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Direct Oxa-Pictet−Spengler Cyclization to the Natural (3a,5)-*trans*-Stereochemistry in the Syntheses of (+)-7-Deoxyfrenolicin B and (+)-7-Deoxykalafungin

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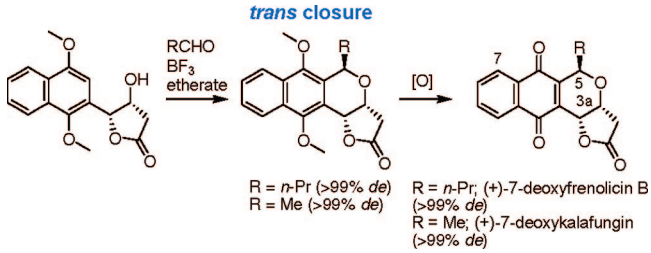
Received September 2, 2008



The pyranonaphthoquinones (+)-7-deoxyfrenolicin B and (+)-7-deoxykalafungin were synthesized in four steps using an oxa-Pictet−Spengler cyclization that directly provided the natural (3a,5)-*trans*-substituted dihydronaphthopyrans with high diastereoselectivity. This outcome is in contrast to the unnatural (3a,5)-*cis*-substituted dihydronaphthopyrans reported under similar conditions for the syntheses of (+)-frenolicin B and (+)-kalafungin. Computational modeling is presented that provides insight into this unusual stereoselectivity.

The natural products (+)-frenolicin B **1** and (+)-lactoquinomycin A **2** (Figure 1) were recently identified as potent inhibitors of the serine/threonine kinase Akt, also known as protein kinase B (PKB) (Akt1 $IC_{50} = 0.149$ and 0.313 μM, respectively).[1] As part of an SAR effort to rapidly explore the pyranonaphthoquinone's pharmacophore, we developed an efficient four-step synthesis of the C-7, C-8 unsubstituted analogues (+)-7-deoxyfrenolicin B **3** and (+)-7-deoxykalafungin **4**, respectively. This synthetic route was amenable toward further pyran ring modifications at C-5.[2]

We expected to follow a synthetic route similar to those reported for the asymmetric syntheses of (+)-frenolicin B **1**[3] and (+)-kalafungin **5**,[4] which employed a pyran-forming oxa-

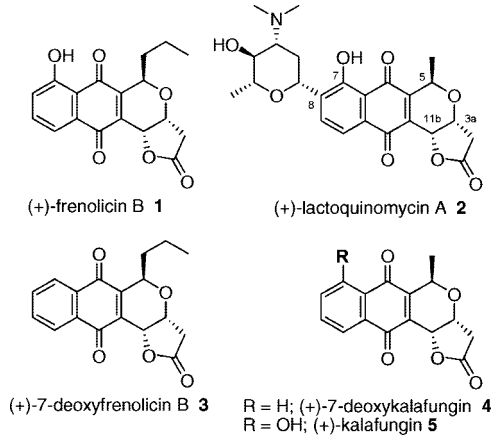


FIGURE 1. Pyranonaphthoquinones of interest.

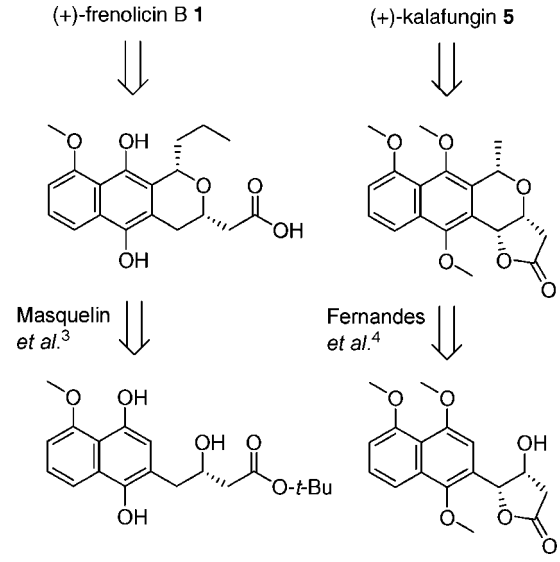


FIGURE 2. Oxa-Pictet−Spengler pyran *cis*-ring closures.

