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A study toward a total synthesis of fostriecin

Yohei Kiyotsuka, Junji Igarashi and Yuichi Kobayashi*

Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan

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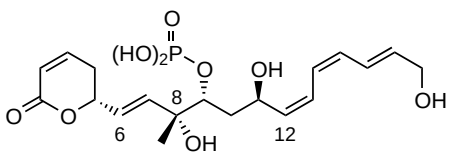
Abstract—In order to synthesize the major C(3)–C(12) part of fostriecin, asymmetric dihydroxylation of several dienes **5a**–**f**, prepared by cross-coupling reactions of several types, was studied, thus providing high dependency on the hydroxyl groups at C(5) and C(11). The best regioselectivity was obtained with **5d** to produce diol **23**, which was later transformed into the advanced intermediate **26**.

Biological investigation of fostriecin has disclosed a variety of biological properties, such as inhibition of cell cycles and that of DNA, RNA and protein synthesis.[1] Due to high efficiency of these properties, fostriecin has attracted much interest as a lead compound for developing a new drug.[2] In order to gain deep understanding on these biological properties, investigation using fostriecin and its analogues is a convenient and efficient way. The absolute structure of fostriecin was determined by Boger[3] recently in 1997, who later succeeded in the first total synthesis in 2001.[4] Shortly after this publication, a synthesis of the C(1)–C(12) (fostriecin numbering) part was reported by Cossy,[5] and then synthesis of the full structure by Jacobsen.[6] However, there still seems an urgent demand to develop a new synthetic method in order to provide analogues of fostriecin. Herein, we report a study toward a synthesis of fostriecin.[7]



fostriecin (**1**)

Our approach to fostriecin (**1**) is illustrated in Scheme 1. Alcohol **2**, which is transferred to **1** by selective phosphorylation at C(9) by Boger,[4] would be prepared by the coupling reaction of alkenyl halide **3** and a dienyl metal **4**. Recently, alkenyl and aryl borates with the 2,2-dimethyl-1,3-propanediol and the Me ligands were developed in order to secure coupling reactions with alkenyl halides of steric hindrance and/or less reactivity to be successful.[8] Halide **3** is one such compound, and thence borate **4** is selected as a reagent in our fostriecin synthesis, and was found to be successful in a model study.[9] With regard to this coupling reaction, Jacobsen also accomplished a similar reaction with dienyl stannane **4** ($M = SnBu_3$) under the ligand-free palladium catalysis. For preparation of the key intermediate **3**, we chose a sequence involving the Sharpless asymmetric dihydroxylation (AD reaction)[10] of diene **5** at the C(8)–C(9) double bond and a subsequent one-carbon elongation, because numerous methods are available for preparation of dienes, for instance, the Sonogashira reaction of **7** and halide **6** followed by reduction of enyne, cross-coupling reaction of organometallic **8** and halide **6**, and vise versa, etc.

According to the results previously obtained from the AD reactions of dienes,[11] an olefin part of higher electron density and/or less steric hindrance is the reaction site for the oxidation. In our case, however, the regioselectivity seemed to be disrupted by the alkoxy groups close to the diene moiety of **5**. Consequently, dienes **5a**–**f** (Table 1) of related structures were chosen in order to find the structural factor indispensable for the high regioselectivity in the AD reaction.

Keeping asymmetric synthesis in mind, substrates and organometallics for construction of dienes **5a**–**f** were prepared by methods summarized in Schemes 2 and 3. Epoxide ring opening of TBS ether of glycidol[12] with

Keywords: fostriecin; asymmetric dihydroxylation; coupling reactions; regioselection.

* Corresponding author. Tel.: +81-45-924-5789; fax: +81-45-924-5789; e-mail: ykobayas@bio.titech.ac.jp

