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Total Synthesis and Structural Validation of Phosdiecin A *via* Asymmetric Alcohol-Mediated Carbonyl Reductive Coupling

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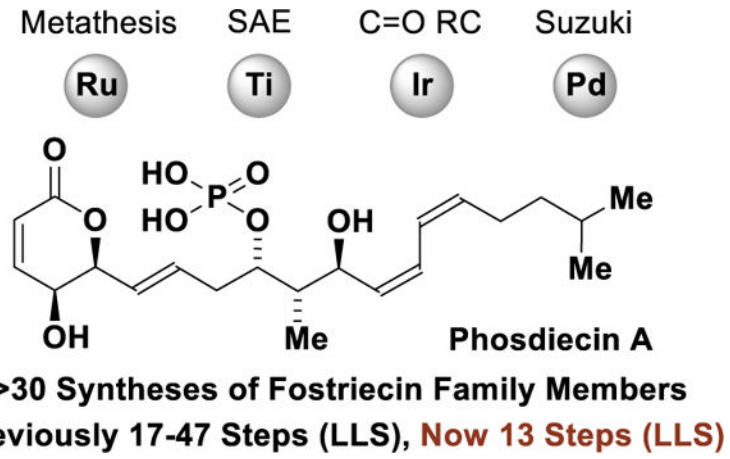
Abstract

The first total synthesis and structural validation of phosdiecin A was accomplished in 13 steps (LLS) through asymmetric iridium-catalyzed alcohol-mediated carbonyl reductive coupling. The present route is the shortest among >30 total and formal syntheses of fostriecin family members.

Graphical Abstract



Fostriecin (CI-920), a metabolite produced by *Streptomyces pulveraceus* isolated from a Brazilian soil sample in 1983,[1] is the forerunner to a ever-growing family of phosphorylated polyketide natural products that modulate signal transduction pathways in mammalian cells, including the regulation of tumor microenvironment functions that support tumor development and protect cancer cells from chemotherapeutic stress.[2] These properties are linked to their protein phosphatase inhibitory action, in particular, the serine/threonine

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Supporting Information Available: 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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phosphatases PP1 and PP2A, which display functional roles that include cell cycle regulation (PP1 and PP2A), RNA splicing (PP1), cell differentiation (PP2A), apoptosis (PP2A), among others.[2] Phase I clinical trials were launched for fostriecin but were halted before the maximum tolerated dose was established, as its instability and unpredictable purity limited supply.[3] In 1992, Ohkuma and coworkers reported the isolation of a metabolite, dubbed sultriecin, from *S. roseiscleroticus* No. L827–7 from an Indian soil sample bearing a related hydroxylated dihydropyranone and a (*Z,Z,E*)-triene linked by an *anti*-1,3-diol tether, which was proposed to incorporate a sulfate moiety at C-9.[4] In 2010, Boger and coworkers reassigned the structure as the C-9 sodium phosphate monoester and established its relative and absolute configuration, renaming it phostriecin.[5] Like fostriecin, phostriecin has garnered interest as a potential chemotherapeutic agent due to its potent and selective inhibition of protein phosphatase 2A (PP2A).[2,5] More recently, Thomasi and coworkers isolated two new phosphorylated polyketides, phosdiecins A and B, from the fermentation broth of *Streptomyces sp.* SS99BA-2 collected on the Brazilian coast.[6] The structural assignment of phosdiecins A and B (including absolute stereochemistry) has not been corroborated by total synthesis and the biological properties of these compounds remain unexplored.

