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Unified Approach toward Syntheses of Juglomycins and Their Derivatives

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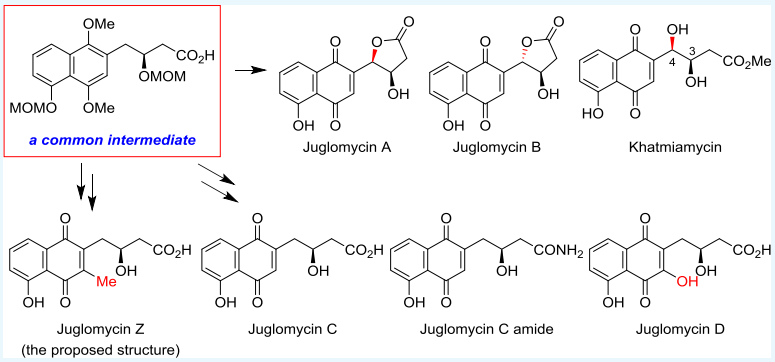
Supporting Information



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 3*R*,4*R* 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-[(3*S*)-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

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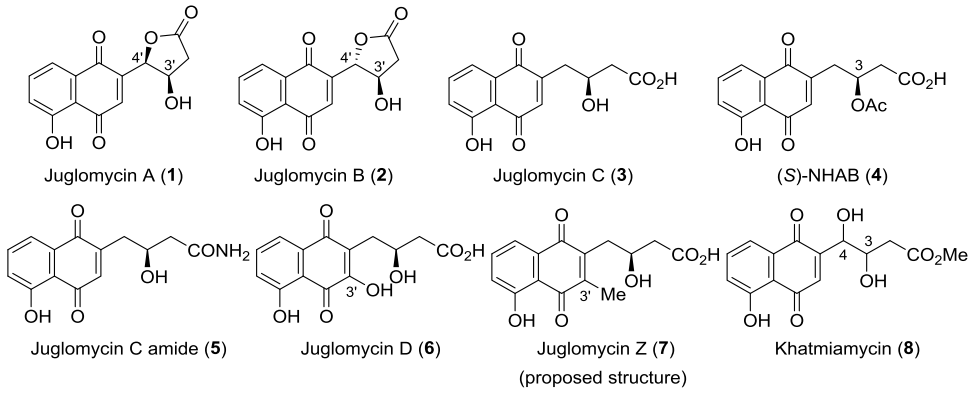

Figure 1. Structures for juglomycins and their derivatives. Selected carbon atoms have been labeled using the IUPAC numbering system.

activities against zoospores as well as potent antibacterial activity against *S. aureus* and *Streptomyces viridochromogenes*.[9]

Several synthetic studies on juglomycins and their derivatives have been reported.[10] The synthesis of (±)-**1** and (±)-**2** was reported by Giles and co-workers.[11] Brimble and co-workers achieved the formal synthesis of (±)-**1** and (±)-**2** via oxidative fragmentation of furo[3,2-*b*]naphtho[2,1-*d*]-furans.[12,13] The racemic and asymmetric synthesis of **1** using a reaction of a naphthol anion with a chiral aldehyde was reported by Kraus and co-workers.[14,15] Min and co-workers synthesized (±)-**1** from 1-hydroxy-5-methoxynaphthalene.[16] The Dötz benzannulation route to the enantioselective synthesis of (−)- and (+)-**1** has been reported by Fernandes and co-workers.[17−19] Both enantiomers of **3** and **4** were synthesized by the stereoselective aldol reaction of chiral sulfoxides with an aldehyde by our group.[20] During the course of our synthesis on juglorubin, **6** was obtained as a byproduct by treatment of **3** with a phosphate buffer (pH 8.5) under aerobic conditions.[21]

In this paper, a unified approach toward the syntheses of juglomycins A−D, juglomycin C amide, khatmiamycin, and the structure proposed for juglomycin Z is reported. Through the synthesis of khatmiamycin and its 4-epimer, determination of the relative and absolute configuration of natural khatmiamycin has been achieved. The spectroscopic data for synthetic juglomycin Z and its methyl ester do not match those reported, suggesting that the structure assigned to juglomycin Z is incorrect.

RESULTS AND DISCUSSION

Our synthetic approach toward the syntheses of juglomycins A−D, Z, juglomycin C amide, and khatmiamycin is outlined in Scheme 1. The optically active compound **9**[22] can be easily converted into the corresponding carboxylic acid (**10**). We envisioned that **10** would serve as a potential common intermediate to access to the member of juglomycins and their related derivatives. Juglomycins A (**1**) and B (**2**) will be synthesized by formation of a lactone through benzylic oxidation of **10**, followed by oxidation of naphthalene and removal of protective groups. Khatmiamycin (**8**) can be prepared by methanolysis of **1** or **2**. Oxidation of the naphthalene in **10** and removal of the protective groups in **13** will afford juglomycin C (**3**). Epoxidation of **3** and isomerization of the corresponding epoxide **14** will give juglomycin D (**6**). Amidation of **10**, oxidation, and removal of the protective groups in **15** will afford juglomycin C amide (**5**). Juglomycin Z (**7**) will be synthesized by introduction 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**[22] with tetra-*n*-butylammonium fluoride (TBAF) gave the corresponding alcohol **17**. Oxidation of the primary alcohol in **17** through Dess−Martin oxidation[23] and Pinnick oxidation[24] 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 **I** (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.[3]

The synthesis and determination of the absolute configuration of khatmiamycin (**8**) were achieved (Scheme 4). Treatment of **1** with *p*-toluenesulfonic acid monohydrate ($TsOH·H_2O$) 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**. Methanolysis of **1** under basic conditions gave a complex mixture. We presume that the equilibrium between **1** and **8** exists. The ^1H and ^{13}C NMR spectra of synthetic **8** agreed with those reported for natural **8**.[9] The specific rotation of synthetic **8** was determined to be $[\alpha]_D^{25}$ −103.3 (*c* 0.10, MeOH). The specific rotation for natural **8** was reported to be $[\alpha]_D^{25}$ −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 3*R*,4*R*. Methanolysis of **2** under the same conditions as **1** gave 4-*epi*-**8** in 43% yield with 19% of recovered **2**. The ^1H and ^{13}C NMR spectra of 4-*epi*-**8** were different from those of natural khatmiamycin. The specific rotation of 4-*epi*-**8** was $[\alpha]_D^{23}$ +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

