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Total Synthesis of Phoslactomycin A

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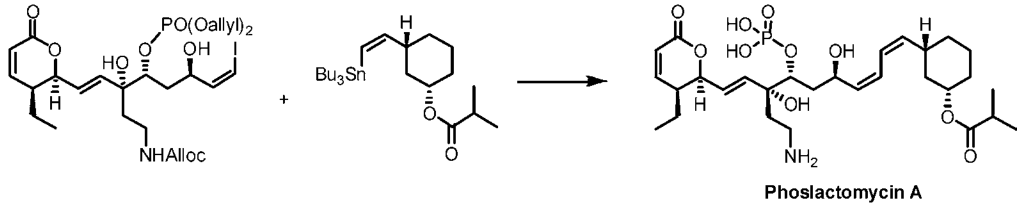
ABSTRACT



A convergent total synthesis of the PP2A-inhibitor phoslactomycin A was achieved using a CuTC-mediated coupling of an alkenyl iodide C1−C13 fragment with an C14−C21 alkenyl stannane in the presence of a protected phosphate. Key features for the assembly of the C1−C13 fragment were an asymmetric dihydroxylation, an Evans−Aldol reaction, and a well-balanced protective group strategy. An asymmetric 1,4-addition to cyclohexenone was the key step in the preparation of the C14−C21 fragment.

Phoslactomycin A, phoslactomycin B, and phoslactomycin F (leustroducsin B) are representative members of the phoslactomycins[1] from *Streptomyces nigrescens* and the leustroducsins[2] from *Streptomyces platensis* (Figure 1). Their various biological activities (induction of colony-stimulating factors, anti-infective, and antitumor) were connected with serine/threonine protein phosphatase 2A inhibition.[3]

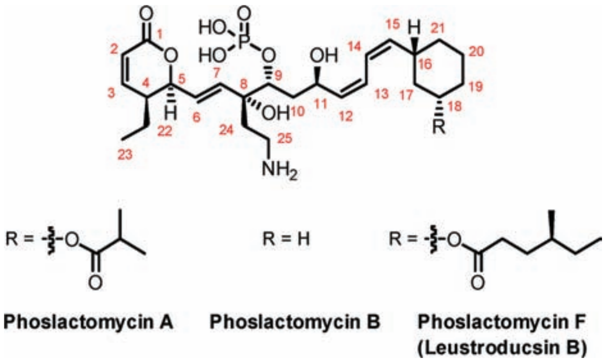


Figure 1. Representative phoslactomycins.

Synthetic efforts in the phoslactomycin field led to total syntheses of phoslactomycin F[4] and phoslactomycin B[5] as well as formal total syntheses of both[6] and a synthesis of the C7−C13 part.[7] Here, we present the first total synthesis of phoslactomycin A.

Our synthetic strategy relied on a very late cross-coupling of an already phosphorylated C1−C13 alkenyl iodide **1** with a C14−C21 stananne **2** (Scheme 1). An Evans−Aldol reaction was chosen for the introduction of the C4,C5 stereocenters and an asymmetric dihydroxylation of a trisubstituted alkene **3** for the formation of the C8,C9 dioxygen functionality. The cis-disubstituted cyclohexane fragment **2** should be prepared via an asymmetric 1,4-addition to cyclohexenone **4**.

The synthesis of the C1−C13 fragment started with a Cu-mediated opening of the epoxide **5**[8] by vinyl-MgBr (Scheme 2). After TIPS protection of the resulting alcohol, oxidative clevage of the alkene gave an aldehyde **6** which was subjected to a Wittig reaction with the phosphorane

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[1] (a) Fushimi, S.; Nishikawa, S.; Shimazu, A.; Seto, H. *J. Antibiot.* **1989**, *42*, 1019–1025. (b) Fushimi, S.; Furihata, K.; Seto, H. *J. Antibiot.* **1989**, *42*, 1026–1036.

