Unified Approach toward Syntheses of Juglomycins and Their Derivatives

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Supporting Information

ABSTRACT: A unified and common intermediate strategy for syntheses of juglomycins and their derivatives is reported. The use of a 1,4-dimethoxynaphthalene derivative as a key intermediate enabled easy access to various juglomycin derivatives. In this study, juglomycins A−D, juglomycin C amide, khatmiamycin and its 4-epimer, and the structure proposed for juglomycin Z were synthesized from this intermediate. The absolute configuration of natural khatmiamycin has been established to be 3R,4R through our synthesis. Unfortunately, the spectroscopic data for synthetic juglomycin Z were not consistent with the data reported for the natural one, strongly suggesting a structural misassignment.

INTRODUCTION

Juglomycins A (1) and B (2) were isolated from Streptomyces sp. 190-2 (Figure 1).1,2 They are composed of 1,4-naphthoquinone with a lactone at the side chain and are diastereomers possessing different stereochemistries at the 4′-position of each structure. The absolute configuration of 1 was determined to be 3′R,4′R with X-ray crystallography.3 The absolute configuration of 2 was subsequently determined to be 3′R,4′S.3 Juglomycin C (3) was isolated from Streptomyces sp. 815 and 3094.4 This compound, which possesses a carboxyl group at the side chain, is a reduced form of 1 and 2 at the 4′-position. Naphthoquinone-8-hydroxy-3-[(3S)-acetoxybutyric acid] [(S)-NHAB, 4], a 3-O-acetylated derivative of 3, was isolated from a disruptant of the actVI-ORFA gene for the biosynthesis of actinorhodin in Streptomyces coelicolor A3(2).5,6 Compound 4 is considered to be a key intermediate in the biosynthesis of juglomycins A−C.7 During the course of the identification of the gene clusters for these natural 1,4-naphthoquinones, juglomycin C amide (5) was isolated from S. coelicolor A3(2) M145.7 Juglomycin D (6), isolated from Streptomyces sp. 815 and 3094, is an oxidized form of 3 at the 3′-position.4 Juglomycin Z (7), isolated from the culture filtrate of Streptomyces tendae Tü 901/8c, has a methyl group at the 3′-position.8 Khatmiamycin (8) was isolated from the culture broth of Streptomyces sp. ANK313. This compound is an ester derivative of 1 or 2, but the absolute configurations at the 3- and 4-positions have not been determined.9

Natural 1,4-naphthoquinones have attractive biological activities.10 Juglomycins A and B show antibacterial activity against Gram-positive bacteria such as Bacillus subtilis, Staphylococcus aureus, and Streptococcus pneumoniae, and Gram-negative bacteria such as Escherichia coli, and Mycobacterium tuberculosis.1,2 Juglomycin C and the methyl ester of juglomycin D exhibit moderate antibacterial activity against B. subtilis and E. coli.4 Juglomycin Z shows antibacterial activity against Gram-positive and Gram-negative bacteria and yeast. The antibacterial activity of this compound against Bacillus brevis is a 10-fold potent than that of juglomycin A.8 Khatmiamycin exhibits potent motility inhibitory and lytic...
Several synthetic studies on juglomycins and their derivatives have been reported. The synthesis of (+)-1 and (±)-2 was reported by Giles and co-workers. Brimble and co-workers achieved the formal synthesis of (+)-1 and (±)-2 via oxidative fragmentation of furo[3,2-d]naphtho[2,1-d]-furans. The racemic and asymmetric synthesis of 10 envisaged that converted into the corresponding carboxylic acid (8), which was reported by Kraus and co-workers. Min and co-workers synthesized (±)-1 from 1-hydroxy-5-methoxynaphthalene. The Dotz benzannulation route to the enantioselective synthesis of (−)-1 and (+)-1 has been reported by Fernandes and co-workers. Both enantiomers of 3 and 4 were synthesized by the stereoselective aldol reaction of chiral sulfoxides with an aldehyde by our group. During the course of our synthesis on juglorubin, a reaction of a naphthol anion with a chiral aldehyde was achieved. The spectroscopic data for synthetic juglomycins A and B are identical with those of natural ones. The synthesis and determination of the absolute configuration of khatmiamycin (8) were achieved (Scheme 4). Treatment of 1 with p-toluenesulfonic acid monohydrate (TsOH·H₂O) in methanol at 50 °C for 2.5 h gave 8 in 38% yield with 37% of recovered 1. Although several conditions were investigated to improve the yield of 8, no significant improvement was achieved. Increased reaction time and reaction temperature caused decomposition of 1 and 8. Methanolation of 1 under basic conditions gave a complex mixture. We presume that the equilibrium between 1 and 8 exists. The ¹H and ¹³C NMR spectra of synthetic 8 agreed with those reported for natural 8. The specific rotation of synthetic 8 was determined to be [α]D25 −103.3 (c 0.10, MeOH). The specific rotation for natural 8 was reported to be [α]D25 −21.0 (c 0.10, MeOH). Although the specific rotation value of synthetic 8 was different from that of natural 8, the sign of synthetic 8 was identical to that of natural 8. The differences in the values should be due to the presence of impurities in natural 8. On the basis of these results, the absolute configuration of natural khatmiamycin was determined to be 3R,4R. Methanolation of 2 under the same conditions as 1 gave 4-epi-8 in 43% yield with 19% of recovered 2. The ¹H and ¹³C NMR spectra of 4-epi-8 were different from those of natural khatmiamycin. The specific rotation of 4-epi-8 was [α]D25 +81.6 (c 0.10, MeOH). The synthesis of juglomycins C (3), D (6), and juglomycin C amide (5) is shown in Scheme 5. Oxidation of the methyl group into the 3’-position of 13, followed by deprotection of the protective groups in 16.

