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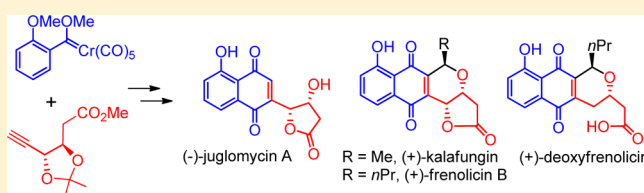
A Chiron Approach to the Total Synthesis of (–)-Juglomycin A, (+)-Kalafungin, (+)-Frenolicin B, and (+)-Deoxyfrenolicin

Rodney A. Fernandes,* Vijay P. Chavan, Sandip V. Mulay, and Amarendra Manchoju

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, Maharashtra, India

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 H₂SO₄-mediated epimerization.



Pyranonaphthoquinones are a class of compounds isolated from various strains of bacteria and fungi¹ 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 agents² 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 4⁶ 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 tandem 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 deoxyfrenolicin⁵ 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 molecules⁷ we utilized Dötz benzannulation⁸ 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 reaction¹⁰ 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-Fuchs¹¹ 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 K₂CO₃ (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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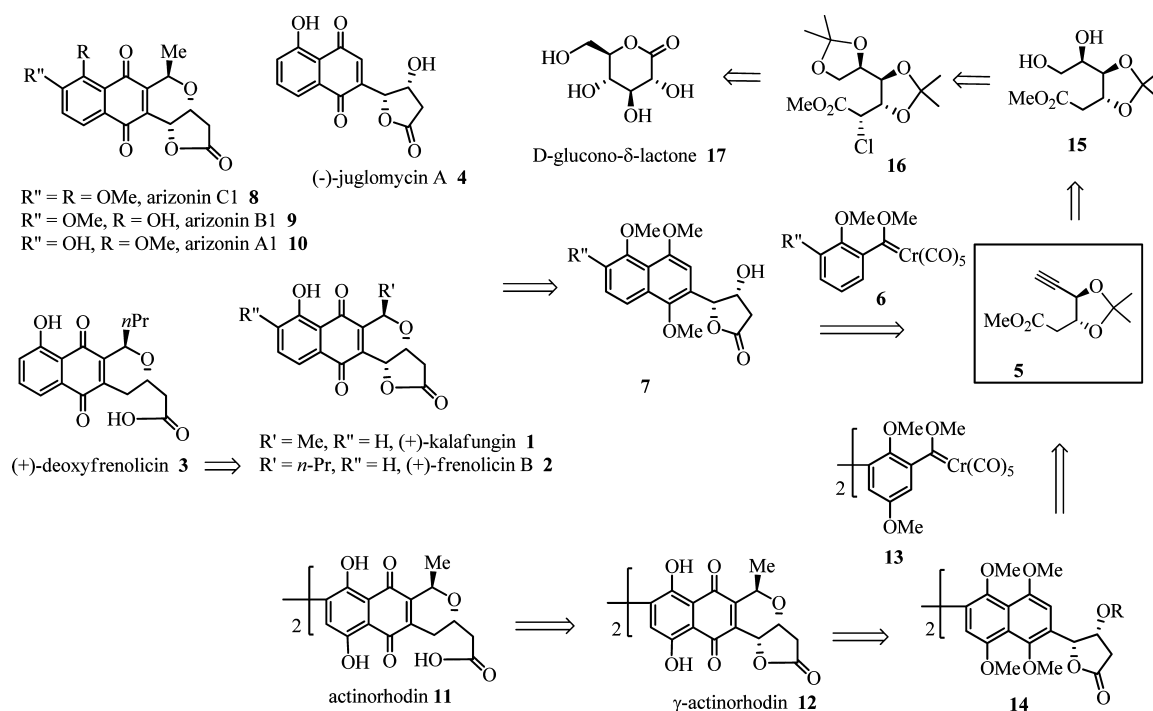
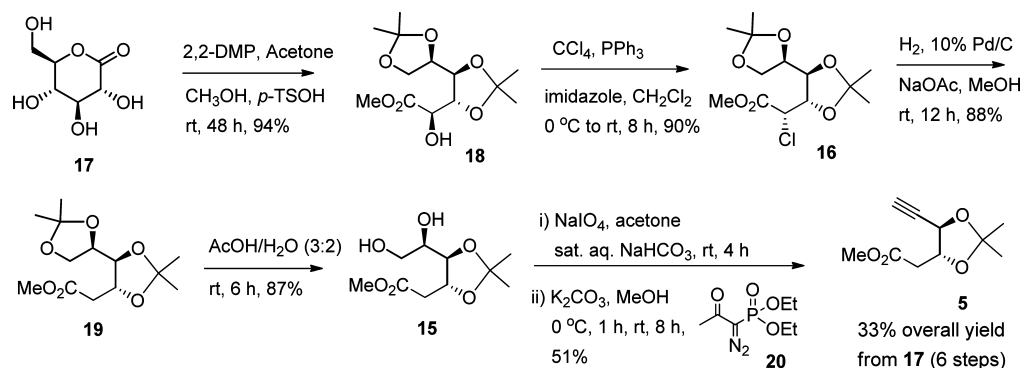
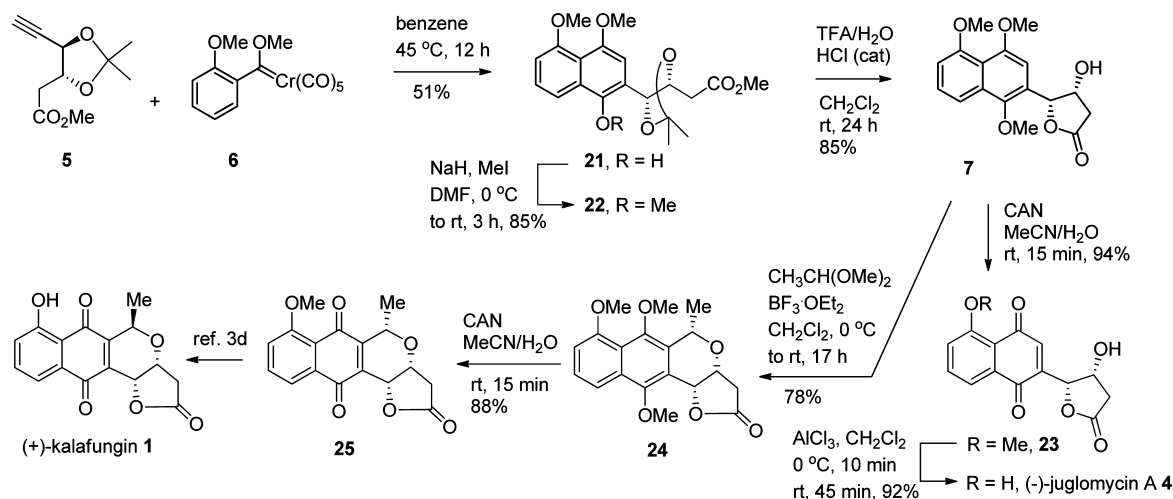


Figure 1. Various pyranonaphthoquinones, related molecules, and a common strategy for their synthesis.

