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Total synthesis of fostriecin (CI-920) *via* a convergent route

Kazuyuki Miyashita, Masahiro Ikejiri, Hitomi Kawasaki, Satoko Maemura and Takeshi Imanishi*
Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan

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Fostriecin, a potent and promising antitumor antibiotic, was stereoselectively synthesized *via* a convergent route involving a three-segement coupling procedure.

Fostriecin (**1**, CI-920), produced by *Streptomyces pulveraceus*,[1] is a promising antitumor antibiotic that is active against leukemia, lung cancer, breast cancer and ovarian cancer *in vitro*.[2] 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, in spite of its potential.[3] Fostriecin is known to be a weak topoisomerase II inhibitor *via* a novel, non-DNA-strand cleavage mechanism,[4] which is quite different from that of classic topoisomerase II inhibitors like anthracyclines and podophyllotoxins, and is also known to be a potent and highly selective protein phosphatase inhibitor against PP2A and PP4.[5] However, as is obvious from the fact that its stereo-structure was disclosed only a few years ago,[6] the mechanism of these biological actions at the molecular level has not been revealed, and the relation between these actions and the antitumor activity is also unknown.

For the reasons described above, fostriecin is an attractive synthetic target and, actually, synthetic study has been reported by some groups.[7] Recently, the first synthesis has been achieved by Boger's group,[8] and subsequently Jacobsen's group[9] also reported its total synthesis.† In order to reveal its mechanism of action, it is important to establish a general synthetic route not only to natural fostriecin but also its various congeners. For this purpose, we also have been conducting the synthesis of fostriecin *via* a convergent route involving three key segments A, B and C according to the strategy shown in Fig. 1. The δ-lactone structure was expected to be synthesized from a Horner–Emmons reagent, segment A. The segment B containing a series of stereogenic centers was planned to be synthesized from (*R*)-malic acid by combination of Wittig reaction and Sharpless asymmetric dihydroxylation. The triene moiety was planned to be constructed by Stille coupling reaction after coupling the segment B with the segment A. We herein describe the total synthesis of fostriecin.

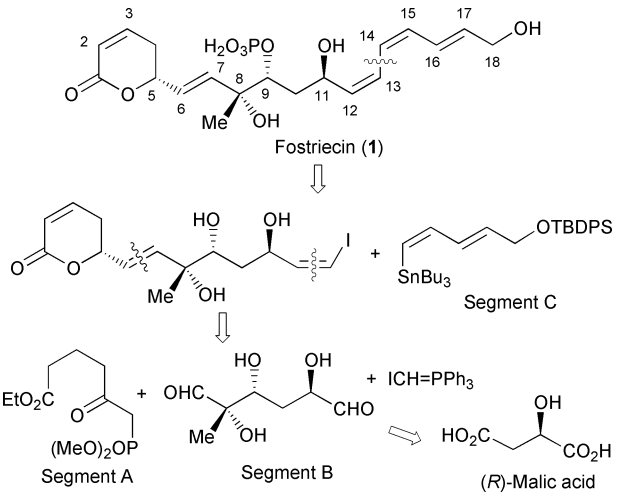
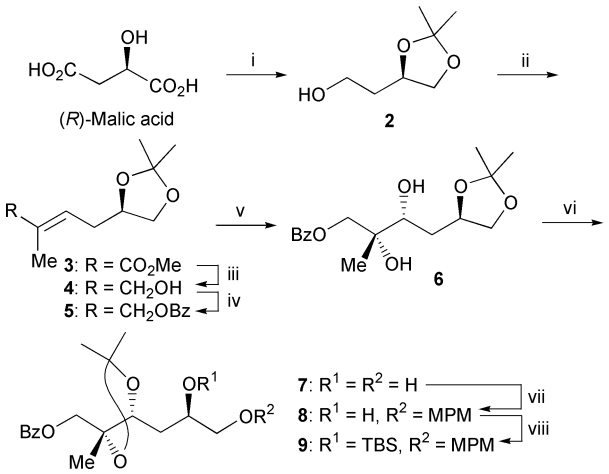


Fig. 1 Retrosynthetic analysis for fostriecin (**1**).

