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Formal Catalytic Asymmetric Total Synthesis of Fostriecin

Kunihiko Fujii,[†] Keisuke Maki,[†] Motomu Kanai,[†,‡] and Masakatsu Shibasaki*,[†]

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and PRESTO, Japan Science and Technology Corporation

mshibasa@mol.f.u-tokyo.ac.jp

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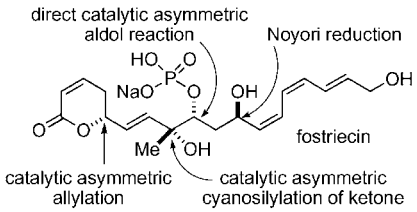
ABSTRACT



The common synthetic intermediate of a potent and promising anticancer agent, fostriecin, was synthesized using a unique method that combines four catalytic asymmetric reactions as shown above.

Fostriecin (**1**, CI-920) is a structurally interesting novel metabolite of *Streptomyces pulveraceus* that was first isolated in 1983 by a research group at Warner Lambert-Parke Davis.[1] Fostriecin displays antitumor activity against a broad range of cancerous cell lines in vitro that is suggested to be intimately related to the potent and highly selective inhibitory activity against serine/threonine phosphatase PP2A.[2] Therefore, fostriecin is a novel lead compound for anticancer drugs, as well as an important biological tool.

In 1997, Boger's group determined the relative and absolute configuration of fostriecin on the basis of synthetic and degradation studies.[3] They later reported the first total synthesis.[4] Since then, five elegant total syntheses have been reported, reflecting the highly focused interest in this compound.[5,6] In this communication, we report our contribution to this field. Our synthetic route is characterized by the fact that all the stereocenters of **1** are constructed by catalytic asymmetric reactions promoted by external chiral asymmetric catalysts. This route might be advantageous for rapid synthesis of stereoisomers of **1**.

Our retrosynthetic plan is shown in Scheme 1. Efforts to synthesize **1** should focus mainly on the following three points: (1) construction of the four chiral stereocenters (including one tetrasubstituted carbon at C-8), (2) construction of the configurationally labile cis−cis−trans-conjugated triene, and (3) selective phosphate ester construction at the C-9 secondary alcohol. To access point 2, we chose a cross-coupling reaction between *cis*-vinyl iodide **2** and *cis*-vinyltin **3** at a late stage.[7] During the course of our studies, Imanishi reported that **2**, containing the proper protection pattern to

* Corresponding author.
[†] The University of Tokyo.
[‡] PRESTO.

(1) (a) Tunac, J. B.; Graham, B. D.; Dobson, W. E. *J. Antibiot*. **1983**, *36*, 1595−1600. (b) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmwe, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot*. **1983**, *36*, 1601−1605.

(2) For reviews, see: (a) Lewy, D. S.; Gauss, C. M.; Soenen, D. R.; Boger, D. L. *Curr. Med. Chem*. **2002**, *9*, 2005−2032. (b) McCluskey, A.; Sim, A. T. R.; Sakoff, J. A. *J. Med. Chem*. **2002**, *45*, 1151−1175. (c) De Jong, R. S.; Mulder, N. H. *Anti-Cancer Drugs* **1997**, *8*, 413−418.

(3) Boger, D. L.; Hikota, M.; Lewis, B. M. *J. Org. Chem*. **1997**, *62*, 1748−1753.

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(5) (a) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **2001**, *40*, 3667−3670. (b) Reddy, Y. K.; Falck, J. R. *Org. Lett*. **2002**, *4*, 969−971. (c) Miyashita, K.; Ikejiri, M.; Kawasaki, H.; Maemura, S.; Imanishi, T. *Chem. Commun*. **2002**, 742−743. (d) Wang, Y.-G.; Kobayashi, Y. *Org. Lett*. **2002**, *4*, 4615−4618. (e) Esumi, T.; Okamoto, N.; Hatakeyama, S. *Chem. Commun*. **2002**, 3042−3043.

(6) For synthetic studies of **1**, see: (a) Cossy, J.; Pradaux, F.; BouzBouz, S. *Org. Lett*. **2001**, *3*, 2233−2235. (b) Kiyotsuka, Y.; Igarashi, J.; Kobayashi, Y. *Tetrahedron Lett*. **2002**, *43*, 2725−2729.