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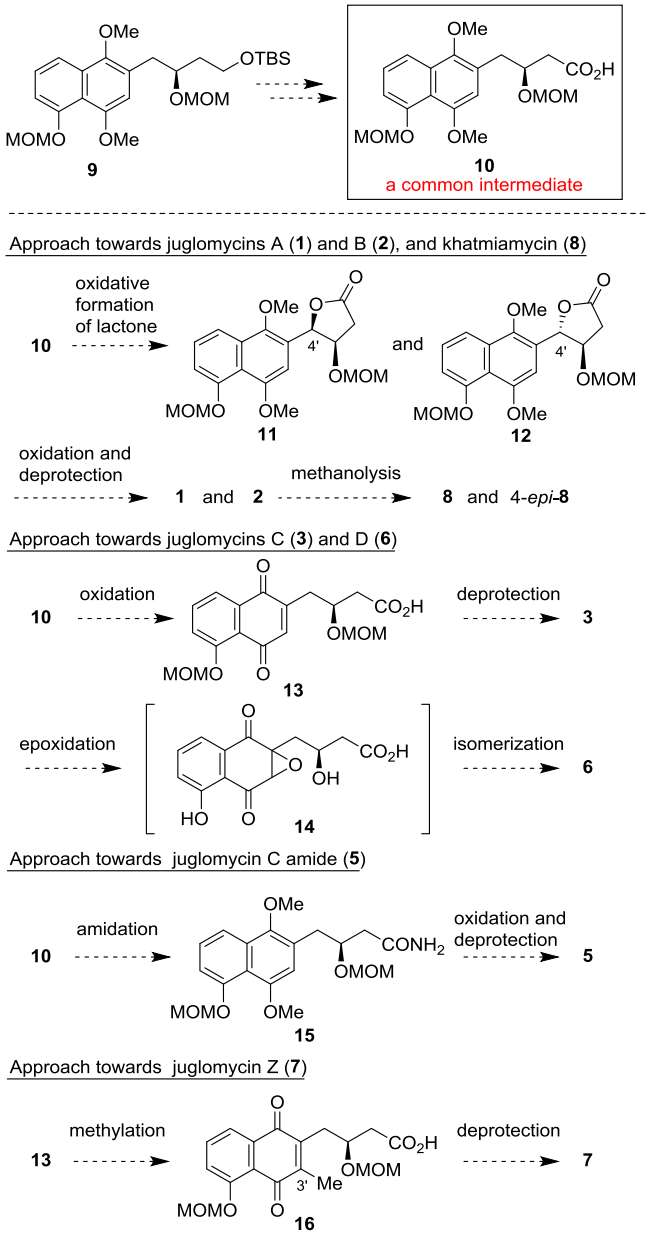
Scheme 1. Synthetic Approach toward Juglomycins and Their Derivatives[a]



[a]Selected carbon atoms have been labeled using the IUPAC numbering system.

naphthalene ring in **10** with CAN followed by removal of the MOM groups gave juglomycin C (**3**). 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 methylation[25] 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 ^{1}H and ^{13}C NMR spectroscopic data for synthetic **7** do not match those reported for the natural one (Table S1 in the Supporting Information).[8] The 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 ^{1}H and ^{13}C 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).[8] The specific rotation value of synthetic **19** {$[\alpha]_D^{26}$ −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**[22] (>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 TBAF 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 $CDCl_3$, this compound was converted into its methyl ester **21** by treatment with trimethylsilyldiazomethane. The ^{1}H and ^{13}C NMR spectroscopic data for synthetic **21** do not match those reported for juglomycin Z methyl ester **19** (Table S3 in the Supporting Information).[8]

The results obtained in Schemes 6 and 7 indicate that the structure proposed for natural juglomycin Z is incorrect. The ^{1}H and ^{13}C NMR signals at the 4,1′,2′,3′,4′-positions as well as the methyl group at the 3′-position in synthetic **7** are quite different from those reported for natural juglomycin Z (Table 1). In particular, the ^{1}H and ^{13}C NMR signals of the methyl group at the 3′-position in synthetic **7** (δ_H = 2.26 ppm; δ_C = 12.7 ppm) are shifted upfield in comparison with those reported for **7** (δ_H = 2.67 ppm; δ_C = 18.5 ppm). These observations indicate that natural juglomycin Z does not have a methyl group at the 3′-positon. The ^{1}H and ^{13}C 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 for 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

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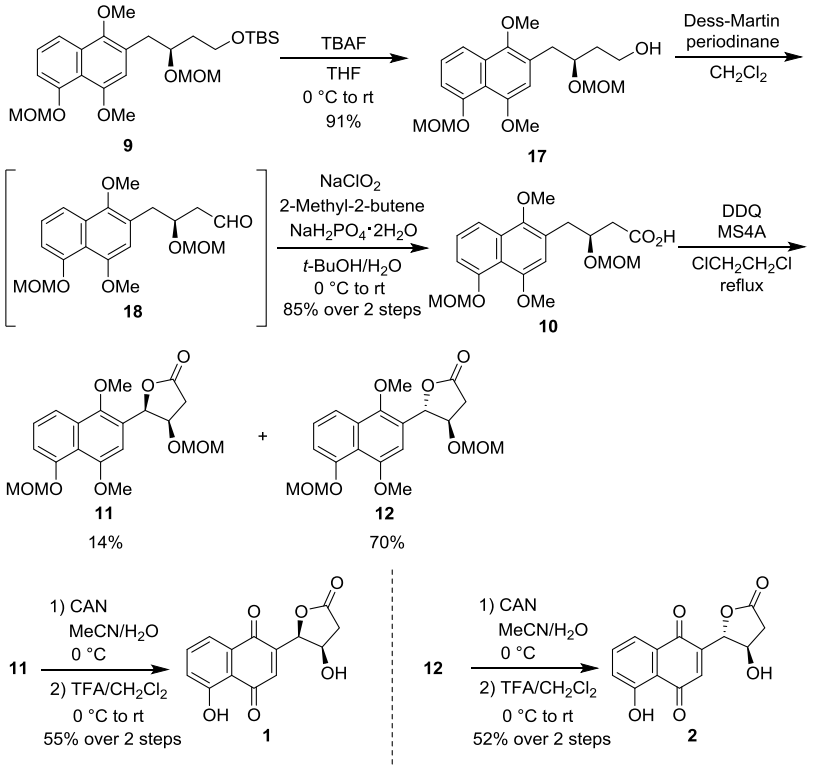
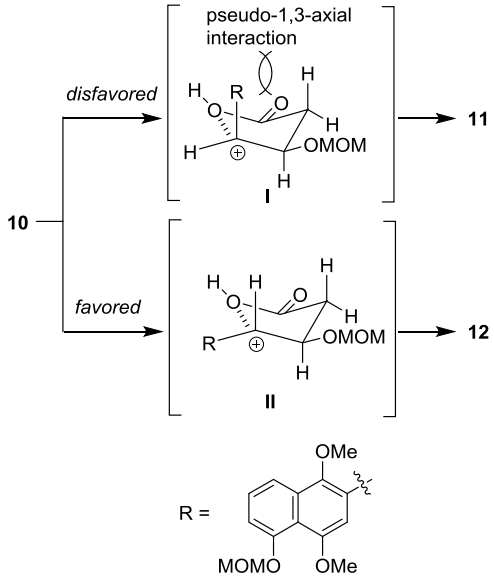
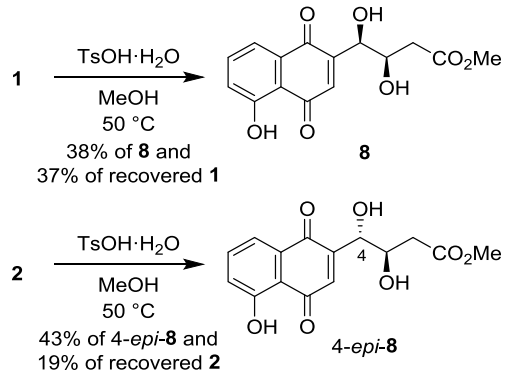
Scheme 2. Synthesis of Juglomycins A (1) and B (2)



