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Total Synthesis of an Antitumor Antibiotic, Fostriecin (CI-920)

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Abstract: The total synthesis of an antitumor antibiotic, fostriecin (CI-920), via a highly convergent route is described. A characteristic feature of the present total synthesis is that the synthesis was achieved via a coupling procedure of three segments A, B, and C. The unsaturated lactone moiety of fostriecin, corresponding to segment A, was constructed from a known Horner−Emmons reagent, and the stereochemistry of the C-5 position was introduced by asymmetric reduction with (*R*)-BINAl−H. Segment B having a series of stereogenic centers was synthesized from (*R*)-malic acid and the stereogenic centers at the C-8 and C-9 positions were prepared by a combination of Wittig reaction and Sharpless asymmetric dihydroxylation reaction. The conjugated *Z*,*Z*,*E*-triene moiety of fostriecin, corresponding to segment C, was eventually constructed by Wittig reaction and Stille coupling reaction. The phosphate moiety, which is known to be essentially important for the antitumor activity, was introduced via two routes: (i) direct phosphorylation of the monohydroxyl derivative in which other hydroxyl groups are protected with silyl groups; (ii) cyclic phosphorylation and selective cleavage of the cyclic phosphate derivative. Although the former route is basically the same as those reported by other groups, the latter route is novel and more effective than the former one. The present total synthesis would serve as a versatile synthetic route to not only fostriecin, but also its various analogues including stereoisomers.

Fostriecin (**1**, CI-920; Figure 1), isolated from *Streptomyces puluveraceus* with its accompanying analogues, PD113270 and PD113271,[1] is known to be active in vitro against leukemia (L1210), lung, breast and ovarian cancer and is also known to show in vivo antitumor activity against L1210 and P388 leukemia.[2] Because of these potentialities, the phase I trial of this compound had been conducted by the National Cancer Institute, but was halted due to problems of purity and stability of the natural material.[3] Fostriecin is a weak topoisomerase II inhibitor, the mechanism of which is not well-known, but was reported to be different from that of known classical topoisomerase II inhibitors, such as anthracyclins and podophyllotoxins.[4] Fostriecin is also known to be the most selective inhibitor against protein phosphatase 2A and 4; hence, it has attracted much attention as a pharmacological reagent as well.[5] Because other protein phosphatase inhibitors, such as okadaic acid, calyculin A, and so on, are generally known to have tumor-promotion activity rather than antitumor activity, the relation between the antitumor activity and the enzyme inhibitory activities of fostriecin is of great interest. It is also noteworthy that fostriecin, which promotes chromatin compaction, radiosensitizes tumor cells.[6] However, despite its interesting biological activities, as is obvious from the fact that the stereostructure, including the absolute stereochemistry, of fostriecin was disclosed in 1997,[7] only limited chemical research had been done and little about the mechanism of action of fostriecin is known.[8]

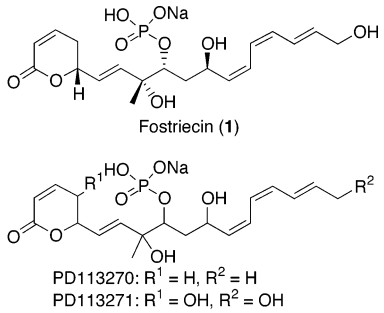

Figure 1. Structures of fostriecin (**1**) and its analogues.

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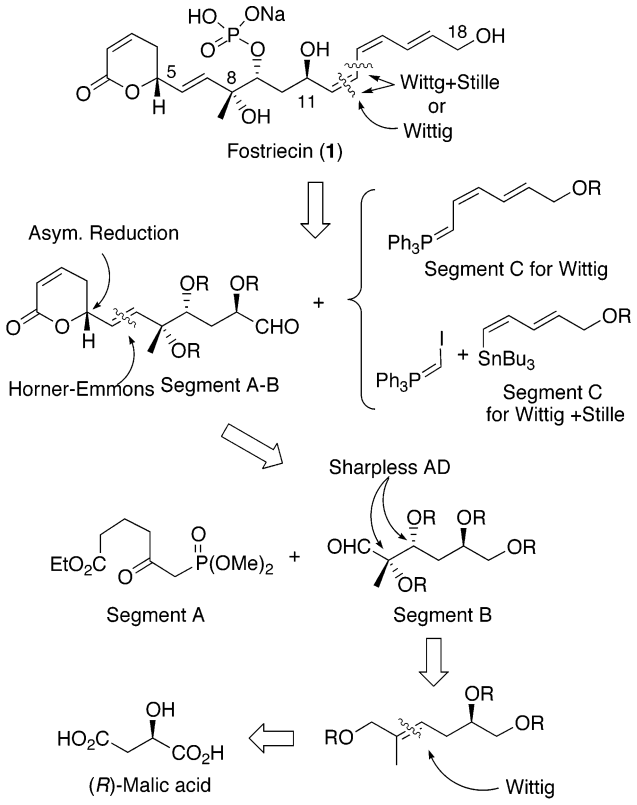

Figure 2. Retrosynthetic analysis of fostriecin (**1**).