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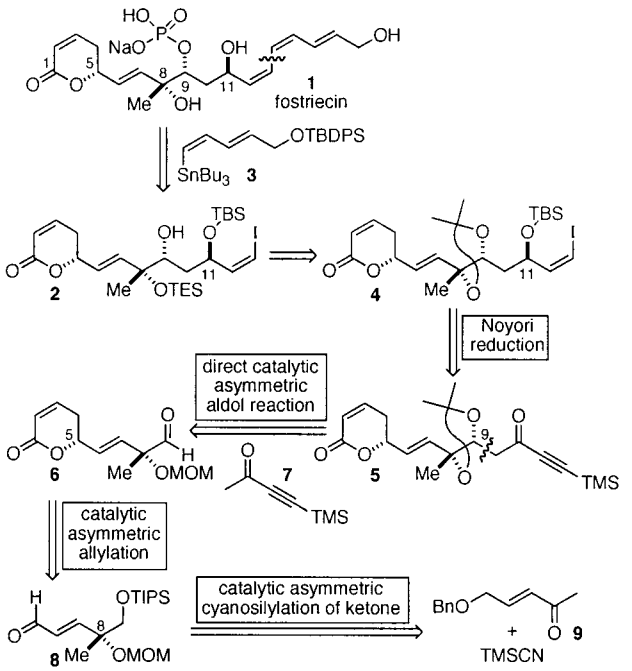
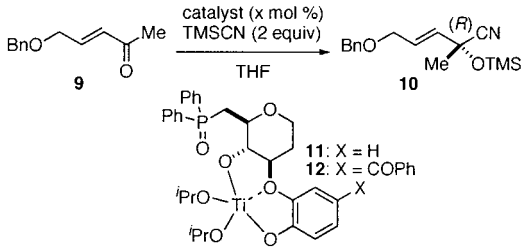
Scheme 1. Retrosynthetic Analysis



access point 3, can be synthesized from **4**.[5c] Thus, we employed **4**, which contains all the chiral stereocenters of fostriecin, as a key intermediate for our synthesis. Partial conformational constraint by the acetonide in **4** should be helpful for purification from other possible contaminating isomers. The chiral secondary alcohol at C-11 should be constructed using a Noyori reduction[8] of the corresponding acetylenic ketone **5**, followed by iodination and diimide reduction of the acetylene.[9] The chiral secondary alcohol at C-9 of **5** should be constructed through a catalytic asymmetric direct aldol reaction[10] of aldehyde **6** and ketone **7** promoted by a Lewis acid−Brönsted base two-center asymmetric catalyst, which was developed in our group.[11,12] α,β-Unsaturated lactone **6** should be synthesized through catalytic asymmetric allylation of aldehyde **8**, followed by ring-closing olefin metathesis (RCM) using Grubbs' catalyst.[13] Finally, the tetrasubstituted chiral center at C-8 should be constructed using the catalytic asymmetric cyanosilylation of ketones promoted by the Lewis acid−Lewis base two-center asymmetric catalyst (**11** or **12**) developed in our group.[14]

We began our synthesis by finding the optimum reaction conditions for the catalytic asymmetric cyanosilylation of ketone **9** (Table 1). On the basis of previous studies,[14] the

Table 1. Catalytic Asymmetric Cyanosilylation of Ketone **9**[a]



entry	catalyst (mol %)	temp, °C	time, h	yield, %[b]	ee, %[c]
1	**11** (10)	−40	120	58	86
2	**11** (5)	−20	36	94	71
3	**12** (5)	−20	48	93	85
4	**12** (2.5)	−20	72	91	81
5[d]	**12** (5)	−25	48	93	85

[a] For detailed experimental procedures, see Supporting Information. [b] Isolated yield. [c] Determined by chiral HPLC analysis after conversion to **14**. [d] Scale of reaction = 50 g.

titanium complex of a D-glucose-derived ligand (catalyst **11** or **12**) generally gives (*R*)-ketone cyanohydrins, which is required for natural fostriecin synthesis. First observed was a significant protecting-group effect of the substrate allylic alcohol on the reactivity and enantioselectivity.[15] Among the ketones studied, benzyl-protected **9** gave the most promising results and cyanohydrin **10** with 86% ee was obtained in 58% yield using **11** as the catalyst (Table 1, entry 1).[16] To improve the yield, the reaction was performed at a higher temperature; however, the enantioselectivity decreased significantly (entry 2). Next, we employed the tuned catalyst **12** containing a benzoyl group at the catechol moiety[14b] under high concentration (>12 M to THF), and the product was obtained in synthetically acceptable reaction time, yield, and enantioselectivity (entry 3). The reaction was performed using 5 mol % of the catalyst on a 50 g scale without any difficulty (entry 5). The chiral ligand was recovered in 95% yield after silica gel column chromatography, which could be used at least several times without any loss of catalyst activity.