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



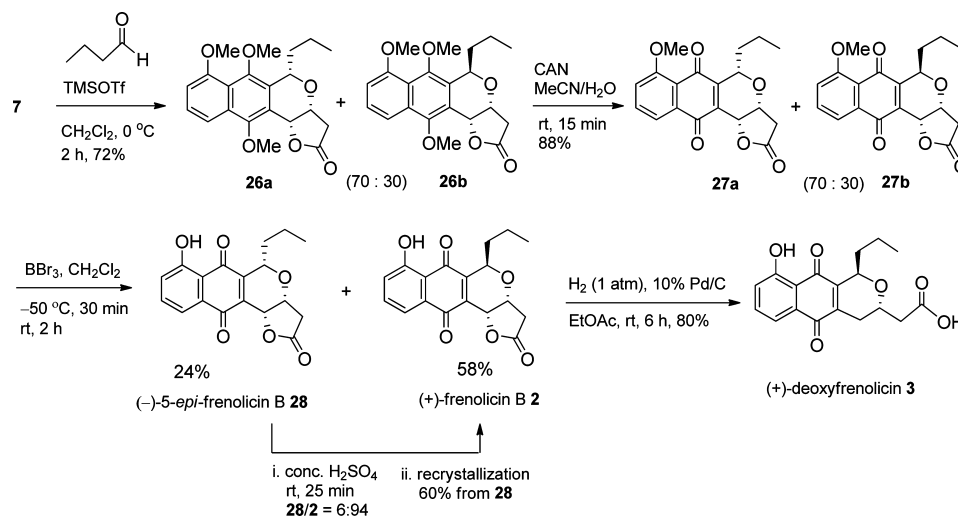
Scheme 2. Synthesis of (–)-Juglomycin A 4 and (+)-Kalafungin 1 from Alkyne 5



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: $[\alpha]_D^{25} -51.8$ (c 0.3, DMSO), lit.^{6a} -51.9 (c 0.42, DMSO). For

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 $\text{BF}_3 \cdot \text{OEt}_2$ 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 ^1H 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**): $[\alpha]_D^{25} +224$ (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 $\text{H}_2/\text{Pd}-\text{C}$ resulted in opening of the lactone to provide (+)-deoxyfrenolicin **3** in good yield of 80%: $[\alpha]_D^{25} +111.8$ (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 . ^1H 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-isopropylidenedioxyhexanoate (15). To diacetone **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. $[\alpha]_D^{25} +8.2$ (c 1.4, CHCl_3); IR (CHCl_3) ν_{max} 3449, 1735, 1439, 1382, 906, 885 cm^{-1} ; ^1H 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 $[\text{C}_{10}\text{H}_{18}\text{O}_6 + \text{Na}]^+$ 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 \times 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. $[\alpha]_D^{25} +1.6$ (c 0.9, CHCl_3); IR (CHCl_3) ν_{max} 3273, 2123, 1743, 1439, 1383, 1372, 995, 906 cm^{-1} ; ^1H 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 $[\text{C}_{10}\text{H}_{14}\text{O}_4 + \text{H}]^+$ 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

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. $[\alpha]_D^{25} +7.2$ (c 0.6, CHCl₃); IR (CHCl₃) ν_{\max} 3372, 1741, 1630, 1602, 1514, 1463, 1438, 986, 911 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/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); ¹³C NMR (100 MHz, CDCl₃) 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 [C₂₀H₂₄O₇ + 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 (Na₂SO₄), 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. $[\alpha]_D^{25} +34.5$ (c 0.3, CHCl₃); IR (CHCl₃) ν_{\max} 1743, 1599, 1588, 1459, 911 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/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); ¹³C NMR (100 MHz, CDCl₃) 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 [C₂₁H₂₆O₇ + 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 CH₂Cl₂ (4 mL) were added TFA/H₂O (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 NaHCO₃ (2 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), 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; $[\alpha]_D^{25} -12.5$ (c 0.6, CHCl₃); IR (CHCl₃) ν_{\max} 3469, 1780, 1734, 1623, 1601, 1586, 981, 905 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/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); ¹³C NMR (100 MHz, CDCl₃) 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 [C₁₇H₁₈O₆ + 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; $[\alpha]_D^{25} -58.2$ (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); $[\alpha]_D^{25} -51.8$ (c 0.3, DMSO), lit.^{6a} –51.9 (c 0.42, DMSO). Spectral and analytical data is same as reported earlier.^{6j}

