °C.
Tetrakis(triphenylphosphine)palladium(0) (Pd(PPh$_3$)$_4$, 908 mg, 0.786 mmol, 0.30 equiv) and copper(I) iodide (148 mg, 0.777 mmol, 0.30 equiv) were added in one portion to the reaction mixture. The resulting suspension was degassed and the degassed suspension was stirred at 23 °C for 2 h. At this point another portion of copper(I) iodide (153 mg, 0.803 mmol, 0.31 equiv) was added. The mixture was degassed and the degassed suspension was stirred at 23 °C for 21 h.

$N$-Acetyl cysteine was added to sequester heavy metal salts and the suspension was stirred at 23 °C for 30 min. The reaction mixture was partitioned between ethyl acetate (300 mL) and saturated aqueous sodium bicarbonate solution (300 mL). The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (gradient elution, 10 → 20 → 30 → 40% ethyl acetate in dichloromethane) to provide the bromoenetriyne 7 (2.73 g, 61%) as a pale yellow foam.

$R_f$ = 0.49 (40% ethyl acetate-hexanes). $^1$H NMR (500 MHz, $C_6D_6$), δ: 8.83 (s, 1H, ArH), 7.55 (dd, 2H, $J$ = 7.0, 3.0 Hz, ArH), 7.46 (m, 3H, ArH, NH), 7.37 (s, 1H, ArH), 7.24–7.15 (m, 5H, ArH, H(5')), 7.08 (d, 1H, $J$ = 8.0 Hz, H(4')), 6.62 (s, 1H, ArH), 6.31 (d, 1H, $J$ = 8.5 Hz, H(12)), 5.89 (m, 1H, H(7')), 5.23 (dd, 1H, $J$ = 8.5, 7.0 Hz, H(11)), 5.10 (dd, 1H, $J$ = 4.0, 4.0 Hz, H(1'''')), 4.76 (d, 1H, $J$ = 6.5 Hz, H(10)), 4.30–4.19 (m, 5H, H(10''), H(14), Ar2CHCH2, OH), 4.09–4.04 (m, 2H, H(3'''), H(5''')), 4.01 (t, 1H, $J$ = 7.0 Hz, Ar2CHCH2), 3.97 (m, 1H, H(14)), 3.86 (m, 1H, H(13)), 3.80 (s, 3H, OCH$_3$), 3.74 (s, 3H, OCH$_3$), 3.18 (dd, 1H, $J$ = 16.0, 5.0 Hz, H(8')), 2.95 (d, 1H, $J$ = 16.5 Hz, H(5)), 2.91 (d, 1H, $J$ = 17.0 Hz, H(5)), 2.86 (dd, 1H, $J$ = 16.0, 7.5 Hz, H(8'')), 2.38 (s, 6H, H(7''''), H(8'''')), 2.16 (t, 1H, $J$ = 4.0 Hz, H(4'''')), 2.01 (m, 1H, H(2'''')), 1.69 (m, 1H, H(2'''')), 1.52 (s, 9H, OC(CH$_3$)$_3$), 1.37 (d, 3H, $J$ = 7.0 Hz, H(6'''')), 1.15 (d, 6H, $J$ = 8.0 Hz, H(11''''), H(12'''')), 1.14 (d, 6H, $J$ = 9.0 Hz, SiCH(CH$_3$)$_3$), 1.07–1.03 (m, 24H, Si(CH$_2$C$_3$)$_3$ × 2, (CH$_3$)$_3$CHSi(CH$_2$C$_3$)$_3$), 0.99 (s, 9H, SiC(CH$_3$)$_3$), 0.69 (q, 6H, $J$ = 8.0 Hz, SiC(CH$_3$C$_3$)$_3$), 0.59 (m, 11H, SiC(CH$_2$C$_3$)$_3$, (CH$_3$)$_2$CHSi(CH$_2$C$_3$)$_3$), 0.29 (s, 3H, $t$-BuSi(CH$_3$)$_2$), 0.19 (s, 3H, $t$-BuSi(CH$_3$)$_2$).

$^{13}$C NMR (126 MHz, $C_6D_6$), δ: 177.0, 171.2, 165.6, 153.8, 151.7, 149.4, 149.3, 147.1, 144.4, 144.2, 142.2, 141.6, 140.5, 134.7, 132.8, 127.9, 127.4, 127.4, 127.3, 126.0, 125.5, 125.4, 124.7, 123.0, 122.6, 122.2, 120.2, 119.4, 108.2, 104.0, 103.9, 103.1, 96.3, 93.9, 90.0, 86.2, 83.1, 82.9, 81.3, 72.0, 70.6, 70.5, 69.4, 66.7, 66.1, 65.6, 62.5, 61.3, 60.7, 50.3, 47.1, 44.6, 39.4, 38.7, 38.2, 31.4, 27.5, 25.9, 21.8, 18.5, 17.6, 16.8, 13.3, 7.9, 7.8, 7.4, 4.8, 4.6, 4.3, 4.2, –4.6, –4.7.

IR (NaCl, thin film), cm$^{-1}$: 3416 (br, w), 2955 (s), 2924 (s), 2862 (s), 2782 (w), 2175 (w), 1744 (m), 1657 (m), 1626 (m), 1565 (m), 1508 (m), 1447 (s), 1390 (m), 1288 (m), 1257 (s), 1242 (s),
1170 (m), 1108 (s), 1010 (s), 836 (m), 780 (m), 739 (s), 724 (s), 672 (w). MS–ESI (m/z): [M+H]$^+$ calcd for C$_{90}$H$_{130}$BrClN$_3$O$_{15}$Si$_4$, 1718.7; found, 1718.8.

Macrolactone 8

A solution of the bromoetriyne 7 (2.21 g, 1.28 mmol, 1 equiv) in tetrahydrofuran (25 mL) and triethylamine (25 mL) was stirred at 23 °C for 48 h. The reaction solution was concentrated to provide a yellow foam. The crude residue was dissolved in benzene (88 mL). This solution was added via syringe pump over a period of 26.5 h to a solution of 2-methyl-6-nitrobenzoic anhydride (MNBA, 697 mg, 2.03 mmol, 1.59 equiv) and 4-dimethylaminopyridine (685 mg, 5.61 mmol, 4.38 equiv) in benzene (1.2 L). After stirring for an additional 30 min, the reaction solution was concentrated. The residue was purified by flash column chromatography (gradient elution, 5→7.5→10→12.5% tetrahydrofuran in 1:1 dichloromethane–hexanes) to provide the macrolactone 8 (1.35 g, 66%) as a pale yellow foam (atropisomeric mixture: ~1.7:1 in C$_6$D$_6$).

