Versatile enantiocontrolled synthesis of (+)-fostriecin†

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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 stereoisomers of the C1–C13 fragment including the C11 stereocenter and the geometry of the $\Delta^{13}$-double bond.

Fostriecin (1, C1–920) 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 trials 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 fostriecin5 and Boger et al. have achieved the first synthesis in 2001. Just recently, three groups6 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 later 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-$\beta$-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, and Sharpless asymmetric dihydroxylation.

According to Aldisson’s procedure,7 dihydrofuran was converted to stannane 7 with perfect $E$-selectivity. After $p$-methoxybenzylation of 7, iodonation of 8 followed by Heck reaction9 of 9 with acrolein afforded aldehyde 10. Brown’s asymmetric allylation11 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 acryloxylation, 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$_2$Cl$_2$ 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 dihydroxylation. However, we were pleased to find that Sharpless dihydroxylation of 13 using AD-mix-$\beta$ 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.5,13

Scheme 1 Retrosynthetic analysis.

Scheme 2 Reagents and conditions: i, $t$-BuLi, THF, –60 to 0 °C, then (Bu$_3$Sn)Cl/Cu(II)I$_2$, –30 to –10 °C, then MeLi, –40 °C to rt, 83%; ii, p-(MeO)PhCH$_2$Cl, NaH, Bu$_4$NI, DMSO, 90%; iii, $t$-BuCH$_2$Cl, 0 °C, 100%; iv, CH$_2$Cl$_2$/CHC(O)Cl, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 73%; v, $\alpha$-$t$-BuOC(CH$_2$)$_2$Me, CH$_2$Cl$_2$, 0 °C, 91%; vi, H$_2$C=CHCH$_2$MgBr, Et$_3$O-toluenate, –78 °C, then 30% H$_2$O$_2$, 3 M NaOH, THF, 81%; vii, H$_2$C=CH(OCl)Br, Bu$_3$N, CH$_2$Cl$_2$, 0 °C, 80%; viii, (C$_2$H$_5$)$_2$P=O/C$_6$H$_5$ONa, CH$_2$Cl$_2$, reflux, 75%; viii, AD-mix-$\beta$, Me$_2$SO$_2$NH$_2$, $t$BuOH–H$_2$O (1:1), 0 °C, 80%; ix, Et$_3$O devis, 2,6-lutidine, CH$_2$Cl$_2$, 78 °C, 91%; x, DDQ, CH$_2$Cl$_2$, 81%; x, DMF, 75%; xii, HCCMeBr, CeCl$_3$, THF, –50 °C, 98%; xii, as in xi, 95%.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b2/b209742g/
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 was 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 acetonitrile 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 acetonitrile at room temperature gave a chromatographically separable 91:9 mixture of 20 and 21 in 69% yield. From Z-isomer 20 either the 11R- or 11S-stereocenter was established selectively via 22 by two methods. After selective desilylation of 20, Evans’ anti-selective reduction of 22 using Me₂NB(OAc)₂H resulted in formation of 11R-diol 23 in 84% de in quantitative yield. On the other hand, NaBH₄ reduction using triethylborane converted 22 to 11S-diol 24 with perfect selectivity in good yield. Similarly, from E-isomer 21 the corresponding 11R-diol 25 and 11S-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 Δ13,19-double bond, we then investigated the conversion of 23 to fostriecin. Selective silylation of 23 afforded Jacobson’s intermediate 27 which was then subjected to palladium-catalyzed Stille coupling with stannane 28 via 22. After selective desilylation of 20, Evans’ anti-selective reduction of 22 using Me₂NB(OAc)₂H resulted in formation of 11R-diol 23 in 84% de in quantitative yield. On the other hand, NaBH₄ reduction using triethylborane converted 22 to 11S-diol 24 with perfect selectivity in good yield. Similarly, from E-isomer 21 the corresponding 11R-diol 25 and 11S-diol 26 were obtained with perfect selectivity, respectively (Scheme 3).

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.

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Notes and references

Prepared from propargyl alcohol in 67% overall yield: i, propargyl alcohol, LiAlH₄; THF, 0 °C then Bu₃SnOTf; rt; ii, (COCl)₂, DMSO; CH₂Cl₂, –78 °C then Et₃N, Ph₃P=CHCO₂Et; rt; iii, t-BuAlH, CH₂Cl₂, –78 °C; iv, t-BuPh₂SiCl, DMAP-Et₃N, CH₂Cl₂, 0 °C. For step x: E. J. Corey and T. M. Eckrich, Tetrahedron Lett., 1984, 25, 2419.


