Direct Total Syntheses of Frenolicin B and Kalafungin via Highly Regioselective Diels–Alder Reactions

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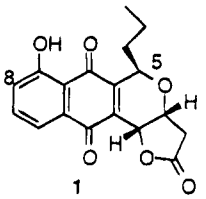
Frenolicin B, an anticoccidial agent, has been synthesized in six steps from ketone **3**. Racemic kalafungin, an antifungal agent, has been synthesized in five steps. The key step in both syntheses, a regioselective Diels–Alder reaction, proceeds with complete regiocontrol and in excellent yield. One rationale for the remarkable stereocontrol is that the lactone ring induces ring-puckering in the quinone subunit which, in consort with electrostatic repulsion, contributes to the regioselectivity.

The synthesis of quinones is a topic of continuing interest because the quinone subunit is contained in a significant number of biologically important natural products.[1] This subunit is present in anticancer agents such as the anthracyclines and mitomycins, antibiotics, antifungal agents such as kalafungin, and anticoccidial agents such as frenolicin B.



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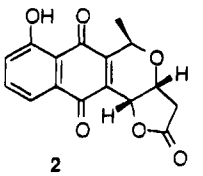

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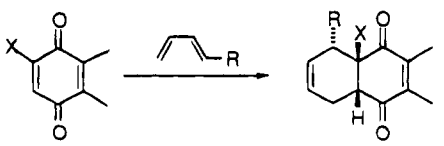
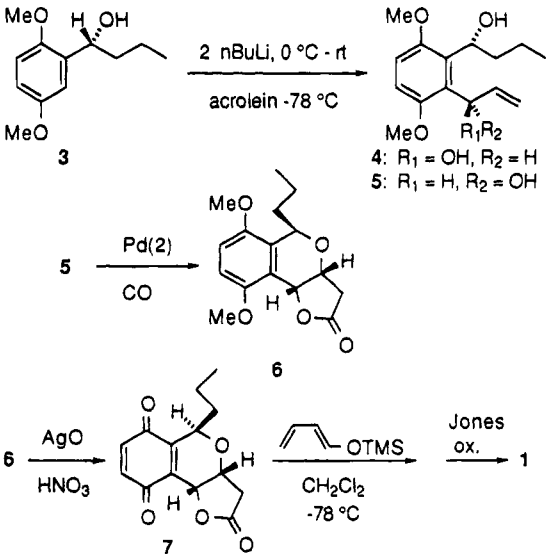
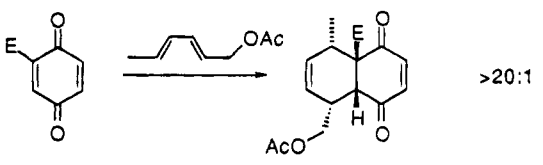
A number of synthetic methods involving cycloadditions, carbanion-mediated annulations, and electrophilic reactions have been reported.[2] Among the pathways featuring a cycloaddition reaction, one of the most general methods for the regiospecfic synthesis of substituted quinones was pioneered by Rapoport and co-workers.[3] This method involves the Diels–Alder reaction of a substituted quinone and is depicted below. The X group is usually chlorine or bromine, but sulfoxides and nitriles can also be employed.[4] However, the necessity of the X group often simply refocusses the synthetic problem to the regioselective synthesis of a substituted haloquinone. Metalation reactions have played a key role in the preparation of intermediates for the synthesis of functionalized quinones. The requirement of a halogen atom imposes certain restrictions on the synthetic route to the quinone.



As part of a program to evaluate the directing effects of functional groups not directly attached to the atoms involved in the cycloaddition reaction, we discovered the highly regioselective Diels–Alder reaction shown below.[5] The allylic ester moiety on the diene appears to be responsible for controlling the excellent regioselectivity,

Scheme 1





since the corresponding alcohol or methyl ether furnished essentially a 1:1 mixture of regioisomeric adducts. We have recently reported that remote substituents on a dienophile can also confer excellent regioselectivity in Diels–Alder reactions.[6] This work led to an extremely direct synthesis of the pyranonaphthoquinone framework and to the first synthesis of frenolicin B (**1**). We now report a full account of the frenolicin B synthesis in addition to a concise synthesis of racemic kalafungin (**2**).

The Synthesis of Frenolicin B. The synthesis of **1** is shown in Scheme 1. The first step involves the reduction of 2,5-dimethoxybutyrophenone using the method of Brown.[7] Proton NMR analysis of the Mosher

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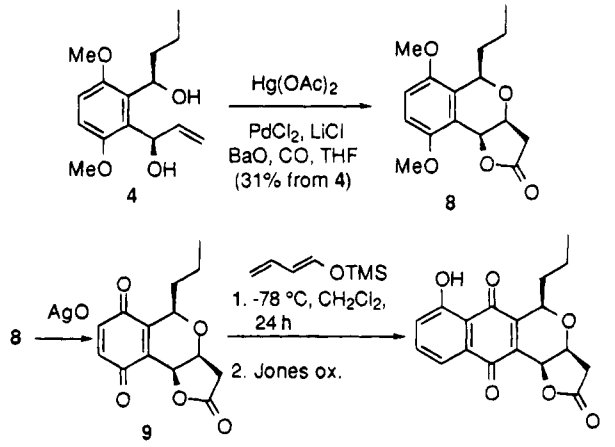
Scheme 2



ester of **3** indicated an enantiomeric excess of approximately 95%. This reaction was superior to the reaction of 2,5-dimethoxybenzaldehyde with dipropylzinc and quinine[8] which proceeded in 83% yield and afforded an enantiomeric excess of only 70%.