Therefore, fostriecin has the potential to be, or to open the door to, a novel type of antitumor agent that is based on a novel mechanism of action.

For the reasons described above, a number of synthetic studies have been conducted, particularly since its stereostructure was revealed by Boger's group in 1997,[7] and the first total synthesis was achieved by his group in 2001.[9] Subsequently, some groups,[10] including ours,[11] have reported its total synthesis.[12] Synthetic studies including the formal total synthesis also have been reported.[13] In this paper, we would like to report details of our total synthesis of fostriecin.[11]

In considering a synthetic strategy for fostriecin, we paid attention particularly to take account that not only fostriecin but also its various analogues can be synthesized efficiently according to the same strategy. For the purpose, we planned to take a convergent route in which the fostriecin molecule is divided into three segments A, B, and C as shown in Figure 2.

Because the triene moiety was easily expected to be unstable, plans were made to couple segment C after the construction of the segment A−B moiety. The triene moiety was expected to be synthesized by Wittig reaction and/or a Pd(0)-catalyzed coupling reaction, which would stereoselectively provide various geometrical isomers, including a natural *Z,Z,E*-isomer.

An unsaturated δ-lactone system is seen as a part of a number of biologically active natural products as well as fostriecin. This structural unit was sometimes connected by the Horner−Emmons reaction employing the lactone moiety as an aldehyde part in syntheses of such natural products,[14] including fostriecin,[9] or, recently, was constructed by ring-closing olefin metathesis. The latter method involves an asymmetric allylation procedure and was also employed in syntheses of natural products[15] and their analogues, including fostriecin.[10b,c,13b] In contrast, we expected that this structural unit would be conveniently constructed by the Horner−Emmons reaction employing the lactone moiety as a Horner−Emmons reagent. Stereoselective reduction of the resultant unsaturated ketone would give both stereoisomers relative to the C-5 position at this stage, allowing a more versatile synthetic route. According to this idea, we employed the Horner−Emmons reagent[16] as segment A.

Concerning segment B having a series of stereogenic centers, we planned to construct the C-8 and C-9 stereogenic centers by Sharpless asymmetric dihydroxylation[17] of the *E*-olefin. The C-11 stereogenic center was assumed to be made from the starting material, (*R*)-malic acid.

Results and Discussion

Synthesis of Segment A−B. Synthesis of segment B was achieved as follows. Alcohol **2** (Scheme 1), which was prepared from (*R*)-malic acid according to a literature procedure,[18] was oxidized by Swern oxidation and treated with a Wittig reagent **4** [19] to give *E*-olefin **3a** in 86% yield from **2**. In contrast, it was also found that the reaction with **5** [20a] gave *Z*-olefin **3b** as a major product under conditions reported by Ando et al.,[20,21] showing that both *E*- and *Z*-isomers of **3** are stereoselectively obtained. Reduction of **3a** and subsequent benzoylation gave olefin **7** in 86% yield. Stereoselective introduction of two hydroxyl groups was achieved as follows. At first, dihydroxylation of **7** without a chiral ligand was examined, affording a mixture of anti- and syn-isomers (Table 1, entry 1). From the proposed model for asymmetric dihydroxylation by Sharpless and co-workers,[17] DHQD as a chiral ligand was expected to give the desired anti-isomer **8a**. In fact, asymmetric dihydroxylation with DHQD gave the anti-isomer **8a** as a main product (entry 2). It is noteworthy that the reaction with $(DHQD)_2PHAL$ as a chiral ligand improves the stereoselectivity (entry 3) and,

