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Total Synthesis of Fostriecin: Via a Regio- and Stereoselective Polyene Hydration, Oxidation, and Hydroboration Sequence

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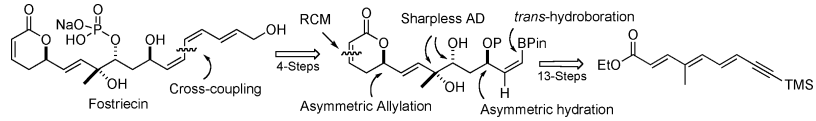
ABSTRACT



A total synthesis of the fostriecin has been achieved in 24 steps from enyne 11. The lactone moiety was installed by a Leighton allylation and Grubbs ring-closing metathesis reaction. The highly reactive *Z,Z,E*-triene moiety was installed via a late-stage Suzuki−Miyaura cross-coupling of a remarkably stable *Z*-vinyl boronate. The relative and absolute stereocenters of the C-8,9,11 triol were generated with a regio- and stereoselective asymmetric hydration/oxidation sequence.

Fostriecin (**1**, CI-920) is a structurally novel phosphorylated polyene-, polyol-, and pyranone-containing natural product, which was isolated from *Steptomyces pulveraceus* in 1983 (Figure 1).[1] In addition to its compelling structural features,

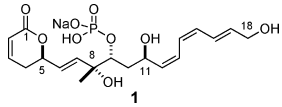


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Figure 1. Fostriecin (**1**, CI-920).

fostriecin has been shown to possess significant cytotoxic activity against a broad range of cell lines,[2] such as leukemia, lung cancer, breast cancer, and ovarian cancer in vitro and also antitumor activity against leukemia in vivo.[3] This cancer cell activity has been linked to the phosphate portion of the molecule and its ability to inhibit the protein phosphatases 1, 2A, and 4 (PP1, PP2A, and PP4). Of particular interest is fostriecin's ability to selectively inhibit phosphatases 2A and 4 over phosphatases 1 (e.g., IC_{50} = 45 nM for PP1, 1.5 nM for PP2A, and 3.0 nM for PP4).[4] Because of its unique structure and compelling biological activity, fostriecin has been extensively studied by both chemists and biologists.

In addition to the mechanism-of-action studies, fostriecin was the subject of several clinical trials at the National Cancer Institute. Although its gross structure was known, the complete stereochemical assignment of fostriecin was determined in 1997 by Boger.[5] These efforts from Boger also led to its first total synthesis.[6a] Fostriecin's potential use as a chemotherapeutic agent has inspired many more total syntheses.[6,7] Similarly, the isolation and structural elucidation of related natural products with similar antitumor,

(1) (a) Tunac, J. B.; Graham, B. D.; Dobson, W. E. *J. Antibiot.* **1983**, *36*, 1595. (b) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Wilmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot.* **1983**, *36*, 1601. (c) Hokanson, G. C.; French, J. C. *J. Org. Chem.* **1985**, *50*, 462.

(2) (a) Lewy, D. S.; Gauss, C.-M.; Soenen, D. R.; Boger, D. L. *Curr. Med. Chem.* **2002**, *9*, 2005. (b) De Jong, R. S.; De Vries, E. G. E.; Mulder, N. H. *Anti-Cancer Drugs.* **1997**, *8*, 413.

(3) Reviews: (a) Jackson, R. C.; Fry, D. W.; Boritzki, T. J.; Roberts, B. J.; Hook, K. E.; Leopold, W. R. *Adv. Enzyme Regul.* **1985**, *23*, 193. (b) Scheithauer, W.; Hoff, D. D. V.; Clark, G. M.; Shillis, J. L.; Elslager, E. F. *Eur. J. Clin. Oncol.* **1986**, *22*, 921.