$^{1}$H NMR (mixture of two atropisomers, 500 MHz, C$_6$D$_6$), δ: Major atropisomer: 8.68 (s, 1H, ArH), 8.06 (d, 1H, J = 9.5 Hz, NH), 7.44 (d, 1H, J = 8.5 Hz, H(5′)), 7.36 (s, 1H, ArH), 7.17 (d, 1H, J = 8.0 Hz, H(4′)), 6.65 (s, 1H, ArH), 6.34 (d, 1H, J = 10.0 Hz, H(12)), 5.72 (m, 1H, H(7′)), 5.23 (dd, 1H, J = 9.5, 7.5 Hz, H(11)), 4.98 (d, 1H, J = 7.5 Hz, H(10)), 4.72 (dd, 1H, J = 3.5, 3.0 Hz, H(1′′′)), 4.43 (dd, 1H, J = 13.0, 3.5 Hz, H(14)), 4.30 (m, 1H, H(10′′′)), 4.24 (m, 1H, H(3′′′)), 4.15 (m, 2H, H(5′′′), OH), 3.93 (dd, 1H, J = 3.0, 2.5 Hz, H(13)), 3.86 (dd, 1H, J = 12.5, 2.0 Hz, H(14)), 3.86 (s, 3H, OCH$_3$), 3.75 (s, 3H, OCH$_3$), 3.22 (dd, 1H, J = 16.0, 4.0 Hz, H(8′)), 3.20 (d, 1H, J = 17.0 Hz, H(5)), 3.00 (d, 1H, J = 17.0 Hz, H(5)), 2.48 (s, 6H, H(7′′′), H(8′′′)), 2.28 (dd, 1H, J = 16.5, 4.5 Hz, H(8′)), 2.20 (t, 1H, J = 4.0 Hz, H(4′′′)), 1.94 (m, 1H, H(2′′′)), 1.64 (m, 1H, H(2′′′)), 1.44 (s, 9H, OC(CH$_3$)$_3$), 1.30 (d, 3H, J = 6.5 Hz, C$_3$H$_7$)
H(6’’’), 1.17 (d, 6H, J = 5.5 Hz, H(11’’’), H(12’’’)), 1.16–0.98 (m, 30H, SiCH(CH3)2), Si(CH2CH3)2 × 2, (CH2)2CHSi(CH2CH3)2, 1.10 (s, 9H, Si(CH3)3), 0.68–0.53 (m, 17H, Si(CH2CH3)3), Si(CH2CH3)3, (CH3)2CHSi(CH2CH3)2, 0.35 (s, 3H, t-BuSi(CH2CH3)2), 0.31 (s, 3H, t-BuSi(CH2CH3)2). Minor atropisomer: 8.89 (s, 1H, ArH), 7.53 (d, 1H, J = 8.0 Hz, NH), 7.37 (s, 1H, ArH), 7.18 (d, 1H, J = 8.0 Hz, H(5’’’)), 7.00 (d, 1H, J = 7.5 Hz, H(4’’’)), 6.62 (s, 1H, ArH), 6.18 (d, 1H, J = 9.5 Hz, H(12)), 5.98 (m, 1H, H(7’’’)), 5.78 (dd, 1H, J = 9.5, 6.0 Hz, H(11)), 4.91 (d, 1H, J = 6.0 Hz, H(10)), 4.89 (m, 1H, H(1’’’)), 4.40 (dd, 1H, J = 14.5, 3.0 Hz, H(14)), 4.29 (m, 1H, H(10’’’)), 4.23 (m, 1H, H(13)), 4.15 (m, 2H, H(3’’’), H(14)), 4.03 (m, 1H, H(7’’’’)), 3.78 (s, 3H, OCH3), 3.73 (s, 3H, OCH3), 3.27 (dd, 1H, J = 15.5, 4.5 Hz, H(8’’’)), 2.80 (d, 1H, J = 17.5 Hz, H(5)), 2.74 (dd, 1H, J = 15.0, 11.0 Hz, H(8’’’)), 2.65 (d, 1H, J = 16.5 Hz, H(5)), 2.33 (s, 6H, H(7’’’’), H(8’’’’)), 2.06 (t, 1H, J = 4.0 Hz, H(4’’’)), 1.98 (m, 1H, H(2’’’’)), 1.64 (m, 1H, H(2’’’’)), 1.45 (s, 9H, OC(CH3)3), 1.28 (d, 3H, J = 7.0 Hz, H(6’’’’)), 1.15 (d, 6H, J = 5.0 Hz, H(11’’’’), H(12’’’’)), 1.16–0.98 (m, 30H, SiCH(CH3)2), Si(CH2CH3)3 × 2, (CH2)2CHSi(CH2CH3)2, 1.04 (s, 9H, Si(CH3)3), 0.68–0.53 (m, 17H, Si(CH2CH3)3, Si(CH2CH3)3, (CH3)2CHSi(CH2CH3)2, 0.28 (s, 3H, t-BuSi(CH2CH3)2), 0.22 (s, 3H, t-BuSi(CH2CH3)2). 13C NMR (126 MHz, C6D6) δ: 177.4, 176.8, 172.2, 170.4, 166.0, 165.4, 155.6, 153.9, 153.8, 149.5, 149.2, 148.4, 148.1, 147.6, 147.0, 146.1, 145.1, 142.3, 142.2, 135.0, 134.5, 133.6, 132.9, 131.4, 126.7, 125.9, 125.1, 123.1, 122.8, 122.3, 122.0, 120.4, 119.5, 119.4, 109.9, 109.1, 104.9, 104.1, 104.0, 103.5, 103.0, 96.8, 96.1, 93.7, 89.6, 89.5, 86.1, 85.9, 85.8, 84.3, 83.5, 83.2, 82.3, 80.0, 72.1, 71.0, 70.7, 70.6, 70.0, 69.8, 69.1, 68.0, 66.0, 65.6, 65.3, 64.9, 61.4, 61.2, 60.7, 60.6, 51.2, 50.7, 44.8, 44.5, 41.0, 39.3, 39.2, 38.4, 37.8, 37.6, 30.9, 29.0, 27.5, 27.4, 26.0, 25.9, 21.9, 18.7, 18.5, 17.6, 17.5, 17.0, 16.5, 13.3, 8.0, 7.9, 7.8, 7.7, 7.4, 7.35, 7.32, 7.30, 4.9, 4.8, 4.6, 4.59, 4.3, 4.2, 4.1, –4.4, –4.5, –4.7, –4.8. IR (NaCl, thin film), cm⁻¹: 3405 (br, w), 3333 (br, w), 2954 (s), 2933 (s), 2277 (w), 2174 (w), 1744 (s), 1660 (s), 1554 (s), 1397 (s), 1333 (m), 1297 (m), 1246 (s), 1190 (s), 1113 (s), 1010 (s), 969 (s), 882 (m), 841 (s), 780 (m), 728 (s). MS–ESI (m/z): [M+H]⁺ calcd for C76H118BrClN3O14Si4, 1522.6; found, 1522.1.

Macrolactone 9

Silver nitrate (1.36 g, 8.01 mmol, 9.62 equiv) was added to a solution of the macrolactone 8 (1.27 g, 0.833 mmol, 1 equiv) in tetrahydrofuran (33 mL) and water (11 mL). The resulting solution was stirred at 23 °C for 30 min. Another portion of silver nitrate (380 mg, 2.24 mmol, 2.69 equiv) was added to the reaction mixture and stirring was allowed for 30 min at 23 °C. 2,6-Lutidine (12 ml, 103 mmol, 124 equiv) was added and the resulting suspension was stirred for 20 min. The reaction mixture was filtered through a pad of Celite. The filter pad was washed with ethyl acetate (400 mL). The filtrates were combined and the combined solution was washed
with aqueous hydrochloric acid solution (1 M, 2 × 100 mL), followed by saturated aqueous sodium bicarbonate solution (100 mL). The individual aqueous layers were separately extracted with ethyl acetate (2 × 200 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (gradient elution, 40→50% ethyl acetate in hexanes) to provide the macrolactone 9 (791 mg, 73%) as a pale yellow foam (atropisomeric mixture: ~1.7:1 in C₆D₆).

Rₛ = 0.50 (50% ethyl acetate-hexanes). ¹H NMR (mixture of two atropisomers, 500 MHz, C₆D₆), δ: **Major atropisomer:** 8.70 (s, 1H, Ar H), 8.12 (d, 1H, J = 8.0 Hz, H(4′)), 7.65 (s, 1H, Ar H), 6.59 (d, 1H, J = 9.5 Hz, H(12)), 5.75 (m, 1H, H(7′)), 5.13 (dd, 1H, J = 9.5, 6.5 Hz, H(11)), 4.78 (dd, 1H, J = 6.5, 2.5 Hz, H(10)), 4.72 (t, 1H, J = 3.5 Hz, H(1′′)), 4.42 (dd, 1H, J = 12.5, 3.0 Hz, H(14)), 4.31 (m, 1H, H(10′′)), 4.25 (m, 1H, H(3′′)), 4.11 (m, 2H, H(5′′), OH), 3.87 (m, 1H, H(13)), 3.86 (s, 3H, OCH₃), 3.82 (dd, 1H, J = 12.5, 2.5 Hz, H(8′)), 3.07 (dd, 1H, J = 16.5, 2.5 Hz, H(5)), 2.95 (m, 1H, H(7′′′), H(8′′′)), 2.48 (s, 6H, H(7′′′), H(8′′′)), 2.29 (dd, 1H, J = 16.5, 4.0 Hz, H(8′′′)), 2.22 (t, 1H, J = 4.0 Hz, H(4′′′)), 2.02 (d, 1H, J = 2.5 Hz, H(8)), 1.98 (m, 1H, H(2′′′)), 1.86 (t, 1H, J = 2.5 Hz, H(7)), 1.66 (m, 1H, H(2′′′)), 1.45 (s, 9H, COC(CH₃)₃), 1.32 (d, 3H, J = 7.0 Hz, H(6′′′)), 1.17 (d, 6H, J = 6.0 Hz, H(11′′′)), 1.06–0.98 (m, 12H, SiCH(CH₃)₂), (CH₃)₂CHSi(CH₂CH₃)₂), 0.94 (s, 9H, SiC(CH₃)₃), 0.59–0.55 (m, 5H, SiC(CH₃)₃), 0.25 (s, 3H, t-BuSi(CH₃)₂), 0.21 (s, 3H, t-BuSi(CH₃)₂). ¹³C NMR (126 MHz, C₆D₆) δ: 177.4, 176.8, 172.3, 170.5, 166.0, 165.5, 155.7, 154.7, 153.9, 153.8, 149.4, 149.2, 148.2, 147.8, 147.5, 146.9, 146.0, 145.3, 142.2,
Bromoenetriyne 10