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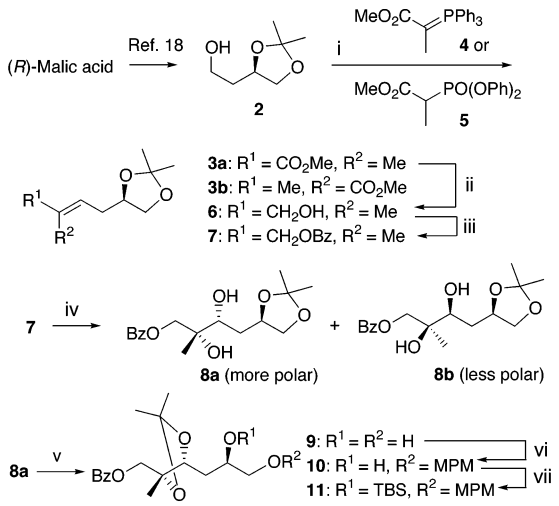
Scheme 1 [a]



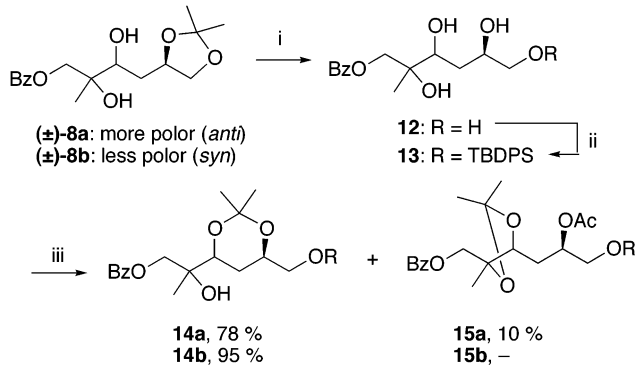
[a] Conditions: (i) Swern oxidation −78 to 0 °C, then **4**, rt, 86%, or (1) Swern oxidation, (2) **5**, DBU, NaI, THF, −78 to 0 °C, 40% (**3b**), 11% (**3a**); (ii) LAH, Et_2O, 0 °C to rt, 98%; (iii) BzCl, Et_3N, CH_2Cl_2, 0 °C, 86%; (iv) Table 1, entry 3; (v) (1) 2,2-dimethoxypropane, *p*-TsOH, rt, (2) $Zn(NO_3)_2 \cdot 6H_2O$, MeCN, 50 °C, 81%, 2 steps; (vi) Bu_2SnO, toluene, reflux, and then MPMCl, Bu_4NI, reflux, 84%; (vii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

Table 1. Asymmetric Dihydroxylation of **7**[a]

entry	ligand	ratio (**8a**:**8b**)	yield (%)
1	none[b]	57:43	95
2	DHQD	72:28	80
3	$(DHQD)_2PHAL$	95:5	92
4	$(DHQ)_2PHAL$	17:83	90

[a] The reactions were performed in *t*-BuOH−H_2O at 0 °C with 2 mol % of $K_2OsO_2(OH)_4$, 3 equiv of $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, 1 equiv of $MeSO_2NH_2$, and 5 mol % of the ligand. [b] The reaction was carried out in acetone−H_2O at room temperature with OsO_4 and NMO.

Scheme 2 [a]



[a] Conditions: (i) 60% AcOH, rt; (ii) TBDPSCl, DMAP, py, rt, 62% from (±)-**8a**, 57% from (±)-**8b**; (iii) (1) 2,2-dimethoxypropane, *p*-TsOH, rt, (2) Ac_2O, py, rt.

as expected, the syn-isomer **8b** was stereoselectively obtained by employing enantiomeric $(DHQ)_2PHAL$ (entry 4).

Although the stereochemistries of **8a** and **8b** were expected to be as shown from the proposed model for the asymmetric dihydroxylation,[17] it was eventually confirmed by NMR analysis of six-membered acetonides **14** derivatized as shown in Scheme 2. Acidic treatment of the more polar isomer of **8a**, which was expected to be an anti-isomer, afforded tetraol **12a**, the primary hydroxyl group of which was protected with a TBDPS group to give triol **13a**. Acetonidation of **13a** gave the six-membered

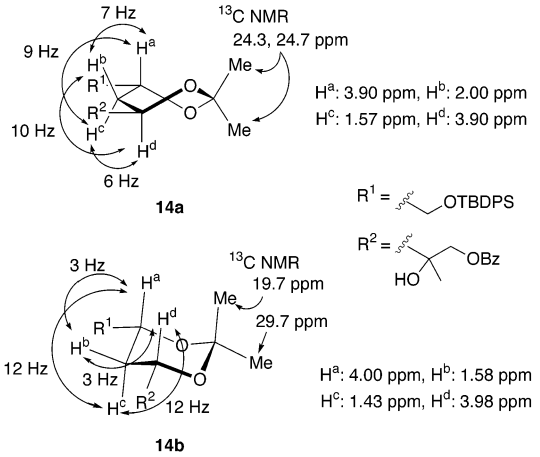


Figure 3. Selected ^1H and ^{13}C NMR data for **14a**,**b**.