(3*R*,5*S*,11*bR*)-3,3*a*,5,11*b*-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 CH₂Cl₂ (10 mL) at 0 °C were added acetaldehyde dimethyl acetal (0.046 mL, 0.44 mmol, 2.0 equiv) and BF₃·OEt₂ (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 NaHCO₃ (5 mL), and the solution was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), 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; $[\alpha]_D^{25} +22.5$ (c 0.2, CHCl₃); IR (CHCl₃) ν_{\max} 1779, 1594, 1574, 996, 906 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/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); ¹³C NMR (100 MHz, CDCl₃) 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 [C₁₉H₂₀O₆ + H]⁺ 345.1338, found 345.1345.

(3*R*,5*S*,11*bR*)-3,3*a*,5,11*b*-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); $[\alpha]_D^{25} -160$ (c 0.3, CHCl₃); IR (CHCl₃) ν_{\max} 1795, 1670, 1640, 1590, 995, 900 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/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); ¹³C NMR (100 MHz, CDCl₃) 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 [C₁₇H₁₄O₆ + H]⁺ 315.0868, found 315.0875.

(+)-Kalafungin (1). To the solution of quinone **25** (0.035 g, 0.111 mmol) in CH₂Cl₂ (5 mL) under N₂ atmosphere at –50 °C was added BBr₃ (1 mL, 1 M solution in CH₂Cl₂, 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 CH₂Cl₂ (3 × 10 mL), and the combined organic layers were washed with water, dried (Na₂SO₄), 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 H₂SO₄ (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 CH₂Cl₂ (30 mL). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (2 × 30 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), 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; $[\alpha]_D^{25} +160.6$ (c 0.3, CHCl₃), lit.^{3c} +160 (c 0.3, CHCl₃); IR (CHCl₃) ν_{\max} 1795, 1730, 1670, 1655, 1625, 905 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/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); ¹³C NMR (100 MHz, CDCl₃) 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 [C₁₆H₁₂O₆ + H]⁺ 301.0711, found 301.0718.

(3*R*,5*S*,11*bR*)-3,3*a*,5,11*b*-Tetrahydro-6,7,11-trimethoxy-5-propyl-1,4-dioxacyclopent[*a*]anthracen-2-one (26*a*) in a 70:30 Mixture with (3*R*,5*R*,11*bR*)-3,3*a*,5,11*b*-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 $[\text{C}_{21}\text{H}_{24}\text{O}_6 + \text{H}]^+$ 373.1651, found 373.1659.

(3aR,5S,11bR)-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 (3aR,5R,11bR)-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*-diastereomer (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 $[\text{C}_{19}\text{H}_{18}\text{O}_6 + \text{H}]^+$ 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; $[\alpha]_D^{25} +224$ (c 0.6, CH_2Cl_2), lit.^{4f} +226.0 (c 0.84, CH_2Cl_2); IR (CHCl_3) ν_{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 $[\text{C}_{18}\text{H}_{16}\text{O}_6 + \text{H}]^+$ 329.1025, found 329.1032. Data for 5-*epi*-frenolicin B (28): mp 185–187 °C; $[\alpha]_D^{25} -224.1$ (c 0.2, CHCl_3), lit.^{4g} –244 (c 0.1, CHCl_3); IR (CHCl_3) ν_{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 $[\text{C}_{18}\text{H}_{16}\text{O}_6 + \text{H}]^+$ 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 $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (4:1) as eluent to afford (+)-deoxyfrenolicin 3 (8 mg, 80%) as orange solid. Mp 173–175 °C; $[\alpha]_D^{25} +111.8$ (c 0.6, MeOH), lit.^{4a} 118.4 (c 1.0, MeOH); IR (CHCl_3) ν_{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 $[\text{C}_{18}\text{H}_{18}\text{O}_6 + \text{Na}]^+$ 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>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rfernand@chem.iitb.ac.in.

Notes

The authors declare no competing financial interest.

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