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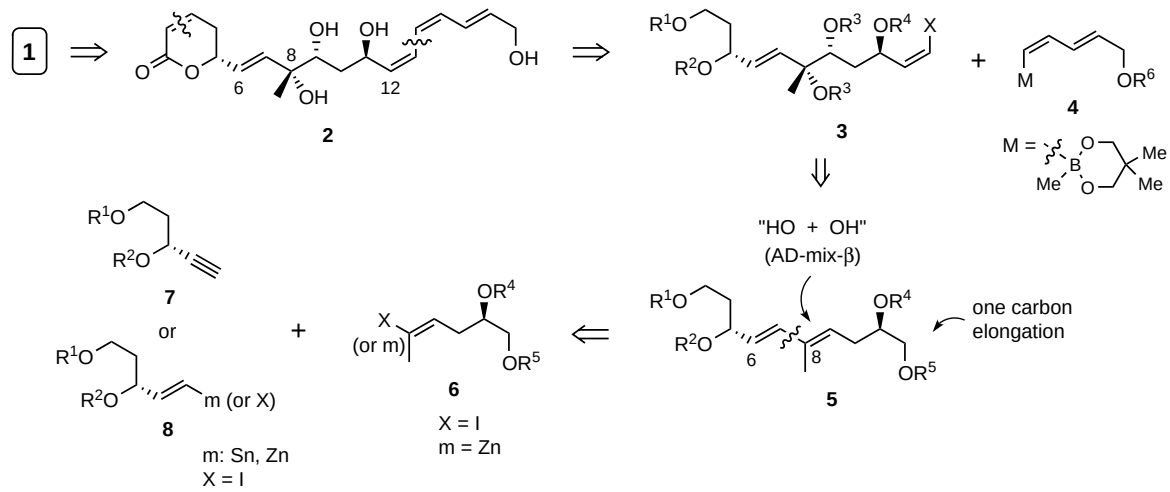
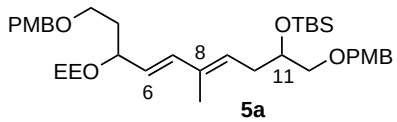
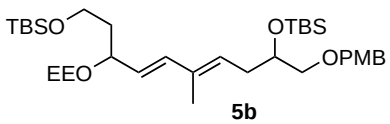
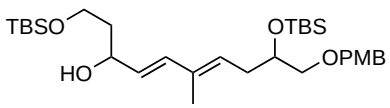
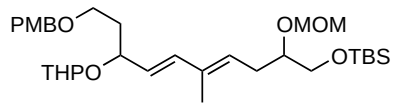
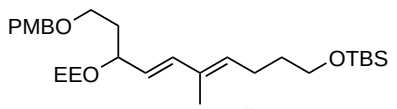
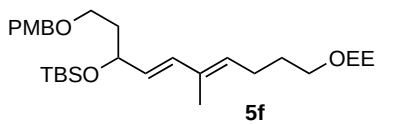


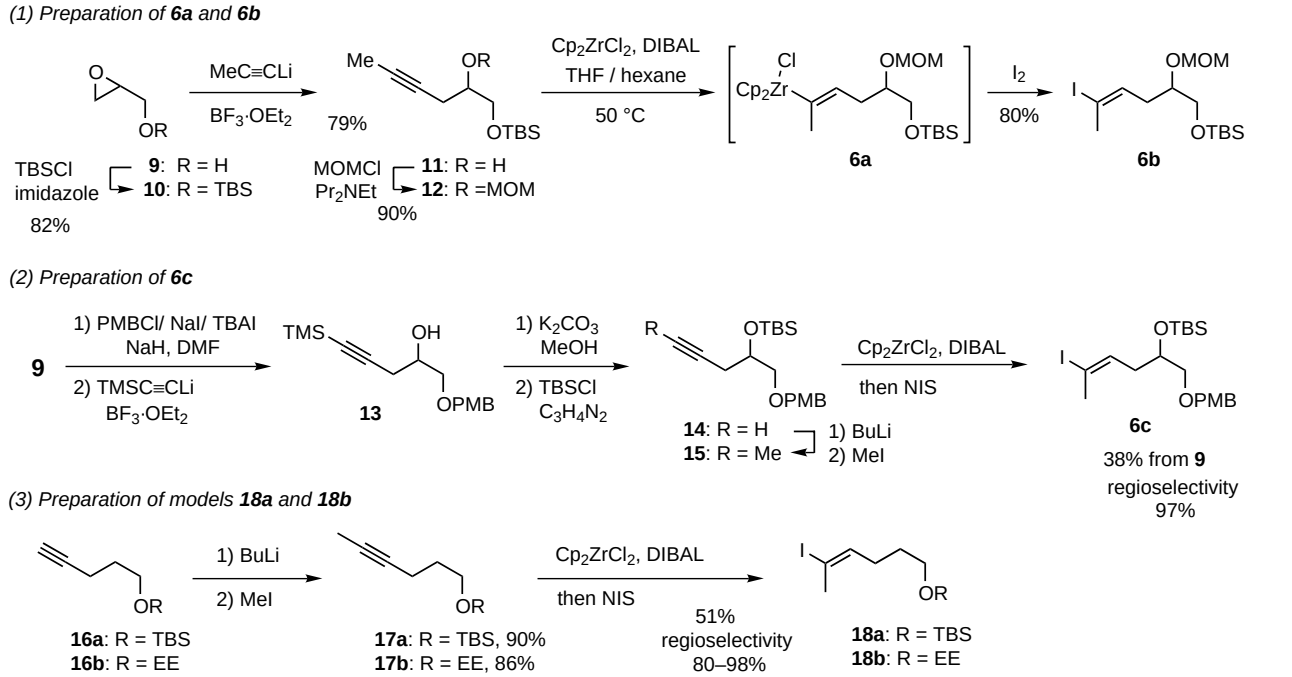
Scheme 1. Retrosynthesis of fostriecin.

