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. 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. 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 products 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. 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 the resulting alcohol. Fragment 3 might be obtained through coupling of alkyne 5 and aldehyde 4.
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. 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. Epoxide 7 was then opened with lithium trimethylsilylacetylide in the presence of BF₃·Et₂O to give homopropargylic alcohol 8. Both the silyl protecting groups were removed with TBAF to give diol 9 that, on acetonide protection, furnished the alkyne fragment 5.

The synthesis of aldehyde fragment 4 is depicted in Scheme 3. Opening of known epoxide 10 with the anion of trimethylsilylacetylene gave compound 11 that on TMS deprotection followed by TBS protection of 12 gave compound 13 in 91% yield. Addition of aldehyde 13 to the known aldehyde 20 gave a diastereomeric mixture of alcohol 14 (1:1) that on DMP oxidation followed by asymmetric reduction of the resulting ketone 15 under Noyori conditions 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 finished the alkyne 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

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**Scheme 2** Synthesis of compound 5

**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-d6 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(4-[(4-Methoxybenzyl)oxy]oxy)-1-[(5-oxiran-2-yl)-butan-2-yl]dimethylsilane (7)

To a stirred solution of compound 6 (5.0 g, 19.8 mmol) in anhydrous CH2Cl2 (100 mL) were added sequentially TBSCI (5.57 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 withaq NaHCO3 (60 mL) and the mixture was stirred for 1 h at 4 °C and 2 h at 0 °C. The reaction mixture allowed to reach rt. The mixture was extracted with EtOAc (2 × 100 mL), the combined organic layers were washed with H2O (20 mL), brine (20 mL), and dried over Na2SO4. The reaction mixture was concentrated under vacuum. Purification of the crude product by column chromatography (SiO2, 15% EtOAc in hexane) afforded the pure compound 7 (631 g, 87%) as a colorless oil; Rf = 0.4 (SiO2, 30% EtOAc in PE); [α]D26 = +15.1 (c 1.8, CHCl3).

IR (neat): νmax = 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), 4.08 (p, J = 6.0 Hz, 1 H), 3.01 (s, 3 H), 3.52 (s, 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), 1.08 (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]⁺.


(35SR)-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 NaHCO3 (60 mL) was added, and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic extract 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; Rf = 0.6 (SiO2, 40% EtOAc in PE); [α]D26 = +65.1 (c 1.8, CHCl3).

IR (neat): νmax = 3396 (br), 3291, 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), 1.72 (m, 4 H).

13C NMR (125 MHz, CDCl3): δ = 159.4, 129.9, 114.0, 81.1, 73.1, 72.3, 70.7, 70.6, 68.5, 55.4, 42.0, 36.9, 27.5.


(4R,6S)-6-[(tert-Butyldimethylsilyl)oxy]-8-[(4-methoxybenzyl)-oxy]-1-(trimethylsilyl)oct-1-yn-1-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·OBz (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 NaHCO3 (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; Rf = 0.6 (SiO2, 30% EtOAc in PE); [α]D25 = +1.2 (c 1.4, CHCl3).

IR (neat): νmax = 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), 4.45 (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).

A stirred solution of TMS-acetylene (8.5 mL, 60 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. BF₃·OEt₂ (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 NH₄Cl (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 (20 mL). After drying over anhydrous Na₂SO₄ and filtering, the solvent was evaporated under reduced pressure to give a residue that, on purification by flash chromatography (SiO₂, 20% EtOAc/hexane), the crude product was purified by column chromatography (SiO₂, 20% EtOAc/hexane) to afford the title compound 13 as a colorless oil (6.76 g, 95%).

The reaction mixture was allowed to warm to rt and stirred for 4 h. Saturated aqueous Na₂SO₄ and filtering, the solvent was evaporated under reduced pressure to give a residue that was subjected to flash chromatography (SiO₂, 12% EtOAc/hexane) to afford compound 14 as a colorless oil (7.14 g, 80%). 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 NH₄Cl (50 mL) was added to the reaction mixture, and the temperature was allowed to rise to rt slowly. The reaction mixture was washed with water (2 × 40 mL) and brine (30 mL). After drying the organic extracts with anhydrous Na₂SO₄ and filtering, the solvent was evaporated under reduced pressure to give a residue that was subjected to flash chromatography (silica gel, 12% EtOAc/hexane) to afford compound 15 as a colorless oil (6.76 g, 95%).
Alkyne 15 (6.5 g, 9.48 mmol) was dissolved in i-PrOH (120 mL) at rt and treated with Ru[5,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 (SiO2, 20% EtOAc/hexane) afforded compound 16 as a colorless oil (5.4 g, 83%). RT = 0.3 (SiO2, 20% EtOAc/hexane); [α]D25 = +5.09 (c 16.5, CHCl3).

HRMS: m/z calcd for C42H61O4Si2 [M + H]+: 685.4107; found: 685.4103.

**HRMS:**


**1H NMR (400 MHz, CDCl3):** 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).

**13C NMR (100 MHz, CDCl3):** δ = 151.3, 138.8, 130.7, 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.

**IR (neat):** 2937, 2858, 2825, 2214, 1414, 1254, 1106, 833, 772, 700, 613 cm–1.

1H NMR (500 MHz, CDCl3): 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).

**HRMS:**

m/z = 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]+.


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**MS (ESI):** m/z = 716 [M + H]+.
were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na2SO4, and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO2, 10% EtOAc/hexane) afforded the ketone as a colorless oil (164 mg, 76%). Rf = 0.4 (SiO2, 20% EtOAc/hexane).

The purified alkynone (164 mg, 0.16 mmol) was dissolved in i-PrOH (4 mL) at rt and treated with [Ru((SS)-Tsdpen)2](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 (SiO2, 15% EtOAc/hexane), afforded the alcohol compound as a colorless oil (143 mg, 87%), Rf = 0.6 (SiO2, 20% EtOAc/hexane).

1H NMR (400 MHz, CDCl3): \( \delta = 7.70–7.64 \text{ (m, 4 H)}, 7.44 \text{ (m, 6 H)}, 7.25–7.22 \text{ (m, 2 H)}, 6.91–6.85 \text{ (m, 2 H)}, 4.43 \text{ (q, J = 11.7 Hz, 2 H)}, 4.31 \text{ (m, 1 H)}, 4.07–3.88 \text{ (m, 2 H)}, 3.80 \text{ (s, 3 H)}, 3.68–3.47 \text{ (m, 6 H)}, 2.35 \text{ (dd, J = 16.5, 4.8 Hz, 1 H)}, 2.59 \text{ (dd, J = 16.5, 3.6 Hz, 1 H)}, 1.88–1.66 \text{ (m, 3 H)}, 1.66–1.58 \text{ (m, 4 H)}, 1.58–1.43 \text{ (m, 5 H)}, 1.42 \text{ (s, 3 H)}, 1.41–1.37 \text{ (m, 7 H)}, 1.41 \text{ (s, 3 H)}, 1.37 \text{ (s, 3 H)}, 1.05 \text{ (s, 9 H)}, 0.89 \text{ (s, 9 H)}, 0.88 \text{ (s, 18 H)}, 0.11 \text{ (s, 3 H)}, 0.09 \text{ (s, 3 H)}, 0.03 \text{ (s, 12 H)}.

13C NMR (100 MHz, CDCl3): \( \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.


Conflict of Interest

The authors declare no conflict of interest.

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