The prospect of developing chemotherapeutic agents based on serine/threonine protein phosphatase inhibition has driven efforts toward the *de novo* chemical synthesis of fostriecin and related phosphorylated polyketide natural products (Figure 1).[7] To date, over 30 total and formal syntheses of “fostriecin family” members have been reported.[7] The reported syntheses of these compounds range between 17–47 steps (LLS) in length. While their complexity is variable and earlier syntheses emphasized structure elucidation, it is clear that the challenges posed by this compound class are not fully resolved. Recently, one of the present authors developed a set of carbonyl reductive couplings and related hydrogen auto-transfer processes that directly convert lower alcohols to higher alcohols.[8] The redox-economy of these processes has been shown to contribute to increased efficiency in polyketide construction.[9] Given the longstanding challenges posed by the synthesis of the fostriecin family of natural products, and to further benchmark the utility of our catalytic methods, a campaign toward phosdiecin A was undertaken. Here, we disclose a 13 step (LLS) total synthesis of phosdiecin A - the shortest among >30 syntheses of fostriecin family members.

Due to uncertainty regarding the structural assignment of phosdiecins A and B, as a prelude to our experimental work DP4+ calculations were undertaken to assess the veracity of the proposed structure (see Supporting Information).[10] In particular, the assignment of relative stereochemistry between the pyran C4–C5 stereotriad with respect to the C9–C11 stereotriad was ambiguous. The computational work validates the relative configuration proposed by Thomasi and coworkers, which emerged from these studies as the most probable stereoisomer. Retrosynthetically, phosdiecin A was envisioned to arise through the convergent assembly of Fragments **A**, **B** and **C** (Figure 2). Fragment **A** was anticipated to be accessible through the Sharpless asymmetric epoxidation (SAE)-kinetic resolution (KR)[11] of furfural adduct **2** (via Achmatowicz reaction) followed by iridium-catalyzed internal redox isomerization.[12] Fragment **B** shows higher complexity due to the C9–C11 stereotriad.[13] For

this fragment, successive use of the present authors carbonyl reductive coupling methodology was employed.[14,15] Specifically, crotylation of the acetylenic aldehyde **6**[14] followed by allylation of the β,γ-stereogenic alcohol **9**[15] was planned. Cross-metathesis of Fragments **A** and **B**, and Suzuki cross-coupling of the resulting vinyl bromide **10** with Fragment **C** would deliver phosdiecin A. Realization of this concise, convergent approach could serve as a prelude to the synthesis of other fostriecin family members, as well as the design of synthetic analogues for structure-activity studies.

Preparation of Fragment **A** begins with addition of vinyl magnesium bromide to furfural **1** (Scheme 1). The resulting allylic alcohol **2** was subjected to conditions for SAE-KR[11] to provide the lactol **3** in 41% yield, 3:1 dr and 92% ee. Next, to install the C4–C5 *syn*-diol, an iridium-catalyzed dynamic kinetic internal redox isomerization was performed.[12] Lactone **4** was obtained in 36% yield as a single stereoisomer (see Supporting Information for determination of relative and absolute stereochemistry). Protection of the secondary alcohol as the PMB-derivative delivers Fragment **A** in a total of four steps (LLS) from furfural **1**.

In pursuit of an efficient route to Fragment **B**, we recently developed the *anti*-diastereo- and enantioselective crotylation of TIPS-protected acetylenic aldehyde **6** through 2-propanol-mediated reductive coupling of α-methyl allyl acetate catalyzed by the iridium-complex (*R*)-Ir-**I**.[14] This reaction was conducted on gram-scale without any erosion in yield or stereoselectivity. To convert the homoallylic alcohol **7** to Fragment **B**, the C11 alcohol was transformed to the PMB ether, the acetylenic TIPS moiety was removed and the resulting terminal alkyne was treated with NBS to form the acetylenic bromide **8**.[16] Selective ozonolytic cleavage of the terminal alkene[17] followed by diimide reduction[18] delivered the vinyl bromide **9**. Finally, direct iridium-catalyzed allylation of the alcohol **9**,[15] which bypasses discrete generation of the configurationally labile chiral α-stereogenic aldehyde, provide Fragment **B** (see Supporting Information for determination of relative and absolute stereochemistry). Here, catalyst-directed diastereoselectivity is amplified by Felkin-Anh selectivity,[19] guiding assembly of the C9–C11 stereotriad with high levels of control (Scheme 2).

