Determination of the Relative and Absolute Stereochemistry of Fostriecin (CI-920)

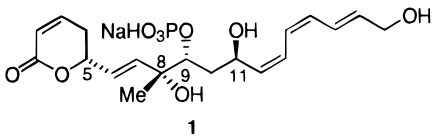
Dale L. Boger,* Masataka Hikota, and Bryan M. Lewis

Department of Chemistry and The Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received November 19, 1996[⊗]

The absolute stereochemistry of fostriecin (**1**, CI-920), a potent antitumor antibiotic presently in Phase I clinical trials at NCI, was determined to be 5*R*,8*R*,9*R*,11*R*. 2D ^{1}H−^{1}H NMR NOE experiments conducted on the cyclic phosphate derivative **2** and acetonide **4** revealed a *syn*-diol stereochemical relationship between C8 and C9 and an *anti*-diol stereochemical relationship between C9 and C11, respectively. The 5*R* absolute configuration assignment was confirmed by synthesis of the degradation product **8** previously disclosed. Additional degradation studies of **1** to provide **7** and chiral-phase HPLC comparison with a sample of known chirality established the absolute stereochemistry of C11 to be *R*. This, along with the relative stereochemical assignments established the full set of absolute stereochemistry assignments for **1**.

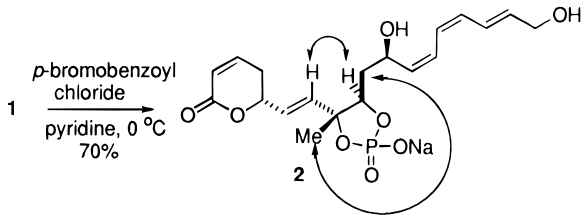
Fostriecin (**1**, CI-920)[1] is a structurally novel phosphate ester produced by *Streptomyces pulveraceus* active *in vitro* against leukemia (L1210, IC_{50} 0.46 μM), lung, breast, and ovarian cancer and displays efficacious *in vivo* antitumor activity against L1210 leukemia in mice.[2] It is currently being investigated in phase I clinical trials at NCI. Fostriecin inhibits DNA topoisomerase II (IC_{50} 40 μM) *in vitro*[3] through a novel, non-DNA-strand cleaving mechanism, but does not induce G_2 arrest like other topoisomerase II inhibitors.[4] Instead, it inhibits the mitotic entry checkpoint,[5] potentially through inhibition of protein phosphatases 1 and 2A (IC_{50} 4 μM and 40 nM, respectively).[6−9] Inhibition of the mitotic entry checkpoint and protein phosphatase are novel properties for a potential clinical antitumor agent. Despite these properties and the clinical potential of **1**, the complete relative and absolute stereochemistry of the molecule is unknown.[10,11] Herein, we detail studies that provide the relative and absolute stereochemistry of fostriecin (Figure 1).



1

Figure 1.

Scheme 1. Preparation of the Cyclic Phosphate Diester



Although the 5*R* absolute stereochemistry of **1** was established in the work leading to the basic tenants of the structure determination,[10] the relative and absolute stereochemistry at C8, C9, and C11 are unknown. The relative stereochemistry between C8 and C9 was determined as follows (Scheme 1). The natural product **1** was converted to the five-membered cyclic phosphodiester **2** (*p*-bromobenzoyl chloride, pyridine, 0 °C, 70%).[12] The closure to **2** was established by ^{31}P NMR (D_2O, 161 MHz, δ) with the observance of a signal at 14.69 characteristic of a five-membered (10−15) versus six-membered (−0.5 to −5.0) cyclic phosphodiester.[13] Upon examination of the 2D ^{1}H−^{1}H ROESY NMR spectrum (D_2O, 400 MHz, δ), NOEs were found between $H_{6,7}$ (5.93−6.00) and H_9 (4.34), as well as between the C8-CH_3 (1.40) and H_{10}

[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1997.

(1) Tunac, J. B.; Graham, B. D.; Dobson, W. E. *J. Antibiot.* **1983**, *36*, 1595. Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot.* **1983**, *36*, 1601.

(2) Jackson, R. C.; Fry, D. W.; Boritzki, T. J.; Roberts, B. J.; Hook, K. E.; Leopold, W. R. *Adv. Enzyme Regul.* **1985**, *23*, 193.

(3) Boritzki, T. J.; Wolfard, T. S.; Besserer, J. A.; Jackson, R. C.; Fry, D. W. *Biochem. Pharmacol.* **1988**, *37*, 4063.

(4) Topoisomerase II inhibitors which induce G2 arrest: (a) etoposide: Chen, G. L.; Yang, L.; Rowe, T. C.; Halligan, B. D.; Tewey, K. M.; Liu, L. F. *J. Biol. Chem.* **1984**, *259*, 13560. (b) Doxorubicin: Tewey, K. M.; Rowe, T. C.; Yang, L.; Halligan, B. D.; Liu, L. F. *Science* **1984**, *266*, 466. (c) Amsacrine: Nelson, E. M.; Tewey, K. M.; Liu, L. F. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3161.

(5) For a review: Murray, A. W. *Nature* **1992**, *359*, 599.

(6) Roberge, M.; Tudan, C.; Hung, S. M. F.; Harder, K. W.; Jirik, F. R.; Anderson, H. *Cancer Res.* **1994**, *54*, 6115.

(7) Ho, D. T.; Roberge, M. *Carcinogenesis* **1996**, *17*, 967.

(8) For a review of protein serine/threonine phosphatases: Ingebritsen, T. S.; Cohen, P. *Eur. J. Biochem.* **1983**, *132*, 255.

(9) Other inhibitors of protein serine/threonine phosphatases: (a) okadaic acid: Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, Y.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469. (b) Microcystins: Botes, D.; Tuinman, A.; Wessels, P.; Viljoen, C.; Kruger, H.; Williams, D. H.; Santikarn, S.; Smith, R.; Hammond, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2311. Painuly, P.; Perez, R.; Fukai, T.; Shimizu, Y. *Tetrahedron Lett.* **1988**, *29*, 11. (c) Calyculin A: Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 2780. (d) Nodularin: Botes, P. B.; Wessels, P. L.; Kruger, H.; Runnegar, M. T. C.; Santikarn, S.; Smith, R. J.; Barna, J. C. J.; Williams, D. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2747. Rinehart, K. L.; Harada, K.; Namikoshi, M.; Chen, C.; Harvis, C.; Munro, M. H. G.; Blunt, J.; Mulligan, P.; Beasley, V.; Dahlem, A.; Carmichael, W. *J. Am. Chem. Soc.* **1988**, *110*, 8557. (e) Tautomycin: Cheng, X.-C.; Ubukata, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 809. (f) Cantharidine: Li, Y.-M.; Casida, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11867. (g) Motuporin: Valentekovich, R. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 9069.

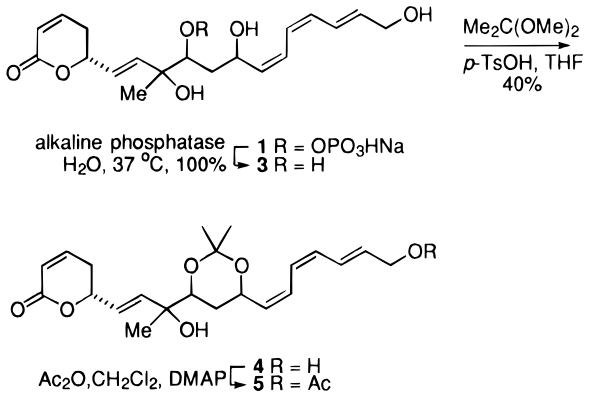
(10) Early work assigned the absolute configuration at C5 as *R*, see: Hokanson, G. C.; French, J. C. *J. Org. Chem.* **1985**, *50*, 462.