Scheme 3. Proposed Mechanism for the Stereoselectivity of the Intramolecular Oxidative Cyclization of 10



Scheme 4. Synthesis of Khatmiamycin (8) and Its 4-Epimer (4-*epi*-8)



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.[7] To date, 11 juglomycins (A–J and Z) have been isolated and characterized.[1,2,4,8,29] Related natural naphthoquinones such as frenolicins[30−32] and nanaomycins[33−36] have also been isolated (Figure 2).[37] Thus, a divergent synthesis from a common intermediate will provide easy access to these natural products.[38]

In this study, we demonstrated that compound **10** is a common intermediate for the divergent synthesis of juglomycins and their derivatives. The most significant feature of the approach described in this paper is that these natural products can be synthesized through only two to four steps from the common intermediate **10**. Further synthetic studies toward related natural naphthoquinones and evaluation of the biological activities of synthetic compounds are currently ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. All solvents and reagents were used without further purification unless otherwise noted. Analytical TLC was performed using Silica gel 60 F_{254} plates (0.25 mm, normal phase) and Silica gel 60RP-18 F_{254S} 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

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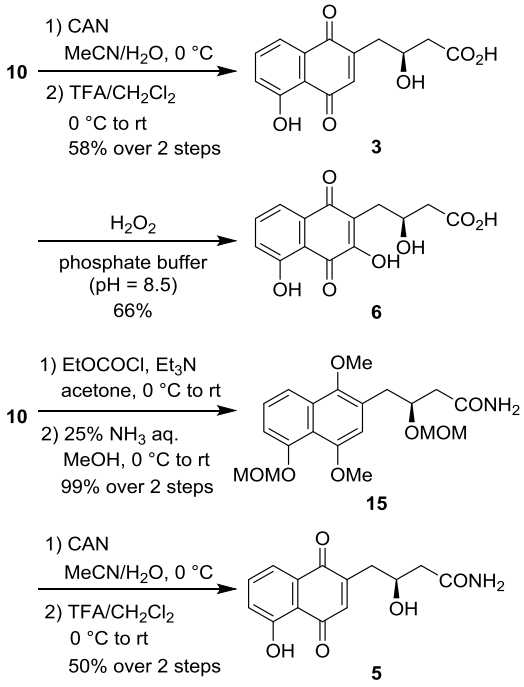
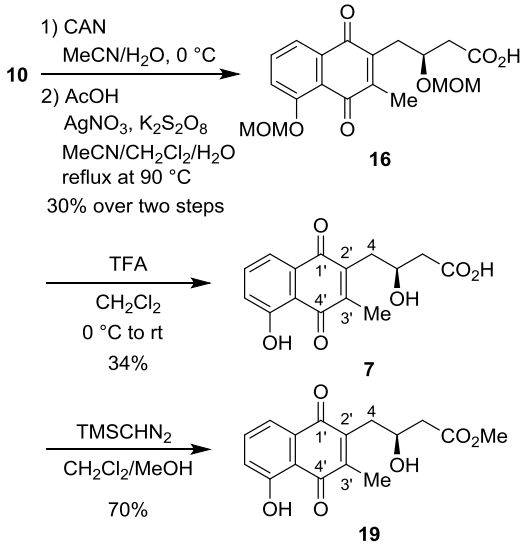
Scheme 5. Synthesis of Juglomycins C (3) and D (6) and Juglomycin C Amide (5)



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



[a]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 $[\alpha]_D$ values (concentration in g/100 mL). IR spectra were recorded on an IR spectrometer using NaCl (neat) or KBr pellets (solid). ^{1}H and proton-decoupled ^{13}C (^{13}C{^{1}H}) NMR spectra were recorded on an NMR spectrometer (400 and 100 MHz, respectively) using chloroform-*d* ($CDCl_3$), acetone-d_6, dichloromethane-d_2 (CD_2Cl_2), and methanol-d_4 (CD_3OD) as solvents. Chemical shift values are expressed in δ (ppm) relative to tetramethylsilane (TMS, δ 0.00 ppm) or the solvent resonance ($CDCl_3$, δ 7.26 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR; acetone-d_6, δ 2.04 ppm for ^{1}H NMR and δ 29.8 ppm for ^{13}C NMR; CD_2Cl_2, δ 5.32 ppm for ^{1}H NMR and δ 53.7 ppm for ^{13}C NMR; CD_3OD, δ 49.0 ppm for ^{13}C 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 5C18-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 $CHCl_3$ 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**[22] (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 Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1, then $CHCl_3$/MeOH = 95/5) to give **17** (1.49 g, 91%) as yellow oil. $[\alpha]_D^{21}$ +14.8 (*c* 1.00, EtOAc); IR (neat) ν_{max}: 3473, 2937, 2898, 2842, 1619, 1598, 1583, 1508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.74 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.40 (dd, *J* = 8.4, 8.0 Hz, 1H), 7.07 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.68 (s, 1H), 5.25 (s, 2H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.53 (d, *J* = 6.8 Hz, 1H), 4.17 (m, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.86 (overlapped, 1H), 3.75 (m, 1H), 3.60 (s, 3H), 3.31 (s, 3H), 3.10 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.92 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.49 (br s, 1H), 1.86 (m, 1H), 1.74 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 154.2, 152.8, 147.8, 131.4, 126.8, 126.6, 118.7, 116.7, 113.4, 108.9, 96.8, 96.4, 76.9, 61.7, 59.7, 56.8, 56.4, 55.8, 37.0, 35.9; HRMS (ESI/FT−ICR−MS) *m*/*z*: $[M + Na]^+$ calcd for $C_{20}H_{28}O_7Na$, 403.1727; found, 403.1721.