With Fragments **A** and **B** in hand, a challenging cross-metathesis was attempted (Scheme 3). This process required extensive experimentation, as the vinyl bromide moiety poses issues of functional group compatibility.[20] Additionally, the vinyl-substituted pyrans are prone to competing olefin isomerization.[21] Ultimately, optimal reaction conditions employing Grubbs 2nd generation catalyst afforded vinyl bromide **10** in 31% yield. Suzuki-Miyaura cross-coupling with Fragment **C**[22] was conducted using McDonald's protocol.[23] The reaction byproducts were most easily removed by subjecting the crude (*Z,Z*)-diene **11** to 1*H*-tetrazole-promoted phosphorylation conditions using diallyl *N,N*-diisopropylphosphoramidite followed by peroxide-mediated oxidation to provide the protected phosphate ester **12** in 56% yield over the two steps.[24] Removal of the PMB protecting group followed by palladium-catalyzed allylic reductive cleavage of the diallyl phosphate ester **12**[25] provided (+)-phosdiecin A as the sodium salt. A work up procedure involving treatment with Dowex-50 provided the protonated material. The spectral data (^{1}H

and ^{13}C NMR) were virtually identical to natural phosdiecin A (see Supporting Information).

In summary, the first total synthesis of phosdiecin A was accomplished in 13 steps (LLS) through asymmetric iridium-catalyzed alcohol-mediated carbonyl reductive coupling. In >30 total and formal syntheses of structurally related natural products, 17–47 steps (LLS) were required. This work validates the initial structure proposed by Thomasi for this natural product.[6] Most importantly, the methods and strategies utilized in the present synthesis should be transferrable to other fostriecin family members and functional analogues. Studies toward this end are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

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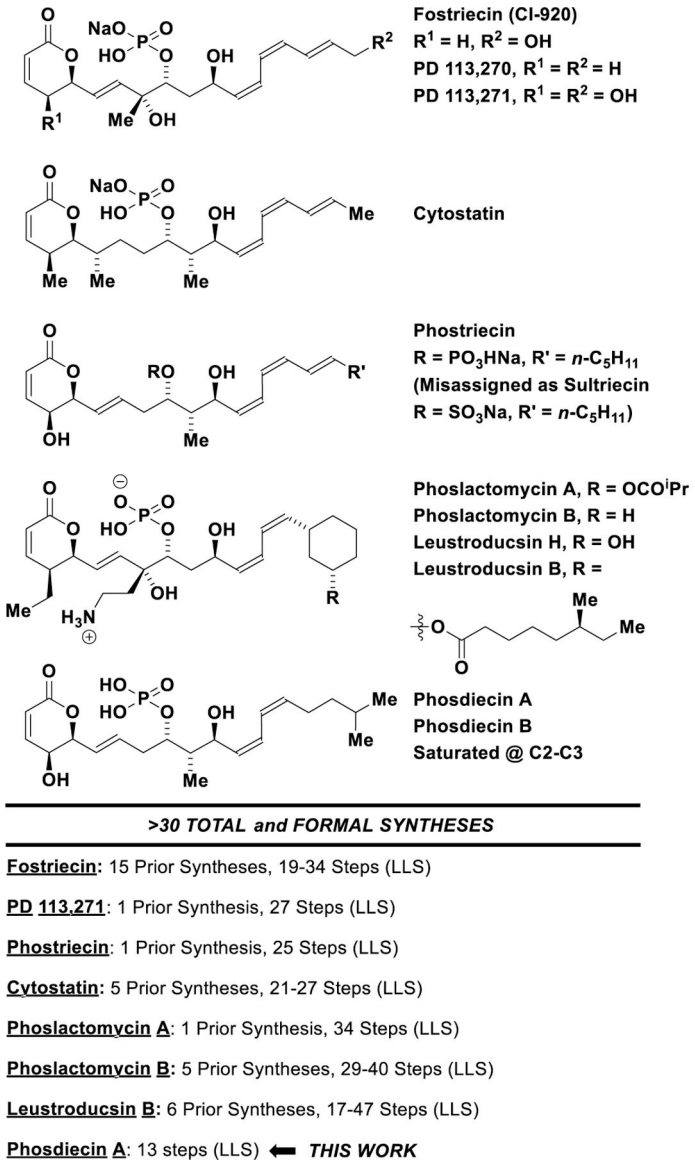


