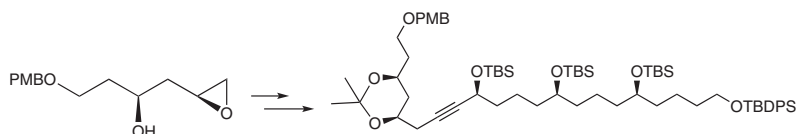


Stereoselective Synthesis of the C19–C39 Fragment of Bastimolide A

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Abstract This paper describes the synthesis of the C19–C39 fragment of the antimalarial natural product bastimolide A via addition of a functionalized C19–C26 alkyne fragment to a C27–C39 aldehyde fragment. Opening of a terminal epoxide and Noyori asymmetric reduction were used as key steps in the synthesis.

Key words bastimolide A, antimalarial activity, stereoselective synthesis, epoxide opening, Noyori asymmetric reduction

Large numbers of novel bioactive secondary metabolites have been isolated from marine organisms and many of them are under clinical development against various diseases.¹ Bastimolide A (**1**, Figure 1), a polyhydroxylated macrolide, was isolated by Gerwick and co-workers from the cyanobacterium *Okeaniahirsuta* collected from the Caribbean coast of Panama.² Detailed NMR studies, followed by single-crystal X-ray diffraction study of a nona-*p*-nitrobenzoate derivative confirmed its structure. Bastimolide A has shown antimalarial activity against four resistant strains of *P. falciparum* with IC₅₀ values between 80 and 270 nM. Its attractive architecture along with potent antimalarial activity and our interest in the total synthesis of complex natural products³ drew our attention to attempt its total synthesis. So far only one synthetic study has been reported by Quintard *et al.* where the synthesis of the C15–C27 fragment of bastimolide A was achieved by implementing enantioselective catalytic reactions.⁴ In this communication, we report the synthesis of a key C19–C39 fragment of bastimolide A.

Retrosynthetically, bastimolide A could be synthesized (Scheme 1) from aldehyde **2** that would be obtained from **3** via deprotection of the PMB ether, followed by oxidation of

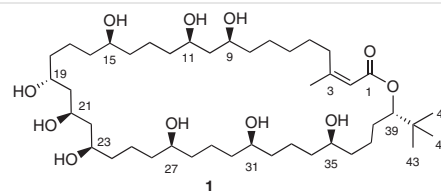
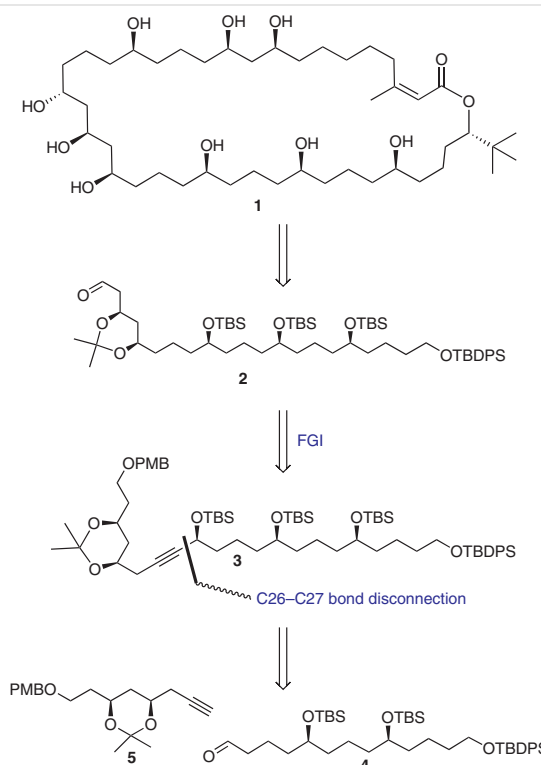


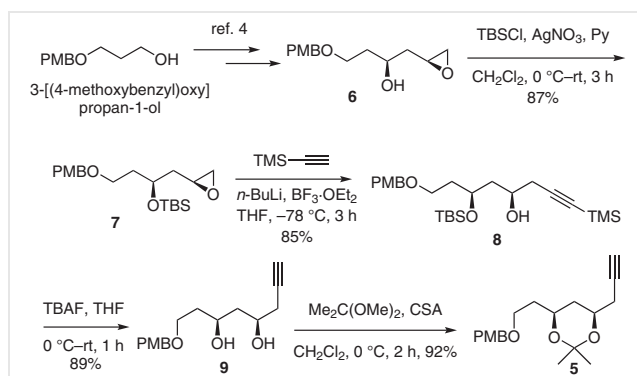
Figure 1 Bastimolide A (**1**)

the resulting alcohol. Fragment **3** might be obtained through coupling of alkyne **5** and aldehyde **4**.



Scheme 1 Retrosynthetic analysis

Following this retrosynthetic plan, the synthesis of **5** was commenced (Scheme 2) from known epoxy alcohol **6**, which was prepared from 3-[(4-methoxybenzyl)oxy]propan-1-ol according to the reported procedure.⁵ TBS protection of **6** under standard conditions afforded **7** in low yield (30%). However TBS protection in presence of AgNO₃ gave **7** in good yield.⁶ Epoxide **7** was then opened with lithium trimethylsilylacetylide⁶ in the presence of BF₃·Et₂O to give homopropargylic alcohol **8**. Both the silyl protecting groups were removed with TBAF⁷ to give diol **9** that, on acetonide protection,⁸ furnished the alkyne fragment **5**.