Metalation of alcohol **3** using 2 equiv of n-butyllithium in ether to generate the dianion followed by reaction with acrolein afforded diols **4** and **5** in a combined yield of only 44%. The major product appeared to be derived from metalation either meta or para to the benzylic alcohol. When the reaction was conducted in 1:10 ether:pentane solution, the alcohols **4** and **5** were isolated in 56% yield, with only 10% of the undesired isomeric product. Diols **4** and **5** were generated in a 1:1.5 ratio and could be separated by flash chromatography. The control of metalation selectivity simply by decreasing the polarity of the solvent may be generally useful. In a related synthesis of hongconin,[9] increasing the proportion of hexane in the ether:hexane solvent mixture also improved the yield of ortho-metalated products. In this case, the effectiveness was limited by the solubility of the anion of the benzylic alcohol. Cyclization of alcohol **5** with palladium acetate and CO in analogy with the work of Semmelhack[10] provided lactone **6** in 65% yield. Oxidation of lactone **6** with AgO[11] provided **7** in 95% yield.

In order to determine whether the lactone moiety influenced the regioselectivity of the Diels–Alder reaction, we examined a Diels–Alder reaction of quinone **7**. Treatment of benzoquinone **7** with 1-[(trimethylsilyl)oxy]-butadiene afforded a Diels–Alder adduct which was immediately treated with excess Jones reagent to provide frenolicin B in 80% isolated yield from **7**. There were no traces of an isomeric quinone. Our product was identical by proton NMR, IR, TLC, and ^{13}C NMR to an authentic sample of frenolicin B supplied by the Hoffmann-LaRoche Co. Interestingly, the ^{13}C NMR of frenolicin B was somewhat concentration dependent. In order to be absolutely certain that the regioselective reaction actually generated the desired product, we also determined the structure of our compound by X-ray crystallography.[12]

The excellent regioselectivity was welcome but was not expected. In order to better understand the origins of the selectivity in terms of the structure of the quinone, we prepared the isomeric quinone **9** from diol **4** (Scheme 2). This molecule was synthesized to probe the steric effect of the propyl group. The reaction of **9** with 1-[(trimethylsilyl)oxy]-1,3-butadiene followed by Jones oxidation of the unpurified adduct afforded 5-*epi*-frenolicin B in 65% yield. Thus, the regioselectivity of the Diels–Alder reaction was excellent in cycloadditions both with quinones bearing an exo propyl group and with quinones bearing an endo propyl group.

Molecular Electrostatic Potentials. A Rationale for Regioselectivity. In order to better understand the role of the ring substituents on the regioselectivity of the Diels–Alder reaction discussed above, the molecular geometries of **7** and **9** were optimized without symmetry constraints at the AM1[13] level of theory and verified as minima by calculating numerically and then diagonalizing the Hessian (matrix of energy second derivatives). Although the initial optimizations resulted in structures in which the propyl group on the dihydropyran ring is equatorial (hereafter referred to as **7e** and **9e**), subsequent studies indicated that the conformations with axial propyl groups (**7a** and **9a**) are slightly lower in energy. At the AM1 level of theory, the free energy[14] at −78 °C (ΔG_{195}) for **7e** (**9e**) is 1.9 (2.7) kcal/mol higher than **7a** (**9a**). Single point RHF/6-31G(d)[15] energy calculations using the AM1 geometries and frequencies (denoted RHF/6-31G(d)//AM1) resulted in very similar ΔG_{195}'s: 3.0 kcal/mol for **7** and 2.4 kcal/mol for **9**. The conclusions drawn regarding the observed regioselectivity are independent of whether the propyl group is axial or equatoral, as will be shown below.

The RHF/6-31G(d) wave functions were then used to calculate molecular electrostatic potentials (MEPs).[16] Here, a MEP is defined as the potential felt by a +1 test charge due to the molecular charge density, evaluated over a grid of points in a given plane of the molecule. The contour map thus generated identifies relative positively and negatively charged regions of the molecule and can be used, for example, to indicate likely sites for electrophilic and nucleophilic attack. All calculations were performed with the electronic structure program GAMESS.[17]

Figure 1 shows two MEPs of **7a** evaluated in planes 2 Å below (Figure 1a) and 2 Å above (Figure 1c) and parallel with the dienophile (DP) plane. Figure 1b schematically depicts the orientation of **7a** in the MEPs. Both MEPs show a positive center region (solid lines) with negative regions (dotted lines) at either side. The plane above the ring shows an almost equal negative charge distribution on either side. The plane below the ring shows more negative charge on the left side, presumably due mostly to the lactone ring-oxygen, and only one negative contour on the right side. Compare this to the MEP of the diene 2 Å above the σ_v symmetry plane, shown in Figure 2. The MEP shows significantly more negative charge on the substituent side of the diene, presumably due to an oxygen lone pair, *in the region most*

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(14) Changes in enthalpy are within 0.1 kcal/mol for all reported changes in free energy.
(15) Harihanan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
(16) *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Thrular, D. G., Eds.; Plenum Press: New York, 1981. Previous studies have successfully used MEPs to explain the regioselectivity in Diels–Alder reactions: Khan, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663. Kraus, G. A.; Li, J.; Gordon, M. S.; Jensen, J. H. *J. Am. Chem. Soc.* **1993**, *115*, 5859. Kraus, G. A.; Li, J.; Gordon, M. S.; Jensen, J. H. *J. Org. Chem.* **1994**, *59*, 2219.
(17) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, A.; Matsunaga, S.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