Tetrahydrofuran (20 mL) and pyridine (10 mL) were added, in that sequence, to a 100-mL, round-bottomed flask charged with copper(II) acetate (406 mg, 2.24 mmol, 60.9 equiv). The resulting blue suspension was stirred at 23 °C for 15 min. Copper(I) iodide (109 mg, 572 μmol, 15.5 equiv) was added to the reaction mixture. The resulting light-green suspension was stirred at 23 °C for 5 min, then was warmed to 60 °C. After stirring for 15 min, a solution of the macrolactone 9 (47.7 mg, 36.8 μmol, 1 equiv) in a 2:1 mixture of tetrahydrofuran and pyridine (30 mL) was added via cannula over 10 min. After stirring for 5 min at 60 °C, the dark-green suspension was allowed to cool to ambient temperature. The cooled suspension was partitioned between ether (200 mL) and aqueous copper(II) sulfate solution (1 M, 100 mL). The organic layer was separated and washed with aqueous copper(II) sulfate solution (1 M, 2 × 100 mL), followed by saturated aqueous sodium bicarbonate solution (100 mL), then saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to a volume of ~3 mL. The residue was purified by flash column chromatography (gradient elution, 70 → 80 → 90% ether in pentane) to provide the cyclic bromoenetriyne 10 (atropisomeric mixture: ~9:1 in C_{6}D_{6}). To determine the yield of the reaction, fractions containing pure 10 were combined and the combined solution was concentrated to ~5 mL. The concentrated solution was diluted with C_{6}D_{6} (50 mL) and the resulting solution was concentrated to a volume of ca. 1 mL. A 1H NMR spectrum was taken to confirm purity and that no toluene was present, then an internal standard (toluene, 5 μl, 47 μmol) was added. The yield of 10 was determined by comparing integrated peak areas for 10 relative to toluene (calculated: 21.7 μmol, 59%).
\[ \text{R}_f = 0.51 \text{ (90\% diethyl ether-hexanes).} \]

\[ ^1\text{H NMR (mixture of two atropisomers, 600 MHz, C}_6\text{D}_6) \]

\[ \delta: \text{Major atropisomer:} 8.92 \text{ (s, 1H, ArH), 7.43 \text{ (d, 1H, J = 7.8 Hz, NH)}, 7.37 \text{ (s, 1H, ArH), 6.87 \text{ (d, 1H, J = 7.8 Hz, H(4'))}, 6.77 \text{ (d, 1H, J = 7.8 Hz, H(5')), 6.62 \text{ (s, 1H, ArH), 5.97 \text{ (d, 1H, J = 9.0 Hz, H(12))}, 5.91 \text{ (m, 1H, H(7'))}, 5.73 \text{ (dd, 1H, J = 9.0, 1.2 Hz, H(11))}, 5.02 \text{ (br s, 1H, C4-OH), 4.93 \text{ (s, 1H, H(10))}, 4.89 \text{ (dd, 1H, J = 6.6, 3.0 Hz, H(1''))}, 4.63 \text{ (dd, 1H, J = 12.0, 4.8 Hz, H(14))}, 4.27 \text{ (m, 1H, H(10''))}, 4.09-4.07 \text{ (m, 2H, H(13), H(3''))}, 4.00 \text{ (d, 1H, J = 4.8 Hz, H(14))}, 3.90 \text{ (m, 1H, H(5''))}, 3.75 \text{ (s, 3H, OCH3)}, 3.72 \text{ (s, 3H, OCH3)}, 3.39 \text{ (dd, 1H, J = 13.8, 10.8 Hz, H(8'))}, 2.73 \text{ (d, 1H, J = 18.0 Hz, H(5))}, 2.48 \text{ (d, 1H, J = 17.4 Hz, H(5))}, 2.18 \text{ (s, 6H, H(7''), H(8''))}, 1.96 \text{ (m, 1H, H(2''))}, 1.90 \text{ (br s, 1H, H(4''))}, 1.57 \text{ (m, 1H, H(2''))}, 1.46 \text{ (s, 9H, COC(CH3))}, 1.29 \text{ (d, 3H, J = 7.2 Hz, H(6''))}, 1.15 \text{ (d, 6H, J = 6.0 Hz, H(11''), H(12''))}, 1.04 \text{ (m, 6H, SiC(CH3))}, 0.99 \text{ (m, 6H, (CH3)2CHSi(CH3)2)}, 0.98 \text{ (s, 9H, SiC(CH3))}, 0.85 \text{ (m, 1H, SiC(CH3))}, 0.55 \text{ (m, 4H, (CH3)2CHSi(CH2CH3)2)}, 0.21 \text{ (s, 3H, t-BuSi(CH3))}, 0.15 \text{ (s, 3H, t-BuSi(CH3))}. \]

\[ ^{13}\text{C NMR (126 MHz, C}_6\text{D}_6) \]

\[ \delta: 176.8, 170.1, 165.6, 154.7, 154.0, 149.5, 148.0, 147.4, 146.9, 142.2, 137.7, 132.9, 132.8, 125.6, 125.3, 123.5, 122.3, 122.2, 119.4, 104.0, 102.9, 97.0, 93.2, 91.7, 90.3, 89.3, 87.2, 81.0, 73.9, 71.8, 71.4, 70.7, 70.6, 68.4, 66.5, 65.8, 61.2, 60.7, 52.0, 44.2, 41.5, 39.4, 38.7, 30.1, 27.4, 25.8, 21.8, 18.2, 17.6, 17.5, 16.1, 13.3, 13.2, 7.33, 4.31, 4.18, 4.13, -4.44, -4.91. \]

\[ \text{IR (in C}_6\text{D}_6), \text{ cm}^{-1}: 3415 \text{ (br, w), 3303 \text{ (br, w), 2944 \text{ (s), 2933 \text{ (s), 2872 \text{ (m), 1744 \text{ (s), 1667 \text{ (s), 1626 \text{ (m), 1564 \text{ (w), 1482 \text{ (s), 1446 \text{ (s), 1431 \text{ (s), 1415 \text{ (m), 1395 \text{ (s), 1292 \text{ (m), 1256 \text{ (s), 1241 \text{ (s), 1185 \text{ (m), 1113 \text{ (s), 1092 \text{ (s), 1010 \text{ (s), 974 \text{ (m), 841 \text{ (s), 780 \text{ (m), 723 \text{ (m).}}} \]

\[ \text{MS–ESI (m/z): [M+H]}^+ \text{ calcd for C}_{64}\text{H}_{88}\text{BrClN}_3\text{O}_{14}\text{Si}_2, 1292.5; \text{ found, 1292.3.} \]

**Dienediyne 11**

4-Å Molecular sieves (activated, 2 g) were added to a solution of the bromoenetriyne 10 (23.1 µmol, 1 equiv) in a 1:1 mixture of THF and toluene (8.0 mL), and the resulting suspension
was stirred at 23 °C for 15 min, then was cooled to −78 °C. A solution of lithium hexamethyldisilazide in tetrahydrofuran (1.0 M, 138 μL, 138 μmol, 5.97 equiv) was added. After 60 sec, a solution of tert-butyllithium in pentane (1.7 M, 120 μL, 204 μmol, 8.83 equiv) was added to the cold reaction mixture (−78 °C). The resulting dark-green solution was quenched immediately (<3 s) with a solution of acetic acid in THF (500 μL of a 1:3 mixture of acetic acid and THF). The reaction mixture was partitioned between a 4:1 mixture of ether and pentane (100 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The aqueous layer was separated and extracted with a 4:1 mixture of ether and pentane (50 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to a volume of ~3 mL. The residue was purified by flash column chromatography (gradient elution, 70→80→90% ether in pentane) to provide the dienediyne 11 as a single atropisomer. To determine the yield of the reaction, fractions containing pure 11 were combined and the combined solution was concentrated to ~5 mL. The concentrated solution was diluted with C6D6 (50 mL) and the resulting solution was concentrated to a volume of ca. 1 mL. A 1H NMR spectrum was taken to confirm purity and that no toluene was present, then an internal standard (toluene, 5 μL, 47 μmol) was added. The yield of 11 was determined by comparing intergrated peak areas for 11 relative to toluene (calculated: 12.1 μmol, 52%).