Synthesis of the segment B was achieved as shown in Scheme 1. Alcohol **2**, which was obtained from (*R*)-malic acid according to literature procedures,[10] was converted into unsaturated ester **3** *via* oxidation and Wittig reaction. The ester **3** was reduced to give allyl alcohol **4**, the hydroxy group of which was protected with a benzoyl group to yield **5**. The stereogenic centers at C-8 and C-9 of fostriecin were successfully introduced by applying Sharpless asymmetric dihydroxylation to **5**.[11] On the reaction using $(DHQD)_2PHAL$ as a chiral ligand, the desired diol **6** was obtained highly stereoselectively. After acetonidation of **6**, regioselective removal of the terminal acetonide group was achieved by treatment with zinc nitrate to afford **7**.[12]

The primary hydroxy group of **7** was selectively protected with a 4-methoxybenzyl (MPM) group, and the residual secondary hydroxy group of **8** was protected with a *tert*-butyldimethylsilyl (TBS) group to give the fully protected segment B (**9**). A characteristic feature of the segment B is that it can be coupled with either segment A or C by selective cleavage of the two terminal protecting groups (Bz and MPM groups).

The segment B was, at first, coupled with the segment A because of the acid-labile property of the conjugated triene moiety. The benzoyl group of **9** was removed. The resultant alcohol **10** was oxidized to give aldehyde **11**, which was coupled with the segment A (**12**)[13] to afford **13** stereoselectively. The stereogenic centre at C-5 of fostriecin was constructed by (*R*)-BINAl-H reduction[14] of **13**, giving **14** in a highly stereoselective manner ($R : S > 20 : 1$). Lactonization of **14** by treatment with acid took place smoothly to yield **15**, which was transformed to unsaturated lactone **17** *via* selenide **16** in a good yield. In order to couple with the segment C, **17** was converted to an iodomethylene derivative as follows. The MPM



Scheme 1 *Reagents and conditions*: i, ref. 10; ii, Swern oxid. −78 to 0 °C, 0.5 h, then $Ph_3P{=}C(Me)CO_2Me$, rt, 1 h, 86%; iii, LAH, Et_2O, 0 °C to rt, 2.5 h; iv, BzCl, TEA, CH_2Cl_2, 0 °C, 3 h, 84% 2 steps; v, $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH–H_2O, 0 °C, 2 h, 92% (*anti* : *syn* = 95 : 5); vi, (1) 2,2-dimethoxypropane, *p*-TsOH, rt, 1 h, (2) $Zn(NO_3)_2{\cdot}6H_2O$, MeCN, 50 °C, 3 h, 81% 2 steps; vii, Bu_2SnO, toluene, reflux, 12 h then MPMCl, Bu_4NI, reflux 1.5 h, 84%; viii, TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, quant.

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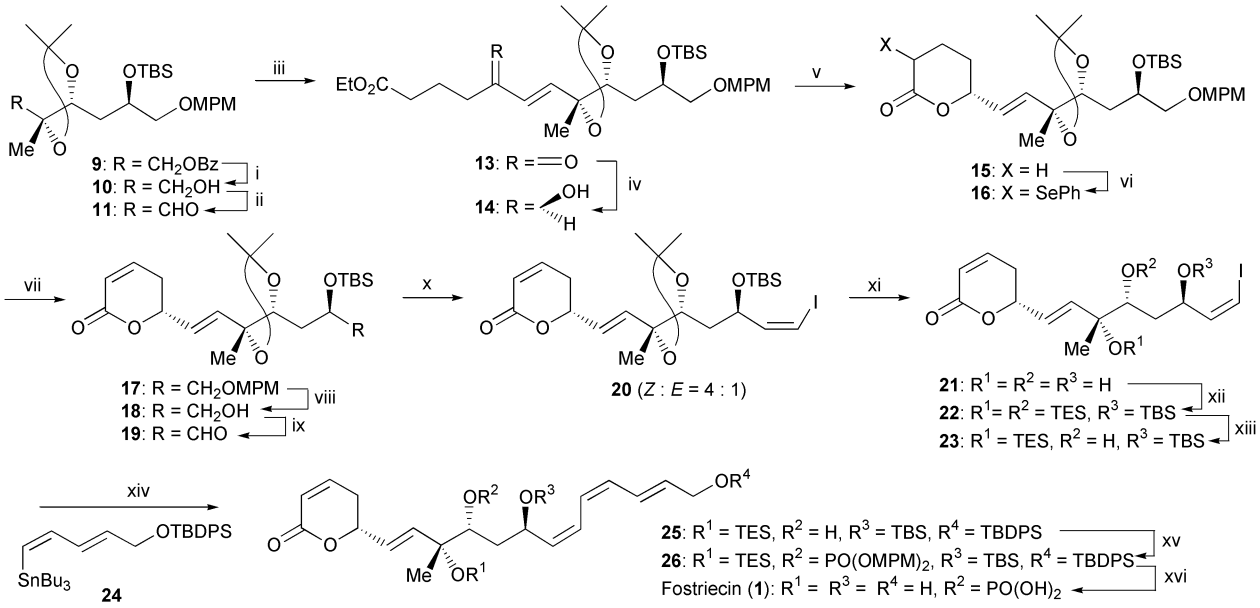

