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Convergent Synthesis of Fostriecin via Selective Alkene Couplings and Regioselective Asymmetric Dihydroxylation

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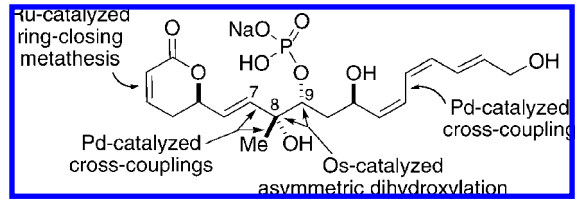
ABSTRACT



A highly convergent synthesis of fostriecin is described, featuring sequential palladium-catalyzed Negishi cross couplings to form the C7−C8 bond and C8−methyl bond, followed by late-stage regio- and stereoselective dihydroxylation of C8−C9.

Fostriecin (**1**, Figure 1) is a phosphate ester metabolite produced by *Streptomyces pulveraceus*.[1] Fostriecin has exhibited potent in vitro activity against leukemia, lung, breast, and ovarian cancer cells.[2] The mechanism of action is attributed to inhibition of mitosis by potent and selective inhibition of certain serine/threonine protein phosphatases (PPs), particularly PP2A (IC_{50} 1.5 nM) and PP4 (IC_{50} 3 nM), and much weaker inhibition of PP1 (45 μM).[3] Unfortunately, the use of fostriecin as a drug has been hampered by its chemical instability. Thus, synthetic approaches to fostriecin will also offer avenues to the discovery of more stable analogue structures, hopefully with bioactivity similar to or even more selective and potent than fostriecin. Although several syntheses of fostriecin and similar phosphate ester natural products have been recorded in the literature,[4,5] we determined that an additional strategy for preparing the fostriecin structure would offer access to analogue structures that might not be as readily available by the other synthetic approaches described to date.

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Our strategy for the synthesis of fostriecin was based on palladium-catalyzed cross-coupling technology of three modules, including the preformed oxacycle of **2** bearing a chiral center at C5, a dibromoenynol **3** with a chiral center at C11, and side-chain synthon **4** (Figure 1). A critical transformation would be the postcoupling regio- and enantioselective *syn*-dihydroxylation[6] of C8 and C9 in order to complete installation of all four chiral centers in fostriecin.

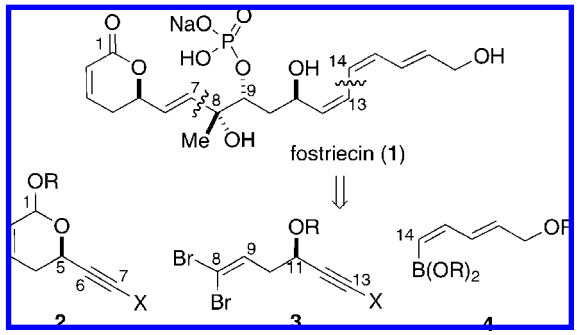

Figure 1. Retrosynthetic analysis for fostriecin (**1**).

The design of synthon **2** with the C1-acetal was based on preliminary indications that the C5-oxygen was prone to facile elimination under basic and acidic conditions when C1 was functionalized as a lactone. In contrast, the acetal module **9** (Scheme 1) was considerably more stable and was efficiently prepared in multigram quantities from the enynol (*R*)-**5**.[7] Acid-catalyzed transetherification of (*R*)-**5** with acrolein diethyl acetal[8] afforded the mixed acetal **6**, which subsequently underwent ring-closing metathesis[9] to give the dihydropyranyl acetal **7**. The sterically bulky triisopropylsilyl group was required for protecting the alkyne from unwanted participation in the metathesis step. After transacetalization to provide the isopropyl acetal **8** as a single anomer,[4b] fluoride-promoted desilylation gave the terminal alkyne of **9** to complete preparation of the C1−C7 module. The C8−C13 dibromoenyne module **13** was also easily prepared, in this case from the trimethylsilyl-protected enynol (*R*)-**10**, involving oxidative cleavage of **11** and Corey−Fuchs reaction of an aldehyde intermediate **12**.[10]

After considerable experimentation, we settled on Negishi cross-coupling for formation of the C7−C8 bond.[11] Hydrozirconation of alkyne **9** proceeded with complete regio- and stereoselectivity to the vinylzirconocene intermediate, followed by transmetalation with zinc bromide to provide **14** (Scheme 2). Palladium-catalyzed, stereoselective cross-coupling with dibromide **13** then formed the C7−C8 bond in compound **15**.[12] The methyl substituent was then installed at C8, with palladium catalysis in the presence of the tri(*tert*-butyl)phosphine ligand, in order to maintain stereospecific formation of **16** in this second cross-coupling step.[13] Mild hydrolysis of the acetal of **16** was followed by oxidation of the corresponding lactol to the lactone **17**.[14]