(4) Reviews: (a) Walsh, A. H.; Cheng, A.; Honkanen, R. E. *FEBS Lett.* **1997**, *416*, 230. (b) Hastie, C. J.; Cohen, P. T. W. *FEBS Lett.* **1998**, *431*, 357.

(5) Boger, D. L.; Hikota, M.; Lewis, B. M. *J. Org. Chem.* **1997**, *62*, 1748.

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antibacterial, and antifungal activities have occurred (e.g., phoslactomycins A−F (**2**),[8] cytostatin (**3**),[9] and leustroducsins A−C and H (**4a**−**c**) in Figure 2).[10]

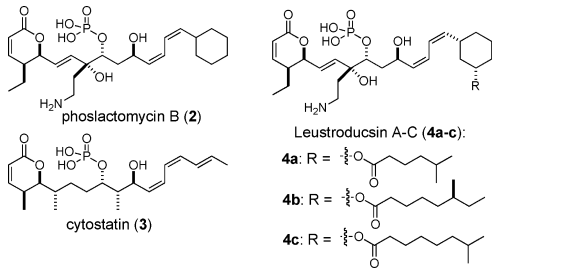


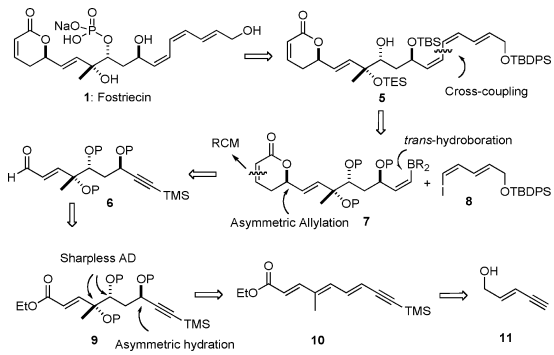
Figure 2. Natural products related to fostriecin.

Unfortunately, because of concerns over the stability of fostriecin, its clinical trials were halted in early phase I.[11] However, interest still exists in new synthetic routes to fostriecin and related molecules. It is hoped that these new routes will provide access to analogues with similar biological activities, yet more desirable physical properties. Furthermore, the unique structural features of fostriecin, which includes an unsaturated lactone, the C-8−C-11 triol monophosphate component, and the conjugated *Z*,*Z*,*E*-trienol, make it an interesting target for synthetic organic chemists.

We became interested in the synthesis of fostriecin out of the same desire to develop a new route to the molecule for SAR-type studies, as well as from our ongoing interest in the synthesis of polyol pyranone-containing natural products.[12] In particular, we wanted to explore the use of our trienoate asymmetric hydration/oxidation reaction sequence for the C-8,9,11 triol portion of the molecule.[13] From a strategic point of view, the pentaene portion of the target molecule made this approach more challenging. Herein we report our successful efforts at regioselectively applying this polyene asymmetric hydration/oxidation reaction sequence in an efficient synthesis of fostriecin. In this regard, our route uniquely uses a late stage *trans*-hydroboration reaction.[14] In addition, it takes advantage of the stereoselective stability of a *Z*-vinyl boronate intermediate,[15,16] which offers a significant alternative for the construction of the *Z*,*Z*,*E*-triene portion of this molecule (vide infra).

Our synthetic efforts started with an investigation of the chemo- and regioselectivity of the asymmetric oxidation and subsequent reduction of yne-trienoate **10** to install the C-11 propargyl alcohol. Although we expected the Sharpless dihydroxylation to occur at the double bond furthest away from the electron-withdrawing group, we have previously found that this reaction can give regioisomers. In practice, our synthesis began with the preparation of the trienoate **10** from commercially available enyne **11** (Scheme 1).

