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A Chiron Approach to the Total Synthesis of (−)-Juglomycin A, (+)-Kalafungin, (+)-Frenolicin B, and (+)-Deoxyfrenolicin

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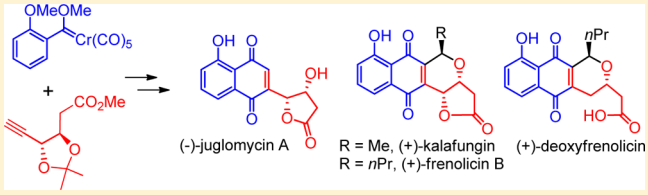
Supporting Information

ABSTRACT: A general, efficient, and common strategy for the synthesis of (−)-juglomycin A, (+)-kalafungin, (+)-frenolicin B, and (+)-deoxyfrenolicin is reported here. The strategy involves the synthesis of a key building block alkyne from a cheap chiral pool material, D-glucono-δ-lactone, Dötz benzannulation, oxa-Pictet-Spengler reaction, and H_2SO_4-mediated epimerization.



Pyranonaphthoquinones are a class of compounds isolated from various strains of bacteria and fungi[1] that exhibit activity against Gram-positive bacteria, pathogenic fungi, and yeasts and possess antiviral activity.[1] They are also proposed to act as bioreductive bis-alkylating agents[2] through the formation of quinone methide intermediates. (+)-Kalafungin **1**,[3] (+)-frenolicin B **2**,[4] and (+)-deoxyfrenolicin **3**[4a,5] are important members of the pyranonaphthoquinone family. The related molecule (−)-juglomycin A **4**[6] lacks a pyran ring but is a precursor to pyran natural products **1**−**3** (Figure 1). Kalafungin **1** was first isolated by Bergy from *Streptomyces tanashiensis*.[3a] It inhibits pathogenic fungi, protozoa, yeasts, and Gram-negative bacteria and as well possesses cytotoxic activity. A variety of approaches[3b−e] have been used in its synthesis including the recent synthesis by Donner through tendem Michael-Dieckman cyclization reaction.[3e] Omura and Coworkers[4a] isolated frenolicin B **2** and deoxyfrenolicin **3** from the fermentation of *Streptomyces roseofulvus* strain no. AM-3867. Frenolicin B shows an excellent anticoccidial activity.[4b] A few racemic and enantioselective syntheses of frenolicin B[4c−k] and racemic syntheses of deoxyfrenolicin[5] have been reported. However, there is no reported enantioselective synthesis of deoxyfrenolicin in the literature. Ono and Coworkers[6a,b] isolated juglomycin A **4** from the culture filtrate of *Streptomyces* sp. 190-2. It shows antibacterial and modest antitumor activity.[6a,b] A few racemic and formal syntheses of **4** are reported.[6c−g] Asymmetric synthesis of **4** was reported first by Kraus and Maeda[6h] followed by the recent syntheses by our group.[6i,j] The most demanding feature for synthesis of this class of compounds is achieving stereoselectively the *anti* placement of substituents at the C-1 and C-3 positions of the pyran ring.

In our earlier syntheses of pyranonaphthoquinones and related molecules[7] we utilized Dötz benzannulation[8] reaction coupled with various asymmetric methods. However our exploration continued toward envisioning a common intermediate through which rapid synthesis of various pyranonaphthoquinones could be achieved. Keeping Dötz benzannulation as a key reaction to rapidly construct the diversely substituted naphthalene ring we visualized alkyne **5** as key intermediate (Figure 1). The Dötz benzannulation of Fischer carbene **6** with alkyne **5** would deliver **7** from which juglomycin A **4**, kalafungin **1**, frenolicin B **2**, and deoxyfrenolicin **3** could be accessed. The strategy holds potential for the synthesis of arizonins **8**−**10**. The use of dimeric Fischer carbene **13** would lead to **14** for bidirectional synthesis of γ-actinorhodin **12** and actinorhodin **11**. The synthesis of **5** was designed based on a chiron approach starting from D-glucono-δ-lactone **17** (Figure 1). The cleavage of diol functionality in **15**, yielding an aldehyde, and subsequent terminal alkyne formation would give the desired intermediate **5**. Compound **15** can be derived from **16** and the latter from D-glucono-δ-lactone **17** through acetonide installation and α-OH to chloride conversion.

The synthesis of alkyne **5** commenced from D-glucono-δ-lactone **17** (Scheme 1), which was converted into diacetonide **18** in 94% yield.[9] The free α-hydroxy group in **18** was processed through Appel reaction[10] to give chloro compound **16** (90%), and subsequent removal of chloride through hydrogenation gave the diacetonide **19** in 88% yield.[9] Regioselective terminal acetonide removal furnished the diol **15** (87% yield). For installation of the desired alkyne moiety, two well-known reaction procedures, Corey-Fuchs[11] and the use of the Bestmann-Ohira reagent,[12] were investigated. The former led to decomposition of the aldehyde from **15**. The latter reagent **20** (1.5 equiv), under optimized reaction conditions using K_2CO_3 (1.2 equiv) gave the alkyne **5** in 51% yield. The overall synthetic sequence from D-glucono-δ-lactone **17** to alkyne **5** required six steps and resulted in 33% overall yield.