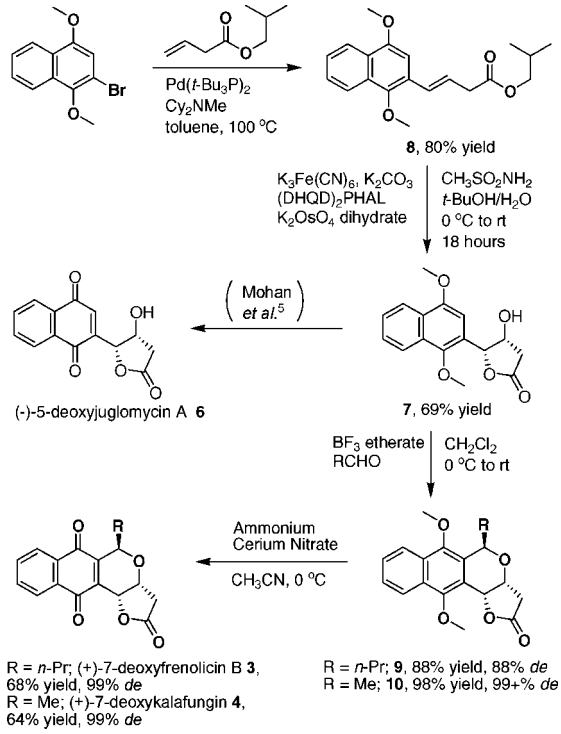
Pictet−Spengler reaction (ArS_E) (Figure 2). These ring closures produced the unnatural (3a,5)-*cis*-relationship within the pyran moiety, necessitating an epimerization at C-5 to obtain the final products. The dimethoxynaphthyl system we used, however, directly provided the natural (3a,5)-*trans*-relationship.

The hydroxylactone **7** necessary for our syntheses had been previously reported by Mohan et al.[5] in the asymmetric synthesis of (−)-5-deoxyjuglomycin A **6** (Scheme 1). The reported synthesis was shortened by using a Heck coupling between 2-bromo-1,4-dimethoxynaphthalene[6] and isobutyl but-3-enoate using $Pd(t\text{-}Bu_3P)_2$/dicyclohexylmethylamine[7] to produce **8** in 80% isolated yield.[8] The asymmetric dihydroxylation of **8** under standard conditions[9] afforded hydroxylactone **7** in 69% isolated yield (99% ee, 99% de).[10] The oxa-Pictet−Spengler reaction of **7** with *n*-butyraldehyde in the presence of boron trifluoride etherate unexpectedly generated dimethoxynaphthopyran **9** with

(1) Toral-Barza, L.; Zhang, W.-G.; Huang, X.; McDonald, L.; Salaski, E. J.; Barbieri, L. R.; Ding, W.-D.; Krishnamurthy, G.; Hu, Y.; Lucas, J.; Bernan, V. S.; Cai, P.; Levin, J. I.; Mansour, T. S.; Gibbons, J. J.; Abraham, R. T.; Yu, K. *Mol. Cancer Ther.* **2007**, *6*, 3028–3038.
(2) Unpublished results.
(3) (a) Contant, P.; Haess, M.; Riegl, J; Scalone, M.; Visnick, M. *Synthesis* **1999**, *5*, 821–828. (b) Masquelin, T.; Hengartner, U.; Streith, J. *Helv. Chem. Acta* **1997**, *80*, 43–58.
(4) Fernandes, R. A.; Bruckner, R. *Synlett* **2005**, *8*, 1281–1285.
(5) Mohan, H. R.; Rao, A. S. *Synth. Commun.* **1993**, *23*, 2579–2585.
(6) Ungnade, H. E.; Hein, H. *J. Org. Chem.* **1949**, *14*, 911–914.
(7) Littke, A. F.; Fu, G. *Org. Synth.* **2004**, *81*, 63–76.

