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Formal Total Synthesis of Fostriecin via 1,4-Asymmetric Induction Using Cobalt-Alkyne Complex

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ABSTRACT



The synthesis of a protected dephosphofostriecin, and thereby a formal synthesis of fostriecin, has been accomplished. Two of the four chiral centers are controlled by an external chiral auxiliary and the other two are synthesized stereoselectively, one by a novel 1,4-asymmetric induction using cobalt-alkyne complex, and the other by 1,3-asymmetric induction.

Fostriecin (1, CI-920), a novel secondary metabolite of *Streptomyces pulveraceus*, is a selective inhibitor of protein phosphatase 2A (PP2A) that displays antitumor activity against a diverse panel of tumor cell lines and in vivo activity

10.1021/ol800195g CCC: \$40.75 © 2008 American Chemical Society Published on Web 03/04/2008 toward lymphoid leukemias.¹ This important biological activity has attracted the attention of many synthetic chemists. Both the absolute and the relative stereochemistry were determined by Boger,² who also accomplished the first total synthesis in 2001.³ Since then, several excellent asymmetric syntheses have appeared,⁴ as well as a number of synthetic studies.⁵

Structurally fostriecin has four chiral centers and contains a conformationally labile *cis*-*cis*-*trans* triene moiety. Shibasaki^{4g,i,k} and Falck^{4b} constructed all the stereocenters using four different catalytic asymmetric reactions, while three of the four chiral centers were constructed using asymmetric catalytic reactions by Jacobsen,^{4a} Imanishi,^{4c,d} Kobayashi,^{4e} and Trost.^{4h} In these syntheses, asymmetric catalytic reactions have been utilized at least twice. Yadav employed D-glucose as a chiral starting material,

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and three of the four chiral centers are derived from this chiral source. $^{4\mathrm{j}}$

Our synthetic strategy has been to control stereochemistry using pre-existing stereogenic centers as much as possible. Thus, the stereogenic center at C11 was to be constructed via 1,3-asymmetric induction using the C9 chiral center, whereas the stereochemistry at C5 was to be controlled by the chiral center at C8 via 1,4-asymmetric induction using a cobalt-alkyne complex, methodology recently developed in this group.⁶ The only reaction requiring use of an external chiral auxiliary is the asymmetric dihydroxylation of a homoallylic alcohol. Another noteworthy feature is the construction of the labile triene unit, which we planned to synthesize by reduction of the more stable dieneyne at a late stage of the synthesis. Herein we report the realization of this scenario for the synthesis of protected dephosphofostriecin 2, Imanishi's key intermediate (Scheme 1).^{4c,d}



Our synthesis (Scheme 2) commenced with the preparation of cobalt-alkyne complex **7**. 1,3-Propanediol was monoprotected with PMBCl to give **10**, which was oxidized with SO_3 •pyridine⁷ to give the aldehyde. Wittig reaction, followed by reduction and oxidation, gave **13**. The Corey-Fuchs alkyne synthesis⁸ afforded alkyne **14**, which on Sharpless dihydroxylation⁹ gave diol **15** in good yield with excellent enantioselectivity (93% ee).¹⁰ Protection of the diol **15** with TESCl gave **16**. Treatment of **16** with BuLi and ClCO₂Me gave ester **17**. Changing the protecting group from TES to BOM gave **19**. Reduction with DIBAL-H, followed by treatment with TBAF, gave diol **21**. Oxidation with MnO₂ then gave aldehyde **22**. On treatment with Co₂(CO)₈ **22** provided cobalt–alkyne complex **23** in good yield.

Next is the critical 1,4-asymmetric induction. As allyl metal reagents such as allylMgBr gave no selectivity, the Hosomi-Sakurai allylation was investigated, with the results summarized in Table 1. Lewis acid mediated allylation¹¹ and Mukaiyama aldol reaction¹² of dicarbonylhexacarbonyl cobalt of α,β -acetylenic aldehyde is known, and BF₃·Et₂O is reported to be a suitable promoter in the reaction of allyl stannane.11 Although low selectivity was observed with HfCl₄, ZnCl₂, TiCl₃(O-*i*-Pr), TiCl(O-*i*-Pr)₃ and BF₃·OEt₂, moderate selectivity (73:27) was obtained when MgBr₂•OEt₂ was employed. Good selectivity (80:20) was obtained in the presence of TiCl₂(O-*i*-Pr)₂, which increased to 92:8 when the reaction was performed at lower temperature (-40 °C). The bulkiness of the allyltin reagent is important, because Ph₃SnCH₂CH=CH₂ gave a excellent result whereas the corresponding Bu₃Sn analogue gave poor selectivity (entry 9). The relative configuration of newly generated C5 of 24 was determined by the advanced Mosher's MTPA method¹³ after conversion to (R)- and (S)-mono MTPA esters of 25.