acetonide **14a** as a main product (78% yield) with accompanying five-membered acetonide **15a** (10% yield).[22] Less polar isomer **8b** was also transformed into **13b** by the same procedures, and acetonidation gave six-membered acetonide **14b** exclusively.[22] As shown in Figure 3, ^1H NMR and ^{13}C NMR analyses revealed that **14a** derived from the more polar isomer **8a** has a half-chair conformation, while **14b** derived from the less polar isomer **8b** has a chair conformation.[23] These results clearly show that the more polar isomer **8a** has anti-stereochemistry and the less polar one **8b** has syn-stereochemistry, as expected.

To transform into segment B, the diol **8a** was protected with an acetonide group, giving a bisacetonide, the terminal acetonide group of which was selectively removed under Vijayasaradhi's conditions[24] to give **9**. The primary hydroxyl group of **9** was protected with an MPM group via stannoxane,[25] and the residual secondary hydroxyl group of **10** was protected with a TBS group to give **11**, corresponding to segment B.

It is noteworthy that, theoretically, the present synthetic strategy for segment B can provide all of its possible stereoisomers bearing three stereogenic centers by choosing the proper starting material [(*R*)- or (*S*)-malic acid], the geometrical selectivity of the Wittig reaction (**3a** or **3b**), and the chiral ligand for asymmetric dihydroxylation [$(DHQD)_2PHAL$ or $(DHQ)_2PHAL$]. In addition, segment B (**11**) has a characteristic feature in that either segment A or C can be coupled with it by selective removal of one of the two terminal protecting groups, the benzoyl group and the MPM group. In the case of the synthesis of fostriecin, segment A rather than segment C was, at first, coupled with segment B by taking account of the labile property of the triene moiety.

Construction of segment A−B was achieved as shown in Scheme 3. The benzoyl group of **11** was removed by hydrolysis to give alcohol **16**, which was oxidized to aldehyde **17**, and treated with the Horner−Emmons reagent **18** [16] corresponding to segment A to give **19**, selectively. The stereochemistry at the C-5 position was introduced as follows. As reduction of **19** with $NaBH_4$−$CeCl_3$ afforded a mixture of diastereomers, **20a**,**b**,

(22) To obtain six-membered acetonide selectively, it was important to protect the primary hydroxyl group with a benzoyl group.
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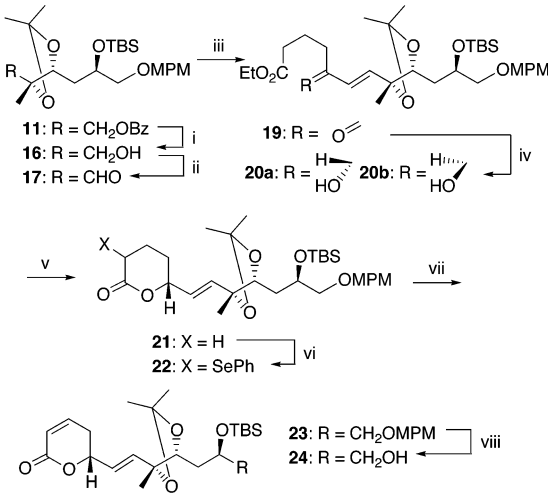
Scheme 3 [a]



[a] Conditions: (i) 3 M KOH(aq):MeOH:THF (1:2:2), rt, 87%; (ii) TPAP, NMO, MS4A, CH_2Cl_2, rt; (iii) $(MeO)_2OPCH_2CO(CH_2)_3CO_2Et$ (**18**), DBU, LiCl, MeCN, rt, 79%, 2 steps; (iv) **20a**, Table 2, entry 4, and **20b**, Table 2, entry 5; (v) *p*-TsOH, benzene, reflux, 92%; (vi) TMSCl, NaHMDS, THF, −78 °C, and then PhSeBr, −78 °C, 94%; (vii) 30% H_2O_2(aq), $NaHCO_3$, AcOEt:THF (1:1), rt, 95%; (viii) DDQ, CH_2Cl_2:H_2O (10:1), rt, 96%.