10.1021/jo801945n CCC: $40.75
Published on Web 11/21/2008

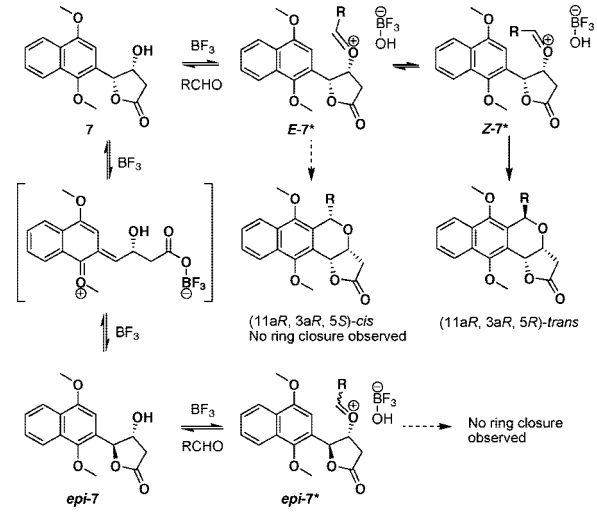
SCHEME 1. Synthesis of (+)-7-Deoxyfrenolicin B 3 and (+)-7-Deoxykalafungin 4



the natural (3a,5)-*trans*-relationship in 88% isolated yield (99% de).[10,11] The same stereochemical result using acetaldehyde was also observed in **10**, isolated in 98% yield (99% de).[10,11] Deprotection of the masked naphthoquinones **9** and **10** with ammonium cerium nitrate in aqueous acetonitrile uneventfully provided (+)-7-deoxyfrenolicin B **3** in 64% (99% de)[11] and (+)-deoxykalafungin **4** in 68% (99% de)[11] isolated yields, respectively. The products were spectroscopically and chromatographically homogeneous (in normal and reverse phase HPLC analyses).

Interestingly, hydroxylactone ***epi*-7** was isolated as an impurity in less than 1% from the oxa-Pictet−Spengler reactions, yet we did not observe the corresponding dihydronaphthopyran products (Scheme 2). Further investigation of the stability of **7** to an equivalent of $BF_3 \cdot OEt_2$ in $CDCl_3$ at room temperature resulted in a 1:1 equilibrium of the two epimers[12] (see

SCHEME 2. Hydroxy Lactone 7 Epimerization and Oxocarbenium Ion Formation



Supporting Information). This was likely the result of lactone ring opening via a mechanism analogous to quinone methide generation.[13]

A computational effort was undertaken to provide insight into how the (3a,5)-*trans*-substituted dihydronaphthopyrans might be obtained from hydroxylactone **7**. Inspection of the intermediate oxocarbenium ion[14] conformations available for ***epi*-7*** failed to identify conformations that had an appropriate geometry as a precursor to nucleophilic intramolecular attack (i.e., local minimum that positioned the reacting carbons relatively closely within an appropriate Burgi−Dunitz angle).[15] In contrast, **7*** predisposes the oxocarbenium ion and the naphthalene ring to lie adjacent to each other. A low energy conformation brings the two reactive centers close and with an angle of approach expected for a 6-*endo-trig* intramolecular nucleophilic attack to an sp^2 carbon through a chair transition state.[16] Other close conformers can bring the two reactive atoms closer (within ca. 3.4 Å) while varying the angle by ±2−3°.

Within the conformational space of oxocarbenium ion isomers available to **7***, two families of regioisomers with substituents oriented *E* and *Z* across the oxocarbenium ion's carbon double bond stand out (Scheme 2). The ***Z*-7*** isomer leads to the observed (11a*R*,3a*R*,5*R*)-*trans*-product, whereas ***E*-7*** isomer leads to the unobserved (11a*R*,3a*R*,5*S*)-*cis*-product. Estimates of the potential energy difference for the local minima of both forms surprisingly suggest that the ***E*-7*** isomer is favored over the ***Z*-7*** (42 kJ/mol using the MMFF94s force field).

With the obvious caveat that the relative energies were obtained in vacuo based on force field calculations, inspection of the conformations available to both isomers provided insight as to why ***Z*-7*** leads to the observed product (Figure 3). The higher potential energy of ***Z*-7*** en route to **9** can be explained by the close proximity of the *n*-propyl group to the napthyl ring.

(8) The isomer resulting from a Heck reaction at the β-carbon was isolated as a minor byproduct in 8% yield. Isobutyl (2*E*)-3-(1,4-dimethoxy-2-naphthyl)but-2-enoate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.21 (m, 1H), 8.12−8.09 (m, 1H), 7.58−7.48 (m, 2H), 6.58 (s, 1H), 6.11 (app quartet, J = 1.4 Hz, 1H), 4.00 (s, 3H), 3.98 (d, J = 6.5 Hz, 2H), 3.82 (s, 3H), 2.65 (d, J = 1.6 Hz, 3H), 2.01 (hept, J = 6.7 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 156.3, 151.9, 146.7, 131.8, 129.1, 127.1, 126.5, 126.1, 122.4, 120.3, 104.4, 70.4, 62.3, 56.0, 28.0, 20.2, 19.5; MS *m/z* 329.2 (M + H); HRMS calcd for $C_{20}H_{24}O_4$ + H, 329.1747; found, 329.1749.