The Dötz benzannulation of alkyne **5** with readily available Fischer carbene **6**[7a] in benzene solvent delivered single regioisomeric naphthol **21** isolated in 51% yield (Scheme 2). The methylation of **21** to **22** (85% yield) and further one-pot acetonide deprotection and lactonization with trifluoroacetic acid/catalytic conc HCl furnished the lactone **7** in 85% yield.

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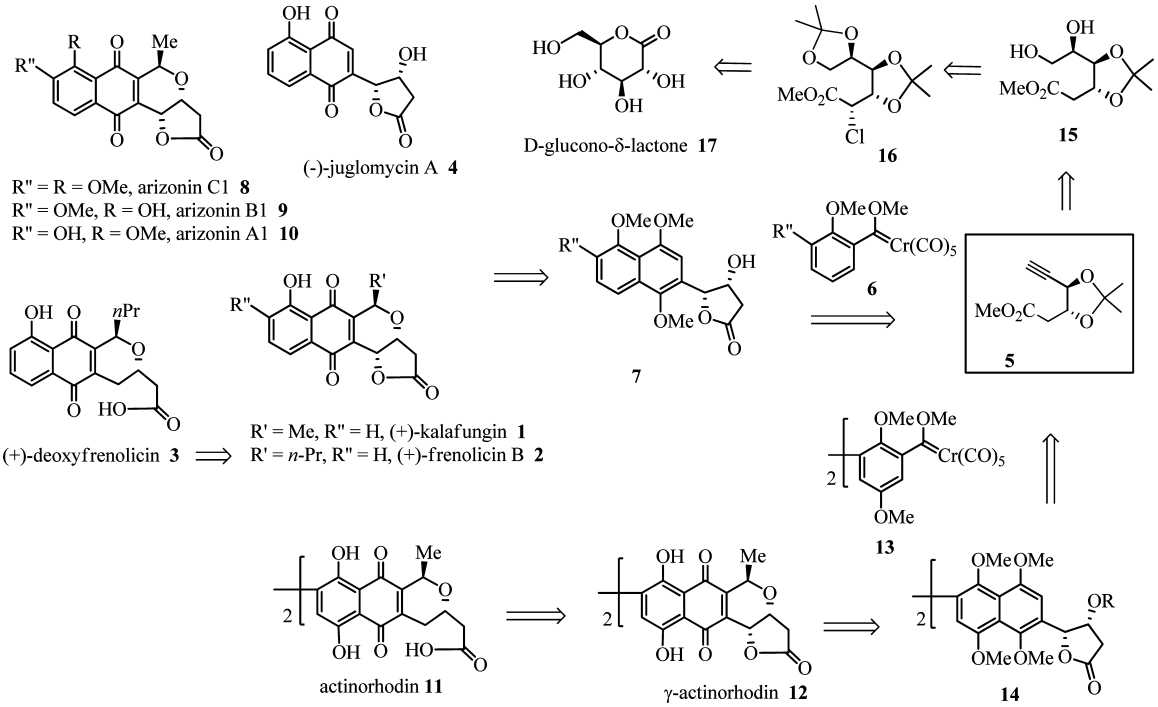
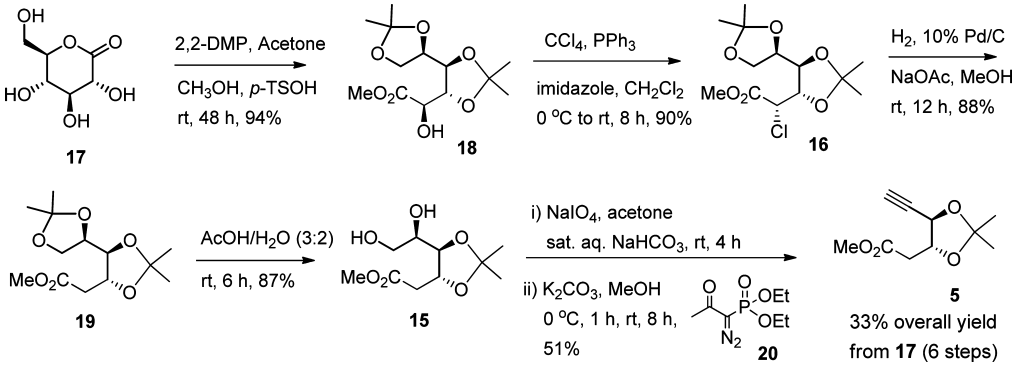
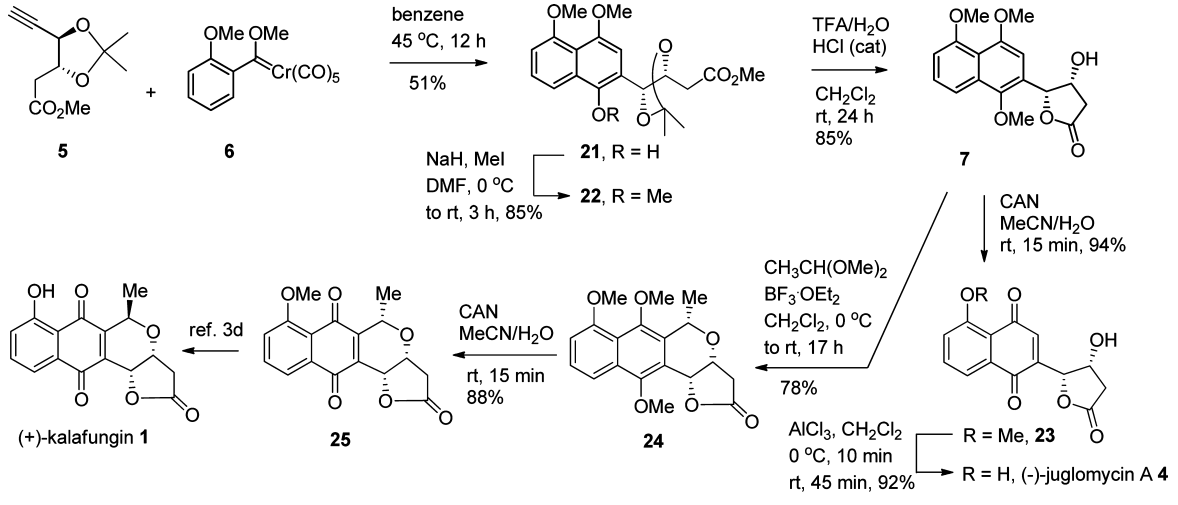