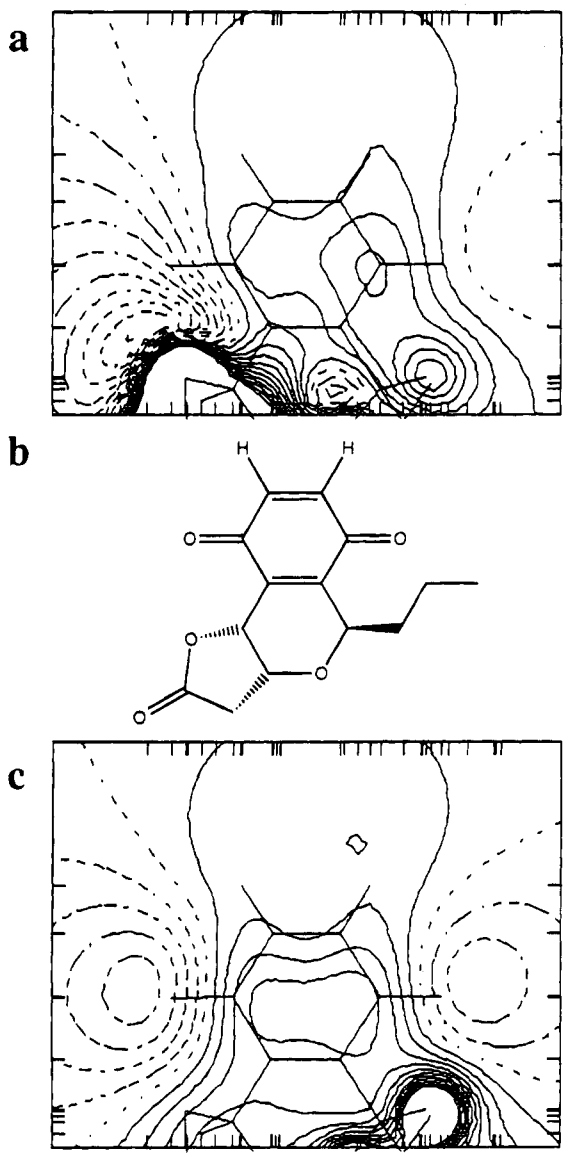

Figure 1. MEPS of **7a** evaluated in planes 2 Å below (a) and above (c) the DP plane. The contour spacing is 5 kcal/mol·e. The more dense the contours, the more electron rich (or deficient) the region. (b) Schematic orientation of **7a** in the MEPs.

likely to interact with dienophile substituents (see Figure 2c and the MEPs in Figure 1). This assumes the TMS group is *cis* to the neighboring CC double bond, which is the orientation that minimizes steric intertacions of the bulky TMS as the diene and dienophile approach. Thus, the MEPs in Figures 1 and 2 indicate that the incoming diene should prefer to react with **7** from below the plane of the ring with the OTMS substituent away from the butyrolactone ring. The other three approaches are disfavored by electrostatic repulsions between the OTMS substituent and the butyrolactone ring- and quinone-oxygens, as depicted schematically in Figure 3. This provides a rationale for the experimentally observed regioselectivity, and the Diels–Alder adduct **A** is predicted as a synthetic intermediate between **7** and **1**. An identical analysis of **7e**[6] results in the same conclusion, and was verified by the isolation and identification, using 2D-NOESY NMR, of **A**.

Figure 4 shows MEPs for **9a** that are analogous to those in Figure 1. These MEPs indicate that the diene should prefer to react with **9** from *above* the plane of the

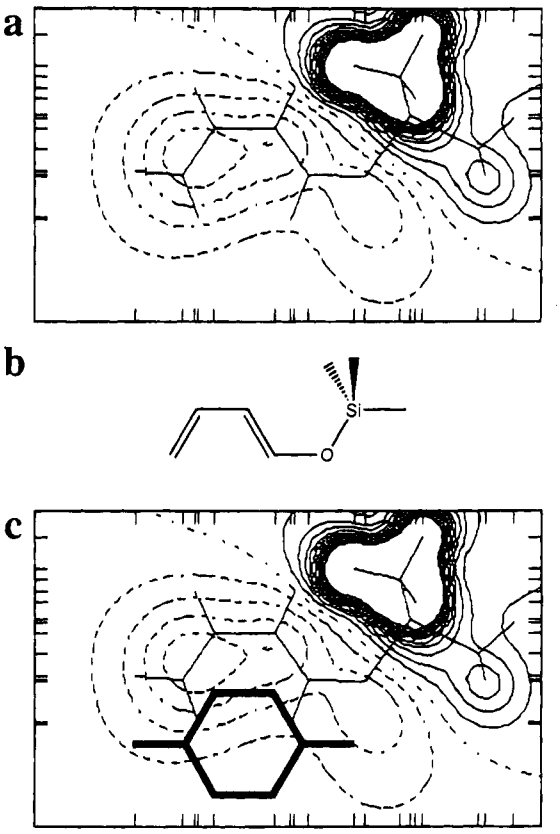

Figure 2. (a) RHF/6-31G(d)//AM1 MEP of 1-[(trimethylsilyl)-oxy]-1,3-butadiene evaluated in a plane 2 Å above the plane of symmetry. The contour spacing is 5 kcal/mol·e. (b) Schematic orientation of the molecule in the MEP. (c) Same as part a but with part of the dienophile structure superimposed (bold lines) to show the regions of the MEP likely to interact with the dienophile substituents as the diene approaches.

ring and with the OTMS substituent away from the butyrolactone ring.

The observed regioselectivity thus appears to be dictated by the unequal charge distribution and the molecular geometry. The quinone oxygens force the reaction to occur on one face of the quinone ring, where the butyrolactone ring-oxygen directs the OTMS substituent away from the butyrolactone ring. The fact that the quinone oxygens disfavors one ring face indicates that the the quinone ring is nonplanar. Figure 5a shows that the quinone ring of **7a** is indeed puckered such that the two quinone oxygens are bent above the DP plane, disfavoring attack from above (Figure 1c). The degree of puckering can be gauged by the dihedral angles between the oxygens and the alkene carbons, defined as τ and τ' in Figure 5: both would be 180° for a planar ring. For **7a**, τ and τ' equal 164° and −170°—a 10°–15° deviation from planarity (negative and positive dihedral angles refer to clockwise and counterclockwise rotation around the center bond; cf. Figure 5b). Figure 5c shows a similar puckering of the quinone ring of **9a**, but in the opposite direction—away from the butyrolactone ring. The deviation from planarity for **9a** is only slighty less than for **7a**, with τ and τ' values of −168° and 172°, respectively. Therefore, it appears that the butyrolactone ring induces the quinone ring-puckering that contributes to the regioselectivity.