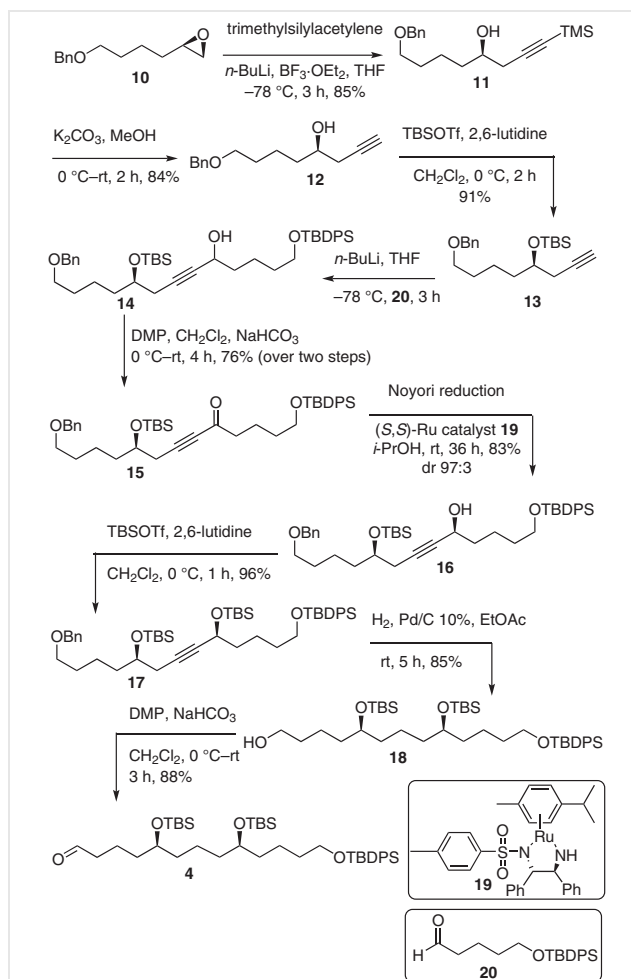


Scheme 2 Synthesis of compound **5**

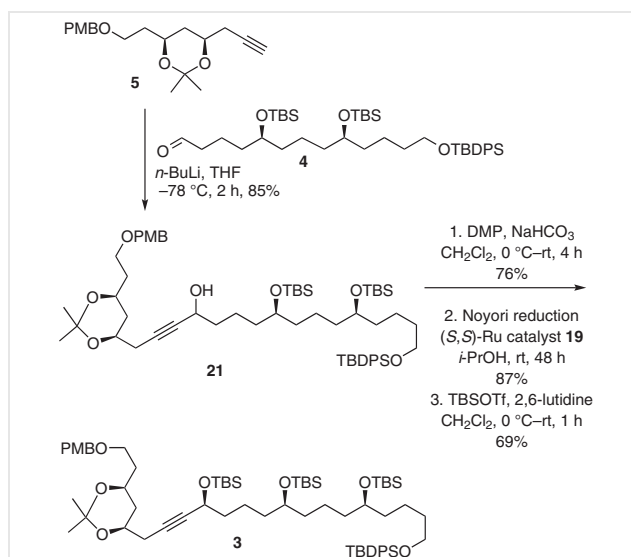
The synthesis of aldehyde fragment **4** is depicted in Scheme 3. Opening of known epoxide **10**⁹ with the anion of trimethylsilylacetylene¹⁰ gave compound **11** that on TMS deprotection followed by TBS protection of **12** gave compound **13** in 91% yield. Addition of alkyne **13** to the known aldehyde **20**¹¹ gave a diastereomeric mixture of alcohol **14** (1:1) that on DMP¹² oxidation followed by asymmetric reduction of the resulting ketone **15** under Noyori conditions¹³ furnished diastereomerically pure compound **16** (dr 97:3). TBS protection of the alcohol **16** followed by one-pot benzyl deprotection and reduction of the alkyne functionality gave primary alcohol **18** that on DMP oxidation furnished the aldehyde fragment **4**.

Having both the fragments **4** and **5** in hand, we planned their coupling (Scheme 4). Accordingly, alkyne **5** on treatment with *n*-BuLi followed by reaction of the resulting anion with the aldehyde **4** furnished alcohol **21**, oxidation of which with DMP afforded the corresponding ynone. Asymmetric reduction of this under Noyori conditions, followed by TBS protection of the resulting alcohol, afforded the pure C19–C39 fragment **3** of bastimolide A after chromatography.

In summary, a convergent approach for a convenient synthesis of C19–C39 fragment of bastimolide A has been achieved via addition of alkyne **5** to an aldehyde **4**. The synthesis was completed in 17 steps from known compounds **10** and **6** with an overall yield of 6.9%. Key reactions used in



Scheme 3 Synthesis of compound **4**



Scheme 4 Synthesis of the C19–C39 fragment of bastimolide A

the synthesis include opening of a terminal epoxide with an alkyne anion and asymmetric reduction of the ynone. Furthermore, the chemistry reported here can be used for the large-scale preparation of **3**.