(11) Just, G.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 753.

(12) This closure could also be effected by treatment with EDCI or DCC, but provided **2** with lower purity due to the difficulty of removing the reaction byproducts. See also: Ozasa, T.; Tanaka, K.; Sasamata, M.; Kaniwa, H.; Shimizu, M.; Matsumoto, H.; Iwanami, M. *J. Antibiot.* **1989**, *42*, 1339.

S0022-3263(96)02166-4 CCC: $14.00

Scheme 2. Preparation of the Six-Membered Ring Acetonide



(1.75−1.90), establishing the cis relationships of the C5-C8 vinyl side chain with H_9 and C8-CH_3 with the C9 side chain on the five-membered cyclic phosphodiester and a *syn*-1,2-diol relationship between C8 and C9.

The relative stereochemistry between C9 and C11 was determined as follows (Scheme 2). The free alcohol **3** was prepared from **1** (alkaline phosphatase, H_2O, 37 °C, 100%) according to the procedure of Hokanson and French[10] and was converted to the acetonide **4** ($Me_2C(OMe)_2$, *p*-TsOH, THF, 25 °C, 10−15 min, 40%). The preferential formation of **4** was anticipated and controlled by use of short reaction times (10−15 min) favoring the kinetic six-membered 1,3-diol acetonide.[14] The alternative possibility of five-membered acetonide formation between C8 and C9 was excluded by the subsequent clean conversion of **4** to monoacetate **5**[14] (excess Ac_2O, Et_3N, CH_2Cl_2, 25 °C, 2 h) versus a diacetate diagnostic of the 1,2-diol acetonide and ultimately confirmed spectroscopically. Extending the reaction time to 1 h led to the generation of small amounts of the five-membered 1,2-diol acetonide (9%) without improving the conversion to **4** (42%).

The acetonide methyl groups of **4** (1.35 and 1.39) displayed similar ^{13}C NMR chemical shifts of 24.49 and 24.89 ($CDCl_3$, 100 MHz, δ) within the range characteristic of an *anti*-1,3-diol acetonide (23.96−25.22) and different from the distinct chemical shifts observed with *syn*-1,3-diol acetonides (18.67−19.98 and 29.74−30.16).[15] In addition, diagnostic cross-peaks observed in the 2D $^1H-^1H$ NOESY NMR spectrum of **4** were observed between one acetonide methyl group (1.35) and H_9 (3.72) and between the other acetonide methyl group (1.39) and H_{11} (4.73) (**A**, Figure 2). This agrees with the existence of an *anti*-1,3-diol derived acetonide adopting a twist boat conformation. Consistent with this assignment, H_9 ($J(H_{10})$ = 6.3, 9.6 Hz) and H_{11} ($J(H_{10})$ = 6.3, 9.5 Hz) exhibit ^1H NMR coupling constants expected with the twist boat conformation and the observed NOEs. Additionally, the alternative *syn*-1,3-diol-derived acetonide **B** would be supported by the observance of three other diagnostic NOEs, one between H_9 and H_{11} and those between the

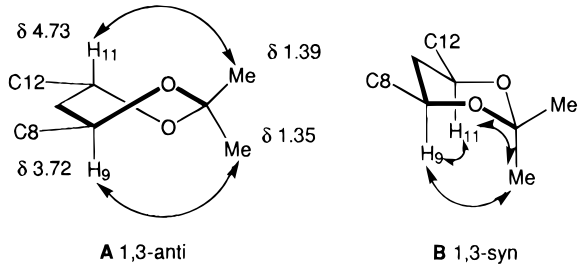
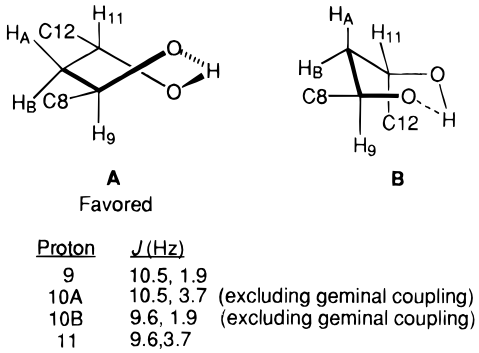


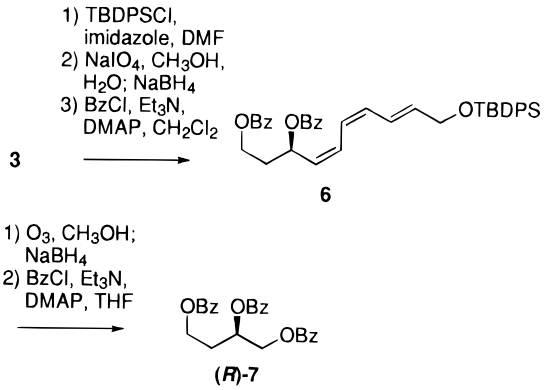
Figure 2.



Proton	*J* (Hz)	
9	10.5, 1.9	
10A	10.5, 3.7	(excluding geminal coupling)
10B	9.6, 1.9	(excluding geminal coupling)
11	9.6,3.7	

Figure 3.

Scheme 3. Degradation of Fostriecin



one axial methyl group of the acetonide and both H_9 and H_{11}. These cross-peaks were not observed in the 2D $^1H-^1H$ NOESY NMR spectrum. From these results which further confirmed the structure of the 1,3- versus 1,2-acetonide, we assigned the relative stereochemistry of the C8−C9 and C9−C11 stereocenters of fostriecin as a *syn*-1,2 and an *anti*-1,3-diol relationship, respectively.

This proved to be consistent with the adoption of a rigid, hydrogen-bonded cyclic structure for **1** and **3** (D_2O, 400 MHz) involving the C9 oxygen substituent and the C11 alcohol which is disrupted upon *O*-acetylation.[10] Our examination of the coupling constants of H_9, H_{10A}, H_{10B}, and H_{11} in **3** had provided us with a preliminary assessment of the *anti*-1,3-diol relationship of C9/C11 adopting a twist boat for the hydrogen-bonded structure (Figure 3).