(*S*)-4-[1′,4′-Dimethoxy-5′-(methoxymethoxy)-naphthalen-2′-yl]-3-(methoxymethoxy)butanoic Acid (10). Dess−Martin periodinane (3.32 g, 7.83 mmol) was added to a solution of **17** (1.49 g, 3.92 mmol) in CH_2Cl_2 (170 mL). The mixture was stirred at rt for 40 min. The mixture was filtrated through a pad of Celite, and the filtrate was concentrated to give a crude aldehyde **18**.

$NaClO_2$ (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 $NaH_2PO_4{\cdot}2H_2O$ (3.06 g, 19.6 mmol) in *tert*-butyl alcohol/H_2O (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 NH_4Cl solution. The resultant mixture was diluted with $CHCl_3$. The organic layer was separated, washed with brine, dried over Na_2SO_4, 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.

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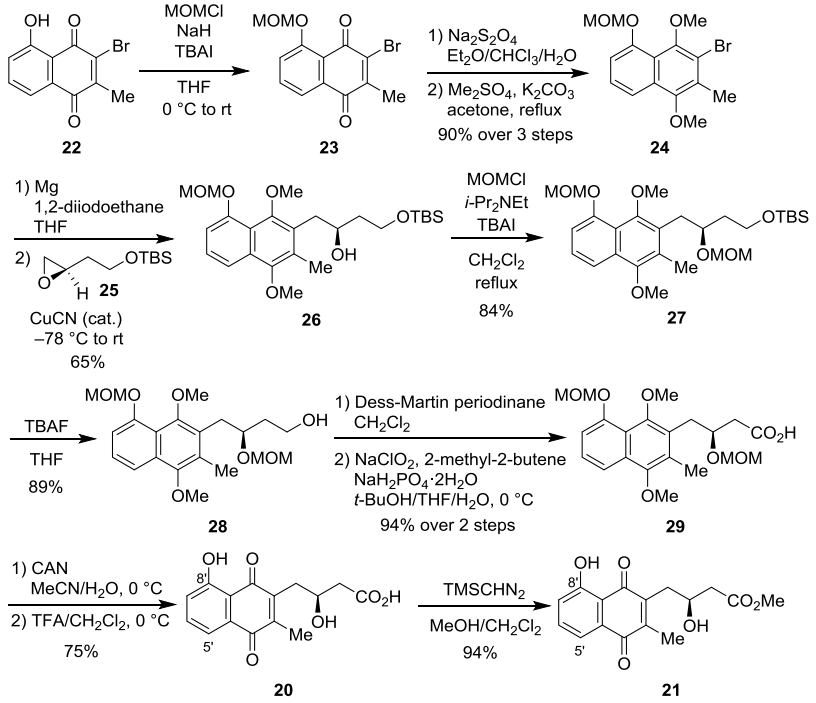
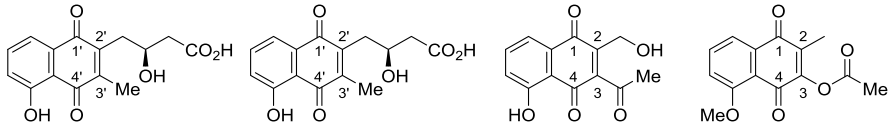
Scheme 7. Synthesis of Juglomycin Z Isomer (20) and Its Methyl Ester 21[a]



[a]Selected carbon atoms have been labeled using the IUPAC numbering system.

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)



natural **7** synthetic **7** bhimamycin E (**30**) **31**

	natural 7[b]		synthetic 7[c]			30[d]		31[e]	
position[a]	δ_C	δ_H	δ_C	δ_H	position[a]	δ_C	δ_H	δ_C	δ_H
1′	182.2		184.8		1	183.1		185.0	
2′ or 3′	148.4		145.9		2	153.7		133.5	
3′ or 2′	149.6		144.2		3	119.9		151.9	
3′-Me	18.5	2.67	12.7	2.26	COMe	30.1	2.34	20.4	2.06
4′	186.6		190.6		4	184.3		176.6	

[a]Carbon atoms have been labeled using the IUPAC numbering system. [b]^{1}H NMR (200 MHz, $CDCl_3/CD_3OD$) and ^{13}C NMR (50.3 MHz, $CDCl_3$).[8] [c]^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$ = 9/1, TMS) and ^{13}C NMR (100 MHz, $CDCl_3$). [d]^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.5 MHz, $CDCl_3$).[27] [e]^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$, TMS).[28]

$[\alpha]_D^{22}$ −1.6 (*c* 1.00, EtOAc); IR (neat) ν_{max}: 3163, 3070, 3010, 2995, 2937, 2844, 1734, 1712, 1660, 1620, 1601, 1583, 1460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.74 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.39 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.07 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.70 (s, 1H), 5.25 (s, 2H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.39 (m, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.59 (s, 3H), 3.25 (s, 3H), 3.16, (dd, *J* = 13.6, 6.8 Hz, 1H), 2.98, (dd, *J* = 13.6, 6.8 Hz, 1H), 2.63, (dd, *J* = 16.0, 7.2 Hz, 1H), 2.56, (dd, *J* = 16.0, 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 176.9, 154.1, 152.8, 147.9, 131.4, 126.6, 126.1, 118.7, 116.8, 113.5, 108.7, 96.8, 96.1, 74.6, 61.7, 56.7, 56.4, 55.5, 39.7, 35.5; HRMS (ESI/FT−ICR−MS) *m*/*z*: [M + Na]$^+$ calcd for $C_{20}H_{26}O_8Na$, 417.1512; found, 417.1512.