The synthesis of juglomycins A (1) and B (2) is depicted in Scheme 2. Deprotection of the tert-butyldimethylsilyl (TBS) group in 9 with tetra-n-butylammonium fluoride (TBAF) gave the corresponding alcohol (17). Oxidation of the primary alcohol in 17 through Dess–Martin oxidation and Pinnick oxidation gave carboxylic acid 10. The desired intramolecular oxidative cyclization proceeded by treatment of 10 with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in the presence of molecular sieves 4A (MS4A) in dichloroethane to give 11 and 12 in 14 and 70% yields, respectively. The selectivity of this reaction can be rationalized by the following hypothesis: the formation of 11 would be disfavored by the pseudo-1,3-diaxial interaction between the naphthyl group and the hydrogen at the pseudo-axial position in intermediate 1 (Scheme 3). Oxidation of the 1,4-dimethoxynaphthalene moiety in 11 and 12 with ceric ammonium nitrate (CAN) followed by removal of two methoxymethyl (MOM) groups afforded 1 and 2, respectively. The spectroscopic data of synthetic 1 and 2 are identical with those of natural ones.

The synthesis and determination of the absolute configuration of khatmiamycin (8) was achieved (Scheme 4). Treatment of 1 with p-toluene sulfonic acid monohydrate (TsOH·H₂O) in methanol at 50 °C for 2.5 h gave 8 in 38% yield with 37% of recovered 1. Although several conditions were investigated to improve the yield of 8, no significant improvement was achieved. Increased reaction time and reaction temperature caused decomposition of 1 and 8. Methanolation of 1 under basic conditions gave a complex mixture. We presume that the equilibrium between 1 and 8 exists. The ¹H and ¹³C NMR spectra of synthetic 8 agreed with those reported for natural 8. The specific rotation of synthetic 8 was determined to be [α]D25 −103.3 (c 0.10, MeOH). The specific rotation for natural 8 was reported to be [α]D25 −21.0 (c 0.10, MeOH). Although the specific rotation value of synthetic 8 was different from that of natural 8, the sign of synthetic 8 was identical to that of natural 8. The differences in the values should be due to the presence of impurities in natural 8. On the basis of these results, the absolute configuration of natural khatmiamycin was determined to be 3R,4R. Methanolation of 2 under the same conditions as 1 gave 4-epi-8 in 43% yield with 19% of recovered 2. The ¹H and ¹³C NMR spectra of 4-epi-8 were different from those of natural khatmiamycin. The specific rotation of 4-epi-8 was [α]D25 +81.6 (c 0.10, MeOH). The synthesis of juglomycins C (3), D (6), and juglomycin C amide (5) is shown in Scheme 5. Oxidation of the methyl group into the 3’-position of 13, followed by deprotection of the protective groups in 16.

The synthesis of juglomycins A (1) and B (2) is depicted in Scheme 2. Deprotection of the tert-butyl dimethylsilyl (TBS) group in 9 with tetra-n-butylammonium fluoride (TBAF) gave the corresponding alcohol (17). Oxidation of the primary alcohol in 17 through Dess–Martin oxidation and Pinnick oxidation gave carboxylic acid 10. The desired intramolecular oxidative cyclization proceeded by treatment of 10 with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in the presence of molecular sieves 4A (MS4A) in dichloroethane to give 11 and 12 in 14 and 70% yields, respectively. The selectivity of this reaction can be rationalized by the following hypothesis: the formation of 11 would be disfavored by the pseudo-1,3-diaxial interaction between the naphthyl group and the hydrogen at the pseudo-axial position in intermediate 1 (Scheme 3). Oxidation of the 1,4-dimethoxynaphthalene moiety in 11 and 12 with ceric ammonium nitrate (CAN) followed by removal of two methoxymethyl (MOM) groups afforded 1 and 2, respectively. The spectroscopic data of synthetic 1 and 2 are identical with those of natural ones.

The synthesis and determination of the absolute configuration of khatmiamycin (8) were achieved (Scheme 4). Treatment of 1 with p-toluene sulfonic acid monohydrate (TsOH·H₂O) in methanol at 50 °C for 2.5 h gave 8 in 38% yield with 37% of recovered 1. Although several conditions were investigated to improve the yield of 8, no significant improvement was achieved. Increased reaction time and reaction temperature caused decomposition of 1 and 8. Methanolation of 1 under basic conditions gave a complex mixture. We presume that the equilibrium between 1 and 8 exists. The ¹H and ¹³C NMR spectra of synthetic 8 agreed with those reported for natural 8. The specific rotation of synthetic 8 was determined to be [α]D25 −103.3 (c 0.10, MeOH). The specific rotation for natural 8 was reported to be [α]D25 −21.0 (c 0.10, MeOH). Although the specific rotation value of synthetic 8 was different from that of natural 8, the sign of synthetic 8 was identical to that of natural 8. The differences in the values should be due to the presence of impurities in natural 8. On the basis of these results, the absolute configuration of natural khatmiamycin was determined to be 3R,4R. Methanolation of 2 under the same conditions as 1 gave 4-epi-8 in 43% yield with 19% of recovered 2. The ¹H and ¹³C NMR spectra of 4-epi-8 were different from those of natural khatmiamycin. The specific rotation of 4-epi-8 was [α]D25 +81.6 (c 0.10, MeOH). The synthesis of juglomycins C (3), D (6), and juglomycin C amide (5) is shown in Scheme 5.
The synthesis of the structure proposed for juglomycin Z (7) is depicted in Scheme 6. Oxidation of the naphthalene ring in 10 with CAN followed by removal of the MOM groups gave juglomycin C amide (5). Oxidation of 3 with hydrogen peroxide in a phosphate buffer (pH = 8.5) afforded juglomycin D (6). Treatment of 10 with ethyl chloroformate gave the corresponding mixed anhydride. Without further purification, the mixed anhydride was reacted with ammonia to afford amide 15. Oxidation of 15 with CAN followed by removal of the MOM groups gave juglomycin C amide (5). The spectroscopic data for synthetic 3, 5, and 6 are identical with the reported data.4,7,21