Rf = 0.51 (90% diethyl ether-hexanes). 1H NMR (single atropisomer, 500 MHz, C6D6), δ: 8.84 (s, 1H, ArH), 7.56 (d, 1H, J = 7.0 Hz, NH), 7.36 (s, 1H, ArH), 6.86 (d, 1H, J = 8.5 Hz, H(4')), 6.70 (d, 1H, J = 7.5 Hz, H(5')), 6.20 (s, 1H, ArH), 6.09 (dd, 1H, J = 1.5, 1.5 Hz, H(12)), 5.94 (m, 1H, H(7''')), 5.47 (br s, 1H, H(8)), 5.11 (d, 1H, J = 3.0 Hz, H(11)), 4.93 (dd, 1H, J = 5.5, 3.0 Hz, H(1'''')), 4.69 (s, 1H, H(10)), 4.37 (dd, 1H, J = 12.0, 3.0 Hz, H(14)), 4.33 (dd, 1H, J = 12.0, 3.0 Hz, H(14)), 4.28 (m, 1H, H(10'')), 4.15 (m, 2H, H(13), H(3'')), 4.03 (m, 1H, H(5'''')), 3.77 (s, 3H, OCH3), 3.74 (s, 3H, OCH3), 3.34 (dd, 1H, J = 14.5, 4.5 Hz, H(8')), 3.02 (dd, 1H, J = 18.0, 1.5 Hz, H(5)), 2.74 (dd, 1H, J = 14.0, 11.0 Hz, H(8')), 2.67 (d, 1H, J = 18.5 Hz, H(5)), 2.26 (s, 6H, H(7''''')), 2.01 (m, 1H, H(4'''')), 1.97 (m, 1H, H(2'''')), 1.60 (m, 1H, H(2'''')), 1.45 (s, 9H, COC(CH3)3), 1.33 (d, 3H, J = 7.0 Hz, H(6'')), 1.16 (d, 6H, J = 6.5 Hz, H(11'')), 1.03 (m, 6H, SiCH(CH3)2), 0.98 (m, 6H, (CH3)2CHSi(CH2CH3)2), 0.92 (dd, 1H, SiC(CH3)3), 0.85 (q, 1H, J = 7.5 Hz, SiCH(CH3)2), 0.55 (q, 4H, J = 8.0 Hz, (CH3)2CHSi(CH2CH3)2), 0.11 (s, 3H, t-BuSi(CH3)2), 0.08 (s, 3H, t-BuSi(CH3)2). 13C NMR (126 MHz, C6D6), δ: 176.8, 170.2, 165.7, 158.1, 154.7, 153.8, 149.5, 147.8, 147.5, 146.9, 142.3, 133.6, 133.1, 132.9, 132.8, 126.0, 124.9, 123.0, 122.3, 119.4, 107.5, 104.1, 103.9, 101.3, 96.9, 91.9, 91.1, 89.1, 84.9, 78.2, 77.2, 71.4, 70.7, 68.8, 67.3, 65.7, 61.3, 60.7, 51.7, 44.3, 41.1, 39.3, 38.7, 31.7, 27.4, 27.2, 25.8, 21.8, 18.2, 17.5,
16.3, 13.3, 7.31, 7.28, 4.27, 4.12, $-4.27,-4.34$. IR (NaCl, thin film), cm$^{-1}$: 3417 (br, w), 3311 (br, w), 2958 (s), 2937 (s), 2863 (m), 2275 (w), 1738 (s), 1663 (m), 1626 (m), 1562 (w), 1487 (s), 1461 (s), 1450 (s), 1429 (s), 1413 (m), 1391 (s), 1295 (m), 1258 (s), 1247 (s), 1189 (m), 1109 (s), 1013 (s), 965 (m), 837 (s), 779 (w), 725 (w).

MS–ESI $(m/z)$: [M+H]$^+$ calcd for C$_{64}$H$_{89}$ClN$_3$O$_{14}$Si$_2$, 1214.6; found, 1214.5. $[\alpha]$$^2_{D}$ (c 0.85, THF): +90.7°.

**Allylic alcohol 12**

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 360 μL, 360 μmol, 5.14 equiv) was added to a solution of the dienediyne 11 (70.0 μmol, 1 equiv) and o-nitrophenol (25.0 mg, 180 μmol, 2.57 equiv) in THF (15 mL) at 23 °C. The resulting orange solution was stirred for 25 min, then was diluted with dichloromethane (100 mL). The mixture was washed with saturated aqueous ammonium chloride solution (50 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 50 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to a volume of ~3 mL. The residue was purified by flash column chromatography (gradient elution, 10→20→30% THF in dichloromethane) to provide the product of bis-deprotection (both the TBS and the pivaloate groups were cleaved). Fractions containing the bis-deprotection product were combined and the combined solution was concentrated to ~1 mL. The concentrate was diluted with dichloromethane (15 mL), whereupon triethylamine (200 μL, 1.43 mmol, 20.5 equiv) and trimethylacetyl chloride (40 μL, 325 μmol, 4.64 equiv) were added, in that order. After stirring at 23 °C for 10 min, the reaction mixture was partitioned between dichloromethane (100 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The aqueous layer was further extracted with dichloromethane (2 × 50 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to a volume of ~3 mL. The residue was purified by flash column chromatography (gradient elution, 10→20→30% THF in dichloromethane) to provide the allylic alcohol 12 as a single atropisomer. To determine the yield of the reaction, fractions containing pure 12 were combined and the combined solution was concentrated to ~5 mL. The concentrated solution was diluted with C$_6$D$_6$ (50 mL) and the resulting solution was concentrated to a volume of ca. 1 mL. A $^1$H NMR spectrum was taken to confirm purity and that no toluene was present, then an internal standard (toluene, 5 μL, 47 μmol) was added. The yield of 12 was determined by comparing integrated peak areas for 12 relative to toluene (calculated: 53.4 μmol, 76%, two steps).
Epoxide 13

4-Å Molecular sieves (activated, 2 g) were added to a solution of the allylic alcohol 12 (53.2 μmol, 1 equiv) in benzene (15.0 mL). After stirring at 23 °C for 15 min, VO(acac)₂ (8.0 mg, 30.2 μmol, 0.57 equiv) was added, and the resulting green suspension was stirred for 5 min. 1,1-Diphenylethylhydroperoxide (50.0 mg, 233.4 μmol, 4.39 equiv) was then added to the reaction
mixture. The resulting red suspension was stirred at 23 °C for 25 min. The reaction mixture was partitioned between dichloromethane (100 mL) and saturated aqueous sodium thiosulfate solution (30 mL). The organic layer was separated and extracted with dichloromethane (50 mL). The organic extracts were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to a volume of ~2 mL. The residue was purified by flash column chromatography (gradient elution, 10→20→30% THF in dichloromethane) to provide the epoxide 138 (atropisomeric mixture: ~1.5:1 in C6D6, ~5:1 in DMSO-d6). To determine the yield of the reaction, fractions containing pure 13 were combined and the combined solution was concentrated to ~5 mL. The concentrated solution was diluted with C6D6 (50 mL) and the resulting solution was concentrated to a volume of ca. 1 mL. A 1H NMR spectrum was taken to confirm purity and that no toluene was present, then an internal standard (toluene, 5 μl, 47 μmol) was added. The yield of 13 was determined by comparing integrated peak areas for 13 relative to toluene (calculated: 15.1 μmol, 28%).

\[
R_f = 0.41 \text{ (80% ethyl acetate-hexanes).} \\
^1H \text{ NMR (600 MHz, C}_6\text{D}_6): \text{Major atropisomer: } 8.88 \text{ (s, 1H, ArH), 7.81 (d, 1H, J = 8.4 Hz, NH), 7.35 (s, 1H, ArH), 6.62 (s, 1H, ArH), 6.60 (d, 1H, J = 7.8 Hz, H(4')), 6.56 (d, 1H, J = 8.4 Hz, H(5')), 6.21 (d, 1H, J = 2.4 Hz, H(12)), 5.68 (m, 1H, H(7)'), 5.32 (d, 1H, J = 3.0 Hz, H(11)), 4.79 (dd, 1H, J = 4.2, 3.6 Hz, H(1''')), 4.23–4.30 (m, 3H, H(10), H(14), H(10'')), 3.87 (br s, 1H, H(13)), 3.84 (s, 3H, OCH3), 3.76 (s, 3H, OCH3), 3.11 (d, 1H, J = 18.0 Hz, H(8')), 2.96 (m, 1H, H(8')), 2.94 (br s, 1H, H(8)), 2.71 (dd, 1H, J = 14.4, 3.6 Hz, H(8')), 2.49 (d, 1H, J = 18.0 Hz, H(5)), 2.34 (s, 6H, H(7''), H(8''), 2.07 (br s, 1H, H(4'')), 1.98–2.03 (m, 1H, H(2'')), 1.63–1.68 (m, 1H, H(2'')), 1.51 (s, 9H, COC(CH3)3), 1.31 (d, 3H, J = 6.6 Hz, H(6'')), 1.16 (d, 6H, J = 6.0 Hz, H(11''), H(12''), 1.02–1.06 (m, 6H, SiCH(CH3)2), 0.97–1.01 (m, 6H, (CH3)2CHSi(CH2CH3)2), 0.86 (m, 1H, SiCH(CH3)2), 0.53–0.61 (m, 4H, (CH3)2CHSi(CH2CH3)2). Minor atropisomer: 8.71 (s, 1H, ArH), 8.29 (d, 1H, J = 8.4 Hz, NH), 7.46 (d, 1H, J = 8.4 Hz, H(4'')), 7.35 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.59 (m, 1H, H(5')), 5.68 (m, 1H, H(7')), 5.41 (d, 1H, J = 2.4 Hz, H(12)), 5.27 (d, 1H, J = 3.0 Hz, H(11)), 4.69 (br s, 1H, H(1''')), 4.34 (s, 1H, H(10)), 4.22–4.32 (m, 3H, H(14), H(10''), H(3'')), 4.15 (m, 2H, H(14), H(5''')), 3.85 (s, 3H, OCH3), 3.81 (br s, 1H, H(13)).