(9) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771. (b) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 6407–6410.

(10) Based on the chiral HPLC analysis against the corresponding racemic sample prepared under the same dihydroxylation condition without the chiral auxiliary, the desired enantiomer was formed exclusively.

(11) The *cis*-isomer was not observed in the crude reaction product by NMR analyses. The *trans*-stereochemistry was supported by nOe NMR experiments, showing a strong interaction between H_{3a} and H_{11b}, and practically no interactions between H_5 and H_{3a} (see Supporting Information).

(12) The enantiomer of **7** was synthesized using hydroquinidine 1,4-phthalazinediyl diether and was subjected to the same conditions with BF_3 etherate. With all four diastereomers available, chiral HPLC analyses concluded that only the benzylic center was epimerized.

(13) (a) Rajski, S. R.; Williams, R. M. *Chem. Rev.* **1998**, *98*, 2723–2795. (b) Brimble, M. A.; Ireland, E.; Phythian, S. J. *Tetetrahedron Lett.* **1991**, *32*, 6417–6420.

(14) (a) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1978**, *43*, 4923–4924. (b) Giles, G. F. G.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3949–3956.

(15) Burgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563–1572.

(16) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736. (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482–483.

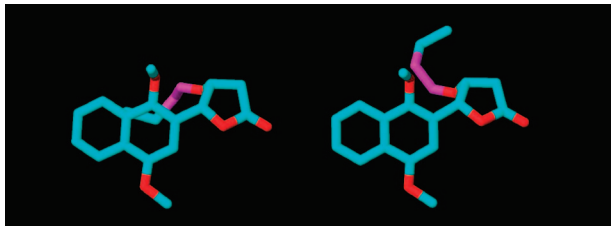


FIGURE 3. Structures of ***E*-7*** (left) and ***Z*-7*** (right). The oxocarbenium ion is colored magenta.

However, the geometry and distance of ***Z*-7*** are already predefined in a manner favorable for the eventual ring-forming reaction. The ***E*-7*** isomer appears to be more stable because it can relieve much of the crowding necessitated by ***Z*-7***. In so doing, ***E*-7*** moves the double bond farther from the nucleophilic center and will eventually have to bring these centers closer together to react. A similar but less crowded situation is also present when the *n*-propyl group is replaced with a methyl group for the formation of **10**.

We assessed the orbital geometries of the ***Z*-7*** and ***E*-7*** isomers prior to ring formation. With the conformations organized for a chair transition state, we calculated both the HOMO and LUMO. Both the ***Z*-7*** and ***E*-7*** isomers appear qualitatively to overlap HOMO and LUMO appropriately (see Supporting Information). A proposed ring forming reaction would cause the hydrogens attached to the newly formed bond to lie gauche for the ***Z*-7*** and anti for the ***E*-7***. Only for the products were the energies in favor of the (11a*R*,3a*R*,5*R*)-*trans*-product.[17]

In contrast, the (3a,5)-*cis*-substituted dihydropyrans synthesized directly from the electron-rich trimethoxy naphthyl systems would be derived from a ***E*-7*** isomer. The increased nucleophilicity of the naphthyl ring would be reflected in an earlier transition state favoring the ***E*-7*** isomer over the ***Z*-7*** isomer. Furthermore, the additional methoxy group may indirectly crowd the potential ***Z*-7*** isomer to favor the ***E*-7*** isomer.

In conclusion, an efficient four-step synthesis of (+)-7-deoxyfrenolicin B **3** and (+)-7-deoxykalafungin **4** has been described with overall 43 and 41% yields, respectively, with high diastereoselectivity (99% de). The oxa-Pictet−Spengler reaction with hydroxylactone **7** directly produced dihydronaphthylpyrans with the natural (3a,5)-*trans*-relationship even though **7** underwent benzylic epimerization during the course of the reaction. The (3a,5)-*trans*-stereochemical outcome of the pyran ring closures were unusual,[18] and few examples occur in the literature.[19] Computational modeling of the oxocarbenium ion intermediates suggests the subtle stereoselectivity of ring closure is a consequence of the dimethoxynaphthyl system's reduced nucleophilicity and that the ***Z*-7*** intermediate is sterically allowed for this system. These parameters combine to produce a late transition state favoring the thermodynamic (3a,5)-*trans*-product.