Table 1. AD reaction of diene with AD-mix-β

entry	diene	conditions	diol 6,7- : 8,9-	yield of major isomer
1	 **5a**	rt., 2 days	1 : 1	52% (83% conversion)
2	 **5b**	rt., 2 days	1 : 1	< 42% (80% conversion)
3	 **5c**	rt., 2 days	1 : < 1	< 20% (complex mixture)
4	 **5d**	rt., 2 days or 0 °C, 3 days	1 : 10	90–93%
5	 **5e**	rt., 2 days	1 : > 17	85%
6	 **5f**	rt., 2 days	1 : 3.6	66%

[a] Reactions were carried out under the conditions specified using AD-mix-β with five-fold more K_2OsO_6 and the DHQD in the reagent.

propyne according to the procedure of Yamaguchi[13] followed by protection of the resulting alcohol **11** with MOMCl provided **12** in good yield. In order to prepare **6b** by iodination at C(8), hydrozirconation of acetylene **12** was carried out under the thermodynamic control using excess $Cp_2Zr(H)Cl$ (2–2.5 equiv.) at 50°C according to Panek[14] and the resulting intermediate was quenched with I_2. When $Cp_2Zr(H)Cl$ generated in situ from Cp_2ZrCl_2 and $LiBEt_3H$ was used,[15] a mixture of **6b** and minor impurities was produced after iodination



Scheme 2. Preparation of the C(8)–C(12) intermediates **6a**–**c** and model compounds **18a**,**b**.

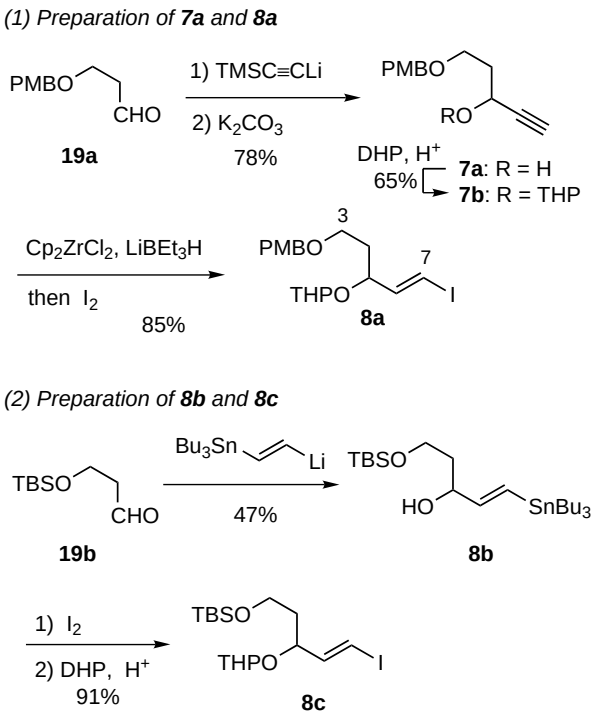
with I_2, though **6b** was isolated in 53% yield with a 7:1 ratio of **6b** and the regioisomer (structure not shown). In contrast, the use of DIBAL as a reducing agent of Cp_2ZrCl_2 resulted in clean production of **6b** in 80% yield. The exclusive formation of **6b** is surprising since Zr species sensitively recognized the small steric difference between the methyl and methylene parts attached to the acetylene moiety. Moreover, this result encourages direct use of the presumed zirconium intermediate **6a** in the formation of diene by the coupling reaction, which is mentioned later.