The next task was to enrich the enantiomeric excess and construct the C-5 chiral carbon through allylation of aldehyde **8** (Scheme 2). Ethanolysis of **10** followed by a two-step reduction gave diol **13**. Enantiomerically pure compound was obtained by recrystallization of the corresponding *p*-nitrobenzoyl ester **14** in 78% yield. After hydrolysis, selective

(7) Jacobsen, Imanishi, Hatakeyama, and Falck utilized Stille or Suzuki cross-coupling for the triene construction. Compound **2** is the common intermediate of Jacobsen, Imanishi, Hatakeyama, and Kobayashi.

(8) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739.

(9) Same strategy was employed in Jacobsen's synthesis.

(10) For a review, see: Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, *67*, 1595−1601.

(11) (a) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178. (b) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871−1873.

(12) For a recent review on two-center asymmetric catalysis, see: Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun*. **2002**, 1989−1999.

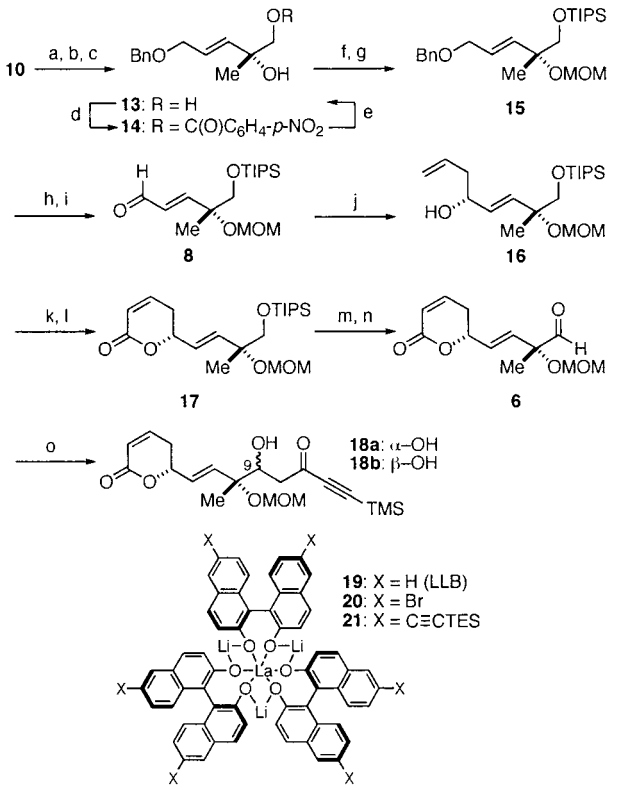
(13) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.

(14) (a) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412−7413. (b) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett*. **2001**, *42*, 691−694.

(15) See Supporting Information for details.

(16) The absolute configuration of **10** was determined by conversion to the known triol: Partridge, J. J.; Shiuey, S.-J.; Chadha, N. K.; Baggiolini, E. G.; Blount, J. F.; Uskokovic *J. Am. Chem. Soc*. **1981**, *103*, 1253−1255.

Scheme 2[a]



[a] Reagents and conditions: (a) 6 N HCl/EtOH, 60 °C, 83%; (b) DIBAH, CH_2Cl_2, from −78 °C to 0 °C; (c) $NaBH_4$, MeOH, 93% (two steps); (d) *p*-$NO_2C_6H_4COCl$, py, CH_2Cl_2, 100%; recrystallized from CH_2Cl_2/hexane, 78% (>99% ee); (e) K_2CO_3, MeOH−CH_2Cl_2, 100%; (f) TIPSCl, imidazole, DMF, 96%; (g) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 88%; (h) LiDBB, THF, −78 °C, 73%; (i) TPAP (5 mol %), NMO, CH_2Cl_2, 87%; (j) AgF (20 mol %), (*R*)-*p*-tol-BINAP (20 mol %), CH_2═$CHCH_2Si(OMe)_3$, MeOH, 80% (dr = 28:1); (k) acryloyl chloride, Et_3N, CH_2Cl_2, 76%; (l) $(Cy_3P)_2RuCl_2$(═CHPh) (15 mol %), CH_2Cl_2, 94%; (m) 3HF·NEt_3, THF, 90%; (n) DMP, CH_2Cl_2, 92%; (o) **19** (10 mol %), **7** (6 equiv), THF, 65% (**18a**/**18b** = 3.6/1).