(4*R*,5*R*)-5-[1′,4′-Dimethoxy-5′-(methoxymethoxy)-naphthalen-2′-yl]-4-(methoxymethoxy)dihydrofuran-2(3*H*)-one (11) and (4*R*,5*S*)-5-[1′,4′-Dimethoxy-5′-(methoxymethoxy)naphthalen-2′-yl]-4-(methoxymethoxy)dihydrofuran-2(3*H*)-one (12). DDQ (1.38 g, 6.08 mmol) was added to a suspension of **10** (800 mg, 2.03 mmol) and MS4A (1 g) in $ClCH_2CH_2Cl$ (150 mL) at rt. The mixture was refluxed by heating in an oil bath under a nitrogen atmosphere for 4.5 h. The mixture was cooled to rt and filtrated through a pad of Celite. The filtrate was diluted with $CHCl_3$ and water. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to give **11** (107.8 mg, 14%) as orange oil and **12** (555.4 mg, 70%) as orange needles. **11**: $[\alpha]_D^{24}$ −17.2 (*c* 0.50, $CHCl_3$); IR (neat) ν_{max}: 3570, 3014, 2937, 2898, 1784, 1601, 1585, 1460 cm^{-1}; ^{1}H NMR (400

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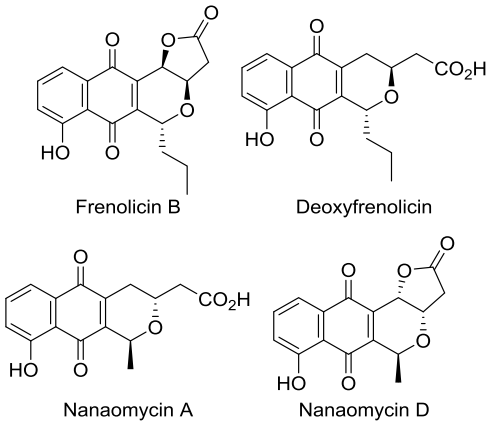

Figure 2. Structures for frenolicin B, deoxyfrenolicin, and nanaomycins A and D.

MHz, $CDCl_3$, TMS): δ 7.73 (dd, J = 8.0, 1.2 Hz, 1H), 7.43 (dd, J = 8.0, 8.0 Hz, 1H), 7.13 (dd, J = 8.0, 1.2 Hz, 1H), 6.93 (s, 1H), 5.96 (d, J = 4.0 Hz, 1H), 5.28 (d, J = 6.4 Hz, 1H), 5.26 (d, J = 6.4 Hz, 1H), 4.78 (dd, J = 5.2, 4.0 Hz, 1H), 4.26 (d, J = 6.8 Hz, 1H), 4.17 (d, J = 6.8 Hz, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.61 (s, 3H), 2.98 (dd, J = 17.6, 5.2 Hz, 1H), 2.97 (s, 3H), 2.79 (d, J = 17.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.3, 154.4, 153.1, 146.3, 130.6, 126.8, 123.1, 119.5, 116.5, 114.2, 104.9, 96.8, 95.3, 80.6, 73.9, 62.1, 56.7, 56.4, 55.4, 37.6; HRMS (ESI/FT−ICR−MS) m/z: $[M + Na]^+$ calcd for $C_{20}H_{24}O_8Na$, 415.1363; found, 415.1362. **12**: mp 57−59 °C; $[\alpha]_D^{23}$ −11.3 (c 1.00, $CHCl_3$); IR (neat) ν_{max}: 3564, 2997, 2943, 2898, 2846, 2827, 1790, 1599, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.75 (dd, J = 8.4, 1.0 Hz, 1H), 7.45 (dd, J = 8.4, 7.7 Hz, 1H), 7.14 (dd, J = 7.7, 1.1 Hz, 1H), 6.62 (s, 1H), 5.86 (d, J = 2.8 Hz, 1H), 5.26 (s, 2H), 4.76 (m, 2H), 4.51 (m, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.60 (s, 3H), 3.37 (s, 3H), 2.91 (dd, J = 17.9, 6.6 Hz, 1H), 2.66 (dd, J = 17.9, 3.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.5, 154.4, 153.8, 146.9, 131.3, 127.2, 125.2, 119.6, 116.6, 114.2, 102.5, 96.7, 95.8, 83.0, 78.6, 62.4, 56.7, 56.4, 55.8, 35.3; HRMS (ESI/FT−ICR−MS) m/z: $[M + Na]^+$ calcd for $C_{20}H_{24}O_8Na$, 415.1363; found, 415.1362.

Juglomycin A, 5-Hydroxy-2-[(2′*R*,3′*R*)-3′-hydroxy-5′-oxotetrahydrofuran-2′-yl]naphthalene-1,4-dione (1). CAN (140 mg, 0.26 mmol) was added to a solution of **11** (40.0 mg, 0.102 mmol) in a 1:1 mixture of MeCN and water (5 mL) at 0 °C. The mixture was stirred at 0 °C for 45 min. The reaction was quenched by the addition of water. The resultant mixture was diluted with $CHCl_3$. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated to give a crude naphthoquinone.

TFA (2 mL) was added to a solution of the crude naphthoquinone in CH_2Cl_2 (6 mL) at 0 °C. The mixture was stirred at rt for 5 h and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10/1) and preparative reverse phase HPLC (MeCN/H_2O = 2/3) to give **1** (15.4 mg, 55% over two steps) as yellow solids. mp 172−174 °C (decomp.), lit.[2] 172 °C (decomp.); $[\alpha]_D^{27}$ −74.1 (c 1.00, MeOH), lit.[3] $[\alpha]_D^{25}$ −74.1 (c 0.1, MeOH); IR (KBr) ν_{max}: 3529, 3394, 2924, 1780, 1647, 1614, 1462 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 11.92 (s, 1H), 7.78 (dd, J = 8.4, 7.6 Hz, 1H), 7.62 (dd, J = 7.6, 1.0 Hz, 1H), 7.34 (dd, J = 8.4, 1.0 Hz, 1H), 6.94 (d, J = 1.7 Hz, 1H), 5.70 (dd, J = 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); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): 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 $C_{14}H_{10}O_6Na$, 297.0370; found, 297.0371.

Juglomycin B, 5-Hydroxy-2-[(2′*S*,3′*R*)-3′-hydroxy-5′-oxotetrahydrofuran-2′-yl]naphthalen-1,4-dione (2). CAN (297 mg, 0.542 mmol) was added to a solution of **12** (85.0 mg, 0.217 mmol) in a 1:1 mixture of MeCN and water (9 mL) at 0 °C. The mixture was stirred at 0 °C for 40 min. The reaction was quenched by the addition of water. The resultant mixture was diluted with $CHCl_3$. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated to give a crude naphthoquinone.

TFA (3 mL) was added to a solution of the crude naphthoquinone in CH_2Cl_2 (9 mL) at 0 °C. The mixture was stirred at rt for 4 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/H_2O = 3/2) to give **2** (31.1 mg, 52% over two steps) as yellow solids. mp 199−202 °C (decomp.), lit.[2] 202 °C (decomp.); $[\alpha]_D^{15}$ +103.1 (c 0.16, MeOH), lit[3] $[\alpha]_D^{25}$ +102 (c 0.23, MeOH); IR (KBr) ν_{max}: 3435, 2927, 1784, 1651, 1614, 1460 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6, TMS): 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); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ 190.8, 184.1, 175.9, 162.1, 148.1, 137.7, 134.0, 133.2, 125.1, 119.7, 115.8, 84.8, 71.9, 36.6; HRMS (ESI/FT−ICR−MS) m/z: $[M + Na]^+$ calcd for $C_{14}H_{10}O_6Na$, 297.0370; found, 297.0370.