[2] (a) Kohama, T.; Enokita, R.; Okazaki, T.; Miyaoka, H.; Torikata, A.; Inukai, M.; Kaneko, I.; Kagasaki, T.; Sakaida, Y.; Satoh, A.; Shiraishi, A. *J. Antibiot.* **1993**, *46*, 1503–1511. (b) Kohama, T.; Nakamura, T.; Kinoshita, T.; Kaneko, I.; Shiraishi, A. *J. Antibiot.* **1993**, *46*, 1512–1519.

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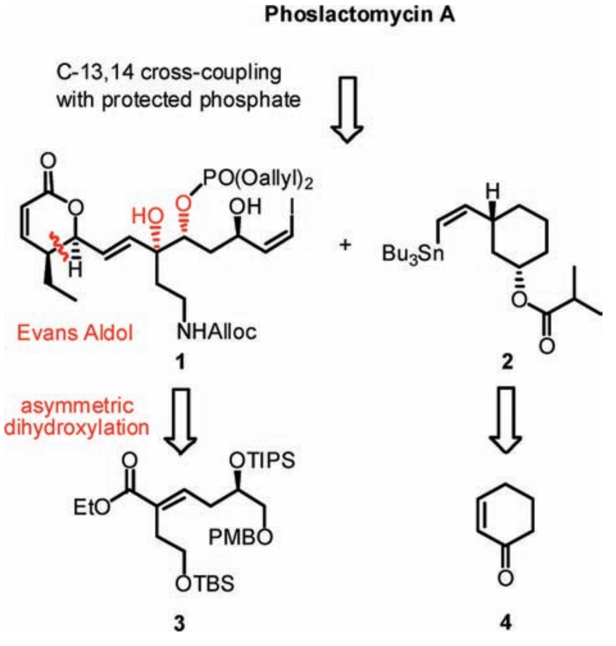
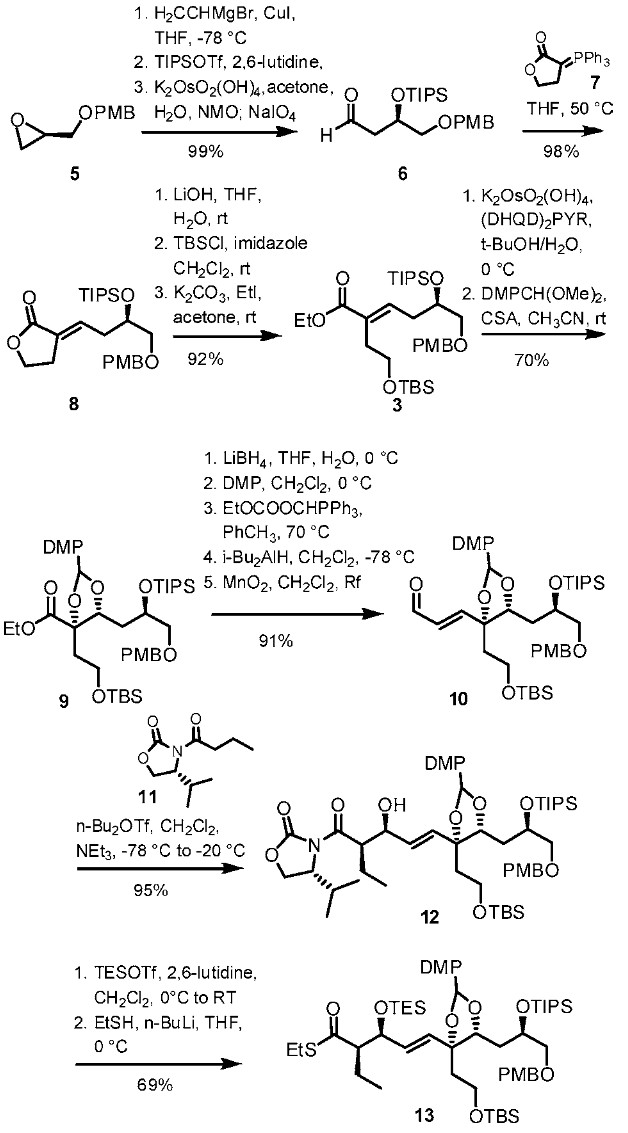
Scheme 1. Retrosynthetic Analysis of Phoslactomycin A



