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Asymmetric Total Synthesis of (+)-Fostriecin†

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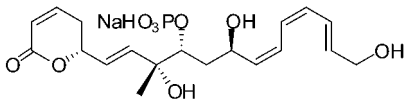
ABSTRACT



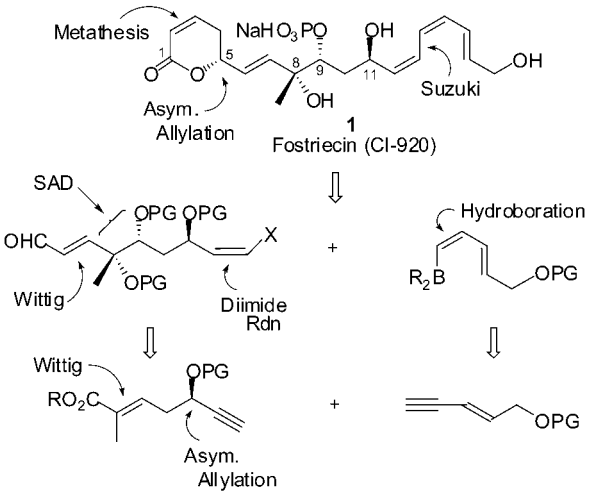
Fostriecin (CI-920)

The title compound, a potent protein phosphatase inhibitor and anticancer agent, was prepared by an efficient, multiconvergent asymmetric synthesis. Key transformations include a ring forming olefin metathesis leading to the α,β-unsaturated lactone and creation of the triene moiety via Suzuki cross-coupling.

Fostriecin (**1**, CI-920), a novel secondary metabolite of *Streptomyces pulveraceus*,[1] displays potent antineoplastic activity in vitro against a diverse panel of tumor cell lines and in vivo toward lymphoid leukemias.[2] More recent investigations revealed that **1** (i) inhibits DNA topoisomerase II by a unique, non-DNA strand cleavage mechanism;[3] (ii) selectively blocks the catalytic subunit of type 2A[4] and 4[5] protein phosphatases (IC_{50} 1.5 and 3 nM, respectively); (iii) ameliorates myocardial infarct size;[6] and (iv) partially protects cardiomyocytes from ischemic injury.[7]

The relative and absolute stereochemistries of **1** were established by a series of elegant spectroscopic[1,8] and degradative[9] studies culminating in total syntheses by Boger et al.[10] and Chavez and Jacobsen.[11] Herein, we describe an efficient and conceptually distinct asymmetric total synthesis[12] of **1** utilizing a multiconvergent strategy designed to postpone introduction of the sensitive unsaturated lactone, phosphate, and triene subunits until advanced stages of the work plan (Scheme 1). Anticipating that natural **1** would be

Scheme 1. Retrosynthetic Analysis



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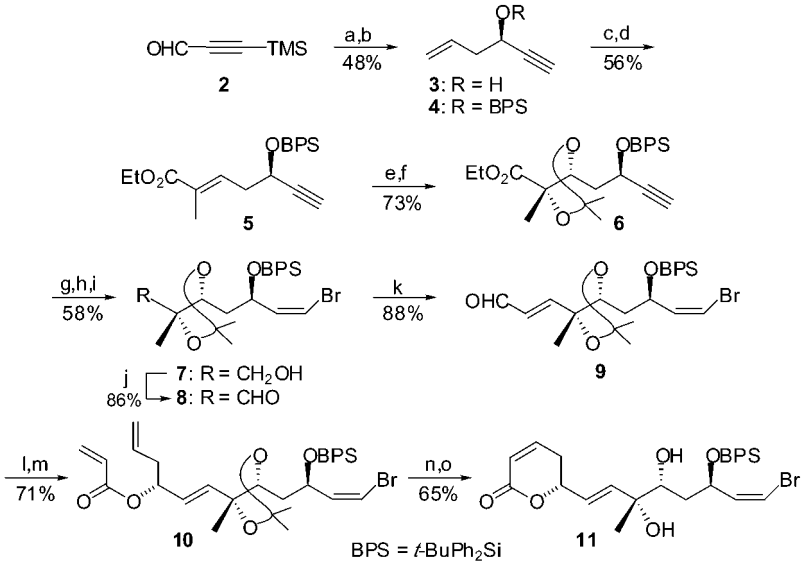
Scheme 2[a]



[a] Reagents and conditions: (a) (+)-Ipc$_2$BOMe, allylmagnesium bromide, Et$_2$O, −100 °C, 1 h; 30% H_2O_2, 3 N NaOH, 0 °C, 12 h; (b) *t*-BuPh$_2$SiCl, ImH, CH_2Cl_2, 23 °C, 4 h; (c) OsO_4, NMO, Me_2CO/H_2O (9:1), 0 °C, 4 h; $NaIO_4/SiO_2$, CH_2Cl_2, 23 °C, 4 h; (d) $EtO_2CC(Me)PPh_3$, C_6H_6, 23 °C, 12 h; (e) AD-mix-*β*, *t*-BuOH/H_2O (1:1), 4 °C, 48 h; (f) 2-methoxypropene, PPTS (cat.), CH_2Cl_2, 23 °C, 8 h; (g) NBS, $AgNO_3$, Me_2CO, 23 °C, 2 h; (h) $(KO_2CN{=})_2$, AcOH, THF, 23 °C, 24 h; (i) $LiAlH_4$, THF, 0° to 23 °C, 3 h; (j) $(ClCO)_2$, DMSO, Et_3N, −78 °C, 2 h; (k) $OHCCHPPh_3$, CH_2Cl_2, 40 °C, 8 h; (l) (+)-Ipc$_2$BOMe, allylmagnesium bromide, Et_2O, −100 to 23 °C, 1.5 h; 30% H_2O_2, pH 7 buffer, 23 °C,12 h; (m) acryloyl chloride, DIPEA, CH_2Cl_2, 0 °C, 2 h; (n) Grubbs's cat., CH_2Cl_2, 23 °C, 12 h; (o) Montmorillonite K 10, CH_2Cl_2, 23 °C, 10 h.