Table 2. Asymmetric Reduction of **19**

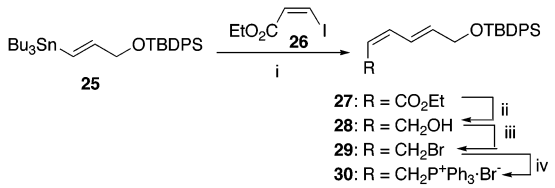
entry	conditions	ratio (**20a**:**20b**)	yield of **20** (%)
1	$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C	1:2	80
2	(*S*)-CBS, BH_3·THF, THF, 0 °C	3:1	95
3	(*S*)-CBS, BH_3·DMS, THF, 0 °C	3:1	96
4	(*R*)-BINAl−H, THF, −100 to −78 °C	>20:1	73 (**21**: 12%)[a]
5	(*S*)-BINAl−H, THF, −100 to −78 °C	**20b** only	70 (5-epi-**21**: 9%)[a]

[a] The ratio was determined after conversion to **20** with K_2CO_3 and EtOH.

in a ratio of ca. 1:2 (Table 2, entry 1), we examined asymmetric reduction of **19**. Although the desired (*R*)-isomer **20a** was obtained as a major product on treatment with a chiral borane reagent,[26] the stereoselectivity was unsatisfactory (entries 2 and 3). In contrast, the reduction with (*R*)-BINAl−H[27] afforded good stereoselectivity (entry 4) in good chemical yield. As expected, the isomer **20b** was almost exclusively obtained by the reduction with (*S*)-BINAl−H (entry 5). Although the stereochemistry at the C-5 position of **20** was expected to be as shown from the proposed transition states for the reduction,[26,27] it was eventually confirmed by modified Mosher's method (see Supporting Information).[28] Lactonization and dehydrogenation via α-phenylselenide **22** afforded unsaturated lactone **23**, the MPM group of which was removed by oxidative treatment to give **24**, corresponding to segment A−B. The present method to construct the unsaturated lactone moiety is straightforward and is characterized by the fact that both stereoisomers are distinctly obtained by choosing the asymmetric reducing agent, (*R*)- or (*S*)-BINAl−H.

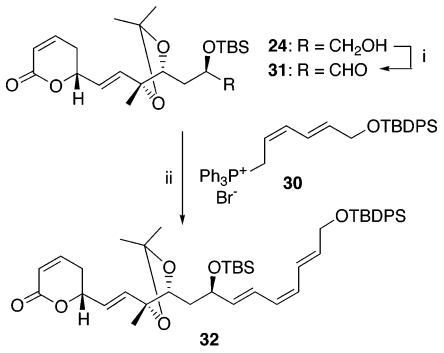
Synthesis of Fostriecin by Direct Phosphorylation. Some examples have been reported that the Wittig reaction of a phosphorus ylide conjugated with an *E*-olefin affords *Z*-stereoselectivity.[29] However, to the best of our knowledge, no report of a Wittig reaction with that conjugated with a *Z*-olefin, like segment C, has been reported. Expecting formation of a *Z*-olefinic bond, we at first selected a Wittig reaction with Wittig salt **30**, which was prepared alternatively as shown in Scheme 4. Vinylstannane **25**[30] was coupled with alkenyl iodide **26**[31] under Pd(0)-catalyzed conditions[32] to give **27** stereoselectively, which was reduced to yield alcohol **28**. Bromination and quartenalization with triphenylphosphine afforded the Wittig salt **30**.

Scheme 4 [a]



[a] Conditions: (i) $PdCl_2(MeCN)_2$, **26**, DMF, rt; (ii) DIBAl−H, CH_2Cl_2, −78 °C, 86%, 2 steps; (iii) NBS, Me_2S, CH_2Cl_2, −20 °C to rt, 68%; (iv) Ph_3P, MeCN, rt, 96%.

Scheme 5 [a]



[a] Conditions: (i) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; (ii) NaHMDS, **30**, THF, −78 to 0 °C, 76%, (*E*:*Z* = 12:1).

The alcohol **24** was oxidized with Dess−Martin reagent[33] and then reacted with the Wittig salt **30** to give *E*-isomer **32** as a major product (Scheme 5). We examined several conditions of the Wittig reaction to obtain the *Z*-isomer, but the results were unsuccessful, probably due to serious steric repulsion of the *Z*,*Z*,*E*-geometry. In addition, deprotection of the acetonide group of **32** was also examined to introduce a phosphate moiety to the hydroxyl group at the C-9 position, but this attempt failed, forming a complex mixture. Therefore, it was found that the desired *Z*-selectivity cannot be obtained by the Wittig reaction of the phosphorus ylide conjugated with a *Z*-olefinic bond and that the acetonide group should be removed before formation of the triene moiety.

Considering the facts described above, we consequently utilized the Stille coupling reaction after formation of the *Z*-olefinic bond between the C-12 and C-13 positions by Wittig reaction, to introduce the triene moiety to segment A−B.