protection of the diol, reductive debenzylation using lithium di-*t*-butyl biphenylide (LiDBB), and TPAP-catalyzed oxidation gave aldehyde **8**. For the synthesis of **16**, we first tried Keck allylation[17] using allyltributyltin (2 equiv) and 20 mol % catalyst prepared from $Ti(O^iPr)_4$ and (*R*)-BINOL. The reaction, however, did not proceed well, and the product was obtained in only 39% yield with a diastereomeric ratio (dr) of 7:1. On the basis of the hypothesis that the low catalyst activity is due to the coordination of the MOM oxygen to the Lewis acid, Yamamoto's silver-catalyzed asymmetric allylation was tried next.[18] The use of a soft metal should minimize adverse effect of the oxygen coordination to the catalyst. As expected, using 20 mol % AgF-(*R*)-*p*-tol-BINAP complex, the reaction proceeded smoothly at −20 °C and the desired isomer **16** was obtained in 80% isolated yield after separation of the diastereomer (dr = 28:1).[19] Esterification with acryloyl chloride and RCM using Grubbs' catalyst gave lactone **17**, which was desilylated and oxidized by Dess−Martin periodinane (DMP) to give aldehyde **6**, the substrate for the catalytic asymmetric aldol reaction.

Despite the versatility of acetylenes, there has been no previous use of an acetylenic ketone as a donor in direct catalytic enantioselective aldol reactions.[10,20] Mechanistic studies revealed that deprotonation of the ketone is the rate-determining step.[11a] Therefore, the reaction rate of acetylenic ketones should be higher than that using aromatic ketones. As expected, the reaction between **6** and **7** proceeded smoothly at −20 °C for 4 h (ca. 50% isolated yield) in the presence of the second generation (*S*)-LLB (**19** + KOH + H_2O, 10 mol %), the optimum asymmetric heteropolymetallic complex for direct aldol reaction using phenyl ketones. The diastereoselectivity was low (2:1), however, giving the desired **18a** as the preferred isomer.[21] Due to the high acidity of the α-proton of **7**, the enolate concentration should be higher than that of phenyl ketones. As a result, the background reaction independent of the asymmetric catalyst might be more problematic in the case of **7** than that of phenyl ketones. Thus, we examined less basic conditions using first generation (*S*)-LLB.[11b] As expected, the selectivity was improved to 3.6:1 (16 h, 65% yield).[22] Further decreasing the basicity of the bimetallic complex using the substitution effect of BINOL (catalysts **20** and **21**) did not produce any beneficial results.[23] Although the selectivity was not satisfactory even in the optimized case, the effect of the chiral catalyst is significant considering that the reaction did not proceed with 10 mol % $La(O^iPr)_3$.

The mixture of **18a** and **18b** was directly converted to the corresponding acetonide **22** (Scheme 3). Then, the asymmetric transfer hydrogenation was performed following Noyori's procedure.[8] The stereoselectivity from the desired isomer was extremely high (>97:3), and stereochemically pure **23** was obtained in 49% isolated yield after silica gel column chromatography.[24] Protection of the propargylic alcohol, iododesilylation of the acetylene,[25] and diimide

(17) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543−6544.

(18) Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3701−3703.

(19) All the relative configurations, including C-5, were confirmed after conversion to **4** and comparison of the ^1H and ^{13}C NMR with Imanishi's NMR chart. The stereoselectivity matches that of Yamamoto's transition-state model. AgF-catalyzed reaction in the absence of the chiral ligand resulted in no reaction. Addition of allylmagnesium bromide gave a 1:1 diastereomixture.

(20) The aldol reaction using **7** as a donor proved to be difficult possibly due to a fast retro-aldol reaction. Using 2,2-dimethyl-3-phenylpropanal as a model substrate in a reaction with the lithium enolate derived from **7** gave the product in only 28%. The reaction did not proceed with the zinc enolate. LLB (10 mol %), however, promoted the reaction efficiently, and the product was obtained in 72% yield.