(8) Strong NOE’s were observed between H(8) and H(4') (in both directions, DMSO-d6), establishing the stereochemistry of the epoxide; long-range coupling between H(8) and H(5) was also observed, confirming the position selectivity of the epoxidation reaction. We also observed strong reciprocal NOE’s between H(10) and H(4') (not observed in either the natural product or its sodium borohydride reduction product: Leet, J. E.; Schroeder, D. R.; Langley, D. R.; Colson, K. L.; Huang, S.; Kloor, S. E.; Lee, M. S.; Golik, J.; Hofstead, S. J.; Doyle, T. W.; Matson, J. A. J. Am. Chem. Soc. 1993, 115, 8432.), confirming the stereochemistry of C10.
3.75 (s, 3H, OCH₃), 3.27 (br s, 1H, H(8)), 3.25 (d, 1H, J = 18.0 Hz, H(5)), 2.93–2.98 (m, 1H, H(8')), 2.57 (d, 1H, J = 18.0 Hz, H(5)), 2.55 (s, 6H, H(7'''), H(8''')), 2.38 (br s, 1H, H(4''')), 2.19 (dd, 1H, J = 16.8, 4.8 Hz, H(8')), 2.02–2.05 (m, 1H, H(2''')), 1.68–1.71 (m, 1H, H(1''')), 1.39 (s, 9H, COC(CH₃)₃), 1.35 (d, 3H, J = 6.0 Hz, H(6''')), 1.35 (s, 3H, OCH₃), 1.32 (d, 3H, J = 6.0 Hz, H(6''')), 1.17 (d, 6H, J = 5.4 Hz, H(11'''), H(12''')), 1.02–1.06 (m, 6H, SiCH(C₂H₅)₂), 0.97–1.01 (m, 6H, (CH₃)₂CHSi(CH₂C₂H₅)₂). 1H NMR (500 MHz, DMSO-d₆) δ: 8.78 (d, 1H, J = 8.0 Hz, NH), 8.12 (s, 1H, ArH), 7.83 (d, 1H, J = 8.0 Hz, H(4''')), 7.52 (s, 1H, ArH), 7.43 (d, 1H, J = 15.5, 4.0 Hz, H(8'''), 2.55 (s, 6H, H(7'''), H(8''''), 2.48 (br s, 1H, H(4''''), 2.12 (d, 1H, J = 17.5 Hz, H(5)), 2.02 (m, 1H, H(2''''), 1.65 (dd, 1H, J = 13.0, 5.0 Hz, H(2''''), 1.38 (d, 6H, J = 6.0 Hz, H(11'''), H(12''')), 1.28 (s, 9H, COC(CH₃)₃), 1.08 (d, 3H, J = 5.5 Hz, H(6''''), 0.95–0.99 (m, 12H, SiCH(CH₃)₂), (CH₃)₂CHSi(CH₂C₂H₅)₂), 0.89 (m, 1H, SiCH(CH₃)₂), 0.59 (m, 4H, (CH₃)₂CHSi(CH₂C₂H₅)₂). IR (NaCl, thin film) cm⁻¹: 3417 (br, w), 2957 (s), 2940 (s), 2878 (m), 2278 (w), 1746 (s), 1666 (m), 1622 (m), 1556 (w), 1516 (m), 1485 (s), 1463 (s), 1450 (s), 1432 (s), 1415 (m), 1393 (s), 1331 (w), 1260 (m), 1172 (s), 1013 (s), 1015 (m), 964 (w). MS–ESI (m/z): [M+H]+ calcd for C₅₈H₇₅ClN₃O₁₅Si, 1116.5; found, 1116.6.

Thioglycoside 31

Thiophenol (7.0 mL, 68.2 mmol, 1.64 equiv) and tin(IV) chloride (5.5 mL, 47.0 mmol, 1.13 equiv) were added sequentially to a solution of methyl L-mycaroside 30⁹ (7.33 g, 41.6 mmol, 1 equiv) in dichloromethane (230 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min, then was allowed to warm to 23 °C. At this point saturated aqueous sodium bicarbonate solution (140 mL) was added, followed by saturated aqueous sodium-potassium tartrate solution (240 mL). The resulting suspension was stirred vigorously for 30 min. The aqueous layer was separated and extracted with dichloromethane (2 × 200 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to afford the thioglycoside 31 (6.94 g, 62%) as a 5:1 (α:β) mixture of anomers. These anomers can be partially separated by flash column chromatography.

(9) Methyl L-mycaroside 30 was prepared in one step (88% yield) from the commercial tartrate salt of Tylosin: Hamill, R. L.; Haney, M. E.; Stamper, M.; Wiley, P. F. Antibiotics and Chemotherapy 1961, 6, 328
**Thioglycoside 14**

Imidazole (1.63 g, 23.9 mmol, 5.18 equiv) and chlorotriethylsilane (900 μL, 5.36 mmol, 1.16 equiv) were added sequentially to a solution of the thioglycoside 31 (α:β = 1:3) (1.17 g, 4.61 mmol, 1 equiv) in DMF (15 mL). The resulting solution was stirred at 23 °C for 1.5 h. The reaction mixture was partitioned between a 1:1 mixture of ethyl acetate and hexanes (200 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was separated and the aqueous layer was extracted with a 1:1 mixture of ethyl acetate and hexanes (2 × 200 mL). The organic layers were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (gradient elution, 5→10→15% ethyl acetate in hexanes) to afford the thioglycoside 14 (1.40 g, 82%) as a 1:3 (α:β) mixture of anomers.

\[
\begin{align*}
\text{CH}_3&\quad\text{O} \quad \text{TESCl, Im, DMF} \quad 82\% \\
\text{CH}_3&\quad\text{OH} \\
\text{CH}_3&\quad\text{SPh} \\
\text{CH}_3&\quad\text{O} \quad \text{TESO} \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{SPh} \\
\text{CH}_3&\quad\text{OH} \\
\text{CH}_3&\quad\text{SPh} \\
\end{align*}
\]

R<sub>f</sub> = 0.27 (35% ethyl acetate-hexanes). \(^1\)H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ: \(\alpha\)-anomer: 7.53 (dd, 2H, <var>ArH</var>), 7.04 (t, 2H, <var>J</var> = 6.0 Hz, <var>ArH</var>), 6.96 (t, 1H, <var>J</var> = 6.0 Hz, <var>ArH</var>), 5.33 (d, 1H, <var>J</var> = 6.5 Hz, H(1)), 2.75 (t, 1H, <var>J</var> = 9.5 Hz, H(4)), 2.13 (s, 1H, HO(C3)), 1.88 (d, 1H, <var>J</var> = 14.5 Hz, H(2)), 1.71 (dd, 1H, <var>J</var> = 14.5, 9.0 Hz, H(2)), 1.66 (d, 1H, <var>J</var> = 6.5 Hz, HO(C4)), 1.29 (d, 3H, <var>J</var> = 6.5 Hz, H(6)), 0.95 (s, 3H, H(7)). \(\beta\)-anomer: 7.62 (dd, 2H, <var>J</var> = 6.5, 1.5 Hz, <var>ArH</var>), 7.04 (t, 2H, <var>J</var> = 6.0 Hz, <var>ArH</var>), 6.96 (t, 1H, <var>J</var> = 6.0 Hz, H(1)), 3.49 (m, 1H, H(5)), 2.62 (t, 1H, <var>J</var> = 8.0 Hz, H(4)), 1.91 (dd, 1H, <var>J</var> = 13.5, 1.5 Hz, H(2)), 1.71 (dd, 1H, <var>J</var> = 14.5, 9.0 Hz, H(2)), 1.62 (dd, 1H, <var>J</var> = 14.0, 7.0 Hz, HO(C4)), 1.40 (s, 1H, HO(3)), 1.22 (d, 3H, <var>J</var> = 6.5 Hz, H(6)), 0.83 (s, 3H, H(7)).

**13C** NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 136.8, 134.8, 131.4, 131.2, 129.3, 129.2, 127.4, 83.5, 80.7, 77.1, 73.7, 71.2, 70.5, 66.1, 44.2, 43.1, 27.4, 27.2, 18.9, 18.3. IR (NaCl, thin film) cm<sup>–1</sup>: 3426 (s), 2974 (m), 2933 (w), 1585 (w), 1477 (m), 1441 (m), 1374 (m), 1149 (m), 1082 (s), 1056 (s), 744 (s). HRMS–Cl (m/z): [M+NH<sub>4</sub>]<sup>+</sup> calcd for C<sub>13</sub>H<sub>22</sub>NO<sub>3</sub>S, 272.1320; found, 272.1324.