Figure 1.

Total synthesis of fostriecin and related phosphorylated polyketide natural products. LLS = Longest linear sequence. See Supporting Information and ref. 7 for literature references pertaining to the syntheses of the indicated compounds, graphical summaries of their syntheses and a detailed inventory of step count.

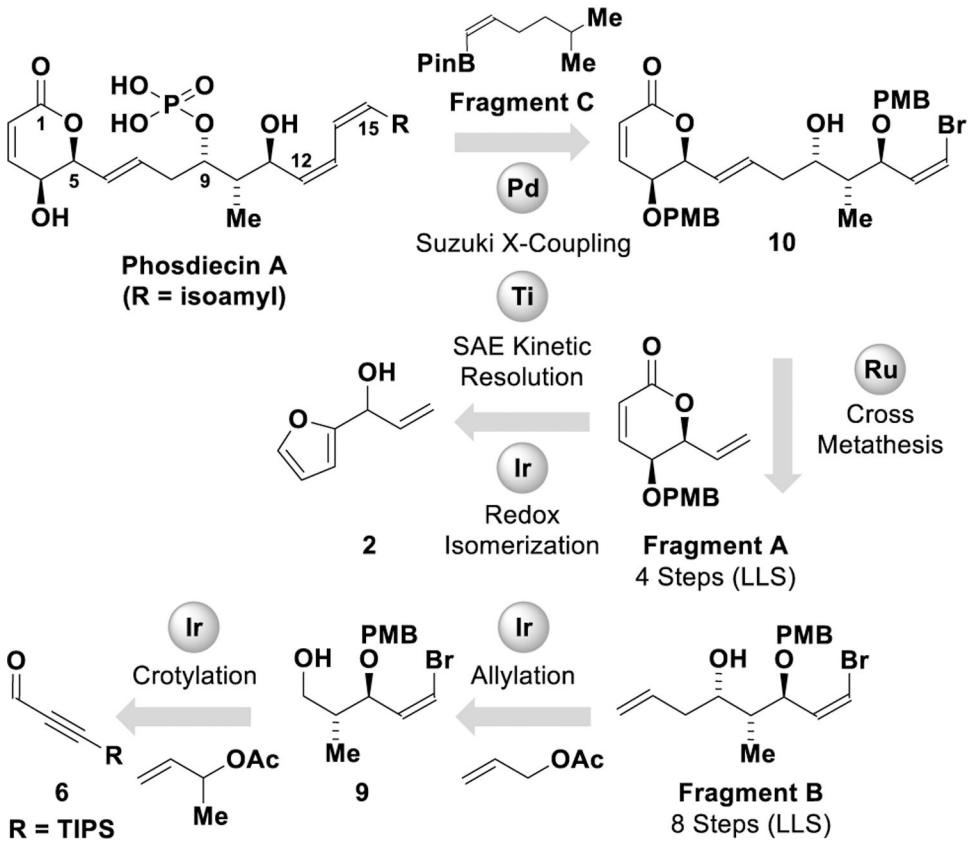
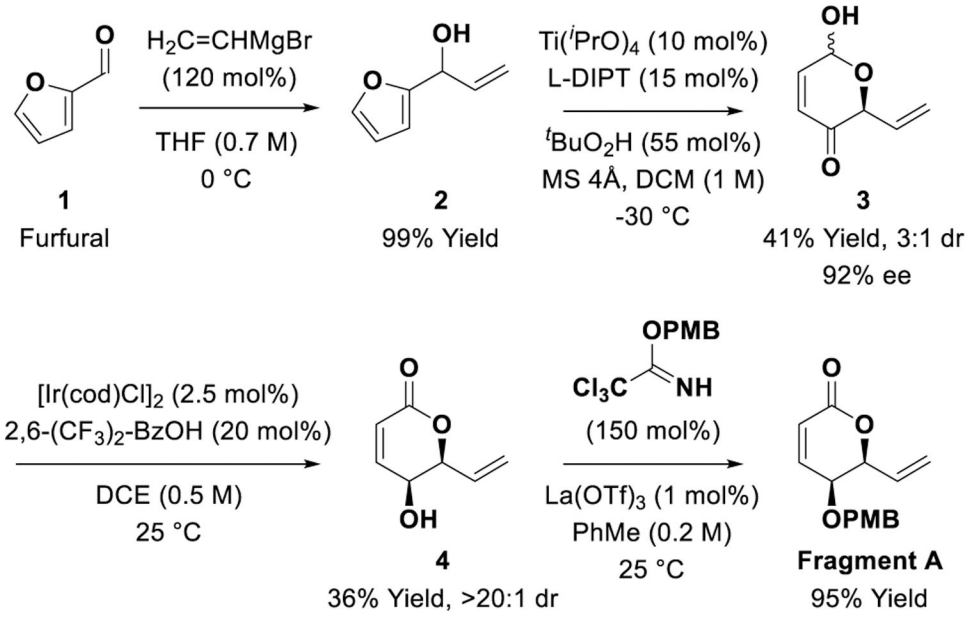