Figure 1. Various pyranonaphthoquinones, related molecules, and a common strategy for their synthesis.

Scheme 1. Synthesis of Key Intermediate Alkyne 5 from D-Glucono-δ-lactone 17



Scheme 2. Synthesis of (−)-Juglomycin A 4 and (+)-Kalafungin 1 from Alkyne 5



The cerium ammonium nitrate (CAN) oxidation of **7** efficiently gave quinone **23** (94%). Subsequent demethylation with $AlCl_3$ resulted in (−)-juglomycin A **4** (92%) as yellow solid: $[\alpha]^{25}_D$ −51.8 (*c* 0.3, DMSO), lit.[6a] −51.9 (*c* 0.42, DMSO). For

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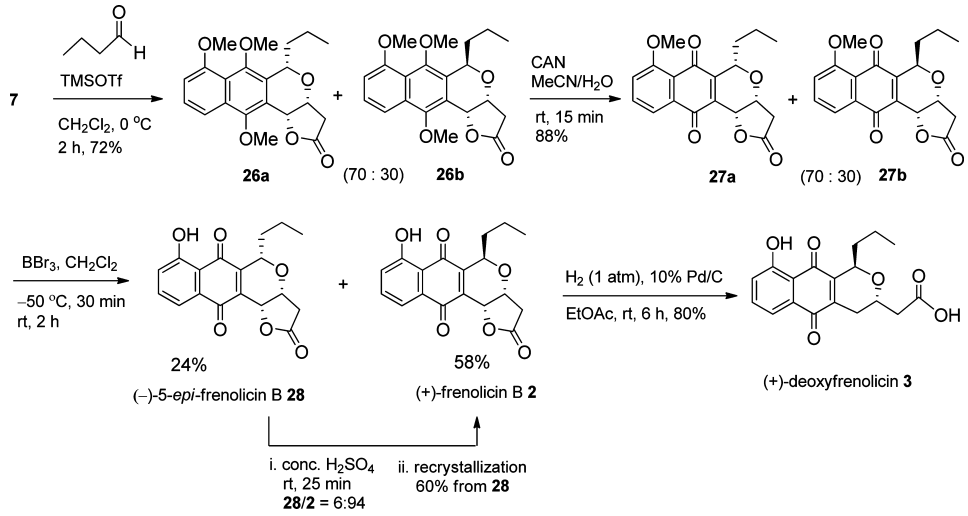
Scheme 3. Synthesis of (+)-Frenolicin B 2 and (+)-Deoxyfrenolicin 3 from Lactone 7



(+)-kalafungin **1** synthesis, the oxa-Pictet-Spengler reaction[4d,g,13] of **7** with acetaldehyde dimethyl acetal and $BF_3{\cdot}OEt_2$ produced all *syn*-pyran product **24** in 78% yield. CAN oxidation of **24** gave **25** (88%). The conversion of **25** to (+)-kalafungin **1** was achieved following literature report.[3d]

The oxa-Pictet-Spengler reaction of **7** with butyraldehyde catalyzed by TMSOTf provided the *syn*/*anti* diastereomers **26a** and **26b** (70:30 by ^{1}H NMR, 72%) as inseparable mixture (Scheme 3) Further CAN oxidation provided *syn*/*anti*-quinones **27a** and **27b** (70:30, 88%). Excess BBr_3-mediated demethylation also induced C-5 epimerization affording a mixture of 5-*epi*-frenolicin B **28** and frenolicin B **2**. The mixture could be separated by flash silica gel column chromatography to deliver **28** (24%) and **2** (58%). The epimer **28** on stirring in conc H_2SO_4 for 25 min induced C-5 epimerization giving **28** and **2** in 6:94 ratio. A single recrystallization provided (+)-frenolicin B **2** (60% yield from **28**): $[\alpha]^{25}_D$ +224 (*c* 0.6, CH_2Cl_2), lit.[4f] +226.0 (*c* 0.84, CH_2Cl_2). The spectroscopic and analytical data of **2** were in full agreement with that reported.[4f] Hydrogenation of frenolicin B **2** with H_2/Pd–C resulted in opening of the lactone to provide (+)-deoxyfrenolicin **3** in good yield of 80%: $[\alpha]^{25}_D$ +111.8 (*c* 0.6, MeOH), lit.[4a] +118.4 (*c* 1.0, MeOH).