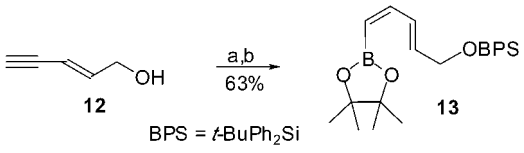
chemically and metabolically labile, we also sought ready access to more robust analogues.[13]

As envisaged in the retrosynthesis above, the C(11)-alcohol was introduced via asymmetric allylation[14] of 3-trimethylsilyl-2-propynal **2**[15] using (+)-*B*-methoxydiisopinocampheylborane and allylmagnesium bromide at low temperature (Scheme 2). Protection of the resultant alcohol **3**[16] (≈ 98% ee) provided silyl ether **4** which was homologated to (*E*)-α,*β*-unsaturated ester **5** by selective oxidative cleavage of the terminal olefin and Wittig condensation with commercial (carbethoxyethylidene)triphenylphosphorane. The stereocenters at C(8) and C(9) were conveniently established via Sharpless asymmetric dihydroxylation[17] (SAD) of the trisubstituted olefin in **5**. Diol protection as the corresponding 1,2-isopropylidene furnished a chromatographically separable mixture (3:1) of **6** and its (*S*),(*R*)-diastereomer. Subsequent terminal alkyne bromination,[18] diimide *cis*-hydrogenation,[19] and LAH reduction of the ester gave rise to alcohol **7** in good overall yield. The final two carbons of the central, linear fragment **9** were added by (triphenylphosphoranylidene)-acetaldehyde homologation of aldehyde **8**, obtained from **7** by Swern oxidation. To construct the α,*β*-unsaturated lactone moiety, **9** was allylated[14] as described above, creating the fourth and final stereocenter at C(5) (≈ 98% de). Acylation of the newly created alcohol with acryloyl chloride evolved **10** and set the stage for a ruthenium-catalyzed ring closing metathesis.[20] Removal of the acetonide using Montmorillonite K 10[21] yielded diol **11**, representing the C(1)−C(13) segment of the total carbon skeleton.

The remaining C(14)−C(18) unit **13** was efficiently secured from 2-(*E*)-penten-4-yn-1-ol (**12**)[22] by alcohol silylation followed by Rh-mediated *trans*-addition[23] of pinacolborane to the terminal acetylene (Scheme 3).

Suzuki−Miyaura[24] cross coupling of **11** and **13** afforded *Z*,*Z*,*E*-diol **14** as the sole product and finalized assembly of

Scheme 3[a]



[a] Reagents and conditions: (a) *t*-BuPh$_2$SiCl, ImH, CH_2Cl_2, 0 °C, 2 h; (b) $[Rh(cod)Cl]_2$, Cy_3P, Et_3N, pinacolborane, C_6H_{12}, 23 °C, 4.5 h.

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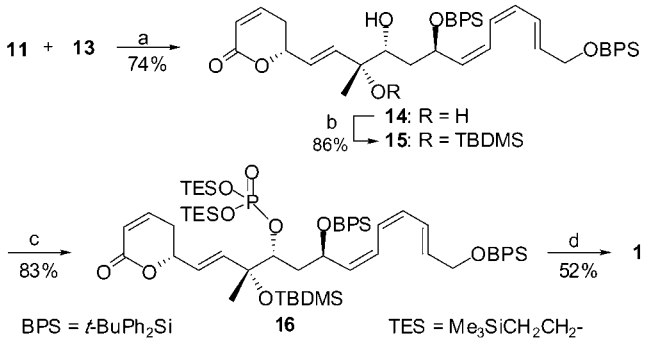
Scheme 4[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, Ag_2O, THF, 65 °C, 8 h; (b) 2,6-lutidine, *t*-$BuMe_2SiOTf$, CH_2Cl_2, −20 °C, 1 h; (c) PCl_3, pyridine, 0 °C, 10 min; $Me_3SiCH_2CH_2OH$, 23 °C, 1 h; 30% H_2O_2, 1 h; (d) HF·py, CH_3CN/H_2O (9:1), 23 °C, 5 d.

the carbon backbone (Scheme 4). Unexpectedly, all efforts to selectively phosphorylate the secondary C(9)-alcohol in **14** resulted in significant amounts of cyclic phosphate involving the tertiary C(8)-alcohol. This was circumvented as recommended by Boger et al.[10] by prior silylation of the interfering hydroxyl using *tert*-butyldimethylsilyl (TBDMS) triflate and 2,6-lutidine to give **15**, thus allowing Evans' three-stage protocol[25] to proceed resulting in bis(2-trimethylsilylethyl)phosphate triester **16.** Global desilylation with excess HF·pyridine at ambient temperature and quenching with $NaHCO_3$ completed the synthesis of **1**, identical in every respect with natural (+)-fostriecin.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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