All the starting materials, reagents, and solvents were used as received without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica-coated plates and components were visualized with UV light. ¹H NMR and ¹³C NMR spectra were recorded at 500 and 400 MHz on Bruker spectrometers in either CDCl₃ or DMSO-*d*₆ with TMS as an internal standard. IR spectra were obtained on a Bruker Alpha spectrophotometer (Opus 8.2). Mass spectra were obtained on an AB SCIEX QTrap 5500 LCMS/MS system. The mass spectra (HRMS) were recorded using either a TOF or double focusing spectrometer.

tert-Butyl(1-((S)-4-[(4-Methoxybenzyl)oxy]-1-[(S)-oxiran-2-yl]-butan-2-yl)oxy)dimethyl Silane (7)

To a stirred solution of compound **6** (5.0 g, 19.8 mmol) in anhydrous CH₂Cl₂ (100 mL) were added sequentially TBSCl (5.97 g, 39 mmol), AgNO₃ (6.74 g, 39 mmol), and pyridine (1.75 mL, 21 mmol) at 0 °C under nitrogen, and the mixture was stirred for 1 h at 0 °C and 2 h at rt. The reaction mixture was quenched with aq NaHCO₃ (60 mL) and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with H₂O (100 mL) and brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. Purification of the crude product by column chromatography (SiO₂, 15% EtOAc in hexane) afforded the pure compound **7** (6.31 g, 87%) as a colorless oil; *R*_f = 0.4 (SiO₂, 30% EtOAc in PE); [α]_D²⁶ -15.1 (c 1.8, CHCl₃).

IR (neat): ν_{max} = 2933, 2378, 2115, 1513, 1463, 1248, 1037, 832, 678 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.25 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.41 (q, *J* = 8.4 Hz, 2 H), 4.06 (p, *J* = 6.0 Hz, 1 H), 3.81 (s, 3 H), 3.52 (t, *J* = 6.5 Hz, 2 H), 3.04 (m, 1 H), 2.75 (t, *J* = 4.5 Hz, 1 H), 2.44 (dd, *J* = 5.0, 2.7 Hz, 1 H), 1.85 (q, *J* = 6.4 Hz, 2 H), 1.68 (t, *J* = 5.6 Hz, 2 H), 0.88 (s, 9 H), 0.06 (s, 6 H).

¹³C NMR (125 MHz, CDCl₃): δ = 159.3, 130.8, 129.5, 114.0, 72.8, 67.6, 66.7, 55.5, 49.4, 47.0, 40.6, 37.3, 26.0, 18.2, -4.3, -4.5.

MS (ESI): *m/z* = 389 [M + Na]⁺.

HRMS: *m/z* calcd for C₂₀H₃₄O₄SiNa [M + Na]⁺: 389.2119; found: 389.2124.

(4R,6S)-6-[(tert-Butyldimethylsilyloxy)-8-[(4-methoxybenzyl)oxy]-1-(trimethylsilyloct-1-yn-4-ol (8)

To a stirred solution of TMS-acetylene (3 mL, 43.5 mmol) in anhydrous THF (40 mL) was added *n*-BuLi (23.84 mL, 1.6 M in hexane 38.14 mmol) at -78 °C under argon, and the mixture was stirred for 30 min. BF₃·OEt₂ (0.7 mL, 50 mmol) was added to the reaction mixture, and it was stirred for 15 min. Compound **7** (dissolved in THF 2 × 10 mL; 4 g, 10.9 mmol) was added via cannula to the above reaction mixture, and the resultant mixture was stirred at -78 °C. After completion of reaction (TLC), aqueous NH₄Cl (40 mL) was added, and the reaction mixture allowed to reach rt. The mixture was extracted with EtOAc (2 × 150 mL), the combined organic layers were washed with H₂O (100 mL) and brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. Purification of the crude product by column

chromatography (SiO₂, 20% EtOAc in hexane) afforded pure compound **8** (4.30 g, 85%) as a colorless oil; *R*_f = 0.6 (SiO₂, 30% EtOAc in PE); [α]_D²³ +1.2 (c 1.4, CHCl₃).

IR (neat): ν_{max} = 3462, 2928, 2174, 1612, 1512, 1249, 1090, 840, 651 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.24 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 4.42 (d, *J* = 1.5 Hz, 2 H), 4.08 (m, 1 H), 3.87 (m, 1 H), 3.80 (s, 3 H), 3.50 (t, *J* = 5 Hz, 2 H), 3.00 (br s, 1 H), 2.40 (dd, *J* = 6.1, 3.3 Hz, 2 H), 1.87–1.78 (m, 3 H), 1.64 (m, 2 H), 0.88 (s, 9 H), 0.15 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 159.4, 130.6, 129.5, 114.0, 103.6, 87.4, 72.9, 69.7, 68.7, 66.6, 55.46, 42.7, 37.6, 29.2, 26.0, 18.1, 0.3, -4.1, -4.4.

MS (ESI): *m/z* = 465 [M + H]⁺.

HRMS: *m/z* calcd for C₂₅H₄₅O₄Si₂ [M+H]⁺: 465.2851; found: 465.2856.