Khatmiamycin, Methyl(3*R*,4*R*)-3,4-dihydroxy-4-(5′-hydroxy-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)-butanoate (8). TsOH·H_2O (13.9 mg, 73.1 μmol) was added to a solution of **1** (20.0 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 Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (toluene/EtOAc = 3/2) and preparative GPC ($CHCl_3$) to give **8** (8.4 mg, 38%) as yellow solids and recovered **1** (7.4 mg, 37%). mp 152−155 °C (decomp.); $[\alpha]_D^{19}$ −103.3 (c 0.10, MeOH), lit.[9] $[\alpha]_D^{20}$ −21 (c 0.1, MeOH); IR (KBr) ν_{max}: 3458, 3378, 2956, 2856, 1722, 1674, 1647, 1621, 1452 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): δ 11.92 (s, 1H), 7.64 (dd, J = 8.0, 7.6 Hz, 1H), 7.60 (dd, J = 7.6, 1.4 Hz, 1H), 7.28 (dd, J = 8.0, 1.4 Hz, 1H), 7.04 (d, J = 1.2 Hz, 1H), 4.79 (br s, 1H), 4.22 (br d, J = 5.7 Hz, 1H), 3.71 (s, 3H), 3.30 (br s, 1H), 3.13 (br d, J = 7.2 Hz, 1H), 2.78 (dd, J = 16.6, 8.8 Hz, 1H), 2.67 (dd, J = 16.6, 3.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2): δ 190.4, 184.7, 173.3, 161.6, 151.0, 136.7, 135.4, 132.4, 124.7, 119.4, 115.2, 70.5, 69.5, 52.3, 38.5; HRMS (ESI/FT−ICR−MS) m/z: $[M + Na]^+$ calcd for $C_{15}H_{14}O_7Na$, 329.0632; found, 329.0635.

4-*epi*-Khatmiamycin, Methyl(3*R*,4*S*)-3,4-dihydroxy-4-(5′-hydroxy-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)-butanoate (4-*epi*-8). TsOH·H_2O (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

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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 Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (toluene/EtOAc = 2/1) and preparative GPC ($CHCl_3$) to give 4-*epi*-**8** (16.7 mg, 43%) as yellow solids and recovered **2** (6.6 mg, 19%). mp 112 °C; $[\alpha]_D^{23}$ +81.6 (*c* 0.10, MeOH); IR (KBr) ν_{max}: 3381, 2954, 2852, 1730, 1691, 1639, 1608, 1482, 1454 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2): 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 (d, *J* = 1.2 Hz, 1H), 4.97 (d, *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); $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2): 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 $C_{15}H_{14}O_7Na$, 329.0632; found, 329.0637.

Juglomycin C, (*S*)-3-Hydroxy-4-(5′-hydroxy-1′,4′-dioxo-1′,4′-dihydronaphthalen-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 $CHCl_3$. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated to give a crude naphthoquinone.

TFA (4 mL) was added to a solution of the crude naphthoquinone in CH_2Cl_2 (12 mL) at 0 °C. The mixture was stirred at rt for 2 h and concentrated under reduced pressure. 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. The ^1H and ^{13}C NMR spectra were identical with those of our authentic sample.[20]

Juglomycin D, (*S*)-3-Hydroxy-4-(3′,5′-dihydroxy-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)butanoic Acid (6). A 30% aqueous H_2O_2 solution (48 μL, 0.423 mmol) was added in portions to a solution of **3** (100 mg, 0.362 mmol) in 1 M sodium phosphate buffer (pH 8.5, 18.9 mL). The mixture was stirred at rt for 5 h. The mixture was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10/1 with 1% AcOH) to give **6** (69.3 mg, 66%) as yellow solids. The ^1H and ^{13}C NMR spectra were identical with those of our authentic sample.[21]

(*S*)-4-[1′,4′-Dimethoxy-5′-(methoxymethoxy)-naphthalen-2′-yl]-3-(methoxymethoxy)butanamide (15). Ethyl chloroformate (94 μL, 0.99 mmol) was added to a solution of **10** (130 mg, 0.330 mmol) and Et_3N (138 μL, 0.99 mmol) in acetone (20 mL) at 0 °C. The mixture was stirred at rt for 1 h and filtered. The filtrate was concentrated to a crude mixed anhydride.

A 25% aqueous NH_3 solution (12 mL) was added to a solution of the crude mixed anhydride in MeOH (18 mL) at 0 °C. The mixture was stirred at rt for 1.5 h. The mixture was diluted with $CHCl_3$ and water. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1/2, then $CHCl_3$/MeOH = 10/1) to give **15** (128.6 mg, 99%) as orange oil. $[\alpha]_D^{22}$ +4.5 (*c* 1.00, EtOAc); IR (neat) ν_{max}: 3431, 3352, 3197, 3008, 2935, 2904, 2844, 2827, 1678, 1620, 1601, 1583, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 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, 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 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 $C_{20}H_{27}NO_7Na$, 416.1680; found, 416.1674.

Juglomycin C Amide, (*S*)-3-Hydroxy-4-(5′-hydroxy-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)butanamide (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 $CHCl_3$. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated to give a crude naphthoquinone.

TFA (5 mL) was added to a solution of the crude naphthoquinone in CH_2Cl_2 (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 ($CHCl_3$/MeOH = 10/1) to give **5** (35.0 mg, 50% over two steps) as yellow solids. mp 161 °C (decomp.); $[\alpha]_D^{28}$ −117 (*c* 0.01, MeOH); IR (KBr) ν_{max}: 3338, 3167, 2972, 2926, 1670, 1641, 1614, 1454 cm^{-1}. ^1H NMR (400 MHz, CD_3OD, 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, 1H), 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); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD): 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 $C_{14}H_{13}NO_5Na$, 298.0686; found, 298.0687.

(*S*)-3-(Methoxymethoxy)-4-{5′-(methoxymethoxy)-3′-methyl-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl}-butanoic Acid (16). CAN (139 mg, 0.254 mmol) was added to a solution of **10** (40.0 mg, 0.102 mmol) in a 1:1 mixture of MeCN and water (8 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of water. The resultant mixture was diluted with $CHCl_3$. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated to give a crude naphthoquinone.