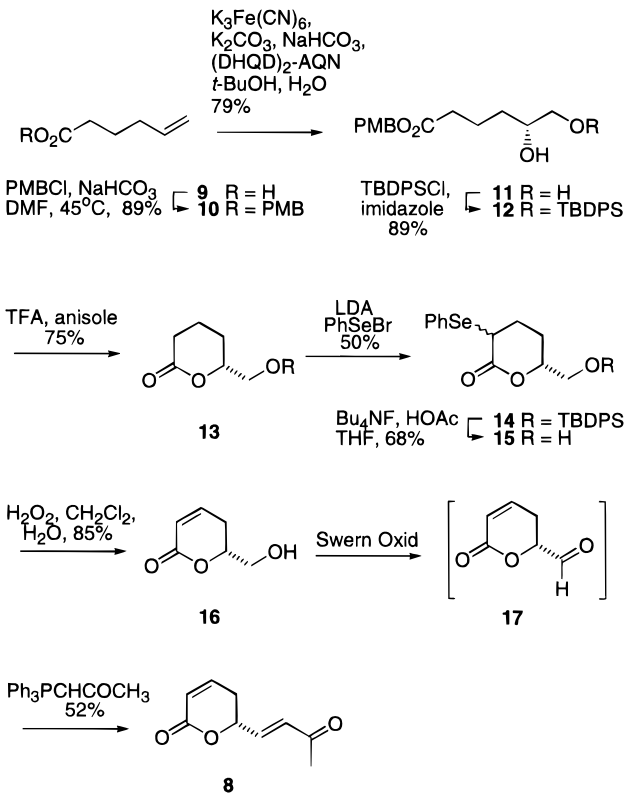
The final task was the determination of the absolute stereochemistry at C11, which when coupled with the relative stereochemistry detailed above and the prior work of Hokanson and French assigning the C5 *R* configuration,[10] would establish the complete absolute stereochemistry of fostriecin (Scheme 3). The free alcohol **3** was cleanly monosilylated (TBDPSCl, imidazole, DMF, 25 °C, 72%) and subjected to oxidative cleavage of the

(13) Egan, W.; Schneerson, R.; Werner, K. E.; Zon, G. *J. Am. Chem. Soc.* **1982**, *104*, 2898. Broeders, N. L. H. L.; Van der Heiden, A. P.; Pecters, I.; Janssen, H. M.; Koole, L. H. *J. Am. Chem. Soc.* **1992**, *114*, 9624.

(14) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883. For **5**: FABHRMS (NBA−NaI) *m/z* 455.2056 ($M^+ + Na^+$, $C_{24}H_{32}O_7$ requires 455.2046).

(15) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

Scheme 4. Preparation of Methyl Ketone Derived from Fostriecin



C8,C9-diol ($NaIO_4$, CH_3OH-H_2O). Immediate reduction ($NaBH_4$, 65% for two steps) of the resulting aldehyde to the diol, and its protection as the dibenzoate (BzCl, Et_3N, DMAP, CH_2Cl_2, 65%) gave **6**. The dibenzoate was subjected to ozonolysis followed by reductive workup (O_3, CH_3OH; $NaBH_4$) and benzoylation (BzCl, Et_3N, DMAP, THF, 65%) to yield the tribenzoate **7**. This material was identical (NMR, IR, MS) to the (*R*)-(+)-tribenzoate **7** and the (±)-tribenzoate prepared from commercially available *R*-(+)-1,2,4-butanetriol and (±)-1,2,4-butanetriol, respectively, and eluted on an analytical Chiracel OD-H HPLC column (0.46 × 20 cm, 20% 2-PrOH/hexane, 0.6 mL/min) with the same retention time as (2*R*)-**7** (11.4 min) versus (2*S*)-**7** (18.4 min). This, combined with the relative configuration assignments, provided the complete relative and absolute stereochemical determination of fostriecin as 5*R*,8*R*,9*R*,11*R*.[16]

Finally, in conjunction with our synthetic efforts on **1** we have conducted a correlation (Scheme 4) that confirms the C5 absolute stereochemical assignment of Hokanson and French.[10] The absolute configuration at C5 was introduced through Sharpless asymmetric dihydroxylation of a terminal olefin.[19] Thus, conversion of hex-5-enoic acid[20] (**9**) to the corresponding *p*-methoxybenzyl ester **10** followed by asymmetric dihydroxylation (3 equiv of $K_3Fe(CN)_6$, 3 equiv of $NaHCO_3$, 3 equiv of K_2CO_3, 0.05 equiv of $(DHQD)_2-AQN$,[21] *t*-BuOH/H_2O 1:1, 0 °C, 48 h, 79%, 88−92% ee) provided the diol **11**. Enrichment to >98% ee was accomplished by one recrystallization (>50% overall, Et_2O)[22] and conveniently monitored by ^1H NMR analysis ($CDCl_3$, 400 MHz) of the corresponding bis-Mosher ester (2.3 equiv of (*R*)-MTPA-Cl, 3 equiv of DMAP, THF, 25 °C, 6 h). Subsequent selective protection of the primary alcohol **11** (1.1 equiv of TBDPSCl, 2.2 equiv of imidazole, DMF, 25 °C, 15 h, 89−92%) cleanly provided **12** and acid-catalyzed lactonization (4 equiv of CF_3CO_2H, 5 equiv of anisole, 25 °C, 0.5 h, 75%) afforded **13**. Formation of the α-phenylselenyl lactone **14** (1.1 equiv of LDA; 1.2 equiv of PhSeBr, THF, −78 °C, 1 h, 50%), deprotection of the TBDPS ether (1.9 equiv of Bu_4NF, 5.8 equiv of HOAc, THF, 25 °C, 3 h, 68%) and oxidation of **15** to the selenoxide (4 equiv of H_2O_2, $CH_2Cl_2-H_2O$, 25 °C, 2 h, 85%) followed by elimination provided the unsaturated lactone alcohol **16**, $[\alpha]^{20}_D$ +160 (*c* 0.85, $CHCl_3$), lit.[23] $[\alpha]^{26}_D$ +175 (*c* 0.92, $CHCl_3$). The correlation of our synthetic **16** with authentic **16**[23] of known absolute configuration established that the Sharpless asymmetric dihydroxylation proceeded with the expected enantioselectivity. Swern oxidation of **16** (10 equiv of $(COCl)_2$, 12 equiv of DMSO, 35 equiv of Et_3N, CH_2Cl_2, −78 °C) followed by *in situ* reaction of **17** with the stabilized Wittig reagent (15 equiv, 0 °C, 30 min, 52% overall) provided **8** ($[\alpha]^{20}_D$ +201 (*c* 0.110, $CHCl_3$), identical in all respects with the degradation product **8**[10] ($[\alpha]_D$ +217 (*c* 1.16, $CHCl_3$) obtained from fostriecin. This latter correlation confirmed the C5 stereochemical assignment of Hokanson and French and provided an advanced synthetic intermediate in our approach to fostriecin. These and related efforts will be disclosed in due time.