In a similar manner, glycidol **9** was converted into acetylene **15** in good yield, and submitted to the hydrozirconation/iodination (by NIS)[16] as mentioned above, to afford iodide **6c** with 97% regioselectivity in 68% yield (38% overall yield). Regioselective formation of **6c** and **6b** strongly indicates the efficiency of Cp_2ZrCl_2 and DIBAL as a hydrozirconation agent.

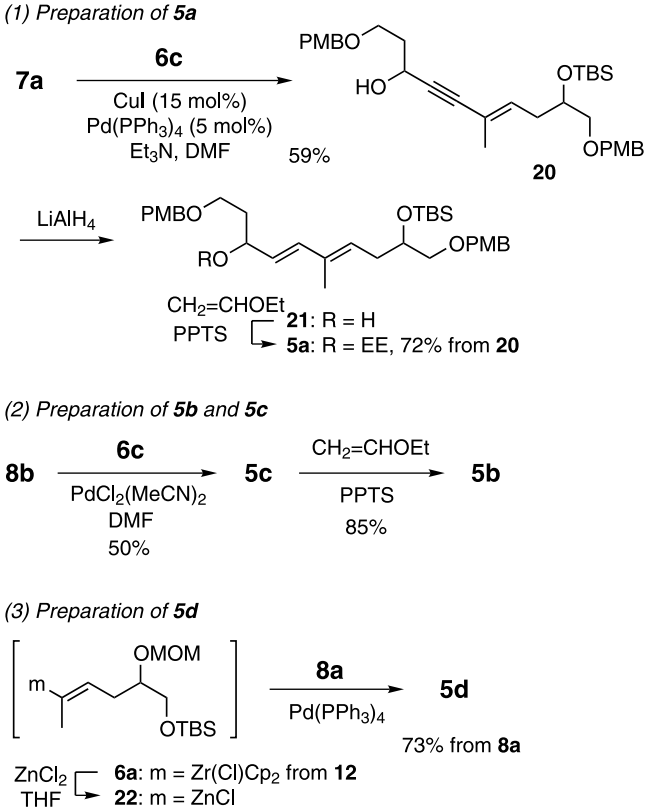
We also prepared iodides **18a** and **18b** as shown in Scheme 2 for construction of model dienes **5e** and **5f** (Table 1). Once again, combination of Cp_2ZrCl_2 and DIBAL as described above provided a good result in the transformation of **17a**,**b** into iodides **18a**,**b**.

Preparation of the C(3)–C(7) parts **7a** and **8a**–**c** in racemic forms is presented in Scheme 3. For the hydrozirconation of **7b**, the conventional protocol was used with success. Note that these intermediates in optically active forms will be available by the reliable methods such as asymmetric reduction of the corresponding ketones,[17] the kinetic resolution of racemic γ-stannyl or γ-iodo allylic alcohols by using the Sharpless reagents,[18] etc.

Coupling reactions between the C(3)–C(7) and the C(8)–C(12) parts to produce the dienes **5a**–**f** were accomplished by sequences or reactions summarized in Scheme 4. Sonogashira reaction[19] of acetylene **7a** and iodide **6c** using $Pd(PPh_3)_4$ and CuI as catalysts and Et_3N as a base in DMF at room temperature proceeded smoothly to afford acetylene **20** in 59% yield, and subsequent hydroalumination with $LiAlH_4$ produced



Scheme 3. Preparation of the C(3)–C(7) intermediates **7a** and **8a**–**c**.



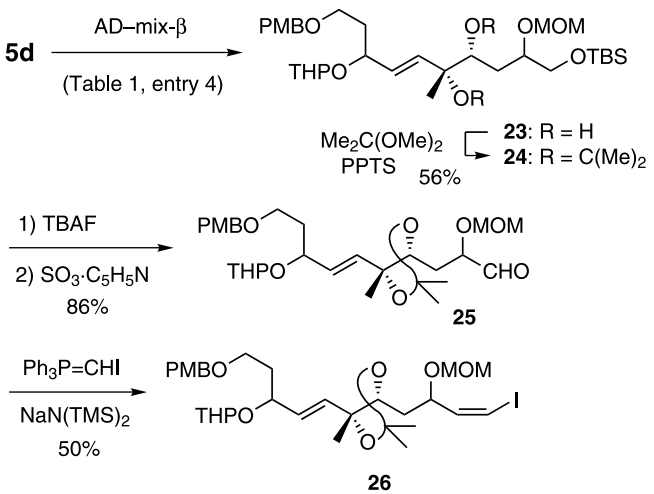
Scheme 4. Preparation of dienes **5a**–**d**. (Model dienes **5e** and **5f** were prepared similarly to **5a**.)