R<sub>f</sub> = 0.53 (10% ethyl acetate-hexanes). \(^1\)H NMR (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ: \(\alpha\)-anomer: 7.66 (m, 2H, <var>ArH</var>), 7.08 (t, 2H, <var>J</var> = 7.8 Hz, <var>ArH</var>), 6.97 (m, 1H, <var>ArH</var>), 5.44 (m, 1H, H(1)), 4.58 (m, 1H, H(1)), 3.09 (d, 1H, <var>J</var> = 9.0 Hz, H(4)), 2.52 (d, 1H, <var>J</var> = 2.4 Hz, HO(C3)), 2.25 (m, 1H, H(2)), 1.79 (m, 1H, H(2)), 1.27 (d, 3H, <var>J</var> = 6.6 Hz, H(6)), 1.03 (s, 3H, H(7)), 0.87 (m, 9H, Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>), 0.49 (m, 6H, Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>). \(\beta\)-anomer: 7.64 (m, 2H, <var>ArH</var>), 7.04 (m, 2H, <var>ArH</var>), 6.96 (m, 1H, <var>ArH</var>), 5.45 (dd, 1H, <var>J</var> = 11.4, 1.8 Hz, H(1)), 3.61 (m, 1H, H(5)), 3.02 (d, 1H, <var>J</var> = 9.0 Hz, H(4)), 2.26 (d, 1H, <var>J</var> = 2.4 Hz, HO(C3)), 2.23 (m, 1H, H(2)), 1.73 (m, 1H, H(2)), 1.21 (d, 3H, <var>J</var> = 6.0 Hz, H(6)), 0.97 (s, 3H, H(7)), 0.85 (m, 9H, Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>), 0.45 (m, 6H, Si(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>). **13C** NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ: 140.1, 135.6, 131.6, 130.2, 129.0, 127.1, 126.2, 84.0, 80.9, 79.4, 78.9, 73.5, 70.7, 70.6, 69.6, 65.8, 43.7, 42.8, 28.3, 28.2, 19.2, 18.8, 7.12, 7.10, 5.69, 5.67. IR (NaCl, thin film) cm<sup>–1</sup>: 3559 (br w), 2954 (s), 2882 (s), 1580 (w), 1477 (m), 1456 (m), 1369 (m), 1303 (m), 1128 (m), 1092 (s), 1056 (s), 744 (s).
Glycosidation Product 15

4-Å Molecular sieves (activated, 0.5 g) were added to a solution of the epoxide 13 (12.2 μmol, 1 equiv), the thioglycoside 14 (7.02 mg, 19.0 μmol, 1.56 equiv), and 2,6-di-tert-butyl-4-methylpyridine (DTBMP, 14.2 mg, 69.2 μmol, 5.67 equiv) in freshly distilled dichloromethane (1.0 mL). After stirring at 23 °C for 15 min, the suspension was cooled to 0 °C. A solution of AgPF₆ in freshly distilled dichloromethane (1.2 M, 40.0 μL, 48.0 μmol, 3.93 equiv) was added, and the resulting suspension was stirred at 0 °C for 10 min. Pyridine (150 μL) was added, and the reaction mixture was allowed to warm to 23 °C. After stirring for 30 min, the mixture was diluted with dichloromethane (100 mL). The diluted mixture was filtered through a pad of Celite. The filtrate was washed with aqueous copper(II) sulfate solution (1 M, 2 × 50 mL), followed by saturated aqueous sodium bicarbonate solution (50 mL) and saturated aqueous sodium chloride solution (50 mL). The individual aqueous layers were separately extracted with dichloromethane (2 × 50 mL). The organic fractions were combined and the combined solution was dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to a volume of ~1 mL. The residue was purified by flash column chromatography (gradient elution, 40→50→60% ethyl acetate in dichloromethane) to provide the glycosidation product 15 (atropisomeric mixture: ~1.5:1 in C₆D₆, ~6:1 in DMSO-d₆). To determine the yield of the reaction, fractions containing pure 15 were combined and the combined solution was concentrated to ~5 mL. The concentrated solution was diluted with C₆D₆ (50 mL) and the resulting solution was concentrated to a volume of ca. 1 mL. A ¹H NMR spectrum was taken to confirm purity and that no toluene was present, then an internal standard (toluene, 5 μL, 47 μmol) was added. The yield of 15 was determined by comparing integrated peak areas for 15 relative to toluene (calculated: 7.20 μmol, 59%).

1005 (s), 974 (m), 826 (m), 733 (s), 687 (m). HRMS–CI (m/z): [M+NH₄]⁺ calcd for C₁₉H₃₆NO₃SSi, 386.2185; found, 386.2175.
R_f = 0.36 (65% ethyl acetate-dichloromethane). \textsuperscript{1}H NMR (600 MHz, C\textsubscript{6}D\textsubscript{6}) δ: Major atropisomer: 8.91 (s, 1H, ArH), 7.82 (d, 1H, J = 8.4 Hz, NH), 7.37 (s, 1H, ArH), 6.63 (s, 1H, ArH), 6.61–6.64 (m, 2H, H(4'), H(5')), 6.15 (d, 1H, J = 3.0 Hz, H(12)), 5.70 (m, 1H, H(7''')), 5.13 (d, 1H, J = 3.0 Hz, H(11)), 4.84 (d, 1H, J = 3.0 Hz, H(1''''')), 4.77 (br s, 1H, H(1''')), 4.36 (s, 1H, H(10)), 4.26–4.32 (m, 3H, H(14), H(10'''), H(5'''')), 4.04 (m, 1H, H(14)), 3.82 (br s, 1H, H(13)), 3.85 (s, 3H, OCH\textsubscript{3}), 3.76 (s, 3H, OCH\textsubscript{3}), 3.63 (s, 1H, HO(C3''''')), 3.26 (br s, 1H, H(8)), 3.24 (d, 1H, J = 9.0 Hz, (H(5'''')), 3.05 (d, 1H, J = 18.0 Hz, H(5')), 2.98 (m, 1H, H(8''')), 2.73 (m, 1H, H(8')), 2.48 (d, 1H, J = 17.4 Hz, H(5)), 2.40 (s, 6H, H(7'''''), H(8''''')), 2.14 (br s, 1H, H(4''''')), 2.01–2.04 (m, 1H, H(2''''')), 1.86 (d, 1H, J = 13.8 Hz, H(2''''')), 1.64–1.72 (m, 1H, H(2'''')), 1.52 (s, 9H, COC(C\textsubscript{6}H\textsubscript{3})), 1.49 (m, 1H, H(2'''')), 1.46 (d, 3H, J = 6.0 Hz, H(6'''')), 1.31 (d, 3H, J = 6.6 Hz, H(6'''')), 1.25 (s, 3H, H(7'''')), 1.16 (d, 6H, J = 5.4 Hz, H(11'''), H(12''')), 0.98–1.07 (m, 21H, Si(CH\textsubscript{2}C\textsubscript{6}H\textsubscript{3})\textsubscript{3})), 0.86 (m, 1H, (CH\textsubscript{3})\textsubscript{2}CHSi(C\textsubscript{6}H\textsubscript{3})\textsubscript{2})), 0.71–0.74 (m, 6H, Si(CH\textsubscript{2}C\textsubscript{6}H\textsubscript{3})\textsubscript{2})), 0.54–0.61 (m, 4H, (CH\textsubscript{3})\textsubscript{2}CHSi(CH\textsubscript{3}C\textsubscript{6}H\textsubscript{3})\textsubscript{2})).

Minor atropisomer: 8.75 (s, 1H, ArH), 8.32 (d, 1H, J = 8.4 Hz, NH), 7.51 (d, 1H, J = 7.8 Hz, H(4')), 7.37 (s, 1H, ArH), 6.69 (d, 1H, J = 7.8 Hz, H(5')), 6.68 (s, 1H, ArH), 5.67 (m, 1H, H(7''')), 5.41 (d, 1H, J = 3.0 Hz, H(12)), 4.97 (d, 1H, J = 3.0 Hz, H(11)), 4.87 (d, 1H, J = 3.6 Hz, H(1'''')), 4.84 (s, 1H, H(10)), 4.67 (br s, 1H, H(1''''')), 4.26–4.32 (m, 2H, H(14), H(10''')), 4.18 (m, 1H, H(3''''')), 3.99–4.04 (m, 3H, H(14), H(5'''''), H(5'''')), 3.85 (s, 3H, OCH\textsubscript{3}), 3.76 (br s, 1H, H(13)), 3.75 (s, 3H, OCH\textsubscript{3}), 3.71 (s, 1H, HO(C3''''')), 3.59 (br s, 1H, H(10)), 3.22 (m, 1H, H(5)), 2.95–3.01 (m, 2H, H(8''), H(4'''''), 2.60 (s, 6H, H(7'''''), H(8'''')), 2.54 (d, 1H, J = 16.2 Hz, H(5')), 2.36 (br s, 1H, H(4''''')), 2.15–2.18 (m, 1H, H(8'')), 2.02–2.05 (m, 1H, H(2''''')), 1.86 (d, 1H, J = 13.8 Hz, H(2''''')), 1.64–1.72 (m, H, H(2''''')), 1.49 (m, 1H, H(2''''')), 1.42 (s, 9H, COC(CH\textsubscript{3})), 1.40 (d, 3H, J = 6.0 Hz, H(6''''')), 1.36 (d, 3H, J = 6.6 Hz, H(6''''')), 1.24 (s, 3H, H(7''''')), 1.17 (m, 6H, H(11'''), H(12''')), 1.02–1.06 (m, 6H, SiCH(CH\textsubscript{3})\textsubscript{2}), 0.97–1.01 (m, 6H, (CH\textsubscript{3})\textsubscript{2}CHSi(CH\textsubscript{3}C\textsubscript{6}H\textsubscript{3})\textsubscript{2}), 0.86 (m, 1H, SiCH(CH\textsubscript{3})\textsubscript{2}), 0.53–0.61 (m, 4H, (CH\textsubscript{3})\textsubscript{2}CHSi(CH\textsubscript{3}C\textsubscript{6}H\textsubscript{3})\textsubscript{2}).