Experimental Section

(1*E*,3*R*,4*R*,6*R*,7*Z*,9*Z*,11*E*)-1-[(6*R*)-2-Oxo-5,6-dihydro-2*H*-pyran-6-yl]-3,4,6,13-tetrahydroxy-3-methyl-1,7,9,11-tridecatetraene 3,4-Cyclophosphate, Sodium Salt (2). A solution of fostriecin (**1**, 2 mg, 4.4 mmol) in pyridine (500 μL) was treated at 0 °C (ice bath) with *p*-bromobenzoyl chloride (1.9 mg, 8.5 μmol), and the mixture was allowed to stir for 45 min at 0 °C. The reaction mixture was concentrated and purified by chromatography on reverse phase silica (0−10% CH_3CN-H_2O) to yield **2** (1.34 mg, 1.8 mg theoretical, 70%): ^1H NMR (D_2O, 400 MHz) δ 7.12 (1H, ddd, *J* = 3.1, 5.6, 9.8 Hz), 6.79 (1H, dd, *J* = 11.0, 15.3 Hz), 6.64 (1H, t, *J* = 11.0 Hz), 6.35 (1H, t, *J* = 11.0 Hz), 6.19 (1H, t, *J* = 11.0 Hz), 6.08 (1H, dd, *J* = 5.9, 15.3 Hz), 6.03 (1H, ddd, *J* = 1.2, 2.3, 9.8 Hz), 6.00−5.93 (2H, m), 5.56 (1H, t, 9.4 Hz), 5.12 (1H, ddd, *J* = 5.3, 5.4, 10.2 Hz), 4.34 (1H, dd, *J* = 3.4, 9.3 Hz), 4.18 (2H, d, *J* = 5.9 Hz), 2.65−2.58 (1H, ddd, *J* = 5.1, 5.2, 18.8 Hz), 2.56−2.52 (1H, dddd, *J* = 3, 3, 10.7, 18.8 Hz), 1.90−1.75 (2H, m), 1.43 (s, 3H); ^{13}C NMR (D_2O, 125 MHz) δ 170.4, 151.8, 137.1, 136.7, 135.7, 133.8, 132.0, 128.7, 127.9, 126.5, 122.2, 87.4, 83.2, 80.9, 66.4, 64.8, 39.6, 31.6, 21.8; ^{31}P NMR (161 MHz, D_2O) δ 14.69; IR (neat) ν_{max} 3358, 2920, 1709, 1383, 1247, 1221, 1109, 1054, 972, 942, 876, 820 cm^{-1}; FABHRMS (NBA−NaI) *m*/*z* 435.1197 (M + Na^+, $C_{19}H_{25}O_8P$ requires 435.1185).

(16) The work is also consistent with and would seem to unambiguously confirm the relative and absolute configuration assignments for the leustroducsins,[17] phoslactomycins,[18] and phospholine[18] whose stereochemistry was tentatively assigned based on the chiroptical properties of Mosher esters of the alcohols. See: Shibata, T.; Kurihara, S.; Yoda, K.; Haruyama, H. *Tetrahedron* **1995**, *51*, 11999.

(17) Leustroducsins: Kohama, T.; Enokita, R.; Okazaki, T.; Miyaoka, H.; Torikata, A.; Inukai, M.; Kaneko, I.; Kagasaki, T.; Sakaida, Y.; Satoh, A.; Shiraishi, A. *J. Antibiot.* **1993**, *46*, 1503. Kohama, T.; Nakamura, T.; Kinoshita, T.; Kaneko, I.; Shiraishi, A. *J. Antibiot.* **1993**, *46*, 1512.

(18) Phoslactomycins: Fushimi, S.; Nishikawa, S.; Shimazu, A.; Seto, H. *J. Antibiot.* **1989**, *42*, 1019. Fushimi, S.; Furihata, K.; Seto, H. *J. Antibiot.* **1989**, *42*, 1026.

(19) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(20) Gilman, H.; Kirby, R. H. *Org. Synth.* **1941**, *1*, 361.

(21) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448.

(22) The corresponding methyl, *tert*-butyl, and benzyl esters were also examined but failed to provide a crystalline diol capable of optical purity enrichment through recrystallization.

(23) Tsubuki, M.; Kanai, K.; Honda, T. *Heterocycles* **1993**, *35*, 281.

The 2D $^1H-^1H$ ROESY NMR spectrum (D_2O, 400 MHz) of **2** displayed the following diagnostic NOE cross-peaks: H_2/H_3, H_3/H_4, H_4/H_5, $H_{6,7}/H_9$, $H_{6,7}/H_{15}$, $H_{6,7}/H_{16}$, $H_{6,7}/H_{17}$, $H_{6,7}/H_{19}$, H_9/H_{10}, H_9/H_{12}, H_9/H_{17}, H_{10}/H_{19}, H_{12}/H_{13}, H_{12}/H_{14}, H_{13}/H_{16}, H_{14}/H_{15}, H_{14}/H_{16}.

(*R*)-6-[(1*E*,3*R*,4*R*,6*R*,7*Z*,9*Z*,11*E*)-3,4,6,13-Tetrahydroxy-4,6-*O*-isopropylidene-3-methyl-1,7,9,11-tridecatetraen-1-yl]-5,6-dihydro-2*H*-pyran-2-one (4). A suspension of **3** (1.0 mg, 2.9 μmol) in THF (1.0 mL) was treated with 2,2-dimethoxypropane (15 μL, 0.12 mmol), followed by a catalytic amount of anhydrous *p*-TsOH at 25 °C. After 10 min of stirring, 3 drops of Et_3N was added, and the mixture was concentrated *in vacuo*. PTLC (SiO_2, 50% EtOAc−hexane) gave **4** (0.4 mg, 1.1 mg theoretical, 40%) as a colorless oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 6.87 (1H, ddd, J = 3.1, 5.4, 12.7 Hz, H_3), 6.71 (1H, dd, J = 11.4, 15.2 Hz, H_{16}), 6.52 (1H, t, J = 11.4 Hz, H_{13}), 6.20 (1H, t, J = 11.4 Hz, H_{14}), 6.09 (1H, t, J = 11.4 Hz, H_{15}), 6.05 (1H, d, J = 12.7 Hz, H_2), 5.96−5.85 (3H, m, H_6, H_7 and H_{17}), 5.51 (1H, rough dd, H_{12}), 4.96 (1H, dt, J = 10.3, 4.7 Hz, H_5), 4.75−4.70 (1H, m, H_{11}), 4.24 (2H, br s, H_{18}), 3.72 (1H, dd, J = 6.3, 9.6 Hz, H_9), 2.50−2.38 (2H, m, H_4), 2.30 (1H, s, C_8-OH), 1.99 (1H, ddd, J = 6.3, 9.6, 12.9 Hz, H_{10}), 1.64 (1H, ddd, J = 6.3, 9.5, 12.9 Hz, H_{10}), 1.39 (3H, s, acetonide CH_3), 1.35 (3H, s, acetonide CH_3), 1.21 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.9, 144.5, 138.0, 134.5, 131.8, 130.4, 126.1, 125.7, 124.9, 123.9, 121.7, 100.8, 77.3, 73.6, 71.7, 63.6, 63.3, 33.2, 29.9, 24.9, 24.5, 22.3; IR (neat) ν_{max} 3440, 2985, 2930, 1715, 1380, 1225, 1060, 1020 cm^{-1}; FABHRMS (NBA−NaI) m/z 413.1952 (M + Na^+, $C_{22}H_{30}O_6$ requires 413.1940).

The 2D $^1H-^1H$ NOESY NMR spectrum ($CDCl_3$, 600 MHz) of **4** displayed the following diagnostic NOE cross-peaks: H_2/H_3, H_3/H_4, H_4/H_5, H_4/H_6, H_5/H_6, H_7/H_9, H_7/H_{19}, H_9/H_{10}, H_9/H_{19}, H_9/acetonide methyl (δ 1.35), H_{10}/H_{11}, H_{10}/H_{12}, H_{10}/H_{19}, H_{11}/H_{14}, H_{11}/acetonide methyl (δ 1.39), H_{12}/H_{13}, H_{13}/H_{14}, H_{13}/H_{16}, H_{14}/H_{15}, H_{15}/H_{17}, H_{16}/H_{18}, H_{17}/H_{18}.