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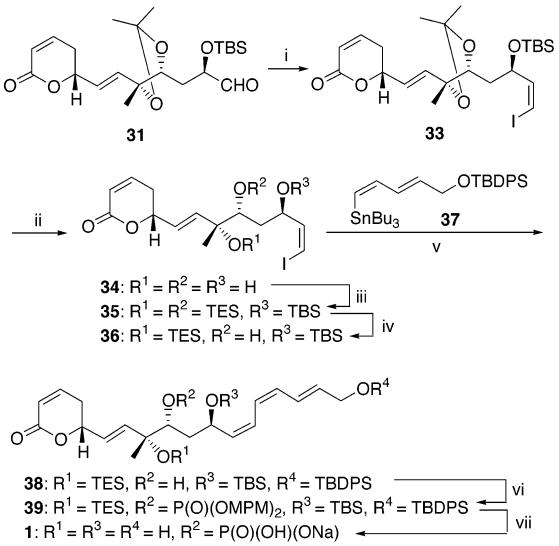
Scheme 6 [a]

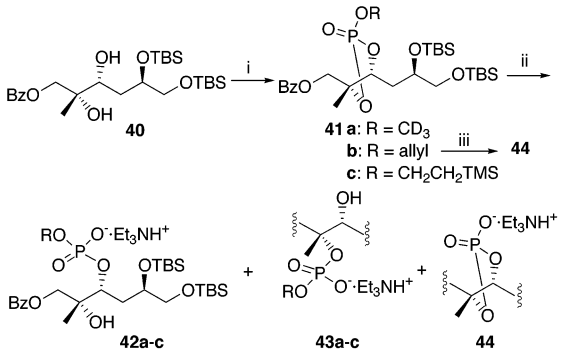


[a] Conditions: (i) $Ph_3P^+CH_2I\cdot I^-$, NaHMDS, HMPA, THF, −100 to 0 °C, 61% from **24** (*Z*:*E* = 4:1); (ii) 1 M HCl(aq):MeOH (1:9), rt, 89%; (iii) (1) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, and then TESOTf, −78 °C, (2) separation 56% (*Z*-isomer); (iv) 1 M HCl(aq):THF:MeCN (1:3:6), −10 °C, 70% (18% recovery of **35**); (v) $PdCl_2(MeCN)_2$, **37**, DMF, rt, 84%; (vi) PCl_3, MPMOH, py, 0 °C to rt, and then *t*-BuOOH, CH_2Cl_2, rt, 56%; (vii) HF(aq)−MeCN and then py, rt, 38%.

Iodomethylenation[34] of the aldehyde **31** gave *Z*-isomer **33** as a major product (*Z*:*E* = ca. 4:1; Scheme 6). Because the geometric isomers were difficult to separate at this stage, the mixture was employed for the subsequent transformation. Deprotection of the acetonide group of **33** was successfully achieved, affording triol **34**. To introduce a phosphoryl group regioselectivey, the hydroxyl groups of **34** were selectively protected as follows. One of the two secondary hydroxyl groups was selectively protected with a TBS group, and the resultant two hydroxyl groups were protected with a TES group. These protection procedures could be accomplished in one pot, and the *Z*-isomer could be separated at this stage by silica gel column chromatography to give **35** in 53% yield. Selective removal of the TES group at the C-8 position was achieved by acidic treatment to give **36**,[35] which was coupled with organostannane **37** [36] under Pd(0)-catalyzed conditions[32] to afford **38**.[35] Phosphorylation of **38** according to Evans' procedure[37] gave **39**, which is a fully protected derivative of fostriecin. Deprotection of **39** by fluoride treatment[9] afforded fostriecin (**1**), which was identified by comparison of the spectral properties (IR, ^{1}H NMR, ^{13}C NMR, $[\alpha]_D$, and TLC behavior) with those of an authentic sample.