Scheme 1. Fostriecin (**1**) Retrosynthesis



In order to protect the terminal acetylene, the primary alcohol of **11** was first protected as a silyl ether (TBSCl/

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(7) For the synthesis of related molecules, see: (a) Cossy, J.; Pradaux, F.; BouzBouz, S. *Org. Lett.* **2001**, *3*, 2233. (b) Kiyotsuka, Y.; Igarashi, J.; Kobayashi, Y. *Tetrahedron Lett.* **2002**, *43*, 2725. (c) Ramachandran, V.; Liu, H.; Reddy, V.-R.; Brown, H. C. *Org. Lett.* **2003**, *5*, 3755. (d) Shimada, K.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 4048. (e) Bialy, L.; Waldmann, H. *Chem.—Eur. J.* **2004**, *10*, 2759. (f) Wang, Y.-G.; Takeyama, R.; Kobayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3320. (g) Lawhorn, B. G.; Boga, S. B.; Wolkenberg, S. E.; Colby, D. A.; Gauss, C.-M.; Swingle, M. R.; Amable, L.; Honkanen, R. E.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 16720. (h) Shibahara, S.; Fujino, M.; Tashiro, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2008**, *10*, 2139. (i) Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. *J. Org. Chem.* **2008**, *73*, 5360. (j) Druais, V.; Hall, M. J.; Corsi, C.; Wendeborn, S. V.; Meyer, C.; Cossy, J. *Org. Lett.* **2009**, *11*, 935. (k) Knig, C. M.; Gebhardt, B.; Schleth, C.; Dauber, M.; Koert, U. *Org. Lett.* **2009**, *11*, 2728. For a synthesis/structural correction of sultriecin, see: (l) Burke, C. P.; Haq, N.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 2157.

(8) (a) Fushimi, S.; Shimazu, A.; Seto, H. *J. Antibiot.* **1989**, *42*, 1019. (b) Fushimi, S.; Furihata, K.; Seto, H. *J. Antibiot.* **1989**, *42*, 1026. (c) Ozasa, T.; Suzuki, K.; Sasamata, M.; Tanaka, K.; Kobori, M.; Kadota, S.; Nagai, K.; Saito, T.; Watanabe, S.; Iwanami, M. *J. Antibiot.* **1989**, *42*, 1331–1338. (d) Ozasa, T.; Tanaka, K.; Sasamata, M.; Kaniwai, H.; Shimizu, M.; Matsumoto, H.; Iwanami, M. *J. Antibiot.* **1989**, *42*, 1339. (e) Shibata, T.; Kurihara, S.; Yoda, K.; Haruyama, H. *Tetrahedron* **1995**, *51*, 1999.

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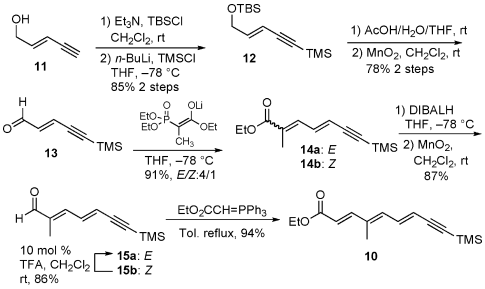
(11) De Jong, R. S.; Mulder, N. H.; Uges, D. R. A.; Sleijfer, D. T.; Hoppener, F. J. P.; Groen, H. J. M.; Willemse, P. H. B.; van der Graaf, W. T.; de Vries, E. G. E. *Br. J. Cancer* **1999**, *79*, 882.

(12) (a) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2005**, 1069. (b) Gao, D.; O'Doherty, G. A. *J. Org. Chem.* **2005**, *70*, 9932.

(13) (a) Guo, G.; Mortensen, M. S.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3149. (b) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087. (c) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 3987. (d) Ahmed, Md. M.; Mortensen, M. S.; O'Doherty, G. *J. Org. Chem.* **2006**, *71*, 7741. For other oxidation/reduction asymmetric hydration approaches, see: (e) Gansauer, A.; Fan, C.-A.; Keller, F.; Keil, J. *J. Am. Chem. Soc.* **2007**, *129*, 3484.

