Total Synthesis of Buergerinin F
via Effective Construction of the Asymmetric Quaternary Carbons
Using Enantioselective Aldol Reaction

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Supporting Information

S1       General Information
S2-10    Experimental Procedure
S11-46   ¹H and ¹³C NMR Data of Compounds

**General Information.** All reactions were carried out under argon atmosphere in dried glassware, unless otherwise noted. Dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4Å, benzene and toluene were distilled from diphosphorus pentoxide, and dried over MS 4 Å, and THF and diethyl ether were distilled from sodium/benzophenone immediately prior to use. All reagents were purchased from Tokyo Kasei Kogyo Co., Ltd., Kanto Chemical Co., Inc. or Aldrich Chemical Co., Inc., and used without further purification unless otherwise noted.

Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. Thin layer chromatography was performed on Wakogel B5F. ¹H and ¹³C NMR spectra were recorded with tetramethylsilane (TMS), chloroform (in chloroform-d) or benzene (in benzene-d₆) as internal standard.
3-Benzyloxy-3,4,5-trihydrofuran-2-one: To a suspension of sodium hydride (60%, 4.70 g, 118 mmol) in THF (60 mL) at 0 °C was added a solution of 3-hydroxy-3,4,5-trihydrofuran-2-one (10.0 g, 98.0 mmol) in THF (40 mL). After the reaction mixture had been stirred for 15 min at rt, benzyl bromide (15.2 mL, 128 mmol) and DMF (10 mL) was added at 0 °C. The reaction mixture was stirred for 46 h at room temperature and then saturated aqueous ammonium chloride was added. The mixture was extracted with diethyl ether, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (AcOEt / hexane = 1 / 10) to afford 3-benzyloxy-3,4,5-trihydrofuran-2-one (15.6 g, 83%) as a pale yellow oil.

Methyl 2-benzyloxy-4-((t-butyldimethylsiloxy)butanoate (7): To a solution of 3-benzyloxy-3,4,5-trihydrofuran-2-one (3.00 g, 15.6 mmol) in methanol (23 mL) at room temperature was added sodium methoxide in methanol (1.50 M, 22.0 mL, 33.0 mmol). The reaction mixture was stirred for 20 min at room temperature and then solvent was removed under the reduced pressure. The reaction mixture was neutralized with 1 M hydrogen chloride in diethyl ether at 0 °C. The residue was dissolved with water and the mixture was extracted with cooled diethyl ether, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent at 0 °C, the crude product was filtered again through a short pad of silica gel 60N (neutral, Kanto Chemical Co., Inc.) with cooled diethyl ether. Concentration of the filtrate by evaporation of the solvent at 0 °C afforded crude methyl 2-benzyloxy-4-hydroxybutanoate as a colorless oil. Above prepared methyl 2-benzyloxy-4-hydroxybutanoate was instantly used in the following reaction without further purification.

To a solution of t-butylchlorodimethylsilane (3.75 g, 25.0 mmol) and imidazole (3.40 g, 49.9 mmol) in DMF (20 mL) at 0 °C was added the above prepared methyl 2-benzyloxy-4-hydroxybutanoate in DMF (11.2 mL). After the reaction mixture had been stirred for 10 min at 0 °C, it was allowed to warm to room temperature. The reaction mixture was
stirred for 2 h at room temperature and then phosphate buffer (pH = 7) was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (AcOEt / hexane = 1 / 20) to afford ester 7 (4.20 g, 80%) as a colorless oil.

(E)-2-Benzylxy-4-(t-butyldimethylsiloxy)-1-methoxy-1-(trimethylsiloxy)butene (6): To a solution of diisopropylamine (1.31 g, 12.9 mmol) in THF (8.3 mL) at 0 °C was added n-butyllithium in hexane (1.66 M, 7.46 mL, 12.4 mmol). After the reaction mixture had been stirred for 10 min at 0 °C, a solution of ester 7 (4.00 g, 11.8 mmol) in THF (4 mL) was added at -78 °C. The reaction mixture was stirred for 30 min at -78 °C and then a solution of chlorotrimethylsilane (1.67 g, 15.4 mmol) in THF (2 mL) was added. After the reaction mixture had been stirred for 10 min at -78 °C, it was warmed to room temperature. The reaction mixture was stirred for 30 min at room temperature, and then it was concentrated by evaporation of the solvent. Petroleum ether was added to the residue, and the suspension was filtered through a short pad of Celite under argon atmosphere. The filtrate was concentrated by evaporation of the solvent to afford ketene silyl acetal 6 (E/Z = 92/8, 4.71 g, 97%) as a pale yellow oil. Above prepared ketene silyl acetal 6 was used in the following reaction without further purification.