\textsuperscript{1}H NMR (600 MHz, DMSO-d\textsubscript{6}) δ: 8.76 (d, 1H, J = 7.8 Hz, NH), 8.13 (s, 1H, ArH), 7.90 (d, 1H, J = 8.4 Hz, H(4')), 7.53 (s, 1H, ArH), 7.46 (d, 1H, J = 9.0 Hz, H(5')), 7.24 (s, 1H, ArH), 6.48 (d, 1H, J = 1.8 Hz, H(12)), 5.99 (s, 1H, HO(C4)), 5.54 (d, 1H, J = 2.4 Hz, H(11)), 5.50 (m, 1H, H(7''')), 5.16 (d, 1H, J = 1.8 Hz, H(1'''')), 4.99 (br s, 1H, H(1''''')), 4.74 (m, 1H, H(10''')), 4.51 (br d, 1H, J = 9.6 Hz, H(14)), 4.40 (s, 1H, H(10)), 4.32 (m, 1H, H(3''''')), 4.19 (m, 1H, H(5''''')), 3.98 (s, 3H, OCH\textsubscript{3}), 3.86 (br s, 1H, H(8)), 3.85 (s, 3H, OCH\textsubscript{3}), 3.81 (m, 2H, H(13), H(14)), 3.71 (m, 1H, H(5'''')), 3.51 (s, 1H, HO(C3''''')), 3.17 (d, 1H, J = 9.6 Hz, H(4''''')), 3.09 (m, 1H, H(8'')), 3.03 (d,
1H, J = 18.6 Hz, H(5)), 2.73 (br d, 1H, J = 12.0 Hz, H(8')), 2.56 (s, 6H, H(7''''), H(8'''')), 2.49 (m, 1H, H(4'''')), 2.17 (d, 1H, J = 18.0 Hz, H(5)), 2.02 (m, 1H, H(2'''')), 1.65–1.82 (m, 2H, H(2''''), H(2''''))), 1.66 (m, 1H, H(2'''')), 1.38 (d, 6H, J = 6.0 Hz, H(11'''), H(12''')), 1.28 (s, 9H, COC(CH3)3), 1.22 (d, 3H, J = 6.6 Hz, H(6''''), 1.08 (d, 3H, J = 6.6 Hz, H(6'''')), 1.05 (s, 3H, H(7'''')), 0.94–0.99 (m, 21H, Si(CH2CH3)3, (CH3)2CHSi(CH2CH3)2), 0.89 (m, 1H, (CH3)2CHSi(CH2CH3)2), 0.58–0.65 (m, 10H, (CH3)2CHSi(C2H5)3, (CH3)2CHSi(CH2CH3)2). MS–ESI (m/z): [M+H]+ calcd for C71H101ClN3O18Si2, 1374.6; found, 1375.0.

Dehydration Product 16

A solution of Martin sulfurane (18.0 mg, 26.8 μmol, 3.83 equiv) in benzene (200 μL) was added to a solution of the glycosidation product 15 (7.00 μmol, 1 equiv) in benzene (1.0 mL) at 23 °C. After stirring for 5 min, the reaction mixture was partitioned between benzene (10 mL) and water (5 mL). The organic layer was separated and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated to a volume of ~0.5 mL. The residue was purified by flash column chromatography (gradient elution, 10→20→30% ethyl acetate in dichloromethane) to provide the dehydration product 16 (atropisomeric mixture: ~1:1 in C6D6, ~3:1 in DMSO-d6). To determine the yield of the reaction, fractions containing pure 16 were combined and the combined solution was concentrated to ~2 mL. The concentrated solution was diluted with C6D6 (50 mL) and the resulting solution was concentrated to a volume of ca. 1 mL. A 1H NMR spectrum was taken to confirm purity and that no toluene was present, then an internal standard (toluene, 5 μL, 47 μmol) was added. The yield of 16 was determined by comparing integrated peak areas for 16 relative to toluene (calculated: 4.53 μmol, 65%).
Rf = 0.41 (30% ethyl acetate–dichloromethane). 1H NMR (500 MHz, C6D6) δ: **Atropisomer One:**
8.92 (s, 1H, ArH), 8.00 (d, 1H, J = 8.0 Hz, NH), 7.36 (s, 1H, ArH), 6.63 (s, 1H, ArH), 6.53 (d, H, J = 8.5 Hz, H(4''')), 6.47 (d, H, J = 8.5 Hz, H(5''')), 6.37 (br s, 1H, H(5)), 6.04 (d, 1H, J = 2.0 Hz, H(12)), 5.58 (m, 1H, H(7')), 5.05 (d, 1H, J = 3.0 Hz, H(11)), 4.77 (d, 1H, J = 3.5 Hz, H(1'''')), 4.75 (br s, 1H, H(1''''')), 4.60 (d, 1H, J = 11.0 Hz, H(14)), 4.39 (s, 1H, H(10)), 4.27–4.34 (m, 2H, H(10''''')), H(3''''), 4.23 (br s, 1H, H(13)), 4.16 (m, 1H, H(5'''')), 3.85 (s, 3H, OCH3), 3.77 (s, 3H, OCH3), 3.74 (m, 1H, H(5'''')), 3.58 (d, 1H, J = 1.5 Hz, H(8)), 3.57 (s, 1H, HO(C3'''')), 3.33 (m, 1H, H(8''')), 3.23 (m, 1H, J = 9.0 Hz, H(4'''')), 2.68 (s, 6H, H(7''''), H(8'''')), 2.53 (dd, 1H, J = 17.5, 3.0 Hz, H(8')), 2.39 (br s, 1H, H(4'''')), 2.09–2.13 (m, 1H, H(2'''')), 1.87 (d, 1H, J = 13.5 Hz, H(2'''')), 1.81–1.89 (m, 1H, H(2''''')), 1.53 (s, 9H, COC(CH3)3), 1.49 (m, 1H, H(2''''')), 1.47 (d, 3H, J = 6.0 Hz, H(6'''')), 1.39 (d, 3H, J = 6.5 Hz, H(6'''')), 1.24 (s, 3H, H(7'''')), 1.18 (d, 6H, J = 6.5 Hz, H(11'''), H(12''''), 1.01–1.08 (m, 21H, Si(CH2CH3)3, (CH3)2CHSi(CH2CH3)2), 0.95 (m, 1H, (CH3)2CHSi(CH2CH3)2), 0.68–0.75 (m, 6H, Si(CH2CH3)3), 0.59–0.63 (m, 4H, (CH3)2CHSi(CH2CH3)2). **Atropisomer two:** 8.74 (s, 1H, ArH), 8.24 (d, 1H, J = 9.0 Hz, NH), 7.58 (d, 1H, J = 7.5 Hz, H(4''')), 7.37 (s, 1H, ArH), 6.73 (d, 1H, J = 8.0 Hz, H(5''')), 6.65 (s, 1H, ArH), 6.43 (br s, 1H, H(5)), 5.60 (m, 1H, H(7')), 5.40 (d, 1H, J = 2.0 Hz, H(12)), 4.97 (s, 1H, H(10)), 4.90 (d, 2H, J = 3.0 Hz, H(11), H(1''''')), 4.79 (br s, 1H, H(1'''')), 4.51 (d, 1H, J = 10.0 Hz, H(14)), 4.27–4.34 (m, 2H, H(10''', H(3'''')), 4.16 (m, 1H, H(5'''')), 4.12 (br s, 1H, H(13)), 3.88 (s, 3H, OCH3), 3.86 (d, 1H, J = 1.5 Hz, H(8)), 3.75 (s, 3H, OCH3), 3.74 (m, 1H, H(5'''')), 3.70 (s, 1H, HO(C3'''')), 3.63 (dd, 1H, J = 12.0, 3.0 Hz, H(14)), 3.29 (m, 1H, H(8''')), 3.24 (d, 1H, J = 9.5 Hz, H(4'''')), 2.71 (s, 6H, H(7'''), H(8'''')), 2.39 (br s, 1H, H(4''')), 2.24 (dd, 1H, J = 17.0, 4.0 Hz, H(4'''')), 2.09–2.13 (m, 1H, H(2'''')), 1.82 (d, 1H, J = 13.5 Hz, H(2''''')), 1.81–1.89 (m, 1H, H(2''''')), 1.49 (m, 1H, H(2'''')), 1.44 (s, 9H, COC(CH3)3), 1.26 (d, 3H, J = 6.5 Hz, H(6'''')), 1.24 (s, 3H, H(7'''')), 1.23 (d, 3H, J = 7.0 Hz, H(6'''')), 1.17 (d, 6H, J = 6.0 Hz, H(11'''), H(12''''), 1.01–1.08 (m, 21H, Si(CH2CH3)3, (CH3)2CHSi(CH2CH3)2), 0.95 (m, 1H, (CH3)2CHSi(CH2CH3)2), 0.68–0.75 (m, 6H, Si(CH2CH3)3), 0.59–0.63 (m, 4H, (CH3)2CHSi(CH2CH3)2). 1H NMR (600 MHz, DMSO-d6) δ: 7.85 (d, 1H, J = 7.5 Hz, NH), 8.07 (s, 1H, ArH), 7.81 (d, 1H, J = 8.0 Hz, H(4''')), 7.50 (s, 1H, ArH), 7.26 (d, 1H, J = 8.5 Hz, H(5'''')), 7.22 (s, 1H, ArH), 6.55 (d, 1H, J = 1.5 Hz, H(12)), 6.14 (br s, 1H, H(5)), 5.57 (d, 1H, J = 3.5 Hz, H(11)), 5.41 (m, 1H, H(7''')), 5.21 (br s, 1H, H(1'''')), 5.15 (br s, 1H, H(1''''')), 4.74 (m, 1H, H(10''')), 4.58 (dd, 1H, J = 1.5, 1.5 Hz, H(13)), 4.51 (br s, 1H, H(10)), 4.36 (m, 1H, H(3'''')), 4.17 (br d, 1H, J = 10.0 Hz, H(14)), 4.10 (br d, 1H, J = 10.5 Hz, H(14)), 3.97 (s, 3H, OCH3), 3.85 (m, 2H, H(8), H(5'''')), 3.84 (s, 3H, OCH3), 3.72 (m, 1H, H(5'''')), 3.51 (s, 1H, HO(C3'''')), 3.18 (d, 1H, J = 9.5 Hz, H(4'''')), 3.13 (m, 1H, H(8''''), 2.78 (m, 1H, J = 12.0 Hz, H(8'''')), 2.56 (s, 6H, H(7'''), H(8'''')), 2.49 (m, 1H, H(4''')), 2.05 (m, 1H, H(2'''')), 1.76–1.83 (m, 2H, H(2''''), H(2''''')), 1.37 (d, 6H, J = 6.0 Hz, H(11'''), H(12''''), 1.27 (s, 9H, COC(CH3)3), 1.24 (d, 3H, J = 6.0 Hz, H(6'''')), 1.18 (m, 1H, H(2'''''), 1.10 (d, 3H, J = 6.5 Hz, H(6'''')), 1.06 (s, 3H, H(7'''')), 0.91–1.01 (m, 22H, Si(CH2CH3)3, (CH3)2CHSi(CH2CH3)2), 0.61–0.66 (m, 10H, Si(CH2CH3)3, (CH3)2CHSi(CH2CH3)2). MS–ESI (m/z): [M+H]+ caleed for C71H86ClN3O7Si2, 1356.6; found, 1357.0.
Synthesis of the Proposed Structure of Kedarcidin Chromophore (1)