Et_3N), and then a TMS group was added to the terminal acetylenic position (*n*-BuLi/trimethylchlorosilane) to give fully protected enynol **12** in 85% yield for two steps (Scheme 2). Selective deprotection of the silyl-ether with aqueous

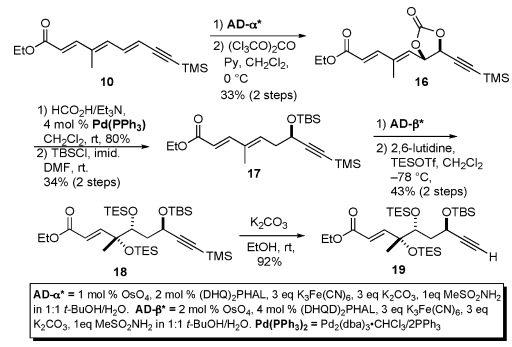
Scheme 2. Synthesis of Trieneoate **10**



acetic acid in THF afforded an allylic alcohol, which was directly oxidized with MnO_2 to provide aldehyde **13** (78%). Horner−Emmons reaction of triethyl-2-phosphonopropionate with aldehyde **13** provided dienynes **14a/b** in 91% yield as a 4:1 mixture of *E*/*Z*-isomers. Although the *E*/*Z*-double bond isomers could be separated by SiO_2 chromatography on a preparative scale, it was easier to carry the mixture forward. Exposure of a CH_2Cl_2 solution of the two isomers **14a/b** with 2.5 equiv of DIBAL-H at −78 °C provided a mixture of allylic alcohols, which without purification were oxidized with MnO_2 to afford aldehydes **15a/b** (87% yield for 2 steps). At this stage, the undesired double bond isomer **15b** was readily converted into the desired isomer **15a** by treating the mixture with 10 mol % TFA in CH_2Cl_2 (86% of >20:1 ratio). Finally, a stabilized Wittig olefination between aldehyde **15a** with $EtO_2CCH{=}PPh_3$ in toluene at reflux gave trienoate **10** in 94% yield (*E*/*Z* ratio >20/1).

With a practical approach to the trienoate **10** in hand, we turned our attention to the asymmetric hydration/oxidation sequence of **10** to provide a suitably protected triol **19** (Scheme 3).[17] This began with an asymmetric dihydroxylation and subsequent palladium-catalyzed reduction of the most electron-deficient double bond of **10**. Exposure of **10** to Sharpless AD-mix-α reagent system regioselectively provided the corresponding diol,[18] which was subsequently converted (triphosgene/Py) to a carbonate **16** (80% for 2 steps). Treatment of **16** with 2.0 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 4.0 mol % PPh_3,and a mild hydride source (3 equiv, Et_3N/HCO_2H) provided a propargylic alcohol, which was then protected to a silyl ether **17** (64% yield for 2 steps). A second Sharpless dihydroxylation with the AD mix-*β*

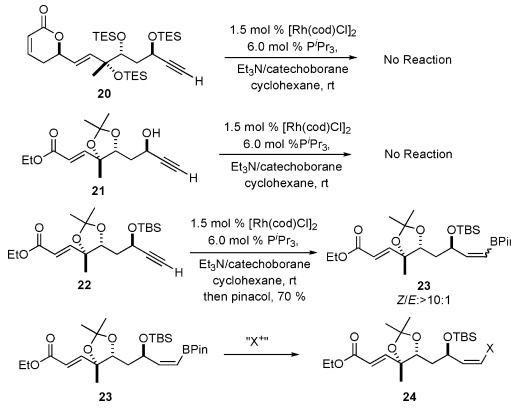
Scheme 3. Asymmetric Hydration and Oxidation of Triene **10**



reagent system of dienoate **17** cleanly gave a diol product, which was then protected as a bis-triethylsilyl ether **18** (TESOTf/2,6-lutidine) in good overall yield (62% for 2 steps) and diastereomeric and enantiomeric purity (>96% ee and dr). The terminal trimethyl silyl group was then selectively removed (K_2CO_3 in EtOH) to give **19** (92%).