A solution of the crude naphthoquinone and $AgNO_3$ (8.6 mg, 51 μmol) in a 1:1:1:1 mixture of AcOH, MeCN, CH_2Cl_2, and water (4 mL) was degassed. A solution of $K_2S_2O_8$ (82.2 mg, 0.304 mmol) in degassed water (6 mL) was added to the mixture at rt. The mixture was refluxed at 90 °C by heating in an oil bath under a nitrogen atmosphere for 2.5 h. The resultant mixture was diluted with $CHCl_3$ and water. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (toluene/EtOAc = 3/2 with 1% AcOH) to give **16** (11.5 mg, 30% over two steps) as brown oil. $[\alpha]_D^{21}$ −5.9 (*c* 0.50, $CHCl_3$); IR (KBr) ν_{max}: 3213, 3072, 2956, 2931, 1732, 1712, 1657, 1627, 1587, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 5.34 (s, 2H), 4.63 (m, 2H), 4.25 (m, 1H), 3.55

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(s, 3H), 3.24 (s, 3H), 3.01 (dd, J = 13.1, 7.5 Hz, 1H), 2.91 (dd, J = 13.1, 6.0 Hz, 1H), 2.67 (dd, J = 15.7, 7.2 Hz, 1H), 2.56 (dd, J = 15.7, 5.0 Hz, 1H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 184.6, 184.3, 176.3, 156.8, 147.5, 140.8, 134.3, 134.1, 121.8, 121.0, 120.5, 96.3, 95.1, 73.9, 56.6, 55.7, 40.4, 32.5, 13.6; HRMS (FAB/double-focusing MS) m/z: $[M + Na]^+$ calcd for $C_{19}H_{22}O_8Na$, 401.1214; found, 401.1212.

Proposed Structure for Juglomycin Z, (*S*)-3-Hydroxy-4-(5′-hydroxy-3′-methyl-1′,4′-dioxo-1′,4′-dihydronaphthalen-2′-yl)butanoic Acid (7). TFA (2 mL) was added to a solution of **16** (11.5 mg, 0.030 mmol) in CH_2Cl_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 = 10/1) and preparative thin-layer 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; $[\alpha]_D^{28}$ −44.3 (c 0.10, MeOH), lit.[8] $[\alpha]_D^{20}$ +144 (c 0.025, MeOH); IR (KBr) ν_{max}: 3402, 3184, 2925, 1728, 1654, 1633, 1606, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3/CD_3OD$ = 9/1, TMS): δ 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, $CDCl_3$): δ 190.1, 184.8, 176.2, 161.2, 145.9, 144.2, 136.1, 131.9, 124.1, 119.2, 114.9, 67.5, 41.2, 34.0, 12.8 HRMS (ESI/FT−ICR−MS) m/z: $[M - H]^-$ calcd for $C_{15}H_{13}O_6$, 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 μmol) in a 1:2 mixture of CH_2Cl_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_2SO_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; $[\alpha]_D^{22}$ −40.9 (c 0.32, MeOH), lit.[8] $[\alpha]_D^{20}$ +37.3 (c 0.01, MeOH); IR (KBr) ν_{max}: 3525, 3020, 2953, 2854, 1731, 1657, 1635, 1610, 1579, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 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), 2.58 (dd, J = 16.6, 7.8 Hz, 1H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 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: $[M + Na]^+$ calcd for $C_{16}H_{16}O_6Na$, 327.0839; found, 327.0842.

3-Bromo-1,4-dimethoxy-5-(methoxymethoxy)-2-methylnaphthalene (24). NaH (60% dispersion in mineral oil, 593.3 mg, 14.8 mmol) was added to a solution of **22**[26] (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_2SO_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.

A solution of $Na_2S_2O_4$ (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_2SO_4, and concentrated. The residue was used for the next reaction without further purification.

Dimethyl sulfate (9.4 mL, 98.5 mmol) and K_2CO_3 (13.6 g, 98.5 mmol) were added to a solution of the crude hydroquinone in acetone (250 mL) under an argon atmosphere. The mixture was refluxed for 13.5 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_2SO_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) ν_{max}: 2999, 2954, 2930, 2841, 1614, 1580, 1571, 1491 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.76 (dd, J = 8.4, 0.7 Hz, 1H), 7.41 (dd, J = 8.4, 7.7 Hz, 1H), 7.14 (dd, J = 7.7, 0.7 Hz, 1H), 5.31 (s, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.60 (s, 3H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 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 (FAB/double-focusing MS) m/z: $[M]^+$ calcd for $C_{15}H_{17}{}^{79}BrO_4$, 340.0310; found, 340.0310.

(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-(1,4-dimethoxy-8-(methoxymethoxy)-3-methylnaphthalen-2-yl)butan-2-ol (26). Magnesium powder (128 mg, 5.27 mmol) was activated by the addition of 1,2-diiodoethane (6.4 mg, 227 μmol) with vigorous stirring for 10 min under an argon atmosphere. A solution of **24** (719 mg, 2.11 mmol) in THF (3.5 mL) was added, and the mixture was stirred at rt for 30 min. The Grignard reagent was added to a solution of **25** (512 mg, 2.53 mmol) and CuCN (9.5 mg, 106 μmol) in THF (20 mL) at −78 °C under an argon atmosphere. The mixture was warmed up to rt and stirred for 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The resultant mixture was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6/1) to give **26** (639 mg, 65%) as pale yellow oil. $[\alpha]_D^{17}$ −13.7 (c 1.00, $CHCl_3$); IR (neat) ν_{max}: 3502, 2954, 2931, 2892, 2856, 1617, 1594, 1572, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, J = 8.4, 0.8 Hz, 1H), 7.35 (dd, J = 8.4, 7.7 Hz, 1H), 7.11 (dd, J = 7.6, 0.8 Hz, 1H), 5.30 (s, 2H), 4.10 (1H, m), 3.89 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.77 (m, 1H), 3.70 (d, J = 2.2 Hz, 1H), 3.59 (s, 3H), 3.03 (d, J = 6.4 Hz, 2H), 2.44 (s, 3H), 1.81 (m, 1H), 1.70 (m, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.9, 150.2, 150.0, 130.2, 129.1, 127.5, 125.7, 119.7, 116.5, 112.0, 96.3, 72.1, 62.4, 61.8, 61.0, 56.4, 38.5, 34.9, 25.8 (3C), 18.1, 13.0, −5.56, −5.58; HRMS (FAB/double-focusing MS) m/z: $[M]^+$ calcd for $C_{25}H_{40}O_6Si$, 464.2594; found, 464.2594.