Synthesis of Fostriecin via Cyclic Phosphate. Not only in our synthesis described above, but also in those reported by other groups,[9,10] the tertiary hydroxyl group at the C-8 position was protected with a silyl group on phosphorylation. It occurred to us that it would be more convenient if the hydroxyl group at the C-9 position could be phosphorylated without protecting the tertiary hydroxyl group. Choosing **40**, which was easily obtained from **8a**, as a model compound, we alternatively examined the posphorylation without protecting the tertiary hydroxyl group. Several attempts to phosphorylate the secondary hydroxyl group of **40** failed, forming diphosphate or cyclic phosphate. We focused on the cyclic phosphate, which would be an intermediate for selective phosphorylation by selective cleavage of the P−O bond. Although some reports concerning hydrolytic cleavage of cyclic phosphates have been reported,[38] regioselectivity of the cleavage of cyclic phosphates has not been known. Cyclic phosphate **41a** (Scheme 7 and Table 3) was obtained as a diastereomeric mixture by treatment with $POCl_3$ in pyridine and then with deuterated methanol, which was employed to simplify the ^{1}H NMR spectrum of the products. After several attempts, we found that cleavage of the cyclic phosphate **41a** smoothly took place by treatment with aqueous acetonitrile (method A) or aqueous THF (method B) in the presence of triethylamine to give hydrated products **42a**, **43a**, and **44**. The desired product **42a** was obtained as a main product in both cases, and the respective ratios obtained by the ^{1}H NMR spectra were almost the same (entries 1 and 2). Although the same reaction in a methanolic solvent afforded a complex mixture, the reaction in *tert*-butyl alcohol (method C) successfully took place. In this reaction, the ratio of **42a** increased, while that of **44** decreased (entry 3 vs entries 1 and 2). As a consequence, it was also found that the reaction in a 2,2,2-trifluoroethanol (method D) gave the best results with respect to both chemical yield and regioselectivity (entry 4). Taking into account application of this method to the synthesis of

Scheme 7 [a]



[a] Conditions: (i) $POCl_3$, py, 0 °C, and then ROH, 0 °C; (ii) Table 3, method A−D; (iii) $Pd(PPh_3)_4$, HCO_2NH_4, THF, rt, 87%.

Table 3. Partial Hydrolytic Cleavage of Cyclic Phosphate **41**

entry	**41**	method[a]	yield from **40** (%)	ratio (**42**:**43**:**44**)
1	**a**	A	81	54:15:31
2	**a**	B	78	57:14:29
3	**a**	C	75	66:15:13
4	**a**	D	83	70:17:13
5	**b**	D	72	77:14:9
6	**c**	D	81	72:14:14

[a] Method A: MeCN:H_2O:Et_3N (20:1:1), room temperature. Method B: THF:H_2O:Et_3N (20:1:1), room temperature. Method C: *t*-BuOH:H_2O:Et_3N (20:1:1), room temperature. Method D: CF_3CH_2OH:H_2O:Et_3N (20:1:1), room temperature.

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(35) This compound **36** was employed as an intermediate in the total synthesis of fostriecin by Jaconsen's group[10a] and Hatakeyama's group[10c] as well. Kobayashi's group reported formal total synthesis of fostriecin by the synthesis of **36**.[13c] The compound **38** was also synthesized by Shibasaki and co-workers in their formal total synthesis of fostriecin.[13d]

(36) Heathcock and co-worker reported the synthesis of a compound having a TBS group in place of the TBDPS group of **37**: Mapp, A. K.; Heathcock, C. H. *J. Org. Chem*. **1999**, *64*, 23. Hatakeyama's group reported alternative synthesis of **37**.[10c]

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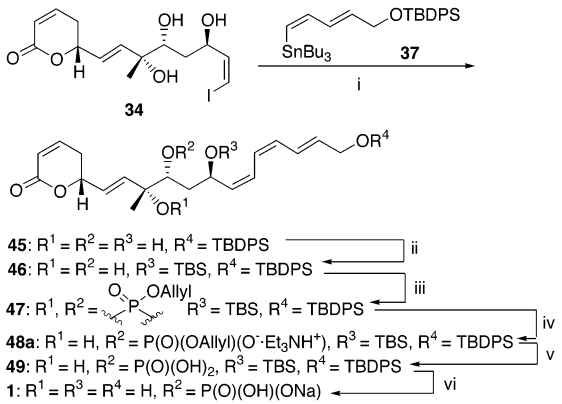
Scheme 8 [a]



[a] Conditions: (i) (1) $PdCl_2(MeCN)_2$, **37**, DMF, rt, (2) separation, 52% (*Z*-isomer); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 88%; (iii) $POCl_3$, py, 0 °C, and then $CH_2{=}CHCH_2OH$, 0 °C; (v) CF_3CH_2OH, Et_3N, H_2O, rt, 81%, 2 steps (80% selectivity); (vi) (1) $Pd(PPh_3)_4$, HCO_2NH_4, PPh_3, THF, rt, (2) HF−py, MeCN, H_2O, rt, 63%, 2 steps.

fostriecin, we next studied the reaction using cyclic phosphates **41b**,**c**, both of which have deprotectable alkoxy groups under mild conditions after introduction of the phosphate moiety. On employing allyl derivative **41b**, the ratio of **42b** slightly increased, and that of **44** slightly decreased, compared with the result of the methyl derivative **41a** (entry 5 vs entry 4). The reaction of 2-(trimethylsilyl)ethyl derivative **41c** afforded the same result as that of **41b**. Therefore, the alkoxy group of the cyclic phosphate would not significantly affect the regioselectivity of the cleavage.