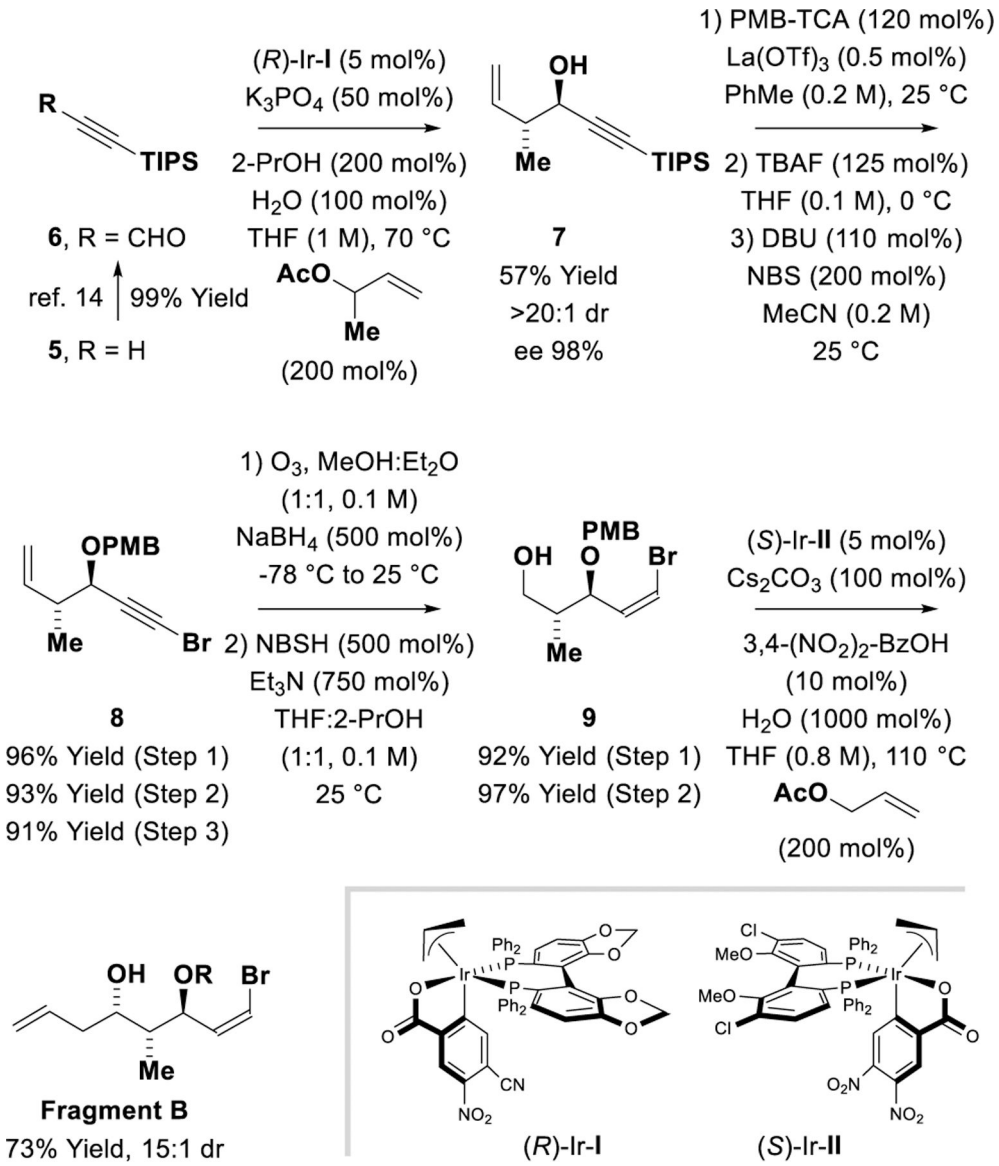
Figure 2.
Retrosynthetic analysis of phosdiecin A.