(3S,5R)-1-[(4-Methoxybenzyl)oxy]oct-7-yne-3,5-diol (9)

To a solution of compound **8** (3.0 g, 6.4 mmol) in anhydrous THF (30 mL) at 0 °C, was added TBAF (32 mL, 32 mmol, 1 M) and the mixture was stirred for 30 min at 0 °C then 30 min at rt. After completion of reaction (TLC), aqueous NH₄Cl (20 mL) was added, and the mixture extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with H₂O (20 mL), brine (20 mL), and dried over Na₂SO₄. After filtration, the solvent was removed under vacuum, and the crude product was purified by column chromatography (SiO₂, 25% EtOAc in hexane) to afford pure compound **9** (1.59 g, 89%) as a colorless oil; *R*_f = 0.6 (SiO₂, 40% EtOAc in PE); [α]_D²³ +6.5 (c 1.8, CHCl₃).

IR (neat): ν_{max} = 3396 (br), 3291 (br), 2922, 2312, 1611, 1512, 1245, 1086, 1032, 821, 644 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.24 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 4.44 (s, 2 H), 4.09–3.97 (m, 3 H), 3.88 (m, 1 H), 3.79 (s, 3 H), 3.72–3.60 (m, 2 H), 2.44–2.29 (m, 2 H), 2.03 (t, *J* = 2.7 Hz, 1 H), 1.72 (m, 4 H).

¹³C NMR (125 MHz, CDCl₃): δ = 159.4, 129.9, 129.5, 114.0, 81.1, 73.1, 72.3, 70.7, 70.6, 68.6, 55.4, 42.0, 36.9, 27.5.

MS (ESI): *m/z* = 301 [M + Na]⁺.

HRMS: *m/z* calcd for C₁₆H₂₂O₄Na [M + Na]⁺: 301.1410; found: 301.1419.

(4S,6R)-4-{2-[(4-Methoxybenzyl)oxy]ethyl}-2,2-dimethyl-6-(prop-2-yn-1-yl)-1,3-dioxane (5)

To a solution of diol **9** (1.0 g, 3.6 mmol) in anhydrous CH₂Cl₂ (10 mL) at 0 °C was added 2,2-dimethoxypropane (0.65 mL, 5.38 mmol) and CSA (417 mg, 1.79 mmol), and the mixture was stirred for 2 h. After completion of reaction (TLC), aqueous NaHCO₃ (5 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), and dried over Na₂SO₄. After filtration, evaporation of the organic extract under vacuum gave crude product that, on purification by column chromatography (SiO₂, 12% EtOAc in hexane), afforded the pure **5** (919 mg, 92%) as a colorless oil; *R*_f = 0.3 (SiO₂, 30% EtOAc in PE); [α]_D²⁶ -26 (c 2.2, CHCl₃).

IR (neat): ν_{max} = 3394, 2994, 2377, 2173, 1512, 1245, 1093, 816, 648 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.25 (d, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 4.45 (d, *J* = 11.6 Hz, 1 H), 4.42 (d, *J* = 11.6 Hz, 1 H), 4.07–3.93 (m, 2 H), 3.81 (s, 3 H), 3.59–3.48 (m, 2 H), 2.47 (dd, *J* = 2.8, 5.2 Hz, 1 H), 2.42 (dd, *J* = 2.8, 5.2 Hz, 1 H), 2.00 (t, *J* = 2.7 Hz, 1 H), 1.79–1.71 (m, 2 H), 1.43 (s, 3 H), 1.38 (s, 3 H), 1.28–1.13 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 159.3, 130.8, 129.4, 114.0, 99.0, 80.5, 72.8, 70.5, 68.0, 66.2, 66.0, 55.4, 36.7, 36.3, 30.3, 26.4, 20.0.

MS (ESI): m/z = 341 [M + Na] $^+$.

HRMS: m/z calcd for $\text{C}_{19}\text{H}_{26}\text{O}_4\text{Na}$ [M + Na] $^+$: 341.1723; found: 341.1719.

(R)-8-(Benzyloxy)-1-(trimethylsilyloxy)-1-yn-4-ol (11)

A stirred solution of TMS-acetylene (8.5 mL, 60.6 mmol) in anhydrous THF (60 mL) was treated with *n*-BuLi (22.75 mL, 1.6 M in hexane, 36.44 mmol) at -78°C under nitrogen, and the mixture was stirred for 30 min. $\text{BF}_3\cdot\text{OEt}_2$ (1.56 mL, 12.1 mmol) was then added and the mixture was stirred for 30 min. Epoxide **10** (5.0 g, 24.2 mmol) dissolved in anhydrous THF (2×10 mL) was added via cannula, and the mixture was stirred for 2 h at -78°C . A saturated solution of aqueous NH_4Cl (80 mL) was added, and the mixture was allowed to reach rt. The reaction mixture was extracted with EtOAc (2×250 mL), and the combined organic extracts were washed with brine (50 mL) and dried over anhydrous Na_2SO_4 . Filtration and evaporation of the organic solvents under reduced pressure provided a crude residue that, on purification by column chromatography (SiO_2 , 8% EtOAc/hexane), furnished compound **11** as a colorless oil (6.26 g, 85%). R_f = 0.3 (SiO_2 , 10% EtOAc/hexane); $[\alpha]_D^{27}$ -12.1 (c 1.9, CHCl_3).