Conclusion. In conclusion we performed an efficient chiral pool synthesis of (−)-juglomycin A, (+)-deoxyfrenolicin, and γ-lactone annulated pyranonaphthoquinones (+)-kalafungin and (+)-frenolicin B. The key alkyne **5** was prepared from chiral pool material D-glucono-δ-lactone in six steps and 33% overall yield. Dötz benzannulation and oxa-Pictet-Spengler reaction provided the desired pyranonaphthoquinone structure and H_2SO_4-mediated epimerization led to the desired stereochemistry of the target molecules. The present paper describes the first asymmetric synthesis of (+)-deoxyfrenolicin. The use of alkyne **5**, possessing the required stereo elements, in a Dötz benzannulation constitutes a de novo strategy that can be readily adopted for the synthesis of related pyranonaphthoquinones.

EXPERIMENTAL SECTION

General Information. Dry reactions were carried out under an atmosphere of Ar or N_2. ^{1}H NMR and ^{13}C NMR were recorded at 400 and 100 MHz, respectively. IR samples were prepared by evaporation from $CHCl_3$ on CsBr plates. HRMS were obtained using positive electrospray ionization by TOF method. Compounds **18**, **16**, and **19** were prepared following literature procedure.[9]

Methyl (3*R*,4*R*,5*R*)-5,6-Dihydroxy-3,4-isopropylidenedioxy-hexanoate (15). To diacetonide **19** (2.24 g, 8.17 mmol) was added a solution of acetic acid/water (3:2, 8 mL), and the mixture was stirred at room temperature for 6 h. Acetic acid and water were removed under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2) as eluent to give diol **15** (1.66 g, 87%) as colorless oil. $[\alpha]^{25}_D$ +8.2 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) υ_{max} 3449, 1735, 1439, 1382, 906, 885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.39 (s, 6H), 2.67 (dd, *J* = 15.9, 7.6 Hz, 1H), 2.83 (dd, *J* = 15.9, 4.4 Hz, 1H), 3.66–3.77 (m, 2H), 3.72 (s, 3H), 3.83 (dd, *J* = 10.9, 2.9 Hz, 2H), 4.41 (dt, *J* = 11.0, 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 27.1, 38.9, 52.0, 64.0, 72.8, 76.0, 80.2, 109.5, 171.9; HRMS *m*/*z* calcd for $[C_{10}H_{18}O_6 + Na]^+$ 257.1001, found 257.1001.

Methyl (3*R*,4*R*)-3,4-Isopropylidenedioxyhex-5-ynoate (5). To a solution of **15** (1.50 g, 6.40 mmol, 1.0 equiv) in acetone (25 mL) were added satd aq $NaHCO_3$ (0.5 mL) and solid $NaIO_4$ (2.74 g, 12.81 mmol, 2.0 equiv). The resulting mixture was stirred at room temperature for 4 h. Acetone was removed under reduced pressure, the residue was filtered through a small pad of silica gel and washed with petroleum ether/EtOAc (7:3), and the filtrate was concentrated to give crude aldehyde (1.29 g).

To a solution of the above crude aldehyde (1.29 g, 6.38 mmol, 1.0 equiv) in MeOH (20 mL) were added freshly prepared Bestmann-Ohira's reagent **20** (2.106 g, 9.57 mmol, 1.5 equiv) and K_2CO_3 (1.06 g, 7.66 mmol, 1.2 equiv) sequentially. The resulting solution was stirred at 0 °C for 1 h and room temperature for 8 h. It was then quenched with satd aq NH_4Cl (10 mL), and MeOH was removed under reduced pressure. The solution was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford alkyne **5** (0.648 g, 51% over two steps) as colorless oil. $[\alpha]^{25}_D$ +1.6 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) υ_{max} 3273, 2123, 1743, 1439, 1383, 1372, 995, 906 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 1.40 (s, 3H), 1.53 (s, 3H), 2.54 (d, *J* = 2.0 Hz, 1H), 2.63 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.69 (dd, *J* = 15.6, 5.1 Hz, 1H), 3.72 (s, 3H), 4.38 (dt, *J* = 7.4, 2.0 Hz, 1H), 4.40 (dd, *J* = 7.3, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 27.0, 37.2, 51.9, 69.6, 75.0, 77.7, 79.9, 110.8, 170.4; HRMS *m*/*z* calcd for $[C_{10}H_{14}O_4 + H]^+$ 199.097, found 199.0988.