No selectivity was observed using the parent aldehyde 22 under the same reaction conditions. Thus, the cobalt–alkyne complex is the key for achieving high selectivity.

The angle of the alkyne triple bond is 180°, whereas that of the alkyne cobalt complex is about 140° (see **7** of Scheme 1). Complexation forces the stereogenic and prestereogenic centers closer, which makes the highly stereoselective 1,4-asymmetric induction possible. C5 stereochemistry has been constructed by the reagent-controlled allylation; Ipc₂B-allyl¹⁴ was used by Falck,^{4b} Hatakeyama,^{4f} Trost,^{4h} and Yadav,^{4j} whereas Shibasaki^{4g,i,k} used the catalytic method of Yamamoto allylation.¹⁵

As the crucial 1,4-asymmetric induction had been successfully achieved, the cobalt was removed by treatment with NMO, then reduction with Red-Al gave trans-alkene **26** in good yield. The unsaturated lactone moiety was constructed by acylation with acryloyl chloride, followed by exposure to Grubbs' second generation catalyst,¹⁶ affording **28** quantitatively.

The next task is installation of the triene moiety via 1,3asymmetric induction. The protecting group of the diol unit and nucleophile were found to be important for obtaining high selectivity. Cleavage of the BOM group afforded the diol **29**, which is Hatakeyama's intermediate.^{4f} The diol **29**

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was protected as its dimethylacetal **30**. Removal of the PMB protecting group, followed by TEMPO oxidation, afforded key intermediate **32**.

The other coupling partner **5** was easily prepared stereoselectively from cis-1,2-dichloroethene via successive Sonogashira reactions (Scheme 3). That is, cis-1,2-dichloroethene (**36**) was reacted with 2-propyne-1-ol and trimethylsilylacetylene successively to generate ene diyne derivative **38** in good yield. Stereoselective reduction with Red-Al,¹⁷ followed by protection of hydroxy group and deprotection of trimetylsilyl group, afforded **5** in good yield.

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 Table 1. Effect of the Lewis Acid on 1,4-Asymmetric

 Induction with 23 Using Allyltin

(CO) ₃ H	(CO) ₃ Co OB(OM OPMB ⁺ CH ₂ =CHC	$H_2SnR_3 \xrightarrow{\text{Lewis acid}} CH_2Cl_2 \xrightarrow{()} 5$	CO) ₃ (CO) ₃ Co-Co OE R - OH OH	3OM OPMB +5S-isomer
23				24	
entry	R	lewis acid	condition	yield[%] ^a	$\operatorname{R:S}{}^{b}$
1	Ph	HfCl_4	−78 °C, 30 m	15	50:50
2	Ph	$ZnCl_2$	−78 °C, 4 h	45	55:45
3	Ph	$BF_3 \cdot OEt_2$	−78 °C, 10 m	40	64:36
4	Ph	$MgBr_2 \cdot OEt_2$	$-78 \sim 0$ °C, 8 h	86	73:27
5	Ph	TiCl ₃ (O- <i>i</i> -Pr)	−78 °C, 30 m	20	60:40
6	Ph	TiCl(O-i-Pr)3	$-78 \sim 0$ °C, 8 h	78	60:40
7	Ph	TiCl ₂ (O- <i>i</i> -Pr) ₂	−20 °C, 4 h	60	80:20
8	Ph	TiCl ₂ (O- <i>i</i> -Pr) ₂	−40 °C, 46 h	60	92:8
9	Bu	$TiCl_2(O-i-Pr)_2$	−45 °C, 12 h	86	45:55

 a Isolated yield. b Diastereomer ratio of C5 of **24** was determined by HPLC analysis.

After extensive experimentation, the diastereoselective coupling of **32** and **5** was successfully accomplished using Fukuyama's protocol.^{18,19} The higher order alkynyl Zn reagent reacted smoothly to yield **33** in good yield with excellent diastereoselectivity. Treatment of **33** with TFA removed both the acetal and TBDPS groups to yield tetraol **34**. Protection of the primary alcohol with TBDPSCl gave **35**. The labile triene unit was successfully constructed using Rieke Zn²⁰ in the presence of buffer solution, affording the protected dephosphofostriecin **2** in good yield. The conversion of **2** to fostriecin has been demonstrated by Imanishi and co-workers.^{4c, d}

In summary, we have accomplished the synthesis of a protected dephosphofostriecin, and thereby a formal synthesis of fostriecin. Two of the four chiral centers are



controlled by an external chiral reagent and the other two are synthesized stereoselectively, one by a novel 1,4asymmetric induction using cobalt-alkyne complex developed by our group⁶ and the second by 1,3-asymmetric induction.

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Supporting Information Available: Detailed experimental procedures, full characterization, and copies of ¹H and ¹³C NMR and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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