The Synthesis of Racemic Kalafungin. Kalafungin is a novel antifungal agent. Kalafungin has been synthesized by Tatsuta, Li, and Kraus.[18] We were interested in extending the strategy developed in the frenolicin B

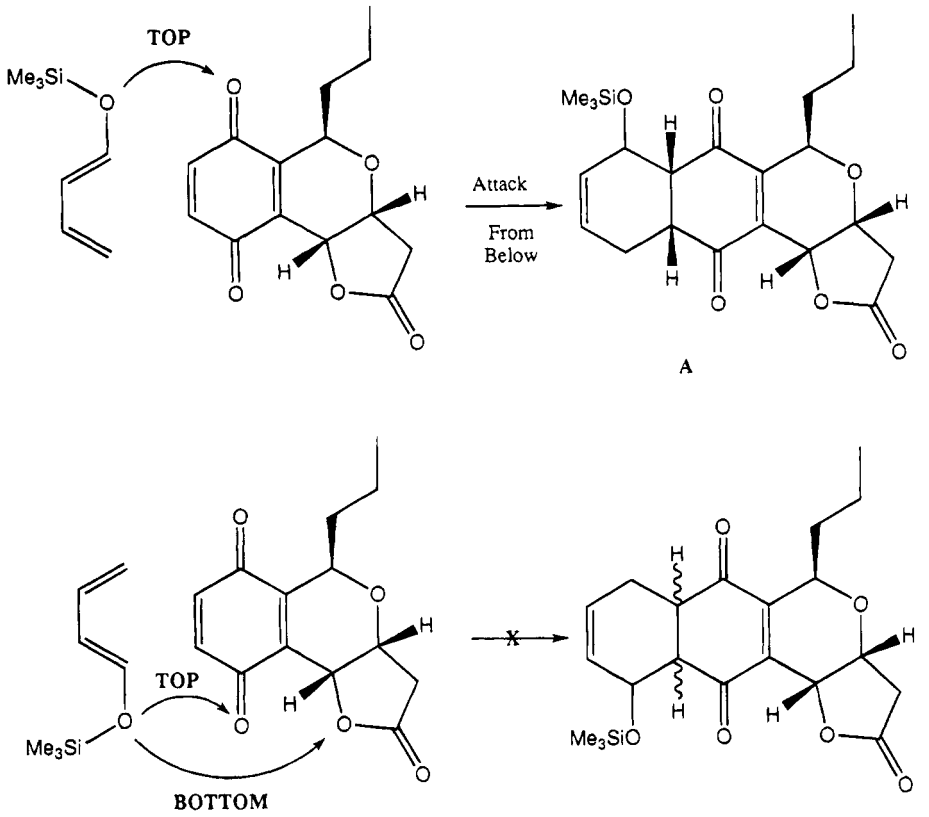

Figure 3. Schematic depiction of the four possible approaches of the dienophile when reacting with **7a**. The curved arrows represent electrostatic repulsions, suggested by the MEPs in Figures 1 and 2, that disfavor that approach.

synthesis to a direct synthesis of kalafungin. Our synthesis of racemic kalafungin (**2**) began with diol **10**, a key intermediate in our synthesis of hongconin.[9] The reaction of **10** with palladium acetate and cupric chloride under an atmosphere of carbon monoxide provided lactone **11** in 61% yield (Scheme 3). Oxidation using the standard Rapoport conditions (AgO, HNO_3) generated benzoquinone **12** in 91% yield. Quinone **12** was treated with 1-[(trimethylsilyl)oxy]-1,3-butadiene in methylene chloride followed by Jones oxidation to provide racemic **2** in 63% yield from **11**. Our spectra of racemic kalafungin were identical to those of a sample synthesized by our group using a completely different synthetic route.[18]

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). The purity of all title compounds was determined to be >95% by 300 MHz proton NMR and/or elemental analysis.

(*R*)-(2,5-Dimethoxyphenyl)propylcarbinol (3). A solution of (+)-IpC_2BCl (10 g, 31 mmol) in THF (20 mL) was cooled to −25 °C, and 2,5-dimethoxybutyrophenone (5.4 g, 26 mmol) was added. The reaction solution was stirred at −25 °C and monitored by TLC. When the reaction was complete, the mixture was raised to rt, and THF was removed at aspirator pressure. The α-pinene liberated during the reaction was removed in vacuo. The residue was dissolved in 100 mL of ethyl ether, diethanolamine (6.28 g, 60 mmol) was added, and the mixture was stirred for 3 h. The resulting solid was filtered off and washed with pentane (2 × 50 mL). The combined filtrates were concentrated. The residue was purified by sgc using 6:1 H:EA. The yield of alcohol **3** was 99% (5.4 g): $[\alpha]^{25}_D$ 24.6° (*c* 2.2, CH_2Cl_2); NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.5, 3 H), 1.24−1.85 (m, 4 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 4.84 (dd, *J* = 5.7, 7.5 Hz, 1 H), 6.72−6.83 (m, 2 H), 6.89 (d, *J* = 3.0, 1 H); IR (neat) cm^{-1} 3438, 1496, 1464, 1275, 1214, 1177, 1027; TLC (H:E = 4:1) R_f = 0.5.