(17) A full conformational search was used Macromodel and MMFF94S forcefield, with 5000 steps of PRCG minimization for each conformation (or until completion, if that occurs sooner). There is a slight potential energy advantage to the (11a*R*,3a*R*,5*R*)-**3** isomer as compared to the (11a*R*,3a*R*,5*S*)-**3** isomer (310 vs 318 kJ/mol, respectively).

(18) Reviewed in: Larghi, E. L.; Kaufman, T. S. *Synthesis* **2006**, *2*, 187–220.

(19) (a) Micale, N.; Zappala, M.; Grasso, S. *Farmaco* **2002**, *57*, 853–859. (b) Bianchi, D. A.; Cipulli, M. A.; Kaufman, T. S. *Eur. J. Org. Chem.* **2003**, *24*, 4731–4736.

Experimental Section

Isobutyl (3*E*)-4-(1,4-Dimethoxy-2-naphthyl)but-3-enoate (8). A solution prepared from 2-bromo-1,4-dimethoxynaphthalene (2.00 g, 7.49 mmol), isobutyl but-3-enoate (2.50 g, 17.6 mmol), and dicyclohexylmethylamine (2.5 mL, 11.7 mmol) in toluene (10 mL) was heated at reflux in the presence of catalytic amount of bis(tri-*tert*-butylphosphine)palladium (79 mg, 0.155 mmol) for 16 h under nitrogen. The reaction mixture was washed with saturated aqueous sodium bicarbonate. The organic phase was dried and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc−hexanes 1:5) to afford **8** (1.96 g, 80%): ^{1}H (300 MHz, $CDCl_3$) δ 8.21−8.18 (m, 1H), 8.07−8.03 (m, 1H), 7.55−7.42 (m, 2H), 7.02 (app d, J = 16.1 Hz, 1 H), 6.89 (s, 1H), 6.41 (dt, J = 16.0, 7.1 Hz, 1H), 4.01 (s, 3H), 3.94 (d, J = 6.7 Hz, 2H), 3.87 (s, 3H), 3.37 (dd, J = 7.1, 1.4 Hz, 2H), 1.98 (hept, J = 6.7 Hz, 1H), 0.96 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 152.1,147.2, 129.0, 128.1, 127.0, 126.7, 125.7, 124.9, 122.8, 122.5, 122.3, 100.7, 71.7, 62.7, 55.8, 39.0, 27.9, 19.3; MS *m*/*z* 329.2 (M + H); HRMS calcd for $C_{20}H_{24}O_4$ + H, 329.1747; found, 329.1758.

(4*R*,5*R*)-5-(1,4-Dimethoxy-2-naphthyl)-4-hydroxydihydrofuran-2(3*H*)-one (7). To a solution of $K_3Fe(CN)_6$ (1.48 g, 4.50 mmol), potassium carbonate (0.61 g, 4.41 mmol), hydroquinidine 1,4-phthalazinediyl diether (11 mg, 14.1 μmol), potassium osmate dihydrate (2.3 mg, 6.24 mmol), and methanesulfonamide (146 mg, 1.53 mmol) in water (8.0 mL) and *tert*-butanol (3.0 mL) at 0 °C was added a solution of **7** (440 mg, 1.34 mmol) in *tert*-butanol (5.0 mL) in one portion. The resulting turbid mixture was allowed to warm to room temperature overnight. Sodium sulfite (1.4 g, 11.1 mmol) was added in one portion, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic portion was washed with 0.5 N HCl (1 × 20 mL) and brine (1 × 30 mL), dried with anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (hexanes−EtOAc, 6:1 to 3:1) afforded 266 mg (69%) of **7** as a solid: ^{1}H (300 MHz, $CDCl_3$) δ 8.28 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.60 (m, 2H), 6.88 (s, 1H), 5.90 (d, J = 3.6 Hz, 1H), 4.85 (app t, J = 4.4 Hz, 1H), 4.01 (s, 3H), 3.94 (s, 3H), 2.95 (dd, J = 17.8, 5.4 Hz, 1H), 2.75 (d, J = 17.5 Hz, 1H), 1.63 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 152.5, 146.1, 127.9, 127.1, 126.8, 126.1, 122.8, 121.6, 121.5, 101.8, 82.0, 69.9, 62.3, 55.9, 38.3; MS *m*/*z* 289.1 (M + H); HRMS calcd for $C_{16}H_{16}O_5$ + H, 289.1071; found, 289.1073; $[\alpha]_D$ −29.6 (*c* 1.0, $CHCl_3$), lit.[5] −30 (*c* 2.115, $CHCl_3$).

