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Versatile enantiocontrolled synthesis of (+)-fostriecin†

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Received (in Cambridge, UK) 7th October 2002, Accepted 29th October 2002
First published as an Advance Article on the web 15th November 2002

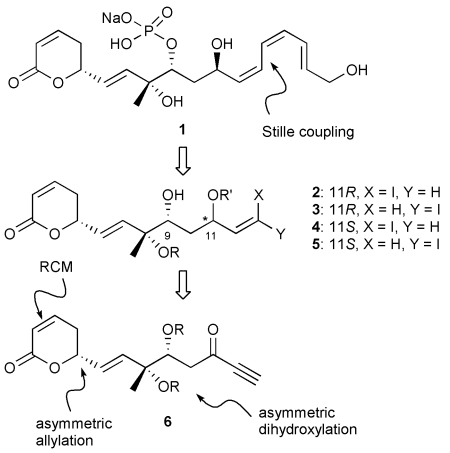
Fostriecin, a potent protein phosphatase inhibitor and antitumor agent, has been enantioselectively synthesized in naturally occurring form *via* a versatile route, which also allows one to secure all possible stereoisomeres of the C1–C13 fragment including the C11 stereocenter and the geometry of the Δ^{12}-double bond.

Fostriecin (**1**, CI-920) is a structurally unique phosphate ester produced by *Streptomyces pulveraceus*.[1,2] This compound displays potent *in vitro* activity against various cancerous cell lines (*i.e.* leukemia, lung cancer, breast cancer, ovarian cancer) as well as *in vivo* antitumor activity.[3] However, despite the high potential of fostriecin as an antitumor drug, phase I clinical trails carried out at NCI were halted relatively early due to concerns over the stability and purity of the natural material.[4] Therefore, an efficient and flexible synthetic route to fostriecin is required for the discovery of analogues that have more desirable physical properties. This situation has spurred much research on the synthesis of fostriecin[5] and Boger *et al.*[3] have achieved the first synthesis in 2001. Just recently, three groups[6] also reported successful total synthesis. We now report a novel enantiocontrolled synthesis of fostriecin, which enables us to prepare various analogues as well.

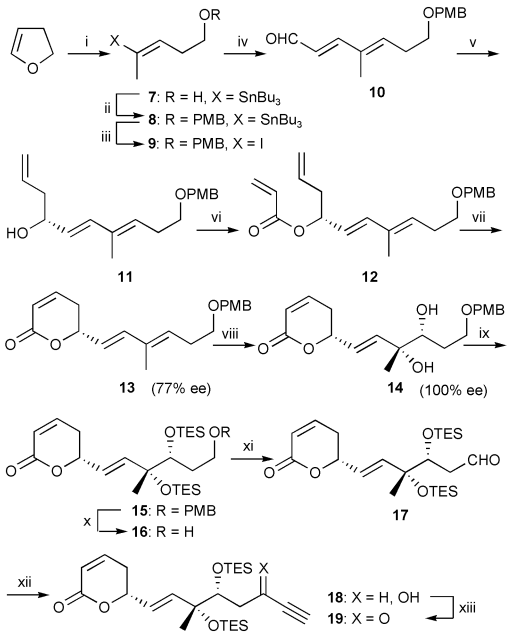
From a retrosynthetic perspective (Scheme 1) we focused on a strategy wherein the phosphate ester and sensitive triene arise from alkenyl iodide **2** late in the synthesis. In order to make our approach flexible, we envisaged ynone **6** as a precursor of **2**. We expected that alkenyl iodide **2** as well as its stereoisomers **3**, **4** and **5** would each be available from **6** by the combination of stereoselective formation of the *E*- or *Z*-β-iodoenone and 9-OH directed *anti*- or *syn*-selective reduction.

Scheme 2 illustrates the asymmetric synthesis of the key ynone based on asymmetric allylation, ring-closing alkene metathesis,[7] and Sharpless asymmetric dihydroxylation.[8]