The 2D $^1H-^1H$ COSY ($CDCl_3$, 600 MHz) of **4** displayed the following diagnostic cross-peaks: H_2 (δ 6.05)/H_3 (δ 6.87), H_3 (δ 6.87)/H_4 (δ 2.38−2.50), H_4 (δ 2.38−2.50)/H_5 (δ 4.96), H_5 (δ 4.96)/H_6 (δ 5.85−5.89), H_9 (δ 3.72)/H_{10} (δ 1.64 and 1.99), H_{10} (δ 1.64 and 1.99)/H_{11} (δ 4.70−4.75), H_{11} (δ 4.70−4.75)/H_{12} (δ 5.51), H_{12} (δ 5.51)/H_{13} (δ 6.52), H_{13} (δ 6.52)/H_{14} (δ 6.20), H_{14} (δ 6.20)/H_{15} (δ 6.09), H_{15} (δ 6.09)/H_{16} (δ 6.71), H_{16} (δ 6.71)/H_{17} (δ 6.90−6.96), H_{17} (δ 6.90−6.96)/H_{18} (δ 4.24).

Alternatively, a suspension of **3** (4.9 mg, 14 μmol) in THF (1.0 mL) was treated with 2,2-dimethoxypropane (30 μL, 0.24 mmol), followed by catalytic anhydrous *p*-TsOH at 25 °C. After 1 h, 3 drops of Et_3N were added and the mixture was concentrated *in vacuo*. PTLC (SiO_2, 33% EtOAc−hexane, elution 2×) gave **4** (2.3 mg, 42%), the corresponding primary alcohol acetal (1.2 mg, 19%), the five-membered ring 1,2-diol acetonide (0.48 mg, 8.8%), and its corresponding primary alcohol acetal (0.30 mg, 4.6%), as colorless oils.[25]

(*R*)-6-[(1*E*,3*R*,4*R*,6*R*,7*Z*,9*Z*,11*E*)-13-[*tert*-Butyldiphenylsilyl)oxy]-3,4,6-trihydroxy-3-methyl-1,7,9,11-tridecatetraen-1-yl]-5,6-dihydro-2*H*-pyran-2-one. A solution of **3** (6.3 mg, 18 μmol) in DMF (0.5 mL) was treated with imidazole (3.7 mg, 54 μmol) and TBDPSCl (7.0 μL, 27 μmol), and the mixture was stirred at 25 °C for 30 min. This sequence was repeated twice. The reaction mixture was diluted with EtOAc (3 mL), washed successively with H_2O (3 × 1 mL) and saturated aqueous NaCl (1 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Chromatography (SiO_2, 50% EtOAc−hexane) provided the TBDPS ether (7.6 mg, 10.6 mg theoretical, 72%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70−7.65 (4H, m), 7.45−7.32 (6H, m), 6.87 (1H, ddd, J = 3.1, 5.3, 9.7 Hz), 6.77 (1H, m), 6.45 (1H, t, J = 11.5 Hz), 6.20 (1H, t, J = 11.5 Hz), 6.08 (1H, t, J = 11.5 Hz), 6.03 (1H, d, J = 9.7 Hz), 5.93 (1H, d, J = 15.7 Hz), 5.88 (1H, dd, J = 4.8, 15.7 Hz), 5.84 (1H, m), 5.58 (1H, t), 5.00−4.92 (2H, m), 4.28 (2H, d, J = 3.7 Hz), 3.82 (1H, dd, J = 6.2, 6.7 Hz), 3.00 (1H, br s), 2.55−2.35 (2H, m), 1.80−1.55 (4H, m), 1.25 (3H, s), 1.06 (9H, s); IR (neat) ν_{max} 3410, 2930, 2855, 1710, 1665, 1430, 1385, 1250, 1110, 1060, 970, 825, 740, 705 cm^{-1}; FABHRMS (NBA−CsI) m/z 721.1942 (M + Cs^+, $C_{35}H_{44}O_6Si$ requires 721.1962).

(3*R*,4*Z*,6*Z*,8*E*)-10-[(*tert*-Butyldiphenylsilyl)oxy]-4,6,8-decatriene-1,3-diol. A solution of the TBDPS ether (6.9 mg, 12 μmol) described above in CH_3OH (2.0 mL) was treated with a solution of $NaIO_4$ (100 mg) in H_2O (10.0 mL, 385 μL, 18 μmol) at 25 °C. After 4 h, $NaBH_4$ (5 mg, 0.1 mmol) was added at 0 °C, and the mixture was stirred for 30 min (0 °C) and 3 h (25 °C). The reaction mixture was diluted with $CHCl_3$ (12 mL), washed with saturated aqueous NaCl (2 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Chromatography (SiO_2, 67% EtOAc−hexane) gave the diol (3.2 mg, 65%) as a colorless oil: ^1H NMR (CD_3OD, 500 MHz) δ 7.68−7.65 (4H, m), 7.43−7.37 (6H, m), 6.79 (1H, dd, J = 11.5, 15.0 Hz), 6.43 (1H, t, J = 11.5 Hz), 6.28 (1H, t, J = 11.5 Hz), 6.06 (1H, t, J = 11.5 Hz), 5.83 (1H, dt, J = 15.0, 5.0 Hz), 5.44 (1H, dd, J = 9.0, 11.5 Hz), 4.79−4.74 (1H, m), 4.29 (2H, d, J = 5.0 Hz), 3.67 (1H, dt, J = 12.5, 6.5 Hz), 3.61 (1H, dt, J = 12.5, 6.5 Hz), 1.83−1.76 (1H, m), 1.68−1.61 (1H, rough dq), 1.06 (9H, s); IR (neat) ν_{max} 3345, 2930, 2860, 1470, 1430, 1110, 1060, 700 cm^{-1}; FABHRMS (NBA−CsI) m/z 555.1344 (M + Cs^+, $C_{26}H_{34}O_3Si$ requires 555.1332).

(2*E*,4*Z*,6*Z*,8*R*)-8,10-Bis(benzoyloxy)-1-[(*tert*-butyldiphenylsilyl)oxy]-2,4,6-decatriene (6). A solution of the diol (2.8 mg, 6.6 μmol) described above in CH_2Cl_2 (2.0 mL) was treated with Et_3N (36 μL, 0.26 mmol), BzCl (10 μL, 86 μmol) and a catalytic amount of DMAP, and the mixture was stirred at 25 °C overnight under N_2. CH_3OH (1.0 mL) was added and after 30 min, the reaction mixture was diluted with EtOAc (10 mL), washed with saturated aqueous $NaHCO_3$ (2 mL), saturated aqueous NaCl (2 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Chromatography (SiO_2, 9% EtOAc−hexane) afforded **6** (2.9 mg, 4.5 mg theoretical, 65%) as a colorless oil: ^1H NMR (CD_3CN, 400 MHz) δ 8.10−7.95 (4H, m), 7.70−7.55 (6H, m), 7.50−7.41 (10H, m), 6.80 (1H, m), 6.61 (1H, t, J = 11.5 Hz), 6.43 (1H, t, J = 11.5 Hz), 6.18−6.09 (2H, m), 5.90 (1H, dt, J = 15.0, 4.9 Hz), 5.61 (1H, m), 4.45 (1H, ddd, J = 5.1, 7.1, 11.3 Hz), 4.38 (1H, ddd, J = 5.3, 6.9, 11.3 Hz), 4.32 (2H, d, J = 4.9 Hz), 2.41−2.30 (1H, m), 2.22−2.13 (1H, m), 1.05 (9H, s); IR (neat) ν_{max} 3070, 2930, 2855, 1720, 1450, 1430, 1315, 1275, 1110, 1070, 1025, 710 cm^{-1}; FABHRMS (NBA−CsI) m/z 763.1836 (M + Cs^+, $C_{40}H_{42}O_5Si$ requires 763.1856).