IR (neat): ν_{max} = 3423 (br), 2937, 2861, 1495, 1432, 1094, 1027, 843, 747, 697, 632 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.29–7.25 (m, 4 H), 7.23–7.18 (m, 1 H), 4.43 (s, 2 H), 3.66 (m, 1 H), 3.41 (t, J = 6.5 Hz, 2 H), 2.37 (dd, J = 17, 5.0 Hz, 1 H), 2.27 (dd, J = 17, 2.0 Hz, 1 H), 1.99 (br s, 1 H), 1.63–1.53 (m, 2 H), 1.51–1.42 (m, 3 H), 1.41–1.32 (m, 1 H), 0.09 (s, 9 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 138.7, 128.6, 127.8, 127.7, 103.5, 87.8, 73.1, 70.4, 70.0, 36.1, 29.8, 29.0, 22.5, 0.3.

MS (ESI): m/z = 305 [M + H] $^+$.

HRMS: m/z calcd for $\text{C}_{18}\text{H}_{29}\text{O}_2\text{Si}$ [M + H] $^+$: 305.1931; found: 305.1931.

(R)-8-(Benzyloxy)oct-1-yn-4-ol (12)

Compound **11** (5.0 g, 16.4 mmol) was dissolved in anhydrous MeOH (150 mL) and treated with anhydrous K_2CO_3 (4.53 g, 32.8 mmol) at 0°C under nitrogen. The reaction mixture was stirred at rt for 2 h and quenched with H_2O (50 mL). MeOH was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (2×80 mL). The combined organic extracts were washed with water (2×40 mL) and brine (20 mL). After drying over anhydrous Na_2SO_4 and filtering, the solvent was evaporated under reduced pressure to give a residue that, on purification by flash chromatography (SiO_2 , 20% EtOAc/hexane), afforded **12** as a colorless oil (3.20 g, 84%). R_f = 0.6 (SiO_2 , 20% EtOAc/hexane); $[\alpha]_D^{30}$ -5.4 (c 2.6, CHCl_3).

IR (neat): ν_{max} = 3418 (br) 3305, 2937, 2862, 2117, 1495, 1432, 1248, 1094, 748, 665, 632 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.28–7.18 (m, 5 H), 4.43 (s, 2 H), 3.68 (m, 1 H), 3.41 (t, J = 6.4 Hz, 2 H), 2.30 (ddd, J = 16.5, 4.8, 2.4 Hz, 1 H), 2.30 (ddd, J = 16.5, 6.8, 2.8 Hz, 1 H), 1.97 (t, J = 2.8 Hz, 1 H), 1.92 (br s, 1 H), 1.62–1.34 (m, 6 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 138.59, 128.45, 127.75, 127.63, 81.10, 72.99, 70.85, 70.27, 69.79, 35.99, 29.63, 27.43, 22.41.

MS (ESI): m/z = 233 [M + H] $^+$.

HRMS: m/z calcd for $\text{C}_{15}\text{H}_{21}\text{O}_2$ [M + H] $^+$: 233.1541; found: 233.1536.

(R)-[[8-(Benzyloxy)oct-1-yn-4-yl]oxy](tert-butyl)dimethylsilane (13)

Compound **12** (3.20 g, 13.7 mmol) was dissolved in anhydrous CH_2Cl_2 (60 mL) and treated with 2,6-lutidine (3.68 mL, 34.4 mmol) and TBSOTf (4.96 mL, 20 mmol) at 0°C . The reaction mixture was stirred for 2 h, quenched with saturated aqueous NaHCO_3 (20 mL) and extracted with EtOAc (2×120 mL). The combined organic extracts were washed with saturated aqueous CuSO_4 (2×40 mL), water (2×40 mL), and brine (50 mL). After drying the organic extract over anhydrous Na_2SO_4 and filtering, the solvent was evaporated under reduced pressure, and the crude product was purified by column chromatography (SiO_2 , 20% EtOAc/hexane), which afforded the title compound **13** as a colorless oil (4.32 g, 91%). R_f = 0.3 (SiO_2 , 20% EtOAc/hexane); $[\alpha]_D^{30}$ $+12.5$ (c 1.8, CHCl_3).

IR (neat): ν_{max} = 3311, 2930, 2856, 2349, 1389, 1253, 1102, 834, 774, 698 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.28–7.18 (m, 5 H), 4.43 (s, 2 H), 3.72 (m, 1 H), 3.41 (t, J = 6.6 Hz, 2 H), 2.26–2.21 (m, 2 H), 1.89 (t, J = 2.7 Hz, 1 H), 1.61–1.52 (m, 3 H), 1.51–1.41 (m, 2 H), 1.29 (m, 1 H), 0.81 (s, 9 H), 0.00 (s, 3 H), -0.01 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 138.9, 128.5, 127.8, 127.7, 81.9, 73.0, 71.5, 70.5, 70.0, 36.6, 30.0, 27.6, 26.1, 22.1, 18.3, -4.3 , -4.4 .

MS (ESI): m/z = 347 [M + H] $^+$.

HRMS: m/z calcd for $\text{C}_{19}\text{H}_{26}\text{O}_4$ [M + H] $^+$: 347.2401; found: 347.2401.

