

Asymmetric Total Synthesis of
(+)-Fostriecin[†]

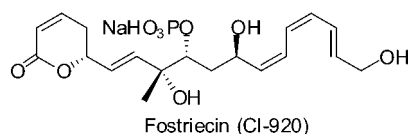
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ABSTRACT



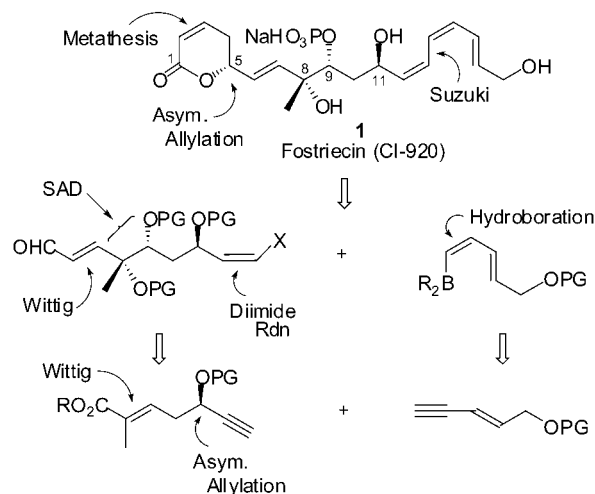
The title compound, a potent protein phosphatase inhibitor and anticancer agent, was prepared by an efficient, multiconvergent asymmetric synthesis. Key transformations include a ring forming olefin metathesis leading to the α,β -unsaturated lactone and creation of the triene moiety via Suzuki cross-coupling.

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 2A⁴ and 4⁵ protein phosphatases (IC₅₀ 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

degradative⁹ 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 synthesis¹² 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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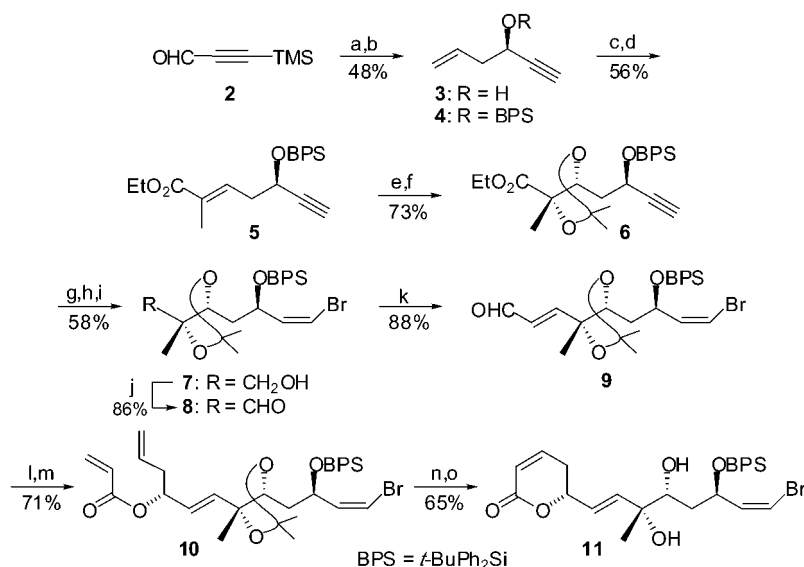
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Scheme 2^a

^a Reagents and conditions: (a) (+)-Ipc₂BOMe, allylmagnesium bromide, Et₂O, -100 °C, 1 h; 30% H₂O₂, 3 N NaOH, 0 °C, 12 h; (b) *t*-BuPh₂SiCl, ImH, CH₂Cl₂, 23 °C, 4 h; (c) OsO₄, NMO, Me₂CO/H₂O (9:1), 0 °C, 4 h; NaIO₄/SiO₂, CH₂Cl₂, 23 °C, 4 h; (d) EtO₂CC(Me)PPh₃, C₆H₆, 23 °C, 12 h; (e) AD-mix-β, *t*-BuOH/H₂O (1:1), 4 °C, 48 h; (f) 2-methoxypropene, PPTS (cat.), CH₂Cl₂, 23 °C, 8 h; (g) NBS, AgNO₃, Me₂CO, 23 °C, 2 h; (h) (KO₂CN=)₂, AcOH, THF, 23 °C, 24 h; (i) LiAlH₄, THF, 0° to 23 °C, 3 h; (j) (ClCO)₂, DMSO, Et₃N, -78 °C, 2 h; (k) OHCCHPh₃, CH₂Cl₂, 40 °C, 8 h; (l) (+)-Ipc₂BOMe, allylmagnesium bromide, Et₂O, -100 to 23 °C, 1.5 h; 30% H₂O₂, pH 7 buffer, 23 °C, 12 h; (m) acryloyl chloride, DIPEA, CH₂Cl₂, 0 °C, 2 h; (n) Grubbs's cat., CH₂Cl₂, 23 °C, 12 h; (o) Montmorillonite K 10, CH₂Cl₂, 23 °C, 10 h.

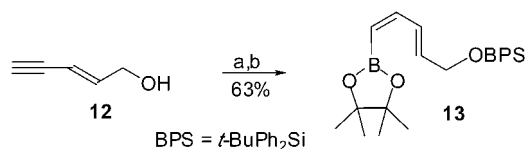
chemically and metabolically labile, we also sought ready access to more robust analogues.¹³

As envisaged in the retrosynthesis above, the C(11)-alcohol was introduced via asymmetric allylation¹⁴ 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 dihydroxylation¹⁷ (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 allylated¹⁴ 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 10²¹ 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*-addition²³ of pinacolborane to the terminal acetylene (Scheme 3).

Suzuki–Miyaura²⁴ 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*-BuPh₂SiCl, ImH, CH₂Cl₂, 0 °C, 2 h; (b) [Rh(cod)Cl]₂, Cy₃P, Et₃N, pinacolborane, C₆H₁₂, 23 °C, 4.5 h.

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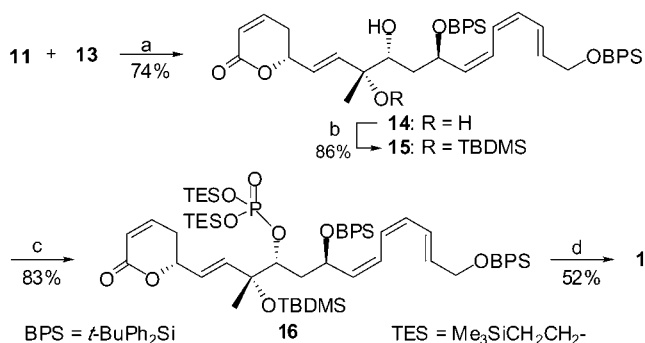
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Scheme 4^a

^a Reagents and conditions: (a) Pd(PPh₃)₄, Ag₂O, THF, 65 °C, 8 h; (b) 2,6-lutidine, *t*-BuMe₂SiOTf, CH₂Cl₂, -20 °C, 1 h; (c) PCl₃, pyridine, 0 °C, 10 min; Me₃SiCH₂CH₂OH, 23 °C, 1 h; 30% H₂O₂, 1 h; (d) HF·py, CH₃CN/H₂O (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 protocol²⁵ to proceed resulting in bis(2-trimethylsilylethyl)phosphate triester **16**. Global desilylation with excess HF·pyridine at ambient temperature and quenching

with NaHCO₃ 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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