(*R*)-[2,5-Dimethoxy-6-(1-hydroxy-2-propenyl)phenyl]-propylcarbinol (5). To the benzylic alcohol (4.3 g, 20.4 mmol) in 220 mL of 1:10 ether:pentane at 0 °C was added nBuLi (19.8 mL, 43 mmol) dropwise with vigorous stirring. The solution was allowed to warm to rt and stirred for 20 h. The solution was then cooled to −78 °C, and a solution of acrolein (3.0 mL, 45 mmol) in 10 mL of pentane was added. After the reaction had stirred for 8 h at −78 °C, it was quenched with saturated ammonium chloride solution and extracted five times with ether/ethyl acetate. The organic layers were dried and concentrated. Purification by sgc using 8:1 and then 4:1 hexanes: ethyl acetate followed by recrystallization from CH_2Cl_2/hexane afforded 42.2% of desired diastereomer, 25.2% of undesired diastereomer: NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3 H), 1.33−1.65 (m, 4 H), 1.88−2.20 (m, 1 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 5.06−5.22 (m, 2 H), 5.65−5.75 (m, 1 H), 6.13−6.26 (m, 1 H), 6.76−6.82 (m, 2 H); IR ($CDCl_3$) cm^{-1} 3606, 3541, 3153, 2960, 2837, 1475, 1464, 1250, 1228, 921, 755; MS: *m/e* 91, 103, 121, 146, 162, 177, 205, 223, 248, 266; HRMS: calcd 266.15181, measured 266.15129; CMR ($CDCl_3$) δ 13.96, 19.64, 39.45, 55.74, 55.92, 69.64, 70.05, 110.30, 110.46, 114.33, 129.09, 131.91, 140.16, 151.90; TLC (H:EA = 2:1) R_f = 0.34.

General Procedure for the Palladium-Mediated Cyclization Reaction. A mixture of diol (2.6 mmol), palladium acetate (0.78 mmol), and $CuCl_2$ (0.85 g, 6.3 mmol) in 50 mL of THF under an atmosphere of CO was vigorously stirred for 24 h. The mixture was concentrated and purified by sgc using hexanes:ethyl acetate.

(*R,R,R*)-6,9-Dimethoxy-3,3a,5,9b-tetrahydro-5-propylfuro[3,2-*c*][2]benzopyran-2-one (6). Purified by sgc using 6:1 and then 4:1 H:EA. The yield was 61%: NMR ($CDCl_3$) δ 0.99 (t, *J* = 7.2 Hz, 3 H), 1.45−1.78 (m, 4 H), 2.66 (d, *J* = 17.7 Hz, 1 H), 2.91 (dd, *J* = 4.8, 17.4 Hz, 1 H), 3.79 (s, 3 H), 3.84 (s, 3 H), 4.61 (dd, *J* = 3.0, 5.1 Hz, 1 H), 4.96 (dd, *J* = 3.9, 9.9 Hz,

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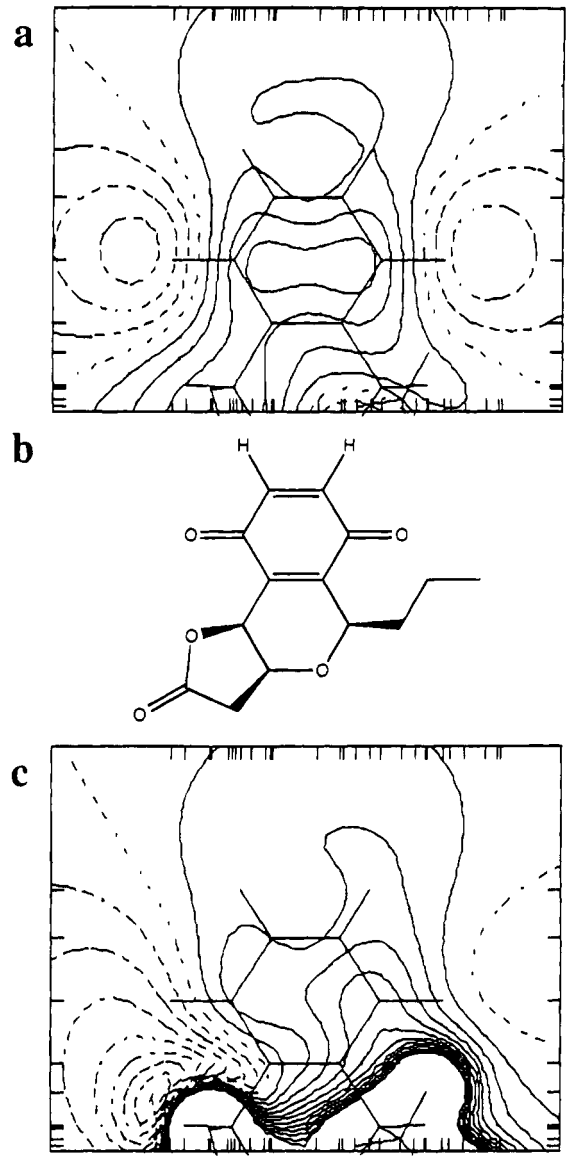


Figure 4. MEPs of **9a** evaluated in planes 2 Å below (a) and above (c) the DP plane. The contour spacing is 5 kcal/mol·e. (b) Schematic orientation of **9a** in the MEPs.

1 H), 5.33 (d, J = 2.7, 1 H), 6.80 (dd, J = 8.7, 21.9 Hz, 2 H); IR ($CDCl_3$) cm^{-1} 3004, 2958, 2937, 2872, 2837, 1777, 1604, 1486, 1463, 1430, 1263, 1201, 1156, 1077; MS: *m/e* 55, 77, 91, 121, 145, 162, 177, 190, 203, 221, 249, 292; HRMS: calcd 292.1311, measured 292.1311; CMR ($CDCl_3$) δ 13.70, 19.43, 33.56, 37.54, 55.68, 56.07, 65.67, 70.74, 71.57, 108.95, 111.48, 117.07, 129.64, 148.60, 152.52, 175.36; TLC (H:E = 2:1) R_f = 0.40. $[\alpha]^{25}_D$ 174.0° (*c* 0.80, CH_2Cl_2).