(2*R*)-1,2,4-Tris(Benzoyloxy)butane (7). A stream of O_3/O_2 was bubbled through a solution of **6** (0.73 mg, 1.16 μmol) in CH_3OH (1.2 mL) at −78 °C for 3 min. After stirring for 15 min, $NaBH_4$ (5 mg, 0.1 mmol) was added, and the mixture was allowed to warm to 25 °C over 30 min. The reaction mixture was diluted with EtOAc (10 mL), washed with H_2O (2 mL) and saturated aqueous NaCl (2 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was dissolved in THF (0.5 mL), and Et_3N (18 μL, 0.13 mmol), BzCl (5.0 μL, 43 μmol), and a catalytic amount of DMAP were added to the solution at 25 °C. After stirring for 8 h, H_2O (1 mL) was added, and the reaction mixture was stirred for 30 min. The mixture was diluted with EtOAc (10 mL), washed with saturated aqueous $NaHCO_3$ (1 mL) and saturated aqueous NaCl (1 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. PTLC (SiO_2, 17% EtOAc−hexane) gave **7** (0.30 mg, 62%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.04−7.98 (6H, m), 7.56−7.49 (3H, m), 7.42−7.35 (6H, m), 5.74−5.69 (1H, m), 4.64 (1H, dd, J = 3.5, 13.5 Hz), 4.553 (1H, dd, J = 7.5, 13.5 Hz), 4.548 (1H, dt, J = 11.5, 6.0 Hz), 4.45 (1H, ddd, J = 5.5, 7.5, 11.5 Hz), 2.38−2.27 (2H, m); IR (neat) ν_{max} 1720, 1600, 1450, 1315, 1270, 1175, 1110, 1070, 1025 cm^{-1}; FABHRMS (NBA−NaI) m/z 441.1334 (M + Na^+, $C_{25}H_{22}O_6$ requires 441.1314).

Chiral phase HPLC analysis on an analytical Chiralcel OD-H column (0.46 × 20 cm, 20% 2-PrOH/hexane, 0.6 mL/min) revealed that **7** (t_R = 11.4 min) derived from **1** eluted with the same retention time as authentic (2*R*)-**7**, t_R = 11.4 min, and not (2*S*)-**7**, t_R = 18.4 min (α = 1.61).

(*R*)- and (±)-1,2,4-Tris(benzoyloxy)butane (7). A stirred solution of (*R*)- or (±)-1,2,4-butanetriol (25.0 mg, 0.236 mmol) in THF (3.0 mL) was treated with Et_3N (656 μL, 4.71 mmol), BzCl (328 μL, 2.83 mmol), and a catalytic amount of DMAP, and the mixture was stirred at 25 °C overnight. H_2O (1.0 mL) was added and after 2 h, the reaction mixture was diluted with

(24) Taylor, R. J. K.; Wiggins, K.; Robinson, D. H. *Synthesis* **1990**, 589.

(25) Characterization is provided in the Supporting Information.

EtOAc (20 mL), washed with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous NaCl (5 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Chromatography (SiO_2, 10% EtOAc−hexane) afforded (*R*)- or (±)-**7** (98.8 mg, 98.7 mg theoretical, 100%) as a colorless oil: both compounds displayed identical ^1H NMR ($CDCl_3$, 500 MHz) and IR (neat) with **7** derived from **1**; FABHRMS (NBA−NaI) *m*/*z* 441.1325 (M + Na^+, $C_{25}H_{22}O_6$ requires 441.1314); (*R*)-1,2,4-butanetriol $[\alpha]^{20}_D$ +49.6 (*c* 0.500, $CHCl_3$).

(4-Methoxyphenyl)methyl Hex-5-enoate (10). Method A. A suspension of hex-5-enoic acid (**9**,[20] 38.00 g, 0.333 mol), 4-methoxybenzyl chloride (57.38 g, 0.366 mol), and $NaHCO_3$ (55.96 g, 0.666 mol) in DMF (190 mL) was stirred at 45 °C for 2 days. Additional 4-methoxybenzyl chloride (5.21 g, 0.0333 mol) was added, and stirring was continued for another 1 day. The reaction mixture was cooled to 25 °C, diluted with EtOAc (300 mL), washed with H_2O (2×100 mL) and saturated aqueous NaCl (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Chromatography (SiO_2, 0−5% EtOAc−hexane gradient elution) afforded **10** (69.55 g, 89%) as a clear colorless oil.

Method B. A solution of hex-5-enoic acid (**9**,[20] 11.4 g, 0.1 mol) in CH_2Cl_2 (250 mL, 0.4 M) was treated sequentially with saturated aqueous $NaHCO_3$ (167 mL), Bu_4NI (48.0 g, 0.13 mol), and 4-methoxybenzyl chloride (18.8 g, 0.12 mol), and the mixture was stirred at 25 °C for 28 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* giving a white solid. This material was triturated with hexanes and filtered, washing the solid with hexanes (4 × 50 mL). The filtrate was concentrated *in vacuo*. Chromatography (SiO_2, 3.5 × 15 cm, 0−10% EtOAc−hexane gradient elution) afforded **10** (11.5 g, 22.1 g theoretical, 52%) as a clear oil: R_f 0.45 (10% EtOAc−hexane); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.28 (2H, d, J = 8.6 Hz), 6.87 (2H, d, J = 8.6 Hz), 5.74 (1H, dddd, J = 6.8, 6.8, 10.2, 17.2 Hz), 5.03 (3H, m), 4.97−4.92 (1H, m), 3.79 (3H, s), 2.32 (2H, t, J = 7.5 Hz), 2.06 (2H, q, J = 7.2 Hz), 1.71 (2H, p, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4, 159.5, 137.6, 130.0, 128.1, 115.3, 113.9, 65.9, 55.2, 33.6, 33.1, 24.0; IR (neat) ν_{max} 2943, 1733, 1610, 1512, 1246, 1164 cm^{-1}; FABHRMS (NBA−NaI) *m*/*z* 257.1159 (M + Na^+, $C_{14}H_{18}O_3$ requires 257.1154).