With the desired triol stereochemistry of fostriecin installed, we next turned to the key rhodium catalyzed *trans*-hydroboration reaction (Scheme 4).[14] Because of the per-

Scheme 4. Substrate Optimization for the *trans*-Hydroboration



ceived instability of the organoborane intermediates, we first investigated the *trans*-hydroboration of late stage intermediates like **20** with the pyranone ring installed. Unfortunately, when terminal alkyne **20** was exposed to Miyaura's typical procedure, no desired products were detected. A similar lack of reactivity was observed for the propargyl alcohol **21**. Success was finally achieved when both the hydroxyl group and pyranone ring were removed. Thus when the TBS-protected propargyl alcohol **22** was exposed to the Miyaura conditions (1.5 mol % $Rh[(cod)Cl]_2$, 6 mol % of P*i*-Pr_3, triethylamine, catechol borane then pinacol)[14] the desired *trans*-hydroboration proceeded smoothly to give *Z*-vinylborane **23** (70%, >10:1). To our surprise the vinyl borane **23** was stable to silica gel chromatography and all attempts to stereoselectively convert the *Z*-vinyl boronate into a vinyl halide like **24** (e.g., NBS and I_2).

(14) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990. For its use in synthesis, see: ref.6c

(15) For an example of a stable vinyl boronate in natural product synthesis, see: Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216.

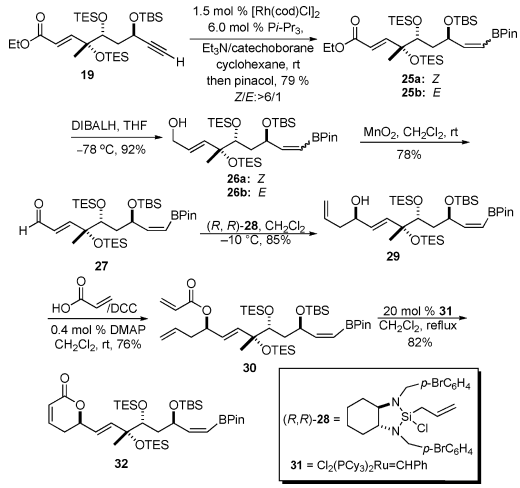
(16) We found that these vinyl-boronates rival the vinyl-trifluoroborates in terms of reaction compatibility, see: Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2008**, *73*, 3885.

(17) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447.

(18) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Zhang, Y.; O'Doherty, G. A. *Tetrahedron* **2005**, *61*, 6337.

For reasons associated with the end-game protecting group strategy, we had to move forward with the bis-TES ether protected vinyl boranes **25a/b** for installation of the pyranone ring and the *E*,*E*,*Z*-triene. When the more suitably protected alkyne **19**, with a bis-TES-ether protecting group, was exposed to the same conditions, a slightly less selective *trans*-hydroboration reaction occurred to give **25a**, along with the undesired *cis*-hydroboration product **25b** in a 6:1 ratio of inseparable isomers. Once again vinyl boronate **25a/b** was remarkably stable to silica gel chromatography and several subsequent synthetic transformations to install the pyranone ring (Scheme 5). To our