The synthesis of the structure proposed for juglomycin Z (7) is depicted in Scheme 6. Oxidation of the naphthalene ring in 10 with CAN gave the corresponding naphthoquinone derivative. Radical methylation25 of the naphthoquinone by treatment with silver nitrate and potassium persulfate in the presence of acetic acid gave 16 in 30% yield over two steps. Removal of the MOM groups with TFA gave the proposed structure for juglomycin Z (7) in 34% yield. Unfortunately, the 1H and 13C NMR spectroscopic data for synthetic 7 do not match those reported for the natural one (Table S1 in the Supporting Information). A specific rotation value of synthetic 7 \( [\alpha]_{D}^{28} = -44.3 \) (c 0.10, MeOH) is completely different from that of the natural one \( [\alpha]_{D}^{20} = +144 \) (c 0.025, MeOH). Synthetic 7 was converted into its methyl ester 19. The 1H and 13C NMR spectroscopic data for synthetic 19 are not identical with those reported for the same compound derived from natural juglomycin Z (Table S2 in the Supporting Information). A specific rotation value of synthetic 19 \( [\alpha]_{D}^{29} = -40.9 \) (c 0.32, MeOH) is different from that of the same compound derived from natural 7 \( [\alpha]_{D}^{20} = +37.3 \) (c 0.01, MeOH).

A juglomycin Z isomer 20 and its methyl ester 21 were also synthesized (Scheme 7). Both 20 and 21 have a hydroxyl group at the 8′-position instead of the 5′-position. The hydroxyl group of 3-bromoplumbagin (22)26 was protected as a MOM ether to give 23. Reduction of the 1,4-naphthoquinone in 23 with sodium hydrosulfite followed by methylation of two hydroxyl groups in the resultant hydroquinone gave 24. A Grignard reagent, which was prepared from 24, was treated with optically active epoxide 25 (>97% ee) in the presence of a catalytic amount of CuCN to give 26 in 65% yield. After protection of the hydroxyl group in 26 as a MOM ether, deprotection of the TBS group in 27 with TBAB afforded 28. Oxidation of the primary alcohol in 28 through Dess–Martin oxidation and Pinnick oxidation gave carboxylic acid 29. Oxidation of 29 with CAN and deprotection of the MOM group gave 20. Because of the low solubility of 20 in CDCl3, this compound was converted into its methyl ester 21 by treatment with trimethylsilyldiazomethane. The 1H and 13C NMR spectroscopic data for synthetic 21 do not match those reported for juglomycin Z methyl ester 19 (Table S3 in the Supporting Information).

The results obtained in Schemes 6 and 7 indicate that the structure proposed for natural juglomycin Z is incorrect. The 1H and 13C NMR signals at the 4,1′,2′,3′,4′-positions as well as the methyl group at the 3′-position in synthetic 7 are different from those reported for natural juglomycin Z (Table 1). In particular, the 1H and 13C NMR signals of the methyl group at the 3′-position in synthetic 7 (δH = 2.26 ppm; δC = 12.7 ppm) are shifted upfield in comparison with those reported for 7 (δH = 2.67 ppm; δC = 18.5 ppm). These observations indicate that natural juglomycin Z does not have a methyl group at the 3′-position. The 1H and 13C NMR signals at the 1′,2′,3′,4′-positions in natural 7 are quite different from those at the 1,2,3,4-positions reported for bhimamycin E (30)27 and 2-methyl-3-acetoxy-5-methoxy-1,4-naphthoquinone (31).28 Furthermore, the chemical shifts of the methyl group in natural 7 are quite different from those derived from the methyl group in the acetyl group in 30 and 31. These spectral comparisons suggest that natural juglomycin Z does not possess an acetyl or acetoxy group at the 3′-position. Therefore, the structure of natural juglomycin Z still remains unclear.

## CONCLUSIONS

2-Alkyl-1,4-naphthoquinones generally act as electrophiles at their electron-deficient α,β-unsaturated ketone moieties. On
the other hand, their tautomers, o-quinone methides, react as both nucleophiles and electrophiles. Natural 1,4-naphthoquinones undergo several biotransformations by both enzymatic and nonenzymatic modifications because of their high reactivities. Juglomycins have remarkable structural diversity by available modifications. To date, 11 juglomycins (A–J and Z) have been isolated and characterized. Related natural naphthoquinones such as frenolicins and nanaomycins have also been isolated (Figure 2). Thus, a divergent synthesis from a common intermediate will provide easy access to these natural products.