With lactone **17** in hand, we then explored the critical *syn*-dihydroxylation to install the remaining C8 and C9 chiral centers. We anticipated that the C2−C3 alkene would be deactivated by conjugation with the lactone carbonyl, and the allylic ester characteristic of the lactone would likewise deactivate the C6−C7 alkene so that the C8−C9 alkene would undergo preferential dihydroxylation. Our initial experiment with the commonly used $(DHQD)_2$-PHAL ligand[5c,6] gave a 1:1 mixture of products arising from dihydroxylation at both C6−C7 and C8−C9 alkenes. We surmised that the binding pocket of the bis(dihydroquinidine) diether provided steric preference to the disubstituted C6−C7 alkene, partially overriding the electronic preference anticipated for the C8−C9 alkene. In support of this hypothesis, we found that the less sterically demanding monomeric ligand DHQD-4-MEQ[15] favored dihydroxylation of the C8−C9 alkene to provide diol **18** as the major product.

From **18**, the remaining steps largely followed the endgame established by other laboratories. Regioselective protection of the tertiary alcohol at C8 was achieved by a slight modification of Imanishi's procedure,[4e] involving initial formation of the C8,C9-bis-TES ethers in situ and then selectively removing the more labile C9 secondary silyl ether under mildly acidic conditions. Conversion of the alkynylsilane to the iodoalkyne and chemo- and stereoselective reduction[16] of this iodoalkyne provided **19**, intercepting an advanced intermediate in the Jacobsen synthesis.[4b]

Chavez and Jacobsen had reported the formation of the C13−C14 bond by Stille cross-coupling. In the interest of

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(7) Enynols (*R*)-**5** and (*R*)-**10** were prepared by lipase-catalyzed resolution of the racemic compounds with vinyl acetate followed by Mitsunobu reaction of the resolved alcohols into the antipodal acetates for efficient production of a single enantiomer from the racemate: (a) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129. (b) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188. (c) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495. (d) Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3203. (e) Robles, O.; McDonald, F. E. *Org. Lett.* **2008**, *10*, 1811.

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(11) (a) Negishi, E.-i.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichim. Acta* **2005**, *38*, 71. (b) Although compound **15** could also be formed from Stille cross-coupling, $Cl_2Pd(PPh_3)_2$-catalyzed hydrostannation of **9** was not as highly regioselective as the corresponding hydrozirconation. Furthermore, the Stille reaction was slower and proceeded in lower yield, even in the presence of $Bu_4N^+Ph_2PO_2^-$: Srogl, J.; Allred, G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376. (c) Huang, Z.; Negishi, E.-i. *Org. Lett.* **2006**, *8*, 3675. (d) Buchwald, S. L.; Lamaire, S. J.; Nelson, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895.