According to Aldisson's procedure,[9] dihydrofuran was converted to stannane **7** with perfect *E*-selectivity. After *p*-methoxybenzylation of **7**, iodination of **8** followed by Heck reaction[10] of **9** with acrolein afforded aldehyde **10**. Brown's asymmetric allylation[11] of **10** gave alcohol **11** in good yield. The optical purity of **11** was not determined at this stage because of its instability under conditions of the HPLC analysis using a chiral column or formation of the corresponding MTPA esters. After acryloylation, ring-closing alkene metathesis of **12** was examined under various conditions and it was found that cyclization took place between the two terminal alkenic double bonds with high site selectivity.[12] Thus, upon treatment of **12** with 0.1 equivalents of Grubbs' catalyst in CH_2Cl_2 at reflux for 22 h, lactone **13** was obtained in 75% yield together with the corresponding dimer in 4% yield. In this particular case, the dimer was the only side-product produced and the conjugated diene moiety did not react at all. The optical purity of **13** was determined to be 77% ee by HPLC using a chiral column, indicating the enantioselectivity of the above-mentioned asymmetric allylation. However, we were pleased to find that Sharpless dihydroxylation of **13** using AD-mix-β produced enantiomerically pure diol **14** in 80% yield. Obviously, the dihydroxylation reaction was accompanied by kinetic resolution and occurred at the most electron-rich and sterically less hindered olefin with perfect regio- and diastereoselectivity.[5c,13]



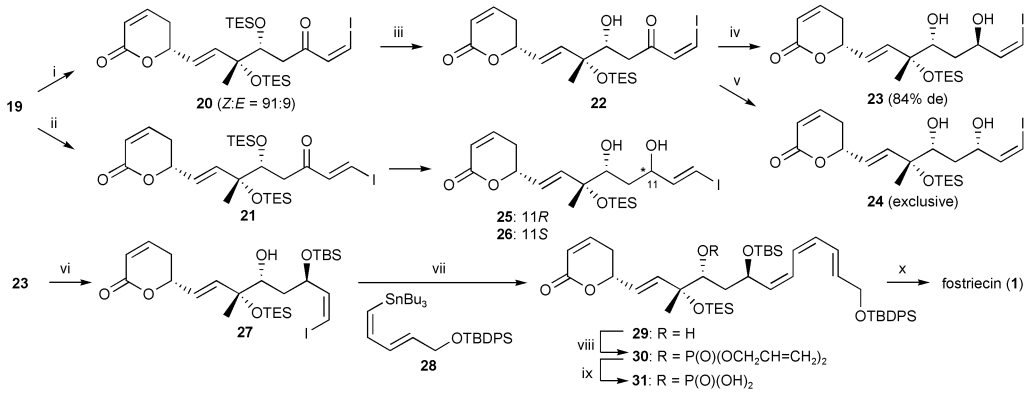
Scheme 1 Retrosynthetic analysis.



Scheme 2 *Reagents and conditions*: i, *t*-BuLi, THF, −60 to 0 °C, then $(Bu_3Sn)_2Cu(CN)Li_2$, −30 to −10 °C, then MeI, −40 °C to rt, 83%; ii, *p*-(MeO)PhCH$_2$Cl, NaH, Bu_4NI, DMSO, 90%; iii, I_2, CH_2Cl_2, 0 °C, 100%; iv, CH_2=CHCHO, $Pd(OAc)_2$ (2 mol%), K_2CO_3, Bu_4NCl, DMF, 73%; v, (+)-Ipc$_2$BOMe, H_2C=CHCH$_2$MgBr, Et_2O–toluene, −78 °C, then 30% H_2O_2, 3 M NaOH, THF, 81%; vi, H_2C=CHC(O)Cl, Et_3N, CH_2Cl_2, 0 °C, 80%; vii, $(Cy_3P)_2Cl_2Ru$=CHPh (10 mol%), CH_2Cl_2, reflux, 75%; viii, AD-mix-β, $MeSO_2NH_2$, *t*-BuOH–H_2O (1:1), 0 °C, 80%; ix, Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 91%; x, DDQ, CH_2Cl_2–H_2O (20:1), 0 °C, 99%; xi, Dess–Martin periodinane, CH_2Cl_2, 0 °C, 100%; xii, HCCMgBr, $CeCl_3$, THF, −50 °C, 98%; xiii, as in xi, 95%.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b2/b209742g/