**EXPERIMENTAL SECTION**

**General Information.** All solvents and reagents were used without further purification unless otherwise noted. Analytical TLC was performed using Silica gel 60 F254 plates (0.25 mm, normal phase) and Silica gel 60RP-18 F254S plates (0.25 mm, reverse phase). Normal phase flash column chromatography was performed using Silica gel 60 (particle size 40–63 μm; 230–400 mesh ASTM). Reverse phase flash column
Scheme 5. Synthesis of Juglomycins C (3) and D (6) and Juglomycin C Amide (5)

1) CAN
MeCN/H2O, 0 °C

2) TFA/CH2Cl2
0 °C to rt
58% over 2 steps

3) H2O2
phosphate buffer (pH = 8.5) 66%

4) EtOCOCI, Et3N
aceton, 0 °C to rt

5) 25% NH3 aq., MeOH, 0 °C to rt
99% over 2 steps

6) CAN
MeCN/H2O, 0 °C

7) TFA/CH2Cl2
0 °C to rt
50% over 2 steps

Scheme 6. Synthesis of the Proposed Structure for Juglomycin Z (7) and Its Methyl Ester 19′

1) CAN
MeCN/H2O, 0 °C

2) AcOH
AgNO3, K2S2O8
MeCN/CH2Cl2/H2O
reflux at 90 °C
30% over two steps

3) TFA
CH2Cl2
0 °C to rt

4) TMSCH3N2
CH2Cl2/MeOH
70%

5) CAN
MeCN/H2O, 0 °C

6) TFA/CH2Cl2
0 °C to rt
34%

7) TMSCH3N2
CH2Cl2/MeOH

“Selected carbon atoms have been labeled using the IUPAC numbering system.”

chromatography was performed using an octadecyl (C18) silica gel (particle size 20–30 μm). Melting point (mp) data were uncorrected. Specific rotations were recorded on a polarimeter and recorded as [α]D values (concentration in g/100 mL). IR spectra were recorded on an IR spectrometer using NaCl (neat) or KBr pellets (solid). 1H and proton-decoupled 13C (13C{1H}) NMR spectra were recorded on an NMR spectrometer (400 and 100 MHz, respectively) using chloroform-d (CDCl3), acetone-d6, dichloromethane-d2 (CD2Cl2), and methanol-d4 (CD3OD) as solvents. Chemical shift values are expressed in δ (ppm) relative to tetramethylsilane (TMS, δ 0.00 ppm) or the solvent resonance (CDCl3, δ 7.26 ppm for 1H NMR and δ 77.0 ppm for 13C NMR; acetone-d6, δ 2.04 ppm for 1H NMR and δ 29.8 ppm for 13C NMR; CD2Cl2, δ 5.32 ppm for 1H NMR and δ 53.7 ppm for 13C NMR; CD3OD, δ 49.0 ppm for 13C NMR). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, br = broad, dd = double doublet, m = multiplet), coupling constants (J; Hz), and integration. Mass spectra were obtained by Fourier transformation–ion cyclotron resonance–mass spectrometry (FT–ICR–MS) using a spectrometer with electrospray ionization (ESI) or on a high-resolution double-focusing mass spectrometer using fast atom bombardment (FAB). Preparative reverse phase high-performance liquid chromatography (HPLC) was performed by the LC-2000 Plus system (pump: PU-2086; UV detector: UV-2075) with a COSMOSIL SC18-MS-II Packed Column (20 mm i.d. × 250 mm). Preparative gel-permeation chromatography (GPC) was carried out using a LC-2000 Plus system equipped with GPC H-2001 and GPC H-2002 (20 × 500 mm) columns using CHCl3 as the eluent.

(S)-4-[(1′,4′-dimethoxy-5′-(methoxymethoxy)naphthalen-2′-yl)-3-(methoxymethoxy)butan-1-ol (17). A 1 M solution of TBAF in tetrahydrofuran (THF, 8.60 mL, 8.60 mmol) was added to a solution of 9 (2.12 g, 4.29 mmol) in THF (200 mL) at 0 °C. The mixture was stirred at room temperature (rt) for 2 h. The reaction was quenched by the addition of water. The resultant mixture was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over Na2SO4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1, then CHCl3) as the eluent.

NaClO2 (80%, 1.33 g, 11.8 mmol) was added to a solution of 17 (1.49 g, 3.92 mmol) in CH2Cl2 (170 mL). The mixture was stirred at rt for 40 min. The mixture was diluted through a pad of Celite, and the filtrate was concentrated to give a crude aldehyde 18. NaClO3 (80%, 1.33 g, 11.8 mmol) was added to a solution of the crude aldehyde 18, 2-methyl-2-butene (4.16 mL, 39.3 mmol), and NaH2PO4 (3.06 g, 19.6 mmol) in tert-butyl alcohol/H2O (1:1, 240 mL) at 0 °C. The mixture was stirred at rt for 1 h. The reaction was quenched by the addition of saturated aqueous NH4Cl solution. The resultant mixture was diluted with CHCl3. The organic layer was separated, washed with brine, dried over Na2SO4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1 with 1% AcOH) to give 10 (1.31 g, 85% over two steps) as orange oil. DOI: 10.1021/acsomega.9b01376
Scheme 7. Synthesis of Juglomycin Z Isomer (20) and Its Methyl Ester 21

Table 1. Comparison of NMR Spectroscopic Data for Natural and Synthetic Juglomycin Z (7), Bhimamycin E (30), and 2-Methyl-3-acetoxy-5-methoxy-1,4-naphthoquinone (31)

| position | \( \delta_C \) | \( \delta_H \) | position | \( \delta_C \) | \( \delta_H \) | position | \( \delta_C \) | \( \delta_H \) | position | \( \delta_C \) | \( \delta_H \) |
|----------|---------------|---------------|----------|---------------|---------------|----------|---------------|---------------|----------|---------------|---------------|
| 1'       | 182.2         |               | 1        | 183.1         |               | 30        |               |               | 3'       | 18.5          | 2.67          |
| 2' or 3' | 148.4         |               | 2        | 153.7         |               | 31        |               |               | 3'-Me    | 12.7          | 2.26          |
| 3'       | 149.6         |               | 3        | 119.9         |               |           |               |               | 4'       | 186.6         |               |