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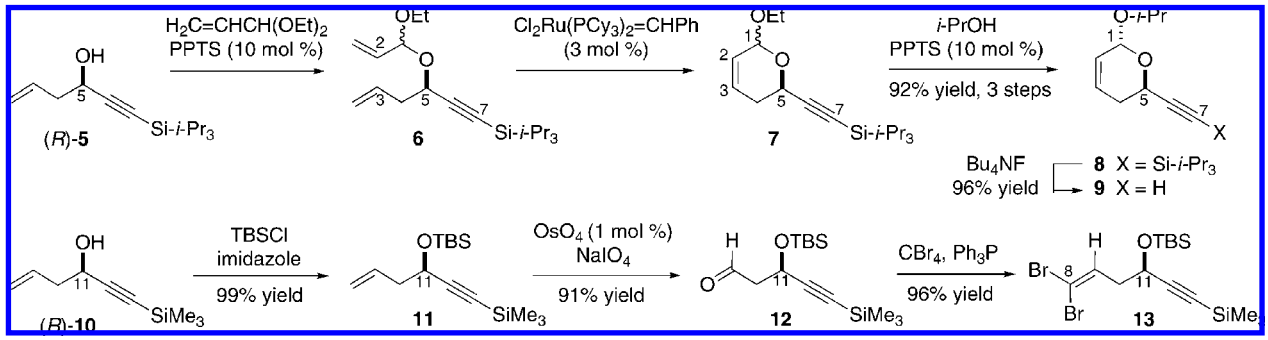
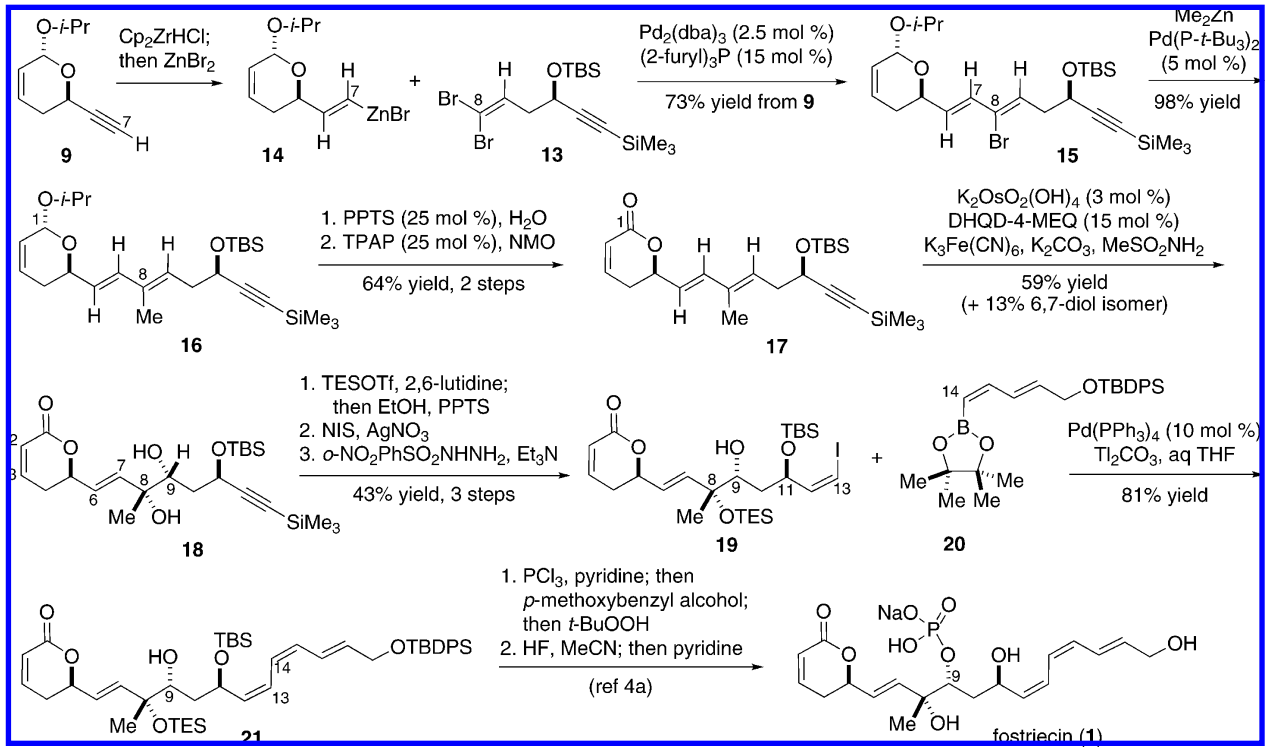
Scheme 1. Preparation of Synthons **9** and **13**



Scheme 2. Short synthesis of Fostriecin, Featuring Palladium-Catalyzed Modular Cross-Couplings



avoiding the use of alkenyltrialkyltin reagents, we explored the Suzuki cross-coupling of iodoalkene **19** with the known vinylboronate module **20**.[4c] In this case, the challenge was to find conditions for cross-coupling at room temperature, as the product was unstable at higher temperatures. Although the use of silver oxide as base provided the desired triene product **21** in moderate yield,[17] higher yields and shorter reaction times were obtained only when the reaction was conducted in the presence of the toxic basic additive thallium carbonate,[18] thus largely negating any benefit that might have been realized from replacing the established Stille coupling with the Suzuki coupling.

In conclusion, we have described a new approach to the structure of fostriecin, via sequential cross-couplings at C8 and regioselective dihydroxylation of the C8−C9 alkene. We anticipate that our convergent strategy can be further exploited to generate a broad array of analogues for thorough exploration of structure−activity relationships in the search for a chemically stable but highly potent and selective inhibitor of protein phosphatase 2A[19] as a novel and

(17) Yields with silver oxide as the base varied from 31% (65 °C, 4 h) to 55% (20 °C, 8 days), whereas the reaction with thallium carbonate proceeded in 81% yield (20 °C, 8 h).

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promising avenue for the development of cancer chemotherapeutics.

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

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