Scheme 2 *Reagents and conditions*: i, 3 M KOH–MeOH–THF (1:2:2), rt 1 h, 87%; ii, TPAP, NMO, MS 4A, CH_2Cl_2, rt, 1 h; iii, $(MeO)_2OPCH_2CO(CH_2)_3CO_2Et$ (**12**), DBU, LiCl, MeCN, rt, 2.5 h, 79% 2 steps; iv, (*R*)-BINAl-H, THF, −100 °C, 6 h, 85% (*R*:*S* > 20:1); v, *p*-TsOH, benzene, reflux, 0.5 h, 92%; vi, NaHMDS, TMSCl, PhSeBr, THF, −78 °C, 4 h, 94%; vii, H_2O_2, $NaHCO_3$, AcOEt–THF, rt, 0.5 h, 94%; viii, DDQ, wet CH_2Cl_2, rt, 0.5 h, 96%; ix, Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 1 h; x, $Ph_3P^+CH_2I\cdot I^-$, NaHMDS, HMPA, THF, −100 to 0 °C, 61% (*Z*:*E* = 4:1) 2 steps; xi, 1 M HCl–MeOH (1:9), rt, 10 h, 89%, xii, (1) TBSOTf, 2,6-lutidine, −78 °C, 10 min, then TESOTf −78 °C to rt (2) separation 56% (*Z*-isomer); xiii, 1 M HCl–THF–MeCN (1:3:6), −10 °C, 2 h, 70% (18% recovery of **22**); xiv, **24**, $PdCl_2(MeCN)_2$, DMF, rt 25 h, 80%; xv, PCl_3, MPMOH, Py, then TBHP–CH_2Cl_2, 56%; xvi, HF–MeCN, then Py, rt, 20 h, 38%.

group of **17** was removed by oxidative treatment. The resultant alcohol **18** was oxidized with Dess–Martin reagent to give aldehyde **19**. Iodomethylenation of **19** by Wittig reaction gave **20** with the *Z*-isomer as a major product. It was essentially important to remove the acetonide group at this stage, because all attempts to remove the acetonide group after coupling with the segment C resulted in failure due to the acid-labile property of the triene moiety. Therefore, the acetonide group of **20** was removed by acidic treatment to give **21**, with concomitant removal of the TBS group. In order to introduce a phosphoryl group regioselectively, the *tert*-hydroxy group and the sterically less hindered *sec*-hydroxy group were selectively protected as follows. All hydroxy groups of **21** were regioselectively protected with a *tert*-butyldimethylsilyl (TBS) group and a triethylsilyl (TES) group in one pot; then the TES group attached to the *sec*-hydroxy group of **22**‡ was selectively removed to give **23**.§

Organotin compound **24** corresponding to the segment C, prepared according to a literature procedure,[15] was coupled with **23** under Pd(0)-catalyzed conditions to give **25** in good yield, which was phosphorylated to give fully protected fostriecin **26**. Deprotection by fluoride-treatment gave fostriecin (**1**), the ^1H NMR data and chromatographic property of which were identical to those of natural fostriecin.

In conclusion, a convergent synthesis of fostriecin (**1**) was achieved, which would be of great use for the synthesis of various fostriecin congeners to obtain a stable analog of fostriecin, and to clarify the mechanism of its biological activity. Synthesis of fostriecin analogs according to the present strategy is in progress in our laboratory.

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Notes and references

† To the best of our knowledge, one study by Hatakeyama's group at Nagasaki University has been orally presented recently in Japan: T. Esumi, N. Okamoto, Y. Iwabuchi and S. Hatakeyama, *Symposium on Progress in Organic Reaction and Synthesis, Abstract*, 2001, **27th**, 202.

‡ Geometric isomers of **22** (*Z*:*E* = 4:1) were separable at this stage by chromatography.

§ The compound **23** was the same as that reported by Jacobsen's group.[9]

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