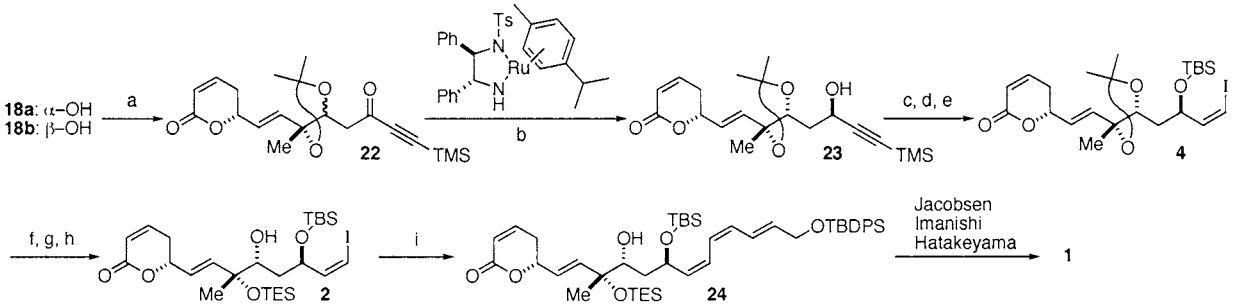
(21) Diastereoisomers could not be separated at this stage. The relative configuration of C-8 and C-9 was determined by NOE measurement on acetonide **22**.

(22) Preliminary studies on the reaction of **7** and a simple aldehyde (2,2-dimethyl-3-phenylpropanal) had a similar tendency: 60% ee with LLB−KOH−H_2O and 72% ee with LLB.

(23) For a beneficial effect of BINOL substitution on a catalytic asymmetric nitroaldol reaction, see: Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256.

(24) Other diastereomers ((9*S*,11*S*)- and (9*S*,11*R*)- derived from **18b**) were separable at this stage (14 and 4%, respectively). The relative configuration of C-9 and C-11 was determined by NOE measurement. See Supporting Information for details.

Scheme 3[a]

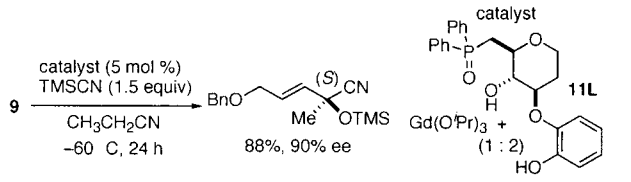


[a] Reagents and conditions: (a) 2,2-dimethoxypropane, PPTS, acetone, 80%; (b) Noyori's catalyst (10 mol %)−KOH (10 mol %), ^{i}PrOH, 49% (other isomers: 18%); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 73%; (d) NIS, $AgNO_3$, acetone, 88%; (e) NBSH, Et_3N, THF/^{i}PrOH, 40% (6% recovery); (f) 1 M HCl (aq)/MeOH, 47%, (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; TESOTf, from −78 °C to −10 °C, 52%; (h) 1 M HCl (aq)/THF/CH_3CN (1:3:6), −10 °C, 52%; (i) $PdCl_2(CH_3CN)_2$, **3**, DMF, 85%.

reduction using *o*-nitrobenzenesulfonylhydrazide (NBSH)[26] gave *cis*-vinyl iodide **4**. Vinyl iodide **2** containing the appropriate protection pattern was synthesized from **4**, using modified Imanishi's procedure. Stille coupling between **2** and **3**[27] under ligand-free conditions[28] gave **24**, which is the common intermediate reported by Jacobsen, Imanishi, and Hatakeyama.[29] Thus, we achieved the formal catalytic asymmetric total synthesis of fostriecin.

To demonstrate the uniqueness of our synthetic strategy, we are currently attempting to synthesize other stereoisomers of fostriecin. Initial results are promising as shown in Scheme 4. Thus, using the (*S*)-selective gadolinium catalyst for ketone cyanosilylation[30] afforded product with the unnatural configuration in 90% ee.

Scheme 4



In summary, we achieved a formal catalytic asymmetric total synthesis of fostriecin. Our strategy is characterized by the fact that all four stereocenters were selectively synthesized by external chiral catalysts. Studies to improve the synthetic efficiency and generate new potent analogues for anticancer agents are currently ongoing.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813−817.
(29) Absolute configuration of **24** was confirmed comparing the sign of the optical rotation to the reported data by Hatakeyama. Two steps (phosphate ester formation and deprotection) are necessary from **24** to **1**.
(30) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908−9909. Ligands **11L** and **12L** are commercially available from Junsei Chemical Co., Ltd. (fax: +81-3-3270-5461).