(*R*,R*,R)-6,9-Dimethoxy-3,3a,5,9b-tetrahydro-5-methylfuro[3,2-*c*][2]benzopyran-2-one (11).** Purified by sgc using 4:1 H:EA. The yield was 60%: NMR ($CDCl_3$) δ 1.47 (d, J = 6.6 Hz, 3 H), 2.63–2.96 (m, 2 H), 3.79 (s, 3 H), 3.84 (s, 3 H), 4.69 (dd, J_1 = 2.7 Hz, J_2 = 4.8 Hz, 1 H), 5.15 (q, J = 6.6 Hz, 1 H), 5.34 (d, J = 2.4 Hz, 1 H), 6.75–6.86 (dd, J_1 = 9 Hz, J_2 = 21.6 Hz, 2 H); IR ($CDCl_3$) 3154, 2938, 2837, 1781, 1603, 1486, 1438, 1404, 1321, 1296, 1262, 1205, 1157, 1078, 988, 921, 755 cm^{-1}; MS *m/e* 55, 77, 91, 103, 121, 145, 162, 190, 203, 221, 233, 249, 264; HRMS *m/e* for $C_{14}H_{16}O_5$ calcd 264.09977, measured 264.09960; CMR ($CDCl_3$) δ 18.09, 37.30, 55.31, 55.67, 65.70, 67.02, 71.26, 108.68, 111.17, 116.49, 129.57, 148.18, 152.13, 175.37; TLC (H:EA = 2:1) R_f = 0.29.

General Procedure for the Oxidation of Hydroquinone Dimethyl Ethers. To a suspension of silver oxide (AgO, Aldrich Chemical Co., 0.18 g, 1.15 mmol) and tricyclic lactone (0.36 mmol) in 9 mL of THF at rt was added 6 N HNO_3 (0.36 mL, 2.17 mmol). After the starting material was gone by TLC, the reaction was worked up by the addition of 20 mL of ether and 5 mL of water. The aqueous layer was extracted three times with ether. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by sgc.

(*R,R,R*)-3,3a,5,9b-Tetrahydro-5-propylfuro[3,2-*c*][2]benzopyran-2,6,9-trione (6). Purification using 2:1 H:EA afforded a 100% yield of tricyclic quinone: NMR ($CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 3 H), 1.50–1.75 (m, 4 H), 2.68 (d, J = 17.7 Hz, 1 H), 2.93 (dd, J = 5.4, 17.7 Hz, 1 H), 4.57 (dd, J = 3.3, 5.1 Hz, 1 H), 4.73 (dd, J = 4.5, 8.7 Hz, 1 H), 5.09 (d, J = 3.0 Hz, 1 H), 6.84 (dd, J = 6.6, 16.8 Hz, 2 H); IR ($CDCl_3$) cm^{-1} 2962, 2933, 2873, 1793, 1665, 1299, 1197, 1149, 1002; MS *m/e* 56, 77, 91, 99, 115, 135, 147, 161, 175, 191, 219, 262; HRMS calcd 262.0841, measured 262.0840; CMR ($CDCl_3$) δ 13.40, 19.34, 33.41, 36.66, 66.15, 68.41, 69.51, 132.12, 136.37, 136.47, 146.82, 174.04, 184.29, 185.11; TLC (H:EA = 2:1) R_f = 0.32; $[\alpha]^{25}_D$ 59.9° (*c* 1.28, CH_2Cl_2).

(*R,S,S*)-3,3a,5,9b-Tetrahydro-5-propylfuro[3,2-*c*][2]benzopyran-2,6,9-trione (9). Purification using 2:1 H:EA afforded a 95% yield of tricyclic quinone: NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3 H), 1.20–1.46 (m, 2 H), 1.78–2.02 (m, 2 H), 2.69–2.91 (m, 2 H), 4.30 (dd, J = 2.7 Hz, 4.5 Hz, 1 H), 4.60–4.63 (m, 1 H), 5.11 (t, J = 2.1 Hz, 1 H), 6.84 (dd, J_1 = 10.2 Hz, J_2 = 19.8 Hz, 2 H); IR ($CDCl_3$) 2963, 2932, 2874, 1791, 1663, 1602, 1405, 1324, 1299, 1260, 1203, 1149, 1048, 1004, 909, 842 cm^{-1}; MS: *m/e* 97, 127, 175, 191, 220, 262; HRMS *m/e* for $C_{14}H_{14}O_5$ calcd 262.08412, measured 262.08458; CMR ($CDCl_3$) δ 14.2, 18.3, 35.3, 37.2, 69.3, 70.9, 71.5, 133.3, 136.1, 137.1, 147.5, 174.5, 184.0, 185.8; TLC (H:EA = 2:1) R_f = 0.35.

(*R*,R*,R)-3,3a,5,9b-Tetrahydro-5-methylfuro[3,2-*c*][2]benzopyran-2,6,9-trione (12).** Purification using 2:1 H:EA afforded a 91% yield of tricyclic quinone: NMR ($CDCl_3$) δ 1.48 (d, J = 6.9 Hz, 3 H), 2.64–2.98 (m, 2 H), 4.84 (dd, J = 3.0 Hz, 5.1 Hz, 1 H), 4.91 (q, J = 6.9 Hz, 1 H), 5.09 (d, J = 3.0 Hz, 1 H), 6.85 (dd, J = 10.2 Hz, 17.4 Hz, 2 H); IR ($CDCl_3$) 2983, 2938, 2874, 1792, 1667, 1308, 1198, 1149, 922, 896, 841, 756, 652 cm^{-1}; MS *m/e* 151, 163, 175, 179, 191, 219, 234; HRMS *m/e* for $C_{12}H_{10}O_5$ calcd 234.05283, measured 234.05311; CMR ($CDCl_3$) δ 18.5, 36.8, 66.2, 66.4, 68.3, 132.1, 136.5, 147.3, 174.0, 184.3, 185.1; TLC (H:EA = 2:1) R_f = 0.27.