7[9] to yield the alkene **8**. The asymmetric dihydroxylation[10] of the trisubstituted double bond in **7** gave with various ligands (DHQD)$_2$PHAL, (DHQD)$_2$PYR, and (DHQD)$_2$AQN a low diastereoselectivity of maximum 3:1 only. After lactone opening to the ethyl ester **3**, the dihydroxylation using (DHQD)$_2$PYR delivered the desired diol with 9:1 selectivity. The major stereoisomer was chromatographically purified and transformed into the DMP-acetal **9**. Conversion of the ester into an unsaturated aldehyde **10** and a subsequent Evans−aldol reaction[11] (dr 95:5) with the oxazolidone **11** gave alcohol **12**. TES protection and removal of the chiral auxilary led to the thiol ester **13**.

Scheme 2. Synthesis of the C1−C13 Fragment Part I



The synthesis of the C1−C13 fragment continued with the construction of the unsaturated lactone. First, the thiol ester **13** was reduced to the corresponding aldehyde. An Ando olefination[12] of this aldehyde gave the unsaturated ester **14**. Selective deprotection of the TES and TBS silyl ethers led to a diol which cyclized to the six-membered lactone **15** upon treatment with catalytic amounts of Ti(OiPr)$_4$ in refluxing benzene (Scheme 3).

Our protection and functionalization strategy made use of experiences from earlier syntheses[4,5] but differed in the timing for the introduction of the phosphate and the amine. So far the phosphate was introduced at the very end of the synthesis after completion of the carbon skeleton.[4,5] We set out to cross-couple fragments **1** and **2** with the protected phosphate already attached to C9.

A zinc azide mediated Mitsunobu reaction[13] was used to convert the primary alcohol **15** into the corresponding

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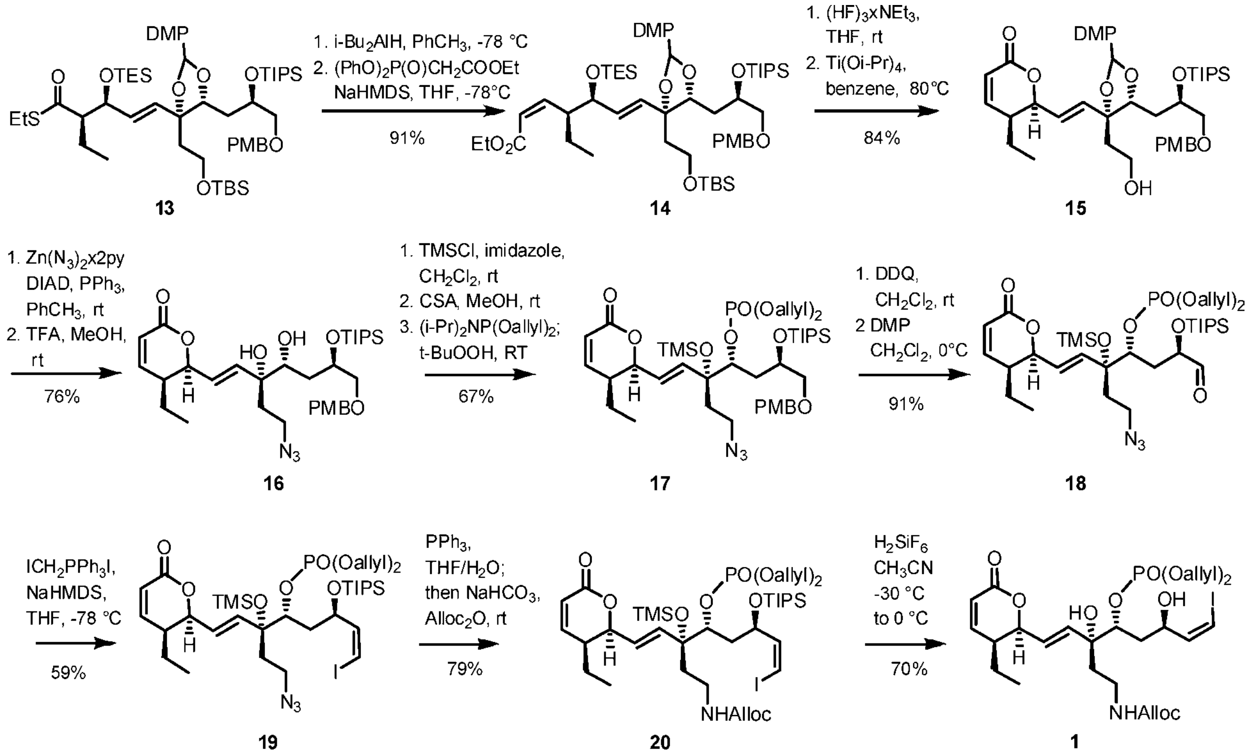
Scheme 3. Synthesis of the C1−C13 Fragment Part II