(3a*R*,5*R*,11b*R*)-6,11-Dimethoxy-5-propyl-3,3a,5,11b-tetrahydro-2*H*-benzo[*g*]furo[3,2-*c*]isochromen-2-one (9). To a solution of **7** (290 mg, 1.09 mmol) and *n*-butyraldehyde (0.1 mL, 1.11 mmol) in dichloromethane (10 mL) at 0 °C was added neat boron trifluoride etherate (0.13 mL, 0.76 mmol) dropwise. The reaction was allowed to warm to room temperature overnight. Saturated aqueous sodium bicarbonate (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (EtOAc−hexanes 3:1) provided 303 mg (88%) of **9** as a light yellow solid: ^{1}H (300 MHz, CD_2Cl_2) δ 8.18−8.08 (m, 2H), 7.65−7.56 (m, 2H), 5.61 (d, J = 2.7 Hz, 1H), 5.21 (m, 1H), 4.68 (m, 1H), 4.12 (s, 3H), 3.97 (s, 3H), 3.02 (dd, J = 17.4, 4.9 Hz, 1H), 2.68 (d, J = 17.4 Hz, 1H), 1.83−1.76 (m, 2H), 1.69−1.56 (m, 2H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 175.7, 153.9, 147.7, 129.8, 128.2, 127.9, 127.7, 126.6, 123.4, 122.9, 118.5, 72.6, 71.7, 66.6, 64.4, 62.4, 38.2, 35.2, 19.8, 13.9; MS *m*/*z* 343.2 (M + H); HRMS calcd for $C_{20}H_{22}O_5$ + H, 343.1540; found, 343.1537; $[\alpha]_D$ +223.0 (*c* 1.0, $CDCl_3$).

(3a*R*,5*R*,11b*R*)-6,11-Dimethoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-benzo[*g*]furo[3,2-*c*]isochromen-2-one (10). The title compound was obtained following the procedure for **9**. Purification by flash chromatography (EtOAc−hexanes 3:1) gave **10** (43 mg, 98%): ^{1}H (400 MHz, $CDCl_3$) δ 8.14−8.11 (m, 1H), 8.07−8.04 (m, 1H), 7.60−7.52 (m, 2H), 5.62 (d, J = 2.8 Hz, 1H), 5.37 (q, J = 6.8 Hz, 1H), 4.77 (dd, J = 4.8, 2.8 Hz, 1H), 4.11 (s, 3H), 3.96 (s, 3H),

3.00 (dd, J = 17.4, 4.8 Hz, 1H), 2.72 (d, J = 17.9 Hz, 1H), 1.56 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 153.7, 147.3, 129.4, 127.9, 127.8, 127.5, 126.3, 123.1, 122.6, 117.7, 72.2, 68.0, 66.4, 64.4, 62.1, 38.0, 19.9; MS m/z 315.2 (M + H); HRMS calcd for $C_{18}H_{18}O_5$ + H, 315.1227; found, 315.1224; $[\alpha]_D$ +144.0 (c 1.0, $CHCl_3$).