General Procedure for the Diels–Alder/Oxidation. To solution of the tricyclic quinone (0.12 mmol) in 1 mL of methylene chloride at −78 °C was added dropwise 1-[(trimethylsilyl)oxy]-1,3-butadiene (0.025 mL, 0.14 mmol). The solution was stirred at −78 °C for 4.5 h (starting material remained by TLC) and then allowed to slowly warm to rt overnight. The solvent was removed in vacuo.

The residue was dissolved in 1.5 mL of acetone, and 2.7 M Jones reagent (0.09 mL, 0.24 mmol) was added at 0 °C. The reaction was stirred for 40 min. The reaction was quenched with 2-propanol, stirred for 5 min, and concentrated in vacuo. The residue was partitioned between saturated ammonium chloride solution (10 mL) and ether (100 mL). The organic layer was washed with saturated NH_4Cl solution and brine and then dried over sodium sulfate. The solvent was concentrated in vacuo and the residue was purified by sgc.

Frenolicin B (1). Purified using 4:1 H:EA. The yield over two steps was 81%: NMR ($CDCl_3$) δ 1.03 (t, J = 7.2 Hz, 3 H), 1.5–1.85 (m, 4 H), 2.71 (d, J = 17.7 Hz, 1 H), 2.96 (dd, J = 5.1, 17.7 Hz, 1 H), 4.62 (dd, J = 3.3, 5.1 Hz, 1 H), 4.91 (dd, J = 3.0, 9.9 Hz, 1 H), 5.26 (d, J = 3.0 Hz, 1 H), 7.25–7.35 (m, 1 H), 7.62–7.76 (m, 2 H), 11.84 (s, 1 H); IR ($CDCl_3$) cm^{-1} 2962, 2933, 2874, 1791, 1652, 1624, 1457, 1283, 1245, 1194, 1148; MS *m/e* 55, 92, 121, 139, 157, 173, 201, 213, 225, 229, 241, 257, 285, 300, 328; HRMS calcd 328.0947, measured 328.0941; CMR ($CDCl_3$) δ 13.53, 19.50, 33.69, 36.81, 66.22, 68.68, 69.60, 114.76, 119.66, 124.79, 131.41, 135.12, 137.11, 149.21, 161.84, 173.84, 181.41, 187.97; TLC (H:EA = 2:1) R_f = 0.45. $[\alpha]^{25}_D$ 226.0° (*c* 0.84, CH_2Cl_2).

Kalafungin (2). Purified using 4:1 H:EA. The yield over two steps was 51%. NMR ($CDCl_3$) δ 1.57 (d, J = 6.9 Hz, 3 H), 2.67–3.01 (m, 2 H), 4.69 (dd, J_1 = 3.0 Hz, J_2 = 4.8 Hz, 1 H), 5.09 (q, J = 6.9 Hz, 1 H), 5.26 (d, J = 3.0 Hz, 1 H), 7.30 (dd, J_1 = 1.8 Hz, J_2 = 7.5 Hz, 1 H), 7.64–7.72 (m, 2 H), 11.84 (s, 1 H); IR ($CDCl_3$) 2937, 1791, 1667, 1651, 1623, 1575, 1457, 1368, 1284, 1243, 1194, 1150, 922, 897, 716, 652 cm^{-1}; MS *m/e* 70,

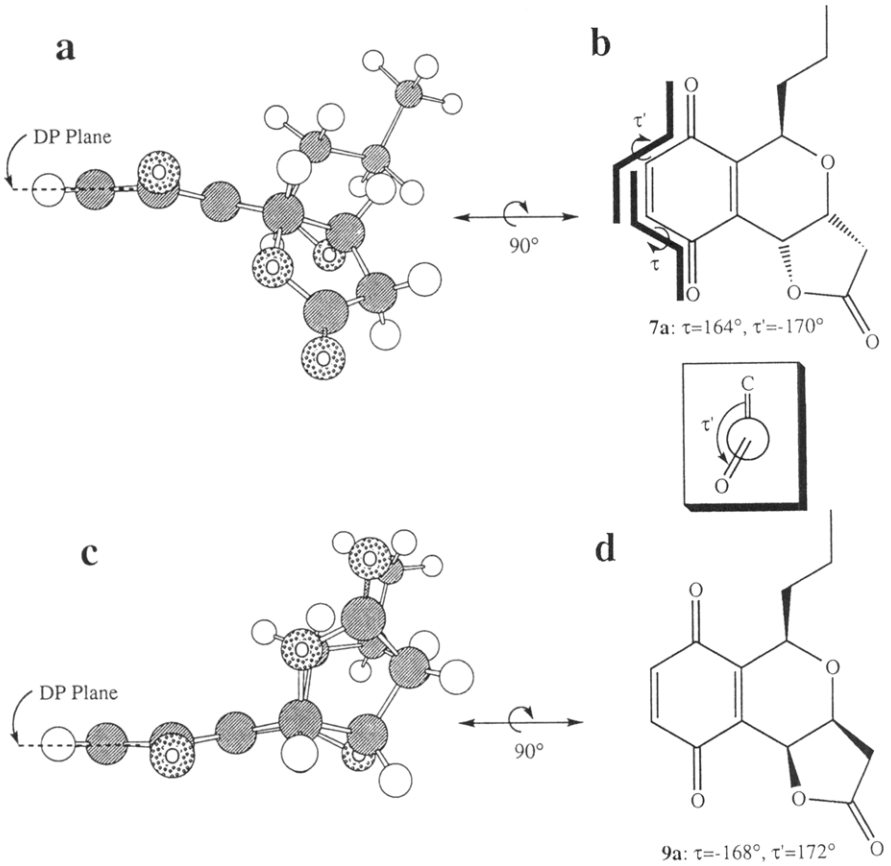
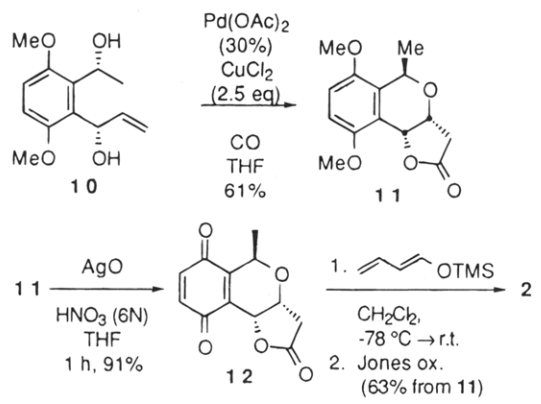