Methyl (2S,3R,4E)-2-benzyloxy-2-(2-[t-butyldimethylsiloxy]ethyl)-3-hydroxyhex-4-enoate (5): To tin(II) trifluoromethanesulfonate (3.55 g, 8.52 mmol) at room temperature were successively added a solution of (S)-1-methyl-2-(1-naphthylaminomethyl)pyrrolidine (2.32 g, 9.65 mmol) in propionitrile (20 mL) and a solution of dibutyltin diacetate (3.19 g, 9.09 mmol) in propionitrile (20 mL). After the reaction mixture had been stirred for 5 min at room temperature, a solution of ketene silyl
acetal 6 (3.50 g, 8.52 mmol) in propionitrile (10 mL) and a solution of crotonaldehyde (398 mg, 5.68 mmol) in propionitrile (10 mL) were added at -78 °C. The reaction mixture was stirred for 41 h at -78 °C and then saturated aqueous sodium hydrogen carbonate was added. The mixture was filtered through a short pad of Celite, and the filtrate was extracted with diethyl ether. The organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (AcOEt / hexane = 1 / 10) to afford aldol 5 (1.72 g, 74%, 94% ee): $[\alpha]_D^{25} = +25.1^\circ$ (c 0.913, benzene); HPLC (CHIRALCEL OD, i-PrOH / hexane = 1 / 50, flow rate = 0.7 mL / min): $t_R = 11.5$ min (3.2%), $t_R = 14.2$ min (96.8%).

(2R,3R,4E)-2-Benzyl-2-(2-[t-butyldimethylsiloxy]ethyl)hex-4-ene-1,3-diol (12): To a solution of aldol 5 (4.47 g, 10.9 mmol) in toluene (186 mL) at -45 °C was added Red-Al® in toluene (65%, 32.8 mL, 109 mmol). The reaction mixture was stirred for 20 min at -45 °C and 1 h at 0 °C and then methanol was added. The mixture was allowed to warm to room temperature and then saturated aqueous potassium sodium tartrate was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (AcOEt / hexane = 1 / 5) to afford diol 12 (4.12 g, 99%) as a pale yellow oil: $[\alpha]_D^{24} = +32.8^\circ$ (c 1.10, benzene).

(2R,3R,4E)-2-(2-[t-Butyldimethylsiloxy]ethyl)hex-4-ene-1,2,3-triol (13): To a solution of 4,4’-di-t-butylbiphenyl (DBB) (26.6 g, 100 mmol) in THF (200 mL) at 0 °C was added lithium (694 mg, 100 mmol). The reaction mixture was stirred for 9 h at room temperature. Thus prepared a solution of lithium di-t-butylbiphenylide (LDBB) in THF (0.50 M) was instantly used in the following reaction.
To a solution of diol 12 (2.22 g, 5.84 mmol) in THF (30 mL) at -78 °C was added LDBB in THF (0.50 M, 164 mL, 81.8 mmol). The reaction mixture was stirred for 9 h at -78 °C and then saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (AcOEt / hexane = 1 / 2) to afford triol 12 (1.69 g, quant.) as a colorless oil: $[\alpha]_D^{23} = +21.6^\circ$ (c 0.70, benzene).

\[ \text{(2R,3R,4E)-2-(2-[t-Butyldimethylsiloxy]ethyl)-2,3-dihydroxyhex-4-enyl acetate (14):} \]

To a solution of triol 12 (578 mg, 1.99 mmol) in dichloromethane (34 mL) at 0 °C were added a solution of triethylamine (1.00 g, 9.88 mmol) in dichloromethane (3 mL) and a solution of acetic anhydride (305 mL, 2.98 mmol) in dichloromethane (3 mL). The reaction mixture was stirred for 20 h at 0 °C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with dichloromethane, and organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (AcOEt / hexane = 1 / 5) to afford acetate 14 (470 mg, 71%) as a colorless oil: $[\alpha]_D^{23} = +25.8^\circ$ (c 1.01, benzene).

\[ \text{(2R,3R,4E)-2-(2-[t-Butyldimethylsiloxy]ethyl)-3-(cumyldimethylsiloxy)-2-hydroxyhex-4-enyl acetate:} \]

To a suspension of silver trifluoromethanesulfonate (771 mg, 3.00 mmol) in toluene (4 mL) at 0 °C was added chlorocumyldimethylsilane (638 mg, 3.00 mmol) in toluene (3.5 mL). The reaction mixture was stirred for 1 h at room temperature and then it was allowed to stand. The top clear layer was instantly used as a solution of cumyldimethylsilyl trifluoromethanesulfonate in toluene (0.40 M) for the following reaction without further purification.