(4-Methoxyphenyl)methyl (*R*)-5,6-Dihydroxyhexanoate (11). A solution of $K_3Fe(CN)_6$ (19.76 g, 60 mmol), K_2CO_3 (8.3 g, 60 mmol), $NaHCO_3$ (5.04 g, 60 mmol), and $(DHQD)_2$−AQN (857 mg, 1 mmol) in *t*-BuOH (100 mL) and H_2O (100 mL) was stirred at 25 °C, warmed slightly to dissolve the materials, and recooled to 25 °C. The mixture was treated with $K_2OsO_2(OH)_2$ (134 mg, 0.4 mmol) and immediately cooled to 0 °C. When precipitates appeared, **10** (4.68 g, 20 mmol) was added at once, and the reaction mixture was stirred at 0 °C for 48 h. Solid Na_2SO_3 (16 g) was added slowly over 10 min at 0 °C. The mixture was warmed to 25 °C and stirred for 45 min. The mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Chromatography (SiO_2, 3.5 × 15 cm, EtOAc) afforded **11** (3.95 g, 5.00 g theoretical, 79%) as a white solid which was 88% ee as determined by preparation of the bis-(*R*)-Mosher ester described below. One recrystallization (Et_2O) provided enantiomerically pure (>98% ee) **11** (2.55 g, 5.00 g theoretical, 51%) as a white solid: R_f 0.5 (EtOAc); mp 57−59 °C (white plates, Et_2O); $[\alpha]^{22}_D$ +2.1 (*c* 0.06, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29 (2H, d, J = 8.6 Hz), 6.89 (2H, d, J = 8.6 Hz), 5.05 (2H, s), 3.81 (3H, s), 3.72−3.66 (1H, m), 3.65−3.60 (1H, m), 3.46−3.40 (1H, m), 2.39 (2H, dt, J = 3.0, 7.3 Hz), 2.24 (1H, d, J = 4.3 Hz, CHO*H*), 1.89 (1H, t, J = 5.7 Hz, CH_2OH), 1.84−1.66 (2H, m), 1.48−1.43 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 159.6, 130.1, 128.0, 113.9, 71.6, 66.6, 66.1, 55.3, 34.0, 32.3, 20.7; IR (neat) ν_{max} 3372, 2933, 2871, 1728, 1610, 1518, 1463, 1254 cm^{-1}; FABHRMS (NBA−NaI) *m*/*z* 291.1212 (M + Na^+, $C_{14}H_{20}O_5$ requires 291.1208). Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.78; H, 7.39.

(4-Methoxyphenyl)methyl (*R*)-5,6-Bis[[(*S*)-α-methoxy-α-(trifluoromethyl)phenyl]acetoxy]hexanoate (bis-Mosher ester of 11). A solution of **11** (5.8 mg, 21.6 μmol) and DMAP (7.9 mg, 64.9 μmol) in THF (108 μL, 0.2 M) was treated with (*R*)-Mosher's chloride ((*R*)-MTPA-Cl, 12.6 mg, 49.8 μmol, 9.4 μL) at 25 °C, and the reaction mixture was stirred for 4 h. The reaction solvent was removed *in vacuo*. Chromatography (SiO_2, 0.5 × 5 cm, 25−50% EtOAc−hexane gradient elution) afforded the *bis*-Mosher ester of **11** (6.0 mg, 15.1 mg theoretical, 40%): R_f 0.4 (25% EtOAc−hexane); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48 (2H, d, J = 7.7 Hz), 7.43 (2H, d, J = 7.1 Hz), 7.40−7.31 (6H, m), 7.28 (2H, d, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 5.31−5.30 (1H, m), 5.04 (2H, s), 4.53 (1H, dd, J = 2.9, 12.4 Hz), 4.24 (2H, dd, J = 5.1, 12.4 Hz), 3.80 (3H, s), 3.43 (3H, d, J = 1.1 Hz), 3.41 (3H, d, J = 1.0 Hz), 2.29 (2H, t, J = 6.9 Hz), 1.73−1.57 (m, 4H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −68.10, −68.13; ^{19}F NMR for racemic material ($CDCl_3$, 376 MHz) δ −67.70, −67.93, −68.10, −68.13; FABHRMS (NBA−CsI) *m*/*z* 833.1169 (M + Cs^+, $C_{34}H_{34}F_6O_9$ requires 833.1161).

(4-Methoxyphenyl)methyl (*R*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-5-hydroxyhexanoate (12). A solution of **11** (500 mg, 1.86 mmol) in DMF (3.7 mL, 0.5 M) was treated sequentially with imidazole (279 mg, 4.1 mmol) and TBDPSCl (564 mg, 2.05 mmol, 534 μL), and the mixture was stirred at 25 °C under Ar for 15 h. The reaction mixture was poured into H_2O (40 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL), dried ($MgSO_4$), and filtered, and the solvent was removed *in vacuo*. Chromatography (SiO_2, 2 × 10 cm, 10−25% EtOAc−hexane gradient elution) afforded **12** (840 mg, 941 mg theoretical, 89%) as a clear oil: R_f 0.5 (25% EtOAc−hexane); $[\alpha]^{22}_D$ −0.92 (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72−7.67 (4H, m), 7.48−7.39 (6H, m), 7.30 (2H, d, J = 8.6 Hz), 6.89 (2H, ddd, J = 2.9, 2.9, 8.6 Hz), 5.06 (2H, s), 3.80 (3H, s), 3.77−3.72 (1H, m), 3.67 (1H, dd, J = 3.5, 10.1 Hz), 3.51 (1H, dd, J = 7.4, 10.1 Hz), 2.54 (1H, br s), 2.36 (2H, t, J = 7.4 Hz), 1.85−1.67 (2H, m), 1.48−1.41 (2H, m), 1.10 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.3, 159.5, 135.5, 133.0, 130.0, 129.8, 128.1, 127.7, 113.8, 71.4, 67.8, 65.8, 55.1, 34.1, 31.9, 26.8, 20.9, 19.1; IR (neat) ν_{max} 3503, 3070, 2931, 2857, 1734, 1612, 1516, 1428, 1248, 1112 cm^{-1}; FABHRMS (NBA−CsI) *m*/*z* 639.1546 (M + Cs^+, $C_{30}H_{38}O_5Si$ requires 639.1543).

(*R*)-6-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (13). A solution of **12** (100 mg, 0.198 mmol) in anisole (107 mg, 107 μL, 1.9 M) was treated with CF_3CO_2H (90 mg, 80 μL), and the mixture was stirred at 25 °C for 30 min. The CF_3CO_2H was evaporated under a N_2 stream (30 min) and *in vacuo* (30 min). Chromatography (SiO_2, 2.5 × 15 cm, 10−25% EtOAc−hexane gradient elution) afforded **13** (55.0 mg, 72.9 mg theoretical, 75%) identical in all respects with authentic racemic material:[24] R_f 0.5 (25% EtOAc−hexane); $[\alpha]^{22}_D$ −12.5 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.70−7.60 (6H, m), 7.50−7.35 (9H, m), 4.45−4.35 (1H, dddd, J = 4.7, 4.8, 5.1, 9.4 Hz), 3.90−3.70 (2H, m), 2.70−2.40 (2H, m), 2.05−1.70 (4H, m), 1.05 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 135.5, 132.9, 129.8, 127.7, 80.2, 65.6, 26.8, 24.4, 19.2, 18.3; IR (neat) ν_{max} 3070, 2930, 2857, 1737, 1241, 1108 cm^{-1}; FABHRMS (NBA−NaI) *m*/*z* 391.1696 (M + Na^+, $C_{22}H_{28}O_3Si$ requires 391.1705).