(R)-5-[4-(Benzyloxy)butyl]-2,2,3,3,16,16-hexamethyl-15,15-diphenyl-4,14-dioxo-3,15-disilaheptadec-7-yn-9-one (15)

To a solution of **13** (4.5 g, 13 mmol) in dry THF (70 mL) under argon, *n*-BuLi (1.6 M in hexane, 9.75 mL, 15.6 mmol) was added at -78°C . After stirring for 30 min at -78°C , aldehyde **20** (7.48 g, 16.9 mmol) dissolved in anhydrous THF (20 mL) was added dropwise via cannula. After stirring for 2.5 h at -78°C , saturated aqueous NH_4Cl (50 mL) was added to the reaction mixture, and the temperature was allowed to rise to rt slowly. The reaction mixture was extracted with EtOAc (2×150 mL), and the combined organic extracts were washed with water (2×40 mL) and brine (30 mL). After drying the organic extracts with anhydrous Na_2SO_4 and filtering, the solvent was evaporated under reduced pressure to give a residue that was subjected to flash chromatography (SiO_2 , 12% EtOAc/hexane) to afford compound **14** as a colorless oil (7.14 g, 80%).

To a solution of compound **14** (7.14 g, 10.3 mmol) in CH_2Cl_2 (100 mL) at 0°C was added NaHCO_3 (2.2 g, 25.7 mmol) under nitrogen. Then DMP (8.8 g, 20 mmol) was added portionwise at the same temperature. The reaction mixture was allowed to warm to rt and stirred for 4 h. Saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL) and saturated aqueous NaHCO_3 (30 mL) were added, and the resultant biphasic mixture was stirred for 50 min and then extracted with EtOAc (2×150 mL). The combined organic extracts were washed with water (50 mL) and brine (40 mL). The organic extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2 , 10% EtOAc/hexane) afforded compound **15** as a colorless oil (6.76 g, 95%). R_f = 0.5 (SiO_2 , 20% EtOAc/hexane); $[\alpha]_D^{30}$ $+3.2$ (c 1.5, CHCl_3).

IR (neat): ν_{max} = 2931, 2856, 2214, 1716, 1427, 1247, 1110, 849, 701, 606 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.63–7.57 (m, 4 H), 7.38–7.26 (m, 8 H), 7.25–7.16 (m, 2 H), 4.43 (s, 2 H), 3.78 (pent, J = 6 Hz, 1 H), 3.59 (t, J = 6.2 Hz, 2 H), 3.40 (t, J = 6.4 Hz, 2 H), 2.45 (t, J = 7.2 Hz, 2 H), 2.41 (d, J = 6 Hz, 2 H), 1.69 (pent, J = 7.2 Hz, 2 H), 1.58–1.47 (m, 6 H), 1.44–1.26 (m, 2 H), 0.98 (s, 9 H), 0.82 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 188.1, 138.8, 135.7, 134.1, 129.8, 128.5, 127.8, 127.7, 91.4, 82.4, 73.1, 70.5, 70.4, 63.6, 45.4, 37.0, 31.9, 29.9, 28.0, 27.0, 26.0, 22.0, 20.7, 19.4, 18.21, -4.3, -4.4.

MS (ESI): m/z = 685 [M + H] $^+$.

HRMS: m/z calcd for $\text{C}_{42}\text{H}_{61}\text{O}_4\text{Si}_2$ [M + H] $^+$: 685.4103; found: 685.4107.

(5R,9S)-5-[4-(Benzyloxy)butyl]-2,2,3,3,16,16-hexamethyl-15,15-diphenyl-4,14-dioxo-3,15-disilaheptadec-7-yn-9-ol (16)

Alkynone **15** (6.5 g, 9.48 mmol) was dissolved in *i*-PrOH (120 mL) at rt and treated with Ru[(*S,S*)-Tsdpen](*p*-cymene) (30 mg, 948 μmol). After stirring for 36 h at rt, the solvent was removed under reduced pressure to give the crude product, that on purification by column chromatography (SiO_2 , 20% EtOAc/hexane) afforded compound **16** as a colorless oil (5.4 g, 83%). R_f = 0.3 (SiO_2 , 20% EtOAc/hexane); $[\alpha]_D^{29}$ +5.09 (c 16.5, CHCl_3).

IR (neat): ν_{max} = 3443 (br), 2930, 2857, 2214, 1414, 1254, 1106, 824, 775, 700, 613 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.63–7.57 (m, 4 H), 7.36–7.28 (m, 6 H), 7.27 (m, 3 H), 7.23–7.17 (m, 2 H), 4.43 (s, 2 H), 4.24 (m, 1 H), 3.71 (pent, 6.4 Hz), 3.60 (t, J = 6.3 Hz, 2 H), 3.40 (t, J = 6.5 Hz, 2 H), 2.27–2.25 (m, 2 H), 1.72 (d, J = 4.8 Hz, 1 H), 1.60–1.49 (m, 7 H), 1.45 (m, 3 H), 1.34–1.30 (m, 1 H), 0.98 (s, 9 H), 0.81 (s, 9 H), 0.00 (s, 3 H), -0.01 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 138.8, 135.8, 134.2, 129.7, 128.5, 127.8, 127.7, 83.1, 82.7, 73.1, 71.1, 70.5, 63.9, 62.9, 38.0, 36.8, 32.4, 30.0, 27.8, 27.1, 26.1, 22.1, 21.7, 19.4, 18.3, -4.2, -4.4.

MS (ESI): m/z = 669 [M + NH_4] $^+$.

HRMS: m/z calcd for $\text{C}_{42}\text{H}_{66}\text{O}_4\text{Si}_2\text{N}$ [M + NH_4] $^+$: 704.4525; found: 704.4524.

