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

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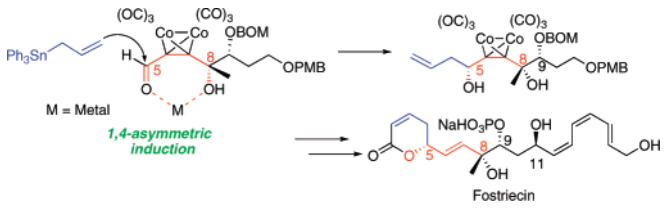
ABSTRACT



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 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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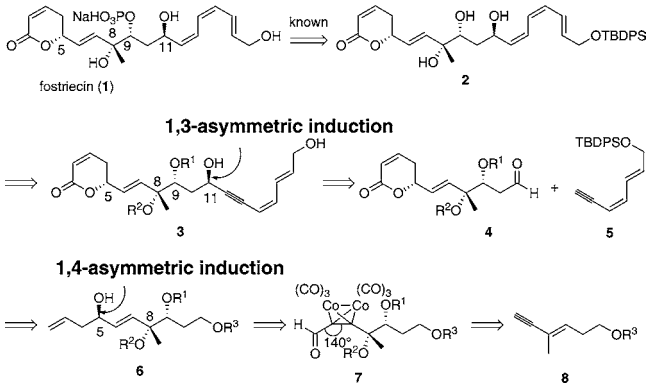
and three of the four chiral centers are derived from this chiral source.[4j]

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]

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



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·pyridine[7] to give the aldehyde. Wittig reaction, followed by reduction and oxidation, gave **13**. The Corey-Fuchs alkyne synthesis[8] afforded alkyne **14**, which on Sharpless dihydroxylation[9] 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 $ClCO_2Me$ 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 MnO_2 then gave aldehyde **22**. On treatment with $Co_2(CO)_8$ **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 allylation[11] and Mukaiyama aldol reaction[12] of dicarbonylhexacarbonyl cobalt of α,β-acetylenic aldehyde is known, and BF_3·Et_2O is reported to be a suitable promoter in the reaction of allyl stannane.[11] Although low selectivity was observed with $HfCl_4$, $ZnCl_2$, $TiCl_3$(O-*i*-Pr), $TiCl$(O-*i*-Pr)$_3$ and BF_3·OEt_2, moderate selectivity (73:27) was obtained when $MgBr_2$·OEt_2 was employed. Good selectivity (80:20) was obtained in the presence of $TiCl_2$(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 $Ph_3SnCH_2CH{=}CH_2$ gave a excellent result whereas the corresponding Bu_3Sn analogue gave poor selectivity (entry 9). The relative configuration of newly generated C5 of **24** was determined by the advanced Mosher's MTPA method[13] 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; Ipc_2B-allyl[14] 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 1,3-asymmetric 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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(10) The enantioselectivity of **15** was determined by chiral HPLC analysis (chiralcel OD−H column, l = 254 nm, *i*PrOH/hexane 1/20, 1.0 mL min^{-1}; t_R = 24.1 min (major), 20.7 min (minor)).
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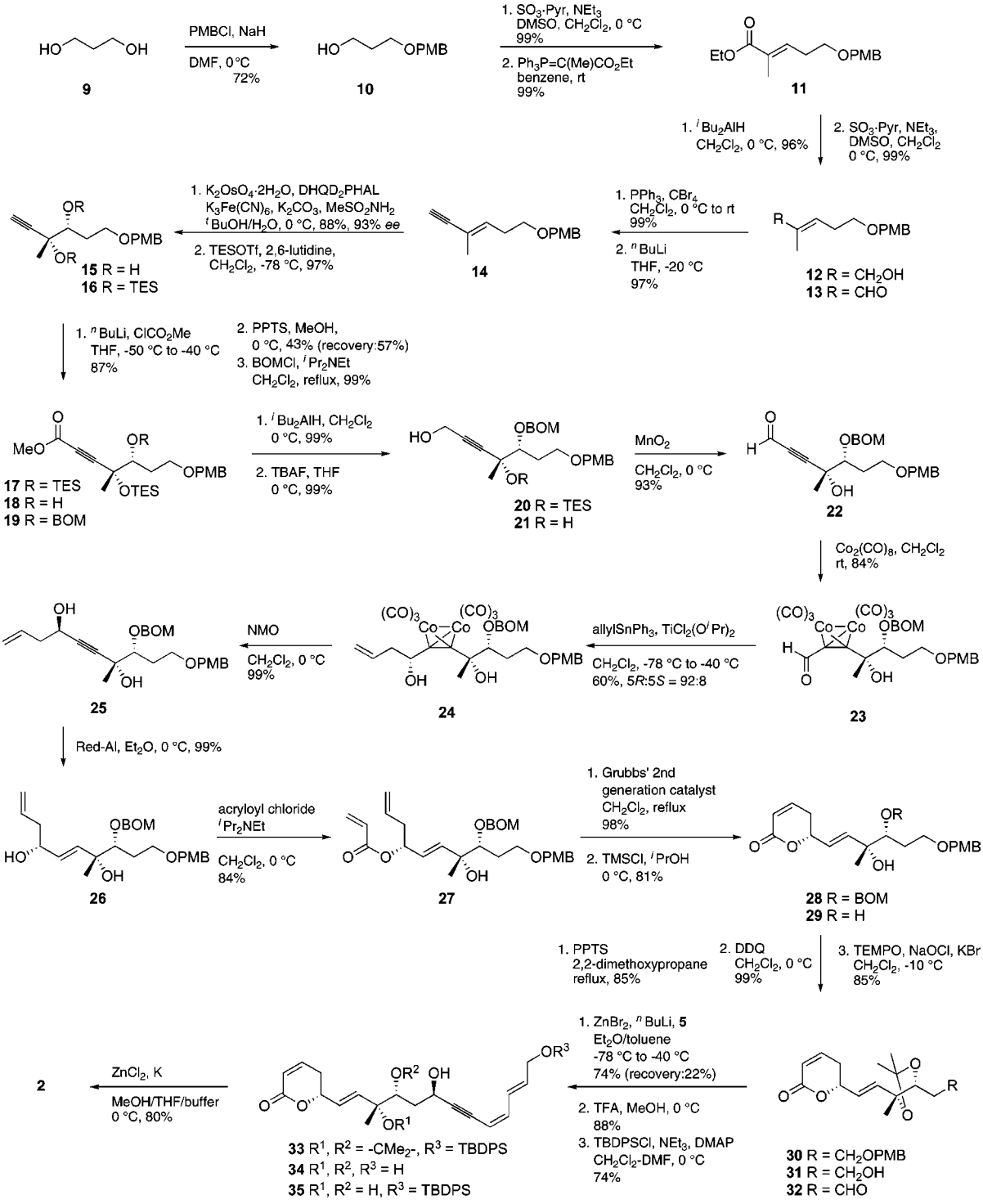
Scheme 2. Synthesis of Fostriecin (**1**)