Methyl (3*R*,4*R*)-4-(1-hydroxy-4,5-dimethoxynaphthalen-2-yl)-3,4-isopropylidenedioxy butanoate (21). To a freshly prepared Fischer carbene complex **6**[7a] (0.2 g, 0.584 mmol, 1.0 equiv) in dry and degassed benzene (10 mL) was added alkyne **5** (0.139 g, 0.701 mmol, 1.2 equiv). The reaction mixture was stirred at 45 °C for 12 h. It was then cooled to room temperature, exposed to

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air, and stirred further for 30 min. The reaction mixture was concentrated, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to give **21** (0.112 g, 51%) as yellow oil. $[\alpha]^{25}_{D}$ +7.2 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) υ_{max} 3372, 1741, 1630, 1602, 1514, 1463, 1438, 986, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.53 (s, 3H), 1.68 (s, 3H), 2.65 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.74 (dd, *J* = 15.2, 4.1 Hz, 1H), 3.65 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 4.36−4.41 (m, 1H), 4.97 (d, *J* = 8.9 Hz, 1H), 6.51 (s, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.85 (dd, *J* = 8.4, 0.8 Hz, 1H), 8.27 (s, 1H, *OH*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8, 27.0, 36.1, 52.0, 56.4, 57.7, 77.20, 82.2, 106.5, 107.1, 109.8, 111.9, 114.7, 118.3, 126.2, 128.7, 145.3, 150.3, 156.6, 170.7; HRMS *m*/*z* calcd for $[C_{20}H_{24}O_7 + H]^+$ 377.1600, found 377.1609.

Methyl (3*R*,4*R*)-4-(1,4,5-Trimethoxynaphthalen-2-yl)-3,4-isopropylidenedioxybutanoate (22). To a solution of naphthol **21** (50 mg, 0.133 mmol, 1.0 equiv) in dry DMF (5 mL) at 0 °C was added NaH (6.4 mg, 0.16 mmol, 60% in mineral oil, 1.2 equiv). The reaction mixture was stirred at room temperature for 20 min and then cooled to 0 °C, and MeI (0.016 mL, 0.266 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 0 °C to room temperature for 3 h. It was then quenched with ice-cold water (5 mL), and the solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to give **22** (44 mg, 85%) as yellow oil. $[\alpha]^{25}_{D}$ +34.5 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) υ_{max} 1743, 1599, 1588, 1459, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.57 (s, 3H), 1.67 (s, 3H), 2.71 (dd, *J* = 16.0, 8.5 Hz, 1H), 2.83 (dd, *J* = 16.1, 3.2 Hz, 1H), 3.61 (s, 3H), 3.86 (s, 3H), 3.97 (s, 6H), 4.24−4.29 (m, 1H), 5.23 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 6.96 (s, 1H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.63 (dd, *J* = 8.4, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 27.3, 36.7, 51.8, 56.5, 56.6, 62.2, 76.7, 78.8, 103.5, 106.9, 109.6, 114.7, 118.4, 125.4, 126.9, 131.1, 147.5, 154.1, 157.5, 171.2; HRMS *m*/*z* calcd for $[C_{21}H_{26}O_7 + H]^+$ 391.1757, found 391.1746.

(4*R*,5*R*)-4-Hydroxy-5-(1,4,5-trimethoxynaphth-2-yl)-dihydrofuran-2(3*H*)-one (7). To a solution of the compound **22** (22 mg, 0.056 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) were added TFA/H_2O (9:1, 0.2 mL) and 2 drops of conc HCl. The resulting solution was stirred at room temperature for 24 h. It was then quenched with satd aq $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to give **7** (15.2 mg, 85%) as white solid. Mp 136−137 °C; $[\alpha]^{25}_{D}$ −12.5 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) υ_{max} 3469, 1780, 1734, 1623, 1601, 1586, 981, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.77 (brs, 1H), 2.72 (d, *J* = 17.5 Hz, 1H), 2.92 (dd, *J* = 17.7, 5.4 Hz, 1H), 3.87 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 4.81−4.83 (m, 1H), 5.84 (d, *J* = 3.5 Hz, 1H), 6.87 (s, 1H), 6.88 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.56 (dd, *J* = 8.4, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.3, 56.5, 56.7, 61.9, 69.7, 81.8, 103.8, 107.1, 114.3, 118.4, 122.4, 127.2, 130.6, 145.8, 153.9, 157.5, 175.7; HRMS *m*/*z* calcd for $[C_{17}H_{18}O_6 + Na]^+$ 341.1001, found 341.0998.