(*S*)-1-*tert*-Butyldimethylsilyloxy-4-[1,4-dimethoxy-8-(methoxymethoxy)-3-methylnaphthalen-2-yl]-3-methoxymethoxybutane (27). MOMCl (370 μL, 4.81 mmol) was added to a solution of **26** (639 mg, 1.37 mmol), *N*,*N*-diisopropylethylamine (850 μL, 4.95 mmol), and TBAI (5.8 mg, 15.7 μmol) in CH_2Cl_2 (20 mL). The mixture was refluxed

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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 $CHCl_3$. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, 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. $[\alpha]_D^{19}$ +1.4 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max}: 2953, 2930, 2887, 2856, 1617, 1593, 1572, 1496, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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 (d, *J* = 6.8 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.44 (d, *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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 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*: $[M]^+$ calcd for $C_{27}H_{44}O_7Si$, 508.2856; found, 508.2856.

(*S*)-4-(1,4-Dimethoxy-8-(methoxymethoxy)-3-methylnaphthalen-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 Na_2SO_4, 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. $[\alpha]_D^{20}$ +16.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max}: 3472, 2949, 2892, 2833, 1616, 1593, 1572, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.12 (d, *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), 3.80 (s, 3H), 3.74 (m, 1H), 3.59 (s, 3H), 3.25 (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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.0, 150.4, 149.9, 130.2, 128.8, 127.4, 125.8, 119.7, 116.5, 111.9, 96.4, 96.3, 77.1, 61.9, 61.1, 59.9, 56.5, 55.6, 37.0, 32.8, 13.1; HRMS (FAB/double-focusing MS) *m/z*: $[M]^+$ calcd for $C_{21}H_{30}O_7$, 394.1992; found, 394.1995.

(*S*)-4-(1,4-Dimethoxy-8-(methoxymethoxy)-3-methylnaphthalen-2-yl)-3-hydroxybutanoic Acid (29). Dess−Martin periodinane (740 mg, 1.74 mmol) was added to a solution of **28** (405 g, 1.03 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at rt for 40 min. The reaction was quenched by the addition of water. The resultant mixture was diluted with $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ three times. The combined organic layer was dried over Na_2SO_4 and concentrated to give a crude aldehyde.

A solution of $NaClO_2$ (80%, 348.5 mg, 3.08 mmol) in H_2O (8 mL) was added to a solution of the crude aldehyde, 2-methyl-2-butene (1.1 mL, 10.3 mmol), and $NaH_2PO_4{\cdot}2H_2O$ (802 mg, 5.14 mmol) in *tert*-butyl alcohol/THF (1:1, 16 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by the addition of water. The resultant mixture was diluted with $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ four times. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 19/1) to give a crude **29**. The crude **29** was further purified by silica gel column chromatography ($CHCl_3$/MeOH = 99/1) to give **29** (395 mg, 94% over two steps) as pale yellow oil. $[\alpha]_D^{20}$ +1.01 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max}: 3164, 3079, 3057, 2987, 2949, 2834, 1734, 1710, 1593, 1572, 1442 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.75 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.34 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.11 (dd, *J* = 7.6, 0.8 Hz, 1H), 5.30 (s, 2H), 4.66 (d, *J* = 7.0 Hz, 1H), 4.57 (d, *J* = 7.0 Hz, 1H), 4.33 (m, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.59 (s, 3H), 3.21 (s, 3H), 3.17, (dd, *J* = 13.3, 6.5 Hz, 1H), 3.09, (dd, *J* = 13.3, 7.7 Hz, 1H), 2.67, (dd, *J* = 15.9, 7.8 Hz, 1H), 2.55 (dd, *J* = 15.9, 4.6 Hz, 1H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 177.3, 153.0, 150.5, 150.0, 130.4, 127.9, 127.4, 125.9, 119.7, 116.5, 112.1, 96.4, 96.0, 74.4, 61.9, 61.1, 56.5, 55.4, 39.8, 32.5, 12.9; HRMS (FAB/double-focusing MS) *m/z*: $[M - H]^-$ calcd for $C_{21}H_{27}O_8$, 407.1706; found, 407.1705.

(*S*)-3-Hydroxy-4-(8-hydroxy-3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanoic Acid (20). CAN (311 mg, 0.834 mmol) was added to a solution of **29** (136 mg, 0.333 mmol) in a 1:1 mixture of MeCN and water (5 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 $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ three times. The combined organic layer was dried over Na_2SO_4 and concentrated to give a crude naphthoquinone.

TFA (3 mL) was added to a solution of the crude naphthoquinone in CH_2Cl_2 (12 mL) at 0 °C. The mixture was stirred at rt for 5 h and concentrated under reduced pressure. The residue was purified by octadecyl silica gel column chromatography (MeOH/H_2O = 3/2) to give **20** (72.9 mg, 75% over two steps) as brownish yellow solids. mp 143−148 °C; $[\alpha]_D^{15}$ −58.0 (*c* 0.15, MeOH); IR (KBr) ν_{max}: 3402, 3184, 2925, 1728, 1654, 1633, 1606, 1454 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): 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), 2.63 (dd, *J* = 15.6, 4.6 Hz, 1H), 2.54 (dd, *J* = 15.6, 8.2 Hz, 1H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): 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*: $[M]^-$ calcd for $C_{15}H_{14}O_6$, 290.0790; found, 290.0791.

Methyl (*S*)-3-hydroxy-4-(8-hydroxy-3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanoate (21). A 2.0 M solution of trimethylsilyldiazomethane in Et_2O (120 μL, 240 μmol) was added to a solution of **20** (17.7 mg, 61.0 μmol) in a 1:1 mixture of CH_2Cl_2 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/acetone = 3/2) to give **21** (17.5 mg, 94%) as yellow solids. mp 86 °C; $[\alpha]_D^{16}$ −89.4 (*c* 0.15, MeOH); IR (KBr) ν_{max}: 3550, 3486, 3028, 3002, 2989, 2978, 2950, 2927, 2873, 1741, 1724, 1657, 1633, 1610, 1570, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 12.11 (s, 1H), 7.62 (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, m), 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ

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190.3, 184.2, 172.9, 161.2, 147.2, 142.9, 136.1, 132.2, 123.9, 119.1, 114.8, 67.6, 51.9, 41.1, 33.3, 13.5; HRMS (FAB/double-focusing MS) m/z: $[M + H]^+$ calcd for $C_{16}H_{17}O_6Na$, 305.1025; found, 305.1025.

■ ASSOCIATED CONTENT

Supporting Information

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

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 ^{13}C NMR spectra for all synthetic compounds (PDF)

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Notes

The authors declare no competing financial interest.

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