**Selected carbon atoms have been labeled using the IUPAC numbering system.**

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resultant mixture was diluted with CHCl₃. The organic layer was separated, washed with water and brine, dried over Na₂SO₄, and concentrated to give a crude naphthoquinone. The mixture was stirred at rt for 5 h and concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) and preparative reverse phase HPLC (MeCN/H₂O = 3/2) to give 2 (31.1 mg, 52% over two steps) as yellow solids. mp 199−202 °C (decomp.), lit.2 172 °C (decomp.); [α]D°C −3.6, 1.7 Hz, 1H), 4.92 (dd, J = 4.5, 3.9 Hz, 1H), 4.77 (dd, J = 4.3, 0.9 Hz, 1H), 3.16 (dd, J = 17.4, 5.4 Hz, 1H), 2.50 (d, J = 17.4 Hz, 1H); 13C{1H} NMR (100 MHz, acetone-d₆): δ 190.8, 183.8, 175.1, 162.1, 147.1, 137.6, 134.9, 133.1, 125.0, 119.5, 115.7, 81.4, 70.2, 39.5; HRMS (ESI/FT−ICR−MS) m/z: [M + Na]+ calcd for C₁₅H₁₄O₇Na, 329.0632; found, 329.0635.

**Khatmiamycin, Methyl(3R,4R)-3,4-dihydroxy-4′-(5′-hydroxy-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)-butanoate (8).** TsOH·H₂O (13.9 mg, 73.1 μmol) was added to a solution of 1 (200.7 mg, 73.0 μmol) in distilled MeOH (9 mL) at rt. The mixture was stirred at 50 °C by heating in an oil bath for 2.5 h. The reaction was quenched by the addition of water. The resultant mixture was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (toluene/EtOAc = 3/2) and preparative GPC (CHCl₃) to give 8 (8.4 mg, 38%) as yellow solids and recovered 1 (7.4 mg, 37%), mp 152−155 °C (decomp.), lit.9 [α]D°C +103.3 (c 0.16, MeOH), IR (KBr) νmax: 3435, 2927, 1784, 1651, 1461, 1416 cm⁻¹; 1H NMR (400 MHz, acetone-d₆): δ 11.87 (s, 1H), 7.80 (dd, J = 8.4, 7.6 Hz, 1H), 7.64 (dd, J = 7.6, 1.2 Hz, 1H), 7.35 (dd, J = 8.4, 1.2 Hz, 1H), 6.82 (d, J = 1.2 Hz, 1H), 5.50 (s, 1H), 5.23 (d, J = 4.0 Hz, 1H), 4.67 (m, 1H), 3.00 (dd, J = 18.0, 6.0 Hz, 1H), 2.43 (dd, J = 18.0, 1.6 Hz, 1H), 2.46 (d, J = 7.6, 1.2 Hz, 1H), 1.25 (3H, CH₃), 13C{1H} NMR (100 MHz, acetone-d₆): δ 190.8, 184.1, 175.9, 162.1, 148.1, 137.7, 134.0, 132.5, 125.1, 119.7, 115.8, 84.8, 71.9, 36.6; HRMS (ESI/FT−ICR−MS) m/z: [M + Na]+ calcd for C₁₅H₁₄O₇Na, 329.0632; found, 329.0632.

**4-epi-Khatmiamycin, Methyl(3R,4S)-3,4-dihydroxy-4′-(5′-hydroxy-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)-butanoate (4-epi-8).** TsOH·H₂O (24.3 mg, 0.128 mmol) was added to a solution of 2 (35.0 mg, 0.128 mmol) in MeOH (12 mL) at rt. The mixture was stirred at 50 °C by heating in...
an oil bath for 2.5 h. The reaction was quenched by the addition of water. The resultant mixture was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (toluene/EtOAc = 2/1) and preparative GPC (CHCl₃) to give 4-epi-8 (16.7 mg, 43%) as yellow solids and recovered 2 (6.6 mg, 19%) mp 112 °C; [α]D²⁰ +8.16 (c 0.10, MeOH); IR (KBr) νmax 3381, 3295, 2954, 2852, 1730, 1691, 1639, 1608, 1482, 1454 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 11.90 (s, 1H), 7.64 (dd, J = 8.0, 7.6 Hz, 1H), 7.60 (dd, J = 7.6, 1.6 Hz, 1H), 7.27 (dd, J = 8.0, 1.6 Hz, 1H), 7.07 (dd, J = 1.2 Hz, 1H), 4.97 (dd, J = 3.2 Hz, 1H), 4.41 (m, 1H), 3.63 (s, 3H), 3.54 (br s, 1H), 3.25 (br s, 1H), 2.55 (dd, J = 16.8, 8.8 Hz, 1H), 2.47 (dd, J = 16.8, 3.6 Hz, 1H); 13C{1H} NMR (100 MHz, CD3OD): δ 190.4, 184.5, 173.5, 161.6, 149.9, 136.8, 135.8, 132.4, 124.8, 119.5, 115.2, 71.3, 70.0, 52.2, 35.5; HRMS (ESI/FT-ICR−MS) m/z: [M + Na]+ calcd for C₁₅H₁₄O₇Na, 392.0632; found, 392.0637.

Juglomycin C Amide, (S)-3-Hydroxy-4-(5′-hydroxy-1′,4′-dioxo-1′,4′-dihydropyridophenal-2′-yl)butanoamide (5). CAN (348 mg, 0.635 mmol) was added to a solution of 15 (100 mg, 0.254 mmol) in a 1:1 mixture of MeCN and water (12 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min. The reaction was quenched by the addition of water. The resultant mixture was diluted with CHCl₃. The organic layer was separated, washed with water and brine, dried over Na₂SO₄ and concentrated to give a crude naphthoquinone.