(2*R*,3*R*)-2-(3-Hydroxy-5-oxotetrahydrofuran-2-yl)-5-methoxynaphthalene-1,4-dione (23). The title compound was prepared from compound **7** (35 mg, 0.11 mmol) following literature procedure[6j] to afford **23** (30 mg, 94%) as yellow solid. Mp 172−175 °C; $[\alpha]^{25}_{D}$ −58.2 (*c* 0.3, MeOH). ^1H NMR (400 MHz, acetone-d_6) δ 2.46 (d, *J* = 17.4 Hz, 1H), 3.12 (dd, *J* = 17.3, 5.3 Hz, 1H), 3.93 (s, 3H), 4.84−4.86 (m, 1H), 5.62 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.73 (d, *J* = 1.6 Hz, 1H), 7.51 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.64 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.76 (dd, *J* = 7.8, 7.6 Hz, 1H). Other spectral and analytical data is same as reported earlier.[6j]

(−)-Juglomycin A (4). The title compound was prepared from **23** (30 mg, 0.104 mmol) following literature procedure[6j] to give **4** (26 mg, 92%) as yellow solid. Mp 172−174 °C (decomp at 171 °C); $[\alpha]^{25}_{D}$ −51.8 (*c* 0.3, DMSO), lit.[6a] −51.9 (*c* 0.42, DMSO). Spectral and analytical data is same as reported earlier.[6j]

(3a*R*,5*S*,11b*R*)-3,3a,5,11b-Tetrahydro-6,7,11-trimethoxy-5-methyl-1,4-dioxacyclopent[*a*]anthracen-2-one (24). To a solution of compound **7** (70 mg, 0.22 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C were added acetaldehyde dimethyl acetal (0.046 mL, 0.44 mmol, 2.0 equiv) and $BF_3{\cdot}OEt_2$ (0.03 mL, 0.24 mmol, 1.1 equiv). The resulting mixture was stirred at 0 °C to room temperature for 17 h. It was then quenched with satd aq $NaHCO_3$ (5 mL), and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford **24** (59.5 mg, 78%) as white solid. Mp 220−224 °C; $[\alpha]^{25}_{D}$ +225 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) υ_{max} 1779, 1594, 1574, 996, 906 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.75 (d, *J* = 6.2 Hz, 3H), 2.78 (d, *J* = 17.3 Hz, 1H), 2.92 (dd, *J* = 17.3, 4.4 Hz, 1H), 3.74 (s, 3H), 4.02 (s, 3H), 4.09 (s, 3H), 4.37 (dd, *J* = 4.4, 2.5 Hz, 1H), 5.07 (q, *J* = 6.3 Hz, 1H), 5.59 (d, *J* = 2.4 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 8.2 Hz, 1H), 7.71 (dd, *J* = 8.5, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 38.4, 56.2, 61.6, 64.4, 70.2, 71.3, 73.0, 107.2, 115.1, 119.2, 121.6, 126.6, 129.1, 130.2, 149.3, 153.1, 156.1, 175.7; HRMS *m*/*z* calcd for $[C_{19}H_{20}O_6 + H]^+$ 345.1338, found 345.1345.

(3a*R*,5*S*,11b*R*)-3,3a,5,11b-Tetrahydro-7-methoxy-5-methyl-1,4-dioxacyclopent[*a*]anthracen-2,6,11-trione (25). CAN oxidation of compound **24** (0.060 g, 0.174 mmol) by a similar procedure as used for conversion of **7** to **23** produced the corresponding quinone **25** (0.048 g, 88%) as an orange crystalline solid. Mp 183−185 °C (decomp); $[\alpha]^{25}_{D}$ −160 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) υ_{max} 1795, 1670, 1640, 1590, 995, 900 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.56 (d, *J* = 6.7 Hz, 3H), 2.72 (d, *J* = 17.6 Hz, 1H), 2.90 (dd, *J* = 17.6, 4.7 Hz, 1H), 4.00 (s, 3H), 4.33 (dd, *J* = 4.5, 2.6 Hz, 1H), 4.78 (dq, *J* = 6.7, 1.5 Hz, 1H), 5.28 (d, *J* = 1.8 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 37.1, 56.4, 68.9, 69.7, 71.1, 118.0, 19.1, 120.1, 132.2, 133.4, 135.3, 152.4, 159.3, 174.6, 182.5, 183.3; HRMS *m*/*z* calcd for $[C_{17}H_{14}O_6 + H]^+$ 315.0868, found 315.0875.

(+)-Kalafungin (1). To the solution of quinone **25** (0.035 g, 0.111 mmol) in CH_2Cl_2 (5 mL) under N_2 atmosphere at −50 °C was added BBr_3 (1 mL, 1 M solution in CH_2Cl_2, 1 mmol, 9 equiv) dropwise over 5 min. After 25 min at −50 °C, the reaction mixture was allowed to warm to room temperature and was stirred for 2 h. Water (5 mL) was added and stirred for 30 min. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography using petroleum ether/EtOAc (2:1 to 3:2) as eluent to give 66:34 mixture of kalafungin **1** and 5-*epi*-**1** (27.4 mg, 82%) as an orange crystalline solid. To the epimer mixture (27.4 mg) was added concentrated H_2SO_4 (1 mL) dropwise at room temperature. The dark red solution was stirred at room temperature for 25 min and carefully poured into brine in a separating funnel. A yellow solid precipitated out. It dissolved upon shaking with CH_2Cl_2 (30 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash silica gel column chromatography using petroleum ether/EtOAc (2:1 to 3:2) as eluent to give a 93:7 mixture of kalafungin **1** and 5-*epi*-**1**. A single recrystallization gave pure (+)-kalafungin **1** (15.3 mg, 56%) as yellow needles. Mp 168−170 °C, lit.[3c] 171−173 °C; $[\alpha]^{25}_{D}$ +160.6 (*c* 0.3, $CHCl_3$), lit.[3c] +160 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) υ_{max} 1795, 1730, 1670, 1655, 1625, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.57 (d, *J* = 6.9 Hz, 3H), 2.70 (d, *J* = 17.7 Hz, 1H), 2.98 (dd, *J* = 17.7, 5.2 Hz, 1H), 4.70 (dd, *J* = 5.1, 3.0 Hz, 1H), 5.01 (q, *J* = 6.9 Hz, 1H), 5.26 (d, *J* = 3.0 Hz, 1H), 7.30 (dd, *J* = 7.1, 2.6 Hz, 1H), 7.64−7.71 (m, 2H), 11.83 (s, 1H, *OH*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 36.8, 66.2, 66.4, 68.6, 114.7, 119.7, 124.8, 131.4, 135.0, 137.2, 149.7, 161.8, 174.0, 181.5, 187.9; HRMS *m*/*z* calcd for $[C_{16}H_{12}O_6 + H]^+$ 301.0711, found 301.0718.