(3a*R*,5*R*,11b*R*)-5-Propyl-3,3a,5,11b-tetrahydro-2*H*-benzo[*g*]-furo[3,2-*c*]isochromene-2,6,11-trione (3). A solution of **9** (16 mg, 47 μmol) in acetonitrile (1.0 mL) at 0 °C was treated with a solution of ammonium cerium nitrate (60 mg, 109 μmol) in water (1.0 mL) in one portion. The reaction was quenched after 10 min with ethyl acetate and water. The organic phase was washed successively with water until the aqueous phase was colorless, dried over anhydrous $MgSO_4$, and concentrated in vacuo to provide **3** (9 mg, 68%): ^{1}H (300 MHz, $CDCl_3$) δ 8.18−8.10 (m, 2H), 7.82−7.61 (m, 2H), 5.29 (d, J = 3.1 Hz, 1H), 4.91 (dd, J = 10.0, 3.0 Hz, 1H), 4.63 (dd, J = 5.1, 3.1 Hz, 1H), 2.99 (dd, J = 17.7, 5.1 Hz, 1H), 2.71 (d, J = 17.7 Hz, 1H), 1.80−1.49 (m, 4H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 183.5, 182.2, 173.9, 148.7, 135.0, 134.4, 134.1, 133.8, 132.5, 126.9, 126.6, 70.4, 68.9, 66.7, 36.9, 33.8, 20.1, 13.9; IR ATR cell (powder) υ_{max} 2960, 1785, 1670, 1288, 1144, 787 cm^{-1}; MS m/z 313.0 (M + H); HRMS calcd for $C_{18}H_{16}O_5$ + H, 313.1071; found 313.1076; $[\alpha]_D$ +155.2 (c 1.0, $CHCl_3$).

(3a*R*,5*R*,11b*R*)-5-Methyl-3,3a,5,11b-tetrahydro-2*H*-benzo[*g*]-furo[3,2-*c*]isochromene-2,6,11-trione (4). The title compound was obtained in 64% yield (10 mg) from **10** (17 mg, 32 μmol) following the procedure for **3**: ^{1}H (400 MHz, C_6D_6) δ 8.08−8.05 (m, 1H), 7.94−7.92 (m, 1H), 7.15−7.11 (m, 2H), 4.87 (q, J = 6.8 Hz, 1H), 4.75 (d, J = 3.2 Hz, 1H), 3.71 (m, 1H), 2.39 (d, J = 17.2 Hz, 1H), 2.18 (dd, J = 17.2, 5.2 Hz, 1H), 1.21 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 183.2, 182.5, 174.0, 149.1, 134.8, 134.3, 134.2, 134.0, 132.4, 126.8, 126.5, 68.8, 66.9, 66.8, 37.1, 18.5; MS m/z 285.1 (M + H); HRMS calcd for $C_{16}H_{12}O_5$ + H, 285.0758; found, 285.0755; $[\alpha]_D$ +100.1 (c 1.0, $CHCl_3$).

(4*R*,5*S*)-5-(1,4-Dimethoxy-2-naphthyl)-4-hydroxydihydrofuran-2(3*H*)-one (*epi*-7). To a solution of **7** (24 mg, 83 μmol) in $CDCl_3$ (3.0 mL) was added boron trifluoride etherate (15 μL, 120 μmol) in one portion at room temperature. (An NMR analysis indicated a ratio of **7** to ***epi*-7** of 1:1.) After 5 min at room temperature, the solution was poured into saturated aqueous sodium bicarbonate (3 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (chloroform) to afford **7** (9 mg, 38%) with the identical chiral HPLC retention as original **7**. Continued elution gave ***epi*-7** (12 mg, 50%): ^{1}H (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.64−7.54 (m, 2H), 6.70 (s, 1H), 5.74 (d, J = 4.8 Hz, 1H), 4.55 (ddd, J = 7.7, 6.4, 4.8 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 3.03 (dd, J = 17.9, 7.4 Hz, 1 H), 2.75 (dd, J = 17.6, 6.4 Hz, 1H), 1.63 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 152.9, 146.3, 128.2, 127.2, 126.6, 126.1, 125.4, 122.8, 121.6, 99.7, 84.4, 74.6, 62.3, 55.9, 37.4, 29.7; ES$^-$ m/z 333.1 (M + formic acid − H); HRMS calcd for $C_{16}H_{16}O_5$ + H, 289.1071; found 289.1073; $[\alpha]_D$ −11.3 (c 1.0, $CHCl_3$).

Acknowledgment. The authors wish to thank Chemical Technology for compound characterization (Mairead Young for chiral HPLC), and Yan Wang for synthetic assistance. We also thank Edward Salaski, Janis Upeslacis, Dennis Powell, Christine Humblet, and Tarek Mansour for their support.

Supporting Information Available: General experimental methods, copies of spectra and chromatograms, and molecular modeling data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801945N