o-Nitrophenol (2.7 mg, 19.4 μmol, 4.83 equiv) and solid tetrabutylammonium fluoride hydrate (10.4 mg, 39.8 μmol, 9.90 equiv) was added to a solution of the dehydration product 16 (4.02 μmol, 1 equiv) in acetonitrile (0.5 mL) at 23 °C. After stirring for 10 min, triethylamine trihydrofluoride (5 μL, 30.7 μmol, 7.64 equiv) was added. The resulting solution was stirred for 2 min at 23 °C. Without work-up, the residue was purified by flash column chromatography (gradient elution, 60→70→80→90% tetrahydrofuran in dichloromethane) to provide the proposed structure of kedarcidin chromophore (1) (atropisomeric mixture: ~1.2:1 in C6D6, ~2:1 in DMSO-d6). To determine the yield of the reaction, fractions containing pure 1 were combined and the combined solution was concentrated to ~1 mL. The concentrated solution was diluted with C6D6 (50 mL) and the resulting solution was concentrated to a volume of ca. 1 mL. A 1H NMR spectrum was taken to confirm purity and that no toluene was present, then an internal standard (toluene, 5 μL, 47 μmol) was added. The yield of 1 was determined by comparing integrated peak areas for 1 relative to toluene (calculated: 2.00 μmol, 50%).

R_f = 0.29 (18% methanol-benzene). 1H NMR (600 MHz, C6D6) δ: Major atropisomer: 12.79 (br s, 1H, HO(C3′)), 8.94 (d, 1H, J = 6.6 Hz, NH), 8.89 (s, 1H, ArH), 7.49 (s, 1H, ArH), 6.59 (s, 1H, ArH), 6.49 (d, J = 8.4 Hz, H(4′)), 6.30 (br s, 1H, H(5)), 6.29 (d, J = 9.0 Hz, H(5′)), 6.00 (d, J = 3.0 Hz, H(12)), 5.26 (m, 1H, H(7′)), 4.92 (d, 1H, J = 3.0 Hz, H(11)), 4.69 (m, 2H, H(1′′), H(1′′′)), 4.60 (br d, 1H, J = 12.6 Hz, H(14)), 4.38 (s, 1H, H(10)), 4.22 (m, 1H, H(10′′), H(10′′′)), 4.09 (s, 3H, OCH3), 4.03 (br s, 1H, H(13)), 3.85 (d, 1H, J = 1.2 Hz, H(8)), 3.84–3.88 (m, 1H, H(3′′), 3.79 (s, 3H, OCH3), 3.65–3.70 (m, 2H, H(5′′), H(5′′′)), 3.61 (s, 1H, HO(C3′′′)), 3.35 (m, 2H, H(14), H(8′)), 2.93 (m, 1H, H(4′′′)), 2.16 (s, 6H, H(7′′), H(8′′)), 2.04 (m, 1H, H(8′)),
1.93 (m, 1H, H(4'''')), 1.86 (m, 1H, H(2'''')), 1.78 (m, 1H, H(2'''')), 1.76 (d, 1H, J = 14.4 Hz, H(2''''))), 1.81–1.89 (m, 1H, H(2'''')), 1.44 (m, 1H, H(2'''')), 1.42 (d, 3H, J = 6.6 Hz, H(6'''')), 1.21 (s, 3H, H(7'''')), 1.12 (d, 6H, J = 6.0 Hz, H(11''), H(12'')), 1.02 (d, 3H, J = 6.6 Hz, H(6'''')). **Minor atropisomer:** 12.87 (br s, 1H, HO(C3')), 9.00 (d, 1H, J = 8.4 Hz, NH), 8.86 (s, 1H, ArH), 7.56 (s, 1H, ArH), 6.98 (d, 1H, J = 7.8 Hz, H(4')), 6.62 (s, 1H, ArH), 6.41 (d, 1H, J = 7.8 Hz, H(5')), 6.36 (br s, 1H, H(5)), 5.54 (m, 1H, H(7')), 5.35 (br s, 1H, H(12)), 4.91 (s, 1H, H(10)), 4.82 (d, 1H, J = 3.0 Hz, H(11)), 4.80 (br s, 1H, H(1'''')), 4.68 (br s, 1H, H(1''')), 4.54 (d, 1H, J = 10.8 Hz, H(14)), 4.21 (m, 1H, H(10''')), 4.15 (br s, 1H, H(13)), 4.07 (s, 3H, OCH3), 3.97 (br s, 1H, H(8)), 3.83–3.90 (m, 1H, H(3'''')), 3.83 (s, 1H, HO(C3'''')), 3.75 (s, 3H, OCH3), 3.66–3.70 (m, 2H, H(5''''), H(5'''')), 3.41 (br d, 1H, J = 11.4 Hz, H(14)), 3.15 (dd, 1H, J = 18.0, 4.8 Hz, H(8')), 2.93 (m, 1H, H(4'''')), 2.39 (m, 1H, H(8')), 2.20 (s, 6H, H(7'', H(8'''')), 1.93 (m, 1H, H(4''')), 1.86 (m, 1H, H(2''')), 1.70 (d, 1H, J = 13.8 Hz, H(2'''')), 1.59–1.63 (m, 1H, H(2'''')), 1.50 (d, 3H, J = 6.6 Hz, H(6'''')), 1.44 (m, 1H, H(2'''')), 1.36 (s, 3H, H(7'''')), 1.13 (d, 6H, J = 6.0 Hz, H(11'''), H(12''')), 1.06 (d, 3H, J = 7.2 Hz, H(6''')). **HRMS–ESI (m/z):** [M+H]⁺ calcd for C53H61ClN3O16, 1030.3740; found, 1030.3738.
* Contains ~10% of the regioisomeric product of cyclic sulfate opening
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