(3a*R*,5*S*,11b*R*)-3,3a,5,11b-Tetrahydro-6,7,11-trimethoxy-5-propyl-1,4-dioxacyclopent[*a*]anthracen-2-one (26a) in a 70:30 Mixture with (3a*R*,5*R*,11b*R*)-3,3a,5,11b-Tetrahydro-6,7,11-trimethoxy-5-propyl-1,4-dioxacyclopent[*a*]anthracen-2-one

(26b). To a solution of compound **7** (95 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) at 0 °C was added *n*-butyraldehyde (0.054 mL, 0.60 mmol, 2.0 equiv) followed by TMSOTf (0.06 mL, 0.33 mmol, 1.1 equiv). The resulting reaction mixture was stirred at 0 °C for 2 h. It was then quenched with satd aq $NaHCO_3$ (5 mL), and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford inseparable mixture of **26a** and **26b** (80 mg, 72%, 70:30 by ^1H NMR) as white solid. Mp 135−137 °C. Spectral data for major *syn*-diastereomer (**26a**): ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 0.88 (t, J = 7.4 Hz, 3H), 1.24−1.47 (m, 2H), 1.95−2.24 (m, 2H), 2.74 (d, J = 17.5 Hz, 1H), 2.90 (dd, J = 17.2, 4.2 Hz, 1H), 3.75 (s, 3H), 4.02 (s, 3H), 4.09 (s, 3H), 4.35 (dd, J = 4.1, 2.3 Hz, 1H), 5.06 (dd, J = 7.1, 2.6 Hz, 1H), 5.59 (d, J = 2.2 Hz, 1H), 6.93 (dd, J = 7.6, 0.9 Hz, 1H), 7.44 (t, J = 8.3 Hz, 1H), 7.73 (dd, J = 8.5, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.3, 37.6, 38.5, 56.2, 61.5, 64.5, 70.9, 73.0 (2C), 107.2, 115.1, 119.5, 121.5, 126.5, 128.0, 130.1, 149.1, 153.0, 156.1, 175.9; HRMS m/z calcd for $[C_{21}H_{24}O_6 + H]^+$ 373.1651, found 373.1659.

(3a*R*,5S,11b*R*)-3,3a,5,11b-Tetrahydro-7-methoxy-5-propyl-1,4-dioxacyclopent[*a*]anthracen-2,6,11-trione (27a) in a 70:30 Mixture with (3a*R*,5*R*,11b*R*)-3,3a,5,11b-Tetrahydro-7-methoxy-5-propyl-1,4-dioxacyclopent[*a*]anthracen-2,6,11-trione (27b). CAN oxidation of mixture **26a** and **26b** (72 mg, 0.19 mmol) by a similar procedure as used for conversion of **7** to **23** produced a mixture of *syn*/*anti* diastereomers **27a** and **27b** (58 mg, 88%) as yellow solid. Mp 125−127 °C (decomp). Spectral data for major *syn*-diastereoomer (**27a**): ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 0.89 (t, J = 7.3 Hz, 3H), 1.27−1.49 (m, 2H), 1.77−2.04 (m, 2H), 2.72 (d, J = 17.4 Hz, 1H), 2.90 (dd, J = 17.4, 4.6 Hz, 1H), 4.01 (s, 3H), 4.32 (dd, J = 4.5, 2.5 Hz, 1H), 4.73−4.75 (m, 1H), 5.29 (d, J = 3.8 Hz, 1H), 7.30 (dd, J = 8.2, 0.9 Hz, 1H), 7.70 (dd, J = 8.0, 8.0 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 18.3, 35.4, 37.3, 56.5, 69.8, 70.9, 72.3, 118.0, 119.3, 120.2, 132.8, 133.61, 135.3, 152.2, 159.4, 174.6, 182.3, 183.4; HRMS m/z calcd for $[C_{19}H_{18}O_6 + H]^+$ 343.1182, found 343.1178.