Scheme 1.

Preparation of Fragment **A**.[a]

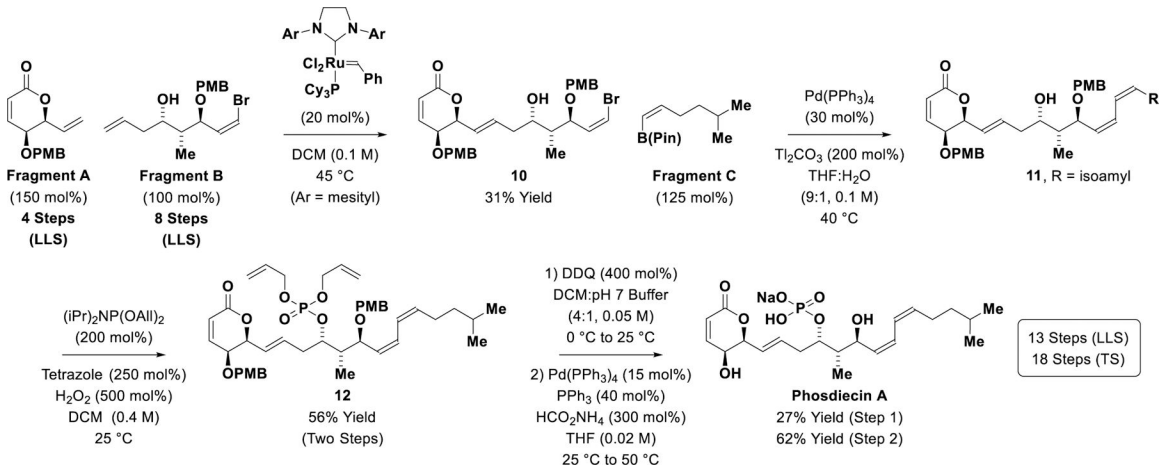
[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for experimental details.



Scheme 2.

Preparation of Fragment **B**.[a]

[a]As described in Scheme 1. See Supporting Information for experimental details.



Scheme 3.

Union of Fragments **A**, **B** and **C** and total synthesis of phosdiecin A.[a]

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for experimental details.