(3*RS*,6*R*)-6-[[(*tert*-Butylphenylsilyl)oxy]methyl]-3-(phenylselenyl)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (14). A solution of **13** (350 mg, 0.95 mmol) in THF (3 mL) was added slowly to a solution of freshly prepared LDA (1.05 mmol, 3.0 mL THF) at −78 °C, and the mixture was stirred at −78 °C for 1 h. PhSeBr (269 mg, 1.14 mmol) in THF (2 mL) was added, and the solution was stirred at −78 °C for 5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O (2 × 20 mL) and saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography (SiO_2, 2.5 × 15 cm, 10−50% CH_2Cl_2−benzene) provided **14** (249 mg, 498 mg theoretical, 50%) as a 2:1 mixture of diastereomers: 83 mg of the less polar isomer; R_f 0.29 (50% CH_2Cl_2−benzene); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.70−7.62 (6H, m), 7.45−7.32 (9H, m), 4.47 (1H, dddd, J = 4.4, 4.6, 4.6, 9.1 Hz), 3.97 (1H, t, J = 7.4 Hz), 3.75 (2H, d, J = 6.3 Hz), 2.42−2.28 (1H, m), 2.10−1.95 (2H, m), 1.85−1.75 (1H, m), 1.05 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 135.8,

135.6, 135.5, 133.0, 132.8, 129.9, 129.3, 128.9, 127.8, 79.5, 65.4, 26.8, 26.2, 24.0; IR (neat) ν_{max} 3052, 2929, 2856, 1732, 1428, 1244, 1113 cm^{-1}; FABHRMS (NBA−NaI) *m/z* 525.1379 (M + H^+, $C_{28}H_{32}O_3SeSi$ requires 525.1364); and 166 mg of the more polar isomer; R_f 0.2 (50% CH_2Cl_2−benzene); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.70−7.65 (6H, m), 7.45−7.30 (9H, m), 4.45−4.35 (1H, dddd, J = 5.0, 5.0, 8.8, 10.4 Hz), 4.03 (1H, t, J = 4.5 Hz), 3.76 (2H, d, J = 5.0 Hz), 2.30−2.10 (3H, m), 1.92−1.82 (1H, m), 1.10 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 135.7, 135.6, 135.5, 133.1, 132.9, 129.8, 129.3, 128.7, 127.8, 80.8, 65.5, 39.8, 26.8, 26.6; IR (neat) ν_{max} 3070, 2929, 2856, 1731, 1427, 1240, 1113 cm^{-1}; FABHRMS (NBA−NaI) *m/z* 525.1380 (M + H^+, $C_{28}H_{32}O_3SeSi$ requires 525.1364).

(3*RS*,6*R*)-6-(Hydroxymethyl)-3-(phenylselenyl)-3,4,5,6-tetrahydro-2*H*-pyran-2-one (15). A solution of **14** (98 mg, 0.187 mmol) in THF (5.0 mL) was treated with HOAc (62 μL, 1.1 mmol) and Bu_4NF hydrate (91 mg), and the mixture was stirred at 25 °C for 3 h. The reaction mixture was diluted with EtOAc (20 mL), washed with H_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Chromatography (SiO_2, 50% EtOAc−hexane) provided **15** (36.2 mg, 53.2 mg theoretical, 68%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67−7.61 (2H, m), 7.37−7.27 (3H, m), 4.52−4.46 (0.5 H, m), 4.46−4.39 (0.5 H, m), 4.02 (0.5 H, ddd, J = 1.0, 4.1, 5.2 Hz), 3.95 (0.5 H, t, J = 7.2 Hz), 3.75 (1H, br d, J = 12.2 Hz), 3.62 (1H, ddd, J = 2.3, 5.4, 12.2 Hz), 2.38−1.67 (5H, m); IR (neat) ν_{max} 3400, 2930, 1720, 1440, 1250, 1190, 1060, 1020, 740, 690 cm^{-1}; FABHRMS (NBA−NaI) *m/z* 287.0180 (M + H^+, $C_{12}H_{14}O_3Se$ requires 287.0186).

(*R*)-6-(Hydroxymethyl)-5,6-dihydro-2*H*-pyran-2-one (16). A stirred solution of **15** (45.4 mg, 0.159 mmol) in CH_2Cl_2 (5.0 mL) and H_2O (100 μL) was treated with 35% H_2O_2 (30.9 μL, 0.318 mmol). After 1 h at 25 °C, the mixture was treated with additional 35% H_2O_2 (30.9 μL, 0.318 mmol) and stirred for 1 h. The organic phase was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 15 mL). The organic phase and the extracts were combined, dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, 50% EtOAc−hexane) provided **16** (17.4 mg, 20.5 mg theoretical, 85%) as a colorless oil: $[\alpha]^{20}_D$ +160 (*c* 0.850, $CHCl_3$) lit. $[\alpha]^{26}_D$ + 175 (*c* 0.92, $CHCl_3$) identical in all respects (NMR, IR, MS) with authentic material.[23]

(*R*)-6-[(*E*)-3-Oxo-1-buten-1-yl]-5,6-dihydro-2*H*-pyran-2-one (8). A solution of oxalyl chloride (28 μL, 0.32 mmol) in CH_2Cl_2 (0.5 mL) was treated with DMSO (27 μL, 0.38 mmol) at −78 °C under Ar, and the mixture was stirred for 15 min. A solution of **16** (4.0 mg, 32 μmol) in CH_2Cl_2 (0.5 mL) was added to the solution, and the mixture was stirred for 15 min. Et_3N (156 μL, 1.12 mmol) was added to the mixture, and stirring was continued for 10 min at −78 °C and 5 min at 0 °C. The reaction mixture was treated with 1-(triphenylphosphoranylidene)-2-propanone at 0 °C for 30 min and passed through a plug of SiO_2 (50% EtOAc−hexane). The material obtained was further purified by PTLC (SiO_2, 60% EtOAc−hexane) to give **8** (2.7 mg, 5.2 mg theoretical, 52%) as a colorless oil: $[\alpha]^{20}_D$ +201 (*c* 0.110, $CHCl_3$), lit.[10] $[\alpha]_D$ +216.8 (*c* 1.16, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.90 (1H, ddd, J = 3.0, 6.0, 10.0 Hz), 6.74 (1H, dd, J = 4.5, 16.0 Hz), 6.43 (1H, dd, J = 1.5, 16.0 Hz), 6.08 (1H, ddd, J = 1.0, 2.5, 10.0 Hz), 5.12 (1H, dddd, J = 1.5, 4.0, 4.5, 11.0 Hz), 2.56 (1H, dddd, J = 1.0, 4.0, 6.0, 18.5 Hz), 2.44 (1H, dddd, J = 2.5, 3.0, 11.0, 18.5 Hz), 2.28 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.5, 163.0, 144.1, 140.7, 130.5, 121.7, 75.6, 29.0, 28.0; IR (neat) ν_{max} 2920, 1720, 1700, 1675, 1360, 1240, 1090, 1060, 805 cm^{-1}; FABHRMS (NBA−NaI) *m/z* 189.0532 (M + Na^+, $C_9H_{10}O_3$ requires 189.0528).

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA 42056), The Skaggs Institute for Chemical Biology, and the sabbatical leave of M.H. from Tanabe Seiyaku Co., Ltd. (1996−1997). We thank Warner-Lambert/Parke-Davis for a sample of fostriecin with which this work was conducted, and we thank the Sharpless group for the $(DHQD)_2$−AQN ligand and the use of a Chiralcel OD-H analytical HPLC column.

Supporting Information Available: ^1H NMR spectra of characterized compounds are provided (20 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.

JO962166H