TFA (5 mL) was added to a solution of the crude naphthoquinone in CH₂Cl₂ (10 mL) at 0 °C. The mixture was stirred at rt for 1.5 h and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl₃/MeOH = 10/1) to give 5 (35.0 mg, 50% over two steps) as yellow solids. mp 161 °C (decomp.); [α]D²⁰ −117 (c 0.01, MeOH); IR (KBr) νmax 3338, 3167, 2972, 2926, 1670, 1641, 1614, 1454 cm⁻¹; 1H NMR (400 MHz, CD₂OD, TMS): δ 7.68 (dd, J = 8.0, 7.6 Hz, 1H), 7.62 (dd, J = 7.6, 0.8 Hz, 1H), 7.27 (dd, J = 8.0, 1.2 Hz, 1H), 6.93 (s, 1H), 4.27 (m, 2H), 2.82 (ddd, J = 13.6, 4.4, 1.2 Hz, 1H), 2.64 (dd, J = 13.6, 8.4 Hz, 1H), 2.43 (m, 2H); 13C{1H} NMR (100 MHz, CD₂OD): δ 191.7, 185.6, 176.4, 162.3, 150.6, 138.0, 137.4, 133.7, 124.8, 120.1, 116.3, 68.1, 44.2, 38.4; HRMS (ESI/FT-ICR−MS) m/z: [M + Na]+ calcd for C_{19}H_{13}NO_{11}Na, 348.0680; 298.0686; found, 298.0687.

(S)-3-(Methoxymethyl)-4-[5′-(methoxymethyl)-3′-methyl-1′,4′-dioxo-1′,4′-dihydropyridophenal-2′-yl]butanoic Acid (3). CAN (417 mg, 0.761 mmol) was added to a solution of 10 (120 mg, 0.305 mmol) in a 1:1 mixture of MeCN and water (12 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min. The reaction was quenched by the addition of water. The resultant mixture was diluted with CHCl₃. The organic layer was separated, washed with water and brine, dried over Na₂SO₄ and concentrated to give a crude naphthoquinone.

The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to give 3 (48.7 mg, 58% over two steps) as yellow solids. mp 190 °C; [α]D²⁰ +81.6 (c 0.01, MeOH); IR (neat) νmax: 3213, 3072, 2956, 2931, 1732, 1712, 1657, 1601, 1583, 1460 cm⁻¹; 1H NMR (400 MHz, CDCl₃, TMS): δ 7.73 (dd, J = 8.0, 0.8 Hz, 1H), 7.39 (dd, J = 8.0, 8.0 Hz, 1H), 7.07 (dd, J = 8.0, 7.8 Hz, 1H), 6.71 (s, 1H), 6.25 (br s, 1H), 6.00 (br s, 1H), 5.25 (s, 2H), 4.68 (d, J = 6.8 Hz, 1H), 4.60 (d, J = 6.8 Hz, 1H), 4.36 (m, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.59 (s, 3H), 3.24 (s, 3H), 3.15 (dd, J = 13.6, 6.4 Hz, 1H), 2.96 (dd, J = 13.6, 6.4 Hz, 1H), 2.46 (m, 2H); 13C{1H} NMR (100 MHz, CDCl₃): δ 173.4, 154.1, 152.8, 147.7, 131.3, 126.5, 126.2, 118.7, 116.6, 113.5, 108.7, 96.7, 95.9, 74.9, 61.6, 56.6, 56.3, 55.5, 41.1, 35.2; HRMS (ESI/FT-ICR−MS) m/z: [M + Na]+ calcd for C_{20}H_{27}NO_{7}Na, 416.1680; found, 416.1674.
A solution of Na$_2$S$_2$O$_4$ (10.7 g, 61.6 mmol) in water (200 mL) was added to a solution of crude 23 in ether (200 mL) and CHCl$_3$ (40 mL). The biphasic solution was stirred vigorously at rt for 10 min. The organic layer was collected and washed with water and brine, dried over Na$_2$SO$_4$, and concentrated. The residue was used for the next reaction without further purification.

Dimethyl sulfate (9.4 mL, 98.5 mmol) and K$_2$CO$_3$ (13.6 g, 98.5 mmol) were added to a solution of crude hydroquinone in acetone (250 mL) under an argon atmosphere. The mixture was refluxed for 3.5 h and was cooled to rt. The reaction was quenched by the addition of water. The resultant mixture was diluted with EtOAc. The organic layer was separated, washed with 28% aqueous NH$_3$ solution, water and brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was passed through silica gel column (toluene) to give 24 (3.98 g, 90% over three steps) as pale yellow solids. mp 57–59 °C; IR (KBr) $\nu_{\text{max}}$: 2999, 2954, 2930, 2841, 1614, 1580, 1571, 1491 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ 7.76 (dd, $J = 8.4, 7.7$ Hz, 1H), 7.14 (dd, $J = 7.7, 0.7$ Hz, 1H), 5.31 (3H, 3H), 3.85 (s, 3H), 3.60 (s, 3H), 2.53 (s, 3H); $^{13}$C(NH) NMR (100 MHz, CDCl$_3$): $\delta$ 152.8, 150.2, 149.3, 130.2, 128.0, 126.6, 120.3, 119.6, 116.5, 112.4, 96.3, 61.47, 61.45, 56.5, 16.9; HRMS (ESI−doubly focusing MS) $m/z$: [M + Na]$^+$ for C$_4$_H$_{11}$BrO$_5$Na$_2$ 430.0310; found, 430.3010.