(5R,9S)-5-[4-(Benzyloxy)butyl]-2,2,3,3,16,16-hexamethyl-15,15-diphenyl-4,14-dioxo-3,15-disilaheptadec-7-yn-9-ol (17)

Compound **16** (6.0 g, 8.7 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL) and treated with 2,6-lutidine (2 mL, 17.4 mmol) and TBSOTf (3.12 mL, 13.1 mmol) at 0 $^\circ\text{C}$. The reaction mixture was stirred for 1 h, quenched with saturated aqueous NaHCO_3 (20 mL), and extracted with EtOAc (2 \times 150 mL). The combined organic extracts were washed with saturated aqueous CuSO_4 (2 \times 50 mL), water (50 mL), and brine (50 mL). After drying the organic extract over anhydrous Na_2SO_4 and filtering, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2 , 20% EtOAc/hexane) to afford **17** as a colorless oil (6.69 g, 96%). R_f = 0.3 (SiO_2 , 20% EtOAc/hexane); $[\alpha]_D^{30}$ +5.2 (c 3.3, CHCl_3).

IR (neat): ν_{max} = 2937, 2858, 2349, 1463, 1370, 1254, 1102, 833, 772, 701, 613 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.67 (m, 4 H), 7.42–7.33 (m, 8 H), 7.29–7.24 (m, 2 H), 4.50 (s, 2 H), 4.30 (m, 1 H), 3.74 (m, 1 H), 3.65 (t, J = 6.2 Hz, 2 H), 3.46 (t, J = 6.6 Hz, 2 H), 2.34 (ddd, J = 16.5, 5.0, 2.0 Hz 1 H), 2.28 (ddd, J = 16.5, 7.0, 2.0 Hz 1 H) 1.67–1.57 (m, 7 H), 1.53–1.45 (m, 4 H), 1.38–1.33 (m, 1 H), 1.04 (s, 9 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 138.9, 135.8, 134.3, 129.7, 128.5, 127.8, 127.7, 83.8, 81.5, 73.1, 71.3, 70.6, 64.1, 63.4, 39.0, 36.6, 32.5, 30.1, 28.0, 27.1, 26.1, 26.1, 22.1, 22.0, 19.4, 18.5, 18.3, -4.2, -4.5, -4.7.

MS (ESI): m/z = 818 [M + NH_4] $^+$.

HRMS: m/z calcd for $\text{C}_{48}\text{H}_{80}\text{O}_4\text{Si}_3\text{N}$ [M + NH_4] $^+$: 818.5390; found: 818.5403.

(5R,9S)-5-[(*tert*-Butyldimethylsilyloxy)-13-[(*tert*-butyldiphenylsilyloxy)tridecane-1,9-diol (18)

A stirred solution of compound **17** (6.5 g, 8.1 mmol) in anhydrous EtOAc (100 mL) was treated with 10% Pd/C (86 mg, 20% w/w) and hydrogenated using a hydrogen-filled balloon at rt for 5 h. The reaction mixture was filtered through a Celite plug, and the plug was washed with EtOAc (2 \times 100 mL). The combined filtrate and washings were concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (SiO_2 , 100–200 mesh, 10% EtOAc/hexane) to afford compound **18** (4.92 g 85%) as a colorless oil. R_f = 0.5 (SiO_2 , 20% EtOAc/hexane); $[\alpha]_D^{25}$ -2.3 (c 1.8, CHCl_3).

IR (neat): ν_{max} = 3071 (br), 2929, 2856, 1413, 1390, 1253, 1108, 833, 772, 700, 613 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.68–7.66 (m, 4 H), 7.44–7.34 (m, 6 H), 3.66–3.60 (m, 6 H), 1.59–1.53 (m, 6 H), 1.45–1.36 (m, 12 H), 1.04 (s, 9 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.03 (s, 6 H), 0.03 (s, 3 H), 0.02 (s, 3 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 135.8, 134.3, 129.7, 127.8, 72.5, 72.4, 64.2, 63.2, 37.6, 37.1, 36.9, 33.2, 33.1, 30.0, 29.8, 27.1, 26.2, 21.9, 21.6, 21.2, 19.4, 18.4, -4.2.

MS (ESI): m/z = 716 [M + H] $^+$.

HRMS: m/z calcd for $\text{C}_{41}\text{H}_{78}\text{O}_4\text{Si}_3\text{N}$ [M + NH_4] $^+$: 732.5232; found: 732.5233.

(5S,9S,13S)-9,13-bis[(*tert*-Butyldimethylsilyloxy)-5-{3-[(4R,6S)-6-{2-[(4-methoxybenzyl)oxy]ethyl}-2,2-dimethyl-1,3-dioxan-4-yl]-prop-1-yn-1-yl}-2,2,3,3,20,20-hexamethyl-19,19-diphenyl-4,18-dioxo-3,19-disilahenicosane (3)

Alcohol **18** (200 mg, 0.28 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and the solution cooled to 0 $^\circ\text{C}$. NaHCO_3 (84 mg, 0.97 mmol) and DMP (294 mg, 0.68 mmol) were added sequentially at the same temperature, and the resulting reaction mixture was stirred under nitrogen for 3 h at rt. Saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) and saturated aqueous NaHCO_3 (10 mL) were added to the reaction mixture, and the resultant biphasic mixture was stirred for 30 min. The mixture was extracted with EtOAc (2 \times 15 mL), and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 , and filtered. The solvents were evaporated under reduced pressure to give aldehyde **4** (175 mg, 88%; R_f = 0.4, 10% EtOAc/hexane), which was used directly for the next reaction.