diene **21** stereoselectively. Finally, protection of the hydroxyl group at C(5) as an EE group furnished diene **5a** in 72%.[20] This two-step formation of diene was successfully applied to coupling between acetylene **7a** and iodides **18a**,**b** to produce dienes **5e** and **5f** in good yields after protection as EE and TBS ethers, respectively (equation not shown). Cross-coupling of stannane **8b** and iodide **6c** was found to proceed under the ligand-free Pd catalysis conditions, thus furnishing **5c** in 50% yield.[21] Reaction of **5c** with CH_2=CHOEt gave another diene **5b** in good yield. Use[14] of the zirconium intermediate **6a** (Scheme 2) in the coupling with iodide **8a** in the presence of $Pd(PPh_3)_4$ was successful to afford diene **5d** in 73% yield.

Although asymmetric dihydroxylation of diene **5a** using AD-mix-β was quite slow under the standard conditions, use of the forcing conditions with the catalyst-rich reagent[22] forwarded the reaction. Unfortunately, almost no regioselectivity was observed. Diene **5b** with the TBS protection at C(3), which is similar to diene **5a** except for PMB protecting group, afforded the same ratio of diols, while **5c** with the hydroxyl group at C(5) furnished worse selectivity with low yield. These results suggest that the size of hydroxyl groups at C(5) and/or C(11) is more important than the inductive effect of the alkoxy group at C(5) or C(11) on the density of olefin in the fostriecin case, and diene **5d** with a smaller MOM-oxy group at C(11) was found to be an ideal substrate to afford the desired diol **23** (structure, see Scheme 5) with a high regioselectivity in good yield.

Conversion of diol **23** to the advanced intermediate **26** was accomplished easily as shown in Scheme 5. After protection of the diol moiety as acetonide, the TBS group at C(12) was removed and oxidation of the resulting alcohol furnished aldehyde **25** in good yield. Finally, Stork–Wittig reaction produced *cis* iodide **26** in 50% yield.

In conclusion, we have figured out the diene **5d** that provides diol **23**, the key intermediate for fostriecin synthesis, with high regioselectivity. The starting compounds of the sequence disclosed herein are available as optically active forms,[23] and thence asymmetric synthesis of fostriecin and analogues would be in our hand. In addition, efficiency of various coupling reactions were assessed for the formation of the diene moiety and the results would be useful in the synthesis of other molecules with a similar diene moiety.



Scheme 5. Synthesis of the fostriecin intermediate **26**.

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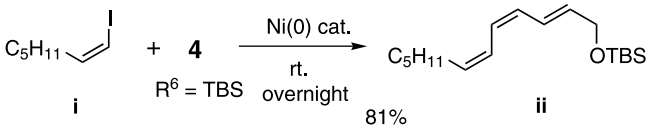

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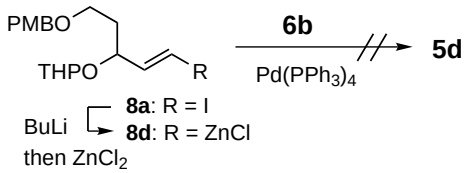
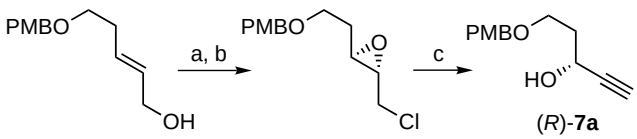
20. Attempted reaction of iodide **6b** and zinc reagent **8d**, which was generated from **8a** by lithiation followed by transmetalation with $ZnCl_2$, in the presence of $Pd(PPh_3)_4$ catalyst in THF resulted in dimerization of **8d** and recovery of **6b**.



21. A similar reduction of the enyne with the TBS-oxy group at C(3) after the Sonogashira reaction resulted in formation of complex mixtures.
22. Kobayashi, Y.; William, A. D.; Tokoro, Y. *J. Org. Chem.* **2001**, *66*, 7903–7906.
23. Optically active (*R*)-**7a** (97% ee) was prepared by the method shown below, while (*R*)-isomer of **6b** was prepared from (*S*)-glycidol ((*S*)-**9**) (>98% ee) by the method described in Scheme 2.



(a) *t*-BuOOH, $Ti(OPr)_4$, D-(–)-DIPT, 84%; (b) CCl_4, PPh_3, $NaHCO_3$, 93%; (c) *n*-BuLi, THF, 92%.