**Proposed Structure for Juglomycin Z, (S)-3-Hydroxy-4-(5′-hydroxy-3′-methyl-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)butanonic Acid (7).** TFA (2 mL) was added to a solution of 16 (11.5 mg, 0.030 mmol) in CH$_2$Cl$_2$ (6 mL) at 0 °C. The mixture was stirred at rt for 1 h and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CHCl$_3$/MeOH = 20/1 with 1% AcOH) to give 7 (3.0 mg, 34%) as yellow solids. mp 88–90 °C; lit.$^8 >300 °C$; $\delta_{\text{D}}$ = 44.3 (c 0.10, MeOH), lit.$^8$ $\delta_{\text{D}}$ = 30.0 (c 0.10, MeOH); IR (KBr) $\nu_{\text{max}}$: 3420, 3184, 2925, 1728, 1654, 1633, 1606, 1454 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$/CD$_2$OD = 9:1, TMS): $\delta$ 7.61 (m, 1H), 7.60 (m, 1H), 7.24 (dd, $J = 7.0, 2.6$ Hz, 1H), 4.23 (m, 1H), 2.89 (d, $J = 6.6$ Hz, 2H), 2.57 (m, 2H), 2.26 (s, 3H); $^{13}$C{1H} NMR (100 MHz, CDCl$_3$): $\delta$ 190.1, 184.8, 176.2, 161.2, 145.9, 144.2, 136.1, 131.9, 124.1, 112.9, 114.9, 67.5, 41.2, 34.0, 12.8 HRMS (ESI−FT−ICR−MS) $m/z$: [M − H]$^+$ for C$_4$_H$_{11}$O$_5$Na$_2$ 289.0707; found, 289.0720.

**Methyl (S)-3-Hydroxy-4-(5′-hydroxy-3′-methyl-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)butanoate (19).** A 0.6 M solution of trimethylsilyldiazomethane in hexane (1.2 mL, 0.72 mmol) was added to a solution of 7 (3.0 mg, 10.3 pmol) in a 1:2 mixture of CH$_2$Cl$_2$ and MeOH (3 mL). The mixture was stirred at rt for 35 min. The reaction was quenched by the addition of AcOH (2 mL). The resultant mixture was diluted with CHCl$_3$ and water. The organic layer was separated, washed with water and brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to give 19 (2.2 mg, 70%) as orange solids. mp 52–53 °C; lit.$^8$ 85 °C; $\delta_{\text{D}}$ = 40.9 (c 0.32, MeOH), lit.$^8$ $\delta_{\text{D}}$ = 37.3 (c 0.01, MeOH); IR (KBr) $\nu_{\text{max}}$: 3525, 3020, 2953, 2854, 1731, 1635, 1610, 1519, 1458 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta$ 12.14 (s, 1H), 7.61 (dd, $J = 7.4, 1.8$ Hz, 1H), 7.57 (dd, $J = 7.8, 7.4$ Hz, 1H), 7.23 (dd, $J = 7.8, 1.8$ Hz, 1H), 4.24 (m, 1H), 3.72 (s, 3H), 3.16 (br s, 1H), 2.87 (m, 2H), 2.65 (dd, $J = 16.6, 4.2$ Hz, 1H), 2.15 (dd, $J = 16.6, 7.8$ Hz, 1H), 2.25 (s, 3H); $^{13}$C{1H} NMR (100 MHz, CDCl$_3$): $\delta$ 190.2, 184.6, 172.8, 161.2, 145.7, 144.4, 136.0, 132.0, 124.0, 119.1, 115.0, 67.7, 51.9, 41.3, 34.0, 12.7; HRMS (ESI−FT−ICR−MS) $m/z$: [M + Na]$^+$ for C$_4$_H$_{11}$O$_5$Na$_2$ 327.0839; found, 327.0842.

**3-Bromo-1,4-dimethoxy-5-(methoxymethoxy)-2-methylphenanthrene (24).** Na$_6$ (60% dispersion in mineral oil, 593.3 mg, 14.88 mmol) was added to a solution of 22$^{16}$ (3.29 g, 12.3 mmol), tetra-n-butylammonium iodide (TBAI, 226 mg, 0.61 mmol), and chlorodimethyl ether (MOMCl, 1.6 mL, 20.9 mmol) in THF (200 mL) at 0 °C. The mixture was stirred under an argon atmosphere at 0 °C for 15 min and at rt for 15 min. The reaction was quenched by the addition of water. The resultant mixture was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over Na$_2$SO$_4$, and concentrated. The residue was washed with hexane to remove mineral oil to afford crude 23. This compound was used for the next reaction.
for 18 h under an argon atmosphere. The mixture was cooled to rt. The reaction was quenched by the addition of water. The resultant mixture was diluted with CHCl₃. The organic layer was separated, washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give 27 (588 mg, 84%) as colorless oil. [α]D₂⁰ +1.4 (c 1.00, CHCl₃); IR (neat) νmax: 3164, 3079, 2987, 2949, 2834, 1734, 1710, 1593, 1572, 1442 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.76 (dd, J = 8.4, 0.9 Hz, 1H), 7.35 (dd, J = 8.4, 7.7 Hz, 1H), 7.12 (dd, J = 7.6, 0.9 Hz, 1H), 5.31 (dd, J = 6.8 Hz, 1H), 5.29 (dd, J = 6.8 Hz, 1H), 4.56 (dd, J = 6.8 Hz, 1H), 4.44 (dd, J = 6.8 Hz, 1H), 4.09 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.73 (m, 2H), 3.59 (s, 3H), 3.13 (dd, J = 13.4, 7.6 Hz, 1H), 3.11 (s, 3H), 3.01 (dd, J = 13.4, 6.4 Hz, 1H), 2.46 (s, 3H), 1.82 (m, 1H), 1.72 (m, 1H), 0.84 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 153.0, 150.5, 149.9, 130.2, 129.3, 127.6, 125.6, 119.8, 116.6, 112.2, 96.6, 95.9, 75.0, 61.9, 61.0, 59.7, 56.4, 55.2, 38.2, 33.1, 25.8 (3C), 18.1, 13.1, −5.37, −5.42; HRMS (FAB/double-focusing MS) m/z: [M]+ calc for C₂⁵H₄₁O₂Si, 508.2856; found, 508.2856.