DOI: 10.1039/b209742g



Scheme 3 *Reagents and conditions*: i, NaI (2 equiv.), AcOH (1 equiv.), acetone, **20** (63%) + **21** (6%); ii, NaI (1.1 equiv.), AcOH (4.4 equiv.), 81%; iii, 47% HF–pyridine–H_2O–MeCN (1:4:2:20), 0 °C, 81%; iv, $Me_4NB(OAc)_3H$, AcOH, MeCN, −30 °C, 99%; v, $NaBH_4$, Et_3B, MeOH–THF, −78 °C, then 30% H_2O_2, $NaHCO_3$, 90%; vi, *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, −78 °C, 88%; vii, **28**, $Pd(MeCN)_2Cl_2$ (2.5 mol%), DMF, 0 °C, 88%; viii $(H_2C{=}CHCH_2O)_2PN(i\text{-}Pr)_2$, tetrazole, CH_2Cl_2, 0 °C, then *t*-BuO_2H, 0 °C, 89%; ix, $Pd(PPh_3)_4$ (10 mol%), HCO_2NH_2, PPh_3, THF, then Dowex-50 (H^+ form), MeOH; x, 47% HF–pyridine–H_2O–MeCN (1:4:2:20), then $NaHCO_3$, 79% from **30**.

Diol **14** was then converted to ynone **19** *via* addition of acetylene to aldehyde **17** in 84% overall yield *via* a five-step sequence.

According to Kishi's methodology,[14] **19** was exposed to 1.1 equivalents of NaI and 4.4 equivalents of acetic acid without solvent at room temperature. In this case, even after 30 min, the kinetically formed *Z*-isomer **20** isomerized to the thermodynamically more stable *E*-isomer **21** to an appreciable extent ($Z:E$ = 76:24) and after 3 h pure **21** was obtained in 81% yield. After experimentation under various conditions using solvent to retard the isomerization, we eventually found that acetone was the solvent of choice for the predominant production of *Z*-isomer **20**. Thus, treatment of **19** with 2 equivalents of NaI and 1 equivalent of acetic acid in acetone at room temperature gave a chromatographically separable 91:9 mixture of **20** and **21** in 69% yield. From *Z*-isomer **20** either the 11*R*- or 11*S*-stereocenter was established selectively *via* **22** by two methods. After selective desilylation of **20**, Evans' *anti*-selective reduction[15] of **22** using $Me_4NB(OAc)_3H$ resulted in formation of 11*R*-diol **23** with 84% de in quantitative yield. On the other hand, $NaBH_4$ reduction using triethylborane[16] converted **22** to 11*S*-diol **24** with perfect selectivity in good yield. Similarly, from *E*-isomer **21** the corresponding 11*R*-diol **25** and 11*S*-diol **26** were obtained with perfect selectivity, respectively (Scheme 3)

Having developed the methodology to attain **23** and all of its isomers including the C11 stereocenter and the geometry of the Δ^{12}-double bond, we then investigated the conversion of **23** to fostriecin. Selective silylation of **23** afforded Jacobsen's intermediate **27**[6a] which was then subjected to palladium-catalyzed Stille coupling[17] with stannane **28**,[18]‡ to produce **29** with perfect stereoselectivity. It should be highlighted that the final phosphorylation-deprotection step employed in the previous syntheses[3,6] was highly improved by use of a diallyl phosphoryl group in place of a di-*p*-methoxybenzyl phosphoryl group. Thus, reaction of **29** with diallyl diisopropylaminophosphine[19] followed by treatment of the resulting phosphite with *tert*-butyl hydroperoxide gave **30** in good yield. Finally, palladium-catalyzed reductive deallylation[20] of **30** followed by desilylation of **31** using HF–pyridine cleanly furnished (+)-fostriecin (**1**). The synthetic substance was identical with natural fostriecin ($[\alpha]_D$, ^1H and ^{13}C NMR, FAB–MS, IR, UV and HPLC).

In conclusion, we have accomplished a total synthesis of (+)-fostriecin from dihydrofuran in 21 steps in 4.5% overall yield. This synthesis provides a flexible route to fostriecin analogues required for biological testing.

We thank Dr R. Schultz of the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute for a sample of natural fostriecin. Partial financial support from the Ministry of Education, Science, Sports and Culture of Japan is gratefully acknowledged.

Notes and references

‡ Prepared from propargyl alcohol in 67% overall yield: i, propargyl alcohol, $LiAlH_4$, THF, 0 °C then Bu_3SnOTf, rt; ii, $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C then Et_3N, $Ph_3P{=}CHCO_2Et$, rt; iii, *i*-Bu_2AlH, CH_2Cl_2, −78 °C; iv, *t*-$BuPh_2SiCl$, DMAP-Et_3N, CH_2Cl_2, 0 °C. For step i: E. J. Corey and T. M. Eckrich, *Tetrahedron Lett.*, 1984, **25**, 2419.

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