To a solution of acetate 14 (187 mg, 0.562 mmol) in pyridine (5.6 mL) at 0 °C was added a solution of cumyldimethylsilyl trifluoromethanesulfonate in toluene (0.40 M,
2.80 mL, 1.12 mmol). The reaction mixture was stirred for 2 h at 0 °C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with diethyl ether, and organic layer was washed with saturated aqueous copper(II) sulfate, water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (AcOEt / hexane = 1 / 10) to afford (2R,3R,4E)-2-(2-[t-butyldimethylsiloxy]ethyl)-3-(cumyldimethylsiloxy)-2-hydroxyhex-4-enyl acetate (265 mg, 93%) as a colorless oil: [α]D23 = +6.3° (c 1.09, benzene).

[2-(1R,2E)-1-(Cumyldimethylsiloxy)but-2-enyl](2R)-2,4-dihydroxybutyl acetate (10): To a solution of (2R,3R,4E)-2-(2-[t-butyldimethylsiloxy]ethyl)-3-(cumyldimethylsiloxy)-2-hydroxyhex-4-enyl acetate (107 mg, 0.211 mmol) in THF (4.2 mL) at -19 °C was added 1 M hydrochloric acid (2.1 mL, 2.1 mmol). The reaction mixture was stirred for 90 min at 0 °C and then saturated aqueous sodium hydrogencarbonate were added. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (AcOEt / hexane = 2 / 3) to afford diol 10 (81.8 mg, 98%) as a colorless oil: [α]D20 = +12.2° (c 2.13, benzene).

((1R,5S,7R)-7-(Cumyldimethylsiloxy)-5-methyl-4,8-dioxabicyclo[3.2.1]octyl)methyl methyl acetate: To a suspension of palladium(II) chloride (56.0 mg, 0.316 mmol) and copper(I) chloride (85.5 mg, 0.864 mmol) in DME (10 mL) at room temperature under oxygen atmosphere was added a solution of diol 10 (249 mg, 0.631 mmol) in DME (2.6 mL). The reaction mixture was stirred for 7 h at room temperature and then the mixture was diluted with diethyl ether. After filtration of the mixture through a short pad of Florisil® and evaporation of the solvent, the crude
product was purified by column chromatography (AcOEt / hexane = 2 / 3) to afford ((1R,5S,7R)-7-(cumyldimethylsiloxy)-5-methyl-4,8-dioxabicyclo[3.2.1]octyl)methyl acetate (218 mg, 88%) as a colorless oil: $[\alpha]_D^{23} = -27.4^\circ$ (c 2.66, benzene).

$\text{HO} \quad \text{Si} \quad \text{O} \quad \text{Si} = \text{PhMe}_2\text{CMe}_2\text{Si}$

$((1R,5S,7R)-7-(\text{Cumyldimethylsiloxy})-5-\text{methyl-4,8-dioxabicyclo[3.2.1]octyl})\text{methanol (15):}$ To a solution of ((1R,5S,7R)-7-(cumyldimethylsiloxy)-5-methyl-4,8-dioxabicyclo[3.2.1]octyl)methylacetate (218 mg, 0.555 mmol) in methanol (6.3 mL) at 0 °C was added potassium carbonate (95.9 mg, 0.694 mmol). The reaction mixture was stirred for 30 min at room temperature and then water was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (AcOEt / hexane = 1 / 1) to afford alcohol 15 (194 mg, quant.) as a colorless oil: $[\alpha]_D^{21} = -43.4^\circ$ (c 2.19, benzene).

$\text{HO} \quad \text{Si} \quad \text{O} \quad \text{Si} = \text{PhMe}_2\text{CMe}_2\text{Si}$

$((1S,5S,7R)-7-(\text{Cumyldimethylsiloxy})-5-\text{methyl-4,8-dioxabicyclo[3.2.1]octyl})\text{formaldehyde:}$ To a suspension of MS 4Å (97.7 mg), potassium carbonate (136.6 mg, 0.988 mmol) and NCS (19.6 mg, 0.147 mmol) in dichloromethane (0.3 mL) at 0 °C were added a solution of alcohol 15 (34.4 mg, 98.1 µmol) in dichloromethane (0.8 mL) and a solution of N-t-butylbenzenesulfenamide (2.5 mg, 13.8 µmol) in dichloromethane (0.4 mL). After the reaction mixture had been stirred for 90 min at room temperature, the mixture was filtered through a short pad of Celite and saturated aqueous ammonium chloride was added to the filtrate. The mixture was extracted with dichloromethane, and the organic layer was washed with saturated aqueous ammonium chloride, water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin
layer chromatography (AcOEt / hexane = 1 / 6) to afford ((1S,5S,7R)-7-(cumyldimethylsiloxy)-5-methyl-4,8-dioxabicyclo[3.2.1]octyl)formaldehyde (34.2 mg, quant.) as a colorless oil: $[\alpha]_D^{21} = -96.2^\circ$ (c 1.45, benzene).