Scheme 5. *trans*-Hydroboration and Pyranone Installation

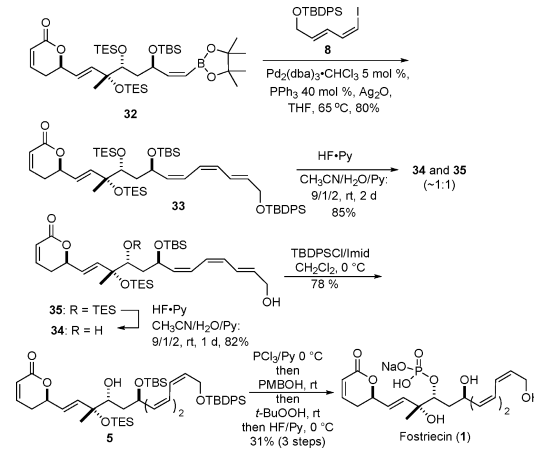


delight, the *Z*-vinyl boronate displayed remarkable stability to the reaction conditions. For instance, when the mixture of esters **25a/b** was exposed to excess DIBALH, a good yield of allyl alcohols **26a/b** was isolated (92% yield, >6/1: *Z*/*E* ratio). Moreover, when the mixture of allylic alcohols was oxidized with MnO_2, only aldehyde **27** was isolated as a single vinylborane isomer in 78% yield. Diastereoselective allylation of aldehyde **27** was achieved by simple exposure to a solution of the Leighton allylsilane reagent (***R,R*)-28** (0.2 M in CH_2Cl_2)[19] at −10 °C, providing allylic alcohol **29** in 85% yield with near perfect stereocontrol (>99% ee and dr). A DCC-promoted esterification with acrylic acid (3 equiv) and allylic alcohol **29** afforded a tetraene **30** in 76% yield. Exposure of a refluxing CH_2Cl_2 solution of the tetraene **30** to the Grubbs catalyst **31** (10 mol %) resulted in a clean cyclization to pyranone **32** in 82% yield.

With both the vinyl boronate **32** and vinyl iodide **8** in hand, we then investigated the Suzuki−Miyaura cross-coupling.[20] Our initial efforts using a $Pd(PPh_3)_4/Ag_2O$ system led to no reaction. Further investigations led to an optimal condition, which used a 20% Pd/PPh_3 system (20% $Pd_2(dba)_3$•$CHCl_3$/80%PPh_3). These conditions smoothly coupled vinyl boronate **32** and vinyl iodide **8** affording the *Z*,*Z*,*E*-triene **33** in excellent alkene stereoselectivity (>20:1) and 80% yield.

(19) Kubota, K.; Leighton, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 946.
(20) For a review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

Scheme 6. Fostriecin End-Game



With all of the carbon atoms and stereocenters in place, all that was needed to complete the synthesis was the selective deprotection and phosphorylation of the C-9 TES-group followed by global deprotection. Unfortunately, the selective deprotection of silyl ether **33** required a three-step sequence. First, exposure of **33** to HF•Py gave products of C-9 TES and C-18 TBDPS deprotection **34** along with monodeprotected products **35**. A subsequent re-exposure of **35** to HF•Py gave improved yields of the bis-deprotected diol **34**. Finally, the primary hydroxyl group of **34** was selectively protected with TBDPSCl/imidazole to give silyl ether **5**. Product **5** was the intermediate reported by Imanishi and others.[6] Using the Imanishi protocol, 2 mg of protected dephospho-fostriecin **5** was converted into fostriecin **1** (∼0.5 mg), ^{1}H NMR (600 MHz in D_2O) and HRMS of which matched those of the natural material.[6a,g,21]

In summary, an enantioselective synthesis of fostriecin has been accomplished in 24 steps from commercially available starting material (**11**). This highly enantio- and diastereocontrolled route illustrates the utility of an iterative Sharpless AD reaction, Noyori asymmetric reduction, asymmetric Leighton allylation, Rh-catalyzed *trans*-hydroboration, and Suzuki−Miyaura cross-coupling reaction sequence. It is also worth noting that these new routes start from achiral sources. Importantly, these key reactions are performed under catalyst control. This strategy should facilitate the syntheses of fostriecin analogues and similar structural natural products. Efforts along these lines will be reported in due course.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The optical rotation data for our synthetic fostriecin did not match that of the natural material. This could be a result of both the different concentration and solvent. However, our optical rotation data for **5** did match that reported by Imanishi; see Supporting Information.