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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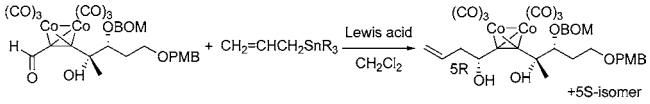
Table 1. Effect of the Lewis Acid on 1,4-Asymmetric Induction with **23** Using Allyltin



23 **24**

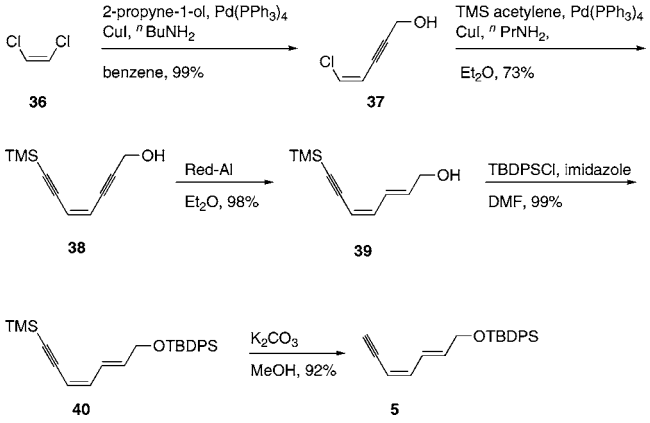
entry	R	lewis acid	condition	yield[%][a]	R:S [b]
1	Ph	$HfCl_4$	−78 °C, 30 m	15	50:50
2	Ph	$ZnCl_2$	−78 °C, 4 h	45	55:45
3	Ph	$BF_3{\cdot}OEt_2$	−78 °C, 10 m	40	64:36
4	Ph	$MgBr_2{\cdot}OEt_2$	−78 ∼ 0 °C, 8 h	86	73:27
5	Ph	$TiCl_3$(O-*i*-Pr)	−78 °C, 30 m	20	60:40
6	Ph	$TiCl$(O-*i*-Pr)$_3$	−78 ∼0 °C, 8 h	78	60:40
7	Ph	$TiCl_2$(O-*i*-Pr)$_2$	−20 °C, 4 h	60	80:20
8	Ph	$TiCl_2$(O-*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 Zn[20] 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 1,4-asymmetric induction using cobalt-alkyne complex developed by our group[6] and the second by 1,3-asymmetric induction.

Scheme 3. Synthesis of Alkynediene Moiety (**5**)



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Supporting Information Available: Detailed experimental procedures, full characterization, and copies of ^1H and ^{13}C 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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