Structures of the products were determined as follows. The cyclic phosphate **44** which was alternatively prepared from **41b** by deallylation and was also differentiated from **42** and **43** by ^{31}P NMR, showed a signal at 11.2 ppm, while **42a** and **43a** showed signals at +1.5 ppm and −2.4 ppm, respectively.[7] The structures of **42a** and **43a** were assigned as shown by comparison of their ^1H NMR spectra, in which the hydrogen at the C-3 position of **42a** and the methyl group at the C-2 position of **43a** shifted to lower field due to the phosphate moiety [**42a**, 4.42 (C-3-H) and 1.13 ppm (C-2-Me); **43a**, 3.89 (C-3-H) and 1.34 ppm (C-2-Me)].

With regard to the reaction mechanism, it has been already reported that, in hydrolytic cleavage of five-membered cyclic phosphate, the endo-cyclic P−O bond is cleaved more easily than the exo-cyclic P−O bond, because of a stereoelectronic effect.[38b] The fact that **42**, not **43**, was a major product in every case would be explained by taking account of the fact that the sterically more hindered P−O bond is likely to be cleaved more easily after attack of H_2O on the phosphorus center of **41**. The fact that a less nucleophilic and more acidic alcohol, 2,2,2-trifluoroethanol, afforded the best result suggests an important role of hydrogen bonding, but the detail is unclear.

Encouraged by the results described above, we applied the method to the synthesis of fostriecin as follows. Compound **34** was coupled with the organotin compound **37** to give **45** (Scheme 8),[39] the hydroxyl group at the C-11 position of which was selectively protected with a TBS group, giving diol **46**.[39] Diol **46** was phosphorylated by treatment with $POCl_3$ and allyl alcohol to give the cyclic triester **47** as a diastereomeric mixture. Without purification, **47** was immediately hydrolyzed, and the P−O bond of **47** was regioselectively cleaved under the same conditions as those described above, affording **48a** as a major product [δ_H, 1.14 ppm (C-8-Me); δ_P, 1.0 ppm]. The minor components were not isolated but were assigned to be C-8-phosphate **48b** and cyclic phosphate diester **48c** from the ^{31}P NMR and ^1H NMR spectra of the crude product, similarly to the reaction of the model compound **41**. The ratio of **48a**:**48b**:**48c** was estimated to be 80:12:8. After deprotection of the allyl group of **48a**,[40] the resultant phosphate **49** was further treated with fluoride to afford fostriecin after chromatographic purification. Spectral properties of the product were identical with those of an authentic sample and of **1** prepared by the method described above. On comparing the two methods, the route from **34** via direct phosphorylation of **38** afforded fostriecin in 7% yield, while that via cyclic phosphate **47** resulted in 23% yield from the same compound **34**, showing that the latter route is obviously more effective.

In conclusion, we have successfully synthesized fostriecin via a highly convergent route involving a three-segment coupling procedure. Introduction of the phosphate moiety was achieved via two routes, direct phosphorylation and partial hydrolytic cleavage of cyclic phosphate. The latter method was shown to be more efficient than the former method. Our present synthetic methodology would be of great use for the synthesis of various fostriecin analogues including stereoisomers and natural products belonging to the fostriecin family[41] as well, and synthetic studies on fostriecin analogues according to the present strategy are in progress toward efforts to reveal the structure−activity relationship of fostriecin.

Experimental Section

Full experimental details are provided as Supporting Information.

Acknowledgment. We gratefully acknowledge Dr. Robert J. Schultz of the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, for the kind gift of natural fostriecin.

Supporting Information Available: Text describing complete experimental details and figures showing ^1H NMR spectra for **3a**, **6**, **7**, **8a**, **9**, **10**, **16**, **19**, **20a**, **21**, **23**, **24**, **35**, **36**, **38**, **46**, and natural and synthetic fostriecin (**1**) and ^{13}C NMR spectra for natural and synthetic fostriecin. This material is available free of charge via the Internet at http://pubs.acs.org.

JA030133V

(39) The compounds **45** and **46** were employed as intermediates in the total synthesis of fostriecin by Boger's group.[9]

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