(5)-4-(1,4-Dimethoxy-8-(methoxymethoxy)-3-methyl-naphthalen-2-yl)-3-(methoxymethoxy)butan-1-ol (28). A 1 M solution of TBAF in THF (1.7 mL, 1.70 mmol) was added to a solution of 27 (588 mg, 1.16 mmol) in THF (10 mL) at rt. The mixture was stirred at rt for 16 h. The reaction was quenched by the addition of water. The resultant mixture was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give 28 (405 mg, 89%) as colorless oil. [α]D₂⁰ +16.5 (c 1.00, CHCl₃); IR (neat) νmax: 3472, 2949, 2892, 2833, 1616, 1593, 1572, 1496 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.76 (d, J = 8.4 Hz, 1H), 7.36 (dd, J = 8.4, 7.6 Hz, 1H), 7.12 (dd, J = 7.6 Hz, 1H), 5.31 (s, 2H), 4.52 (d, J = 6.8 Hz, 1H), 4.42 (d, J = 6.8 Hz, 1H), 4.13 (m, 1H), 3.82 (m, 1H, overlapped), 3.82 (s, 3H), 3.73 (m, 2H), 3.57 (s, 3H), 3.13 (dd, J = 13.3, 7.3 Hz, 1H), 3.00 (dd, J = 13.3, 6.4 Hz, 1H), 2.62 (br s, 1H), 2.45 (s, 3H), 1.83 (m, 2H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ 153.0, 150.5, 149.9, 130.4, 129.4, 126.4, 125.6, 119.8, 116.6, 112.2, 96.6, 95.9, 75.0, 61.9, 61.0, 59.7, 56.4, 55.2, 38.2, 33.1, 25.8 (3C), 18.1, 13.1, −5.37, −5.42; HRMS (FAB/double-focusing MS) m/z: [M]+ calc for C₂₅H₄₁O₂Si, 508.2856. The mixture was stirred at rt for 16 h and concentrated under reduced pressure. The residue was purified by octadecyl silica gel column chromatography (MeOH/H₂O = 3:2) to give 29 (72.9 mg, 75% over two steps) as brownish yellow solids. mp 143−148 °C; [α]D₂⁰ −58.0 (c 0.15, MeOH); IR (KBr) νmax: 3427, 3184, 2925, 1728, 1654, 1633, 1606, 1454 cm⁻¹; ¹H NMR (400 MHz, acetone-d₆): δ 12.15 (s, 1H), 7.70 (dd, J = 8.4, 7.6 Hz, 1H), 7.56 (dd, J = 7.6, 1.0 Hz, 1H), 7.25 (dd, J = 8.4, 1.0 Hz, 1H), 4.34 (m, 1H), 2.93 (dd, J = 12.8, 5.2 Hz, 1H), 2.89 (dd, J = 12.8, 8.4 Hz, 1H), 2.54 (dd, J = 15.6, 6.4 Hz, 1H), 2.23 (s, 3H); ¹³C{¹H} NMR (100 MHz, acetone-d₆): δ 191.3, 184.8, 173.0, 161.9, 147.7, 144.3, 137.0, 133.2, 124.2, 119.2, 115.8, 68.3, 42.6, 34.9, 13.6; HRMS (FAB/double-focusing MS) m/z: [M]+ calc for C₂₅H₄₁O₂Si, 590.2790; found, 590.2791.

Methyl (5)-3-hydroxy-4-(8-hydroxy-3-methyl-1,4-dioxo-1,4-dihyronaphthalen-2-yl)butanoate (21). A 2.0 M solution of trimethylsilyldiazomethane in Et₂O (120 µL, 240 µmol) was added to a solution of 20 (17.7 mg, 61.0 µmol) in a 1:1 mixture of CH₂Cl₂ and MeOH (4 mL). The mixture was stirred at rt for 25 min. The reaction was quenched by the addition of AcOH (100 µL). The resultant mixture was diluted with MeOH and concentrated. The residue was purified by silica gel column chromatography (hexane/acetonitrile = 3:2) to give 21 (17.5 mg, 94%) as yellow solids. mp 86 °C; [α]D₂⁰ −89.4 (c 0.15, MeOH); IR (KBr) νmax: 3550, 3486, 3028, 3002, 2989, 2978, 2970, 2927, 2873, 1741, 1724, 1657, 1633, 1610, 1570, 1458 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, TMS): δ 12.11 (s, 1H), 7.72 (dd, J = 7.5, 1.6 Hz, 1H), 7.58 (dd, J = 8.0, 7.5 Hz, 1H), 7.22 (dd, J = 8.0, 1.6 Hz, 1H), 4.27 (m, 1H), 3.73 (s, 3H), 3.16 (br s, 1H), 2.89 (m, 2H), 2.66 (dd, J = 16.6, 4.0 Hz, 1H), 2.59 (dd, J = 16.6, 8.0 Hz, 1H), 2.25 (s, 3H); ¹³C{¹H} NMR (100 MHz, CDCl₃): δ...
Comparison of NMR spectroscopic data between natural and synthetic juglomycin Z (7), comparison of NMR spectroscopic data between compound 19 derived from natural and synthetic 7, comparison of NMR spectroscopic data between compound 19 derived from natural 7 and compound 21, and copies of 1H and 13C NMR spectra for all synthetic compounds (PDF).

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**Notes**

The authors declare no competing financial interest.

**SUPPORTING INFORMATION**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b01376.
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