$Si = PhMe_2CMe_2Si$

**1S,5R,6R)-6-(Cumyldimethylsiloxy)-1-methyl-2,8-dioxa-5-vinylbicyclo[3.2.1]octane**: To a solution of methyltriphenylphosphonium iodide (880 mg, 2.18 mmol) in THF (2.6 mL) at -78 °C was added KHMDS in toluene (0.50 M, 2.60 mL, 1.30 mmol). After the reaction mixture had been stirred for 30 min at -78 °C, a solution of ((1S,5S,7R)-7-(cumyldimethylsiloxy)-5-methyl-4,8-dioxabicyclo[3.2.1]octyl)formaldehyde (40.0 mg, 0.115 mmol) in THF (1.0 mL) was added. The reaction mixture was stirred for 30 min at room temperature and then the mixture was diluted with hexane. After filtration of the mixture through a short pad of Celite with hexane and evaporation of the solvent, the crude product was purified by thin layer chromatography (AcOEt / hexane = 1 / 4) to afford (1S,5R,6R)-6-(cumyldimethylsiloxy)-1-methyl-2,8-dioxa-5-vinylbicyclo[3.2.1]octane (40.0 mg, quant.) as a colorless oil: $[\alpha]_D^{26} = -19.9^\circ$ (c 1.58, benzene).

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**1S,5R,6R)-1-Methyl-2,8-dioxa-5-vinylbicyclo[3.2.1]octan-6-ol (16)**: To a solution of (1S,5R,6R)-6-(cumyldimethylsiloxy)-1-methyl-2,8-dioxa-5-vinylbicyclo[3.2.1]octane (13.1 mg, 37.8 µmol) in THF (0.5 mL) at 0 °C was added a solution of TBAF in THF (1.0 M, 42.0 µL, 42.0 µmol). The reaction mixture was stirred for 1 h at 0 °C and then phosphate buffer (pH = 7) was added. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (AcOEt / hexane = 1 / 1) to afford alcohol 16 (6.5 mg, quant.) as a colorless oil: $[\alpha]_D^{24} = -17.5^\circ$ (c 1.33, benzene).
(1S,5R,7S)-2-Iodo-7-methyl-4,8,11-trioxatricyclo[5.3.1.01,5]undecane (17): To a solution of alcohol 16 (3.0 mg, 17.6 µmol) in acetonitrile (0.3 mL) at 0 °C were added iodine (6.7 mg, 26.4 µmol) and sodium hydrogencarbonate (9.0 mg, 0.107 mmol). The reaction mixture was stirred for 1 h at room temperature and then saturated aqueous sodium thiosulfate was added. The mixture was extracted with diethyl ether and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (AcOEt / hexane = 1 / 1) to afford iodide 17 (4.2 mg, 80%) as a colorless oil: \([\alpha]_D^{23} = -131.4^\circ\) (c 1.09, benzene).

(1R,5R,7S)-7-Methyl-4,8,11-trioxatricyclo[5.3.1.01,5]undec-2-ene: To a solution of iodide 17 (3.1 mg, 10.5 µmol) in DMSO (1 mL) at room temperature was added potassium t-butoxide (12.0 mg, 0.107 mmol). The reaction mixture was stirred for 5 min at room temperature and then saturated aqueous ammonium chloride was added. The mixture was extracted with diethyl ether, and the organic layer was washed with water and brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (AcOEt / hexane = 1 / 1) to afford (1R,5R,7S)-7-methyl-4,8,11-trioxatricyclo[5.3.1.01,5]undec-2-ene (1.8 mg, quant.) as a colorless oil: \([\alpha]_D^{23} = -44.4^\circ\) (c 0.44, benzene).

(+) -Buergerinin F (1): To a solution of (1R,5R,7S)-7-methyl-4,8,11-trioxatricyclo[5.3.1.01,5]undec-2-ene (1.8 mg, 10.7 µmol) in ethyl acetate (1 mL) at room temperature was added 10% palladium on activated carbon (10.4 mg). The
reaction mixture was stirred for 30 min at room temperature under hydrogen atmosphere. After filtration of the mixture and evaporation of the solvent at 0 °C, the crude product was purified by thin layer chromatography (AcOEt / hexane = 1 / 1) to afford buergerinin F (1) (1.8 mg, quant.) as a colorless oil: $\lbrack \alpha \rbrack_{D}^{23} = +38.1^\circ$ (c 0.41, CHCl$_3$).