Figure 5. (a) Side view of the AM1 optimized structure of **7a** showing the puckering of the quinone ring. (b) Schematic view of **7a**, and definition of the two dihedral angles used to quantify the deviation from planarity for the quinone oxygens. (c) Side view of the AM1 optimized structure of **9a** showing the puckering of the quinone ring. (d) Schematic view of **9a**.

Scheme 3



121, 201, 229, 241, 257, 300; HRMS *m/e* for $C_{16}H_{12}O_5$ calcd 300.06339, measured 300.06252; CMR ($CDCl_3$) δ 18.4, 38.8, 66.2, 66.5, 68.7, 114.6, 119.5, 124.8, 131.2, 135.1, 139.0, 149.9, 161.7, 174.3, 181.5, 187.8; TLC (H:EA = 1:1) $R_f = 0.46$.

5-*epi*-Frenolicin B. Purified using 4:1 H:EA. The yield over two steps was 63%: NMR ($CDCl_3$) δ 0.90 (t, $J = 7.3$ Hz, 3 H), 1.25−1.55 (m, 2 H), 1.86−2.12 (m, 2 H), 2.70−2.95 (m, 2 H), 4.34 (dd, $J = 1.8$ Hz, 2.4 Hz, 1 H), 4.33−4.78 (m, 1 H), 5.28 (t, $J = 1.8$ Hz, 1 H), 7.26−7.32 (m, 1 H), 7.62−7.70 (m, 1 H), 11.73 (s, 1 H); IR ($CDCl_3$) 2962, 2931, 1792, 1668, 1645, 1618, 1457, 1284, 1247, 1148, 1048, 730 cm^{-1}; MS *m/e* 92, 121, 173, 201, 227, 241, 257, 286, 328; HRMS *m/e* for $C_{18}H_{16}O_6$ calcd 328.09469, measured 328.09530; CMR ($CDCl_3$) δ 13.9, 18.2, 35.9, 69.7, 70.8, 71.8, 114.9, 119.5, 124.8, 131.3, 136.1, 137.0, 149.6, 161.6, 174.3, 181.3, 188.6; TLC (H:EA = 2:1) $R_f = 0.47$.

(*R,S,S*)-6,9-Dimethoxy-3,3a,5,9b-tetrahydro-5-propylfuro[3,2-*c*][2]benzopyran-2-one (8). To a solution of the diol **4** (0.80 g, 3.0 mmol) in THF−H_2O (3:1, 40 mL) was added mecuric acetate (1.05 g, 3.3 mmol) and the solution was stirred at rt overnight. The solution was diluted with saturated NaCl solution and extracted three times with ether. The organic layers were dried with magnesium sulfate and concentrated in vacuo. The resulting mercurial could be used directly in the next step.

Anhydrous lithium chloride (0.085 g, 2.0 mmol), palladium chloride (0.177 g, 1.0 mmol), barium oxide (0.153 g, 1.0 mmol), and 5 mL of THF were placed in a dried 25 mL round bottom flask. The flask was flushed thoroughly with carbon monoxide, and 0.5 g (1.0 mmol) of the mercurial was added. A balloon filled with carbon monoxide was connected to the flask, and the reaction mixture was stirred 24 h at rt. The mixture was filtered, and the filtrate was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by sgc using 4:1 H:EA to afford 0.091 g (31% over two steps) of **8**: NMR ($CDCl_3$) δ 0.84 (t, $J = 7.5$ Hz, 3 H), 1.05−1.4 (m, 2 H), 1.82−2.05 (m, 2 H), 2.67−2.87 (m, 2 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 4.27 (dd, $J_1 = 2.1$ Hz, $J_2 = 3.9$ Hz, 1 H), 4.84 (dd, $J_1 = 3.0$ Hz, $J_2 = 5.4$ Hz, 1 H), 5.33 (d, $J = 1.5$ Hz, 1 H), 6.82 (dd, $J_1 = 9.0$ Hz, $J_2 = 29.7$ Hz, 2 H); IR ($CDCl_3$) 3003, 2958, 2934, 2838, 1783, 1602, 1484, 1438, 1349, 1292, 1259, 1204, 1153, 1086, 1041, 980, 802, 736 cm^{-1}; MS *m/e* 84, 115, 149, 165, 207, 222, 249, 292; HRMS *m/e* for $C_{16}H_{20}O_5$ calcd 292.13107, measured 292.13087; CMR ($CDCl_3$) δ 14.1, 17.7, 36.1, 38.2, 55.5, 55.9, 70.6, 72.5, 72.6, 108.9, 112.0, 118.1, 129.0, 149.5, 152.6, 175.9; TLC (H:EA = 2:1) $R_f = 0.40$.

Supplementary Material Available: Copies of ^1H NMR spectra of **1**−**3**, **5**−**9**, **11**, **12**, and 5-*epi*-frenolicin B (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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