To a stirred solution of **5** (238 mg, 0.75 mmol) in dry THF (8 mL) under nitrogen, *n*-BuLi (1.6 M in hexane, 0.4 mL, 0.625 mmol) was added at -78 $^\circ\text{C}$. After stirring for 30 min at -78 $^\circ\text{C}$, crude aldehyde **4** (175 mg, 0.25 mmol) dissolved in THF (2 \times 4 mL) was added dropwise via cannula. After stirring for 45 min at -78 $^\circ\text{C}$, saturated aqueous NH_4Cl (5 mL) was added, and the temperature was allowed to raise to rt slowly. The reaction mixture was extracted with EtOAc (2 \times 15 mL) and the combined organic extracts washed with water (10 mL) and brine (10 mL). After drying the organic extracts over anhydrous Na_2SO_4 and filtering, the solvent was evaporated under reduced pressure to give a crude product that was subjected to flash chromatography (SiO_2 , 15% EtOAc/hexane) to afford **21** as a mixture of diastereomers as a colorless oil (218 mg, 85%).

To a solution of compound **21** (218 mg, 0.21 mmol) in CH_2Cl_2 (10 mL) at 0 $^\circ\text{C}$ was added NaHCO_3 (54 mg, 0.63 mmol) under nitrogen, then DMP (178 mg, 0.42 mmol) was added portion-wise. The reaction mixture was warmed to rt and stirred for 4 h. Saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and saturated aqueous NaHCO_3 (5 mL) were added, and the resultant biphasic mixture was stirred for 10 min and then extracted with EtOAc (2 \times 15 mL). The combined organic extracts

were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2 , 10% EtOAc/hexane) afforded the ketone as a colorless oil (164 mg, 76%). $R_f = 0.4$ (SiO_2 , 20% EtOAc/hexane).

The purified alkynone (164 mg, 0.16 mmol) was dissolved in *i*-PrOH (4 mL) at rt and treated with $\text{Ru}[(S,S)\text{-Tsdpen}](p\text{-cymene})$ (5 mg, 8 μmol). After stirring for 48 h at rt, the solvent was removed under reduced pressure to give that crude product that, on purification by flash chromatography (SiO_2 , 15% EtOAc/hexane), afforded the alcohol compound as a colorless oil (143 mg, 87%). $R_f = 0.6$ (SiO_2 , 20% EtOAc/hexane).

The purified alcohol (143 mg, 0.14 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) and treated with 2,6-lutidine (16 μmL , 0.27 mmol) and TBSOTf (50 μmL , 0.21 mmol) at 0 °C. The reaction mixture was stirred for 1 h and quenched with saturated aqueous NaHCO_3 (5 mL) and extracted with EtOAc (2 \times 10 mL). The combined organic extracts were washed with saturated aqueous CuSO_4 (2 \times 8 mL), water (2 \times 8 mL), and brine (10 mL). After drying over anhydrous Na_2SO_4 and filtering, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2 , 4% EtOAc/hexane), which afforded the target **3** as a colorless oil (111 mg, 69%). $R_f = 0.4$ (SiO_2 , 20% EtOAc/hexane); $[\alpha]_D^{30} -15.9$ (c 1.8, CHCl_3).

IR (neat): $\nu_{\text{max}} = 2929, 2856, 1514, 1464, 1249, 1106, 835, 773, 702$ cm^{-1} .

^1H NMR (400 MHz, CDCl_3): $\delta = 7.70\text{--}7.64$ (m, 4 H), 7.44 (m, 6 H), 7.25–7.22 (m, 2 H), 6.91–6.85 (m, 2 H), 4.43 (q, $J = 11.7$ Hz, 2 H), 4.31 (m, 1 H), 4.07–3.88 (m, 2 H), 3.80 (s, 3 H), 3.68–3.47 (m, 6 H), 2.35 (dd, $J = 16.5, 4.8$ Hz, 1 H), 2.59 (dd, $J = 16.5, 3.6$ Hz, 1 H), 1.88–1.66 (m, 3 H), 1.66–1.58 (m, 4 H), 1.58–1.43 (m, 5 H), 1.42 (s, 3 H), 1.41–1.37 (m, 7 H), 1.41 (s, 3 H), 1.37 (s, 3 H), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.88 (s, 18 H), 0.11 (s, 3 H), 0.09 (s, 3 H), 0.03 (s, 12 H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 159.4, 135.8, 134.4, 131.7, 130.8, 130.8, 129.7, 129.4, 127.8, 114.0, 99.0, 84.2, 80.2, 72.9, 72.5, 72.5, 68.2, 66.2, 66.1, 64.2, 63.4, 55.5, 39.5, 37.7, 37.7, 37.1, 37.0, 36.8, 36.6, 33.1, 30.3, 27.1, 26.8, 26.2, 26.1, 21.9, 21.5, 21.3, 20.1, 19.4, 18.5, 18.4, -4.1, -4.7$.

MS (ESI): $m/z = 1162$ $[\text{M} + \text{NH}_4]^+$.

HRMS: m/z calcd for $\text{C}_{66}\text{H}_{116}\text{O}_8\text{Si}_4\text{N}$ $[\text{M} + \text{NH}_4]^+$: 1162.7773; found: 1162.7772.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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