(+)-Frenolicin B (2) and 5-*epi*-Frenolicin B (28). To a stirred solution of mixture **27a** and **27b** (50 mg, 0.146 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL) at −50 °C was added a solution of BBr_3 (1.5 mL, 1.46 mmol, 1 M in CH_2Cl_2, 10 equiv) dropwise over 10 min. The resulting reaction mixture was stirred at −50 °C for 30 min and then warmed to room temperature and stirred for 2 h. It was then quenched with satd aq $NaHCO_3$ (2 mL), and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford **28** (11.5 mg, 24%) and **2** (27.8 mg, 58%) as yellow solids. Data for (+)-frenolicin B (**2**): mp 162−164; $[\alpha]^{25}_D$ +224 (c 0.6, CH_2Cl_2), lit.[4f] +226.0 (c 0.84, CH_2Cl_2); IR ($CHCl_3$) υ_{max} 3369, 1790, 1665, 1652, 1624, 922, 879 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ = 1.02 (t, J = 7.2 Hz, 3H), 1.57−1.80 (m, 4H), 2.71 (d, J = 17.7 Hz, 1H), 2.97 (dd, J = 17.7, 5.2 Hz, 1H), 4.62 (dd, J = 5.0, 3.0 Hz, 1H), 4.91 (dd, J = 10.3, 3.1 Hz, 1H), 5.26 (d, J = 3.0 Hz, 1H), 7.29 (dd, J = 7.4, 2.1 Hz, 1H), 7.64−7.70 (m, 2H), 11.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 19.5, 33.6, 36.8, 66.2, 68.7, 69.6, 114.8, 119.7, 124.8, 131.4, 135.1, 137.1, 149.2, 161.8, 174.0, 181.5, 188.0; HRMS m/z calcd for $[C_{18}H_{16}O_6 + H]^+$ 329.1025, found 329.1032. Data for 5-*epi*-frenolicin B (**28**): mp 185−187 °C; $[\alpha]^{25}_D$ −224.1 (c 0.2, $CHCl_3$), lit.[4g] −244 (c 0.1, $CHCl_3$); IR ($CHCl_3$) υ_{max} 3505, 1790, 1666, 1645, 1618, 1577, 890, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 0.91 (t, J = 7.3 Hz, 3H), 1.28−1.48 (m, 2H), 1.90−2.09 (m, 2H), 2.73 (d, J = 17.4 Hz, 1H), 2.90 (dd, J = 17.4, 4.4 Hz, 1H), 4.33 (dd, J = 4.6, 2.4 Hz, 1H), 4.77 (dd, J = 4.1, 1.8 Hz, 1H), 5.28 (d, J = 1.9 Hz, 1H), 7.30 (dd, J = 7.6, 1.9 Hz, 1H), 7.65−7.71 (m, 2H), 11.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.9, 18.2, 36.0, 37.3, 69.7, 70.8, 71.8, 115.0, 119.6, 124.8, 131.4, 136.2, 137.1, 149.7, 161.7, 174.4, 181.4, 188.7; HRMS m/z calcd for $[C_{18}H_{16}O_6 + H]^+$ 329.1025, found 329.1036.

(+)-Frenolicin B (2) from 5-*epi*-Frenolicin B (28). To 5-*epi*-frenolicin B **28** (11 mg, 0.0335 mmol) was added conc H_2SO_4 (0.5 mL). The resulting mixture was stirred at room temperature for 25 min. Brine solution (5 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with satd aq $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford a mixture of **2** and **28** in 94:6 ratio. A single recrystallization gave pure (+)-frenolicin B **2** (6.6 mg, 60%) as yellow solid. The analytical and spectral data are the same as above.

(+)-Deoxyfrenolicin (3). To a solution of frenolicin B **2** (10 mg, 0.03 mmol) in EtOAc (5 mL) was added 10% Pd/C (5 mg). The resulting reaction mixture was stirred at room temperature under H_2 atmosphere (balloon pressure) for 6 h. EtOAc was then removed under reduced pressure, and the residue was purified by silica gel column chromatography using CH_2Cl_2/EtOAc (4:1) as eluent to afford (+)-deoxyfrenolicin **3** (8 mg, 80%) as orange solid. Mp 173−175 °C; $[\alpha]^{25}_D$ +111.8 (c 0.6, MeOH), lit.[4a] 118.4 (c 1.0, MeOH); IR ($CHCl_3$) υ_{max} 1724, 1661, 1644, 1618, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 1.00 (t, J = 7.3 Hz, 3H), 1.50−1.61 (m, 1H), 1.63−1.74 (m, 1H), 1.75−1.82 (m, 2H), 2.35 (ddd, J = 19.2, 10.5, 1.9 Hz, 1H), 2.71 (d, J = 6.4 Hz, 2H), 2.85 (dd, J = 19.2, 3.4 Hz, 1H), 4.27−4.34 (m, 1H), 4.85 (t, J = 6.0 Hz, 1H), 7.24 (dd, J = 8.3, 1.8 Hz, 1H), 7.58−7.64 (m, 2H), 12.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.3, 27.7, 34.5, 40.4, 63.1, 70.8, 114.7, 119.2, 124.5, 131.7, 136.3, 142.0, 145.7, 161.6, 175.4, 183.0, 188.4; HRMS m/z calcd for $[C_{18}H_{18}O_6 + Na]^+$ 353.1001, found 353.1011.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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