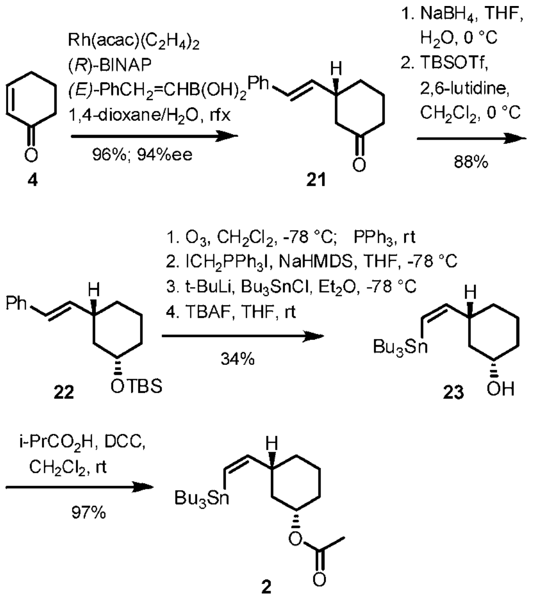


azide. The following cleavage of the DMP acetal to the diol **16** required a careful optimization which finally led to TFA in methanol as the best conditions. Next, the diol was differentiated via formation of the bis TMS ether and subsequent selective cleavage of the secondary TMS ether. The resulting secondary alcohol at C9 was phosphorylated by use of diallyl phosphoroamidite followed by oxidation with *tert*-butyl hydroperoxide.[14]

With the protected C9-phosphate and a C25 azide as latent amine in place, the deprotection of the PMB ether at C12 was addressed next. Treatment of **17** with DDQ delivered the free alcohol, which was oxidized using Dess−Martin conditions[15] to the aldehyde **18**. The latter was converted into the alkenyl iodide **19** according to the Stork−Zhao protocol.[16] The stereoselectivity for this olefination step was >20:1 in favor of the *Z* isomer. The Staudinger reduction of **19** with in situ Alloc-protection gave the carbamate **20**. Compound **20** is a completely functionalized C1−C13 fragment and should be suitable for cross-coupling reactions with the C14−C21 stananne **2**. However, all attempts to use compound **20** in a cross-coupling reaction with a *Z*-alkenylstannanes were unsuccessful. A possible explanation could be the steric shielding of the alkenyl iodide by the bulky TIPS group. Therefore, the TIPS group was removed using 25% aqueous H_2SiF_6 in CH_3CN[17] at −30 → 0 °C, which led to simultaneous removal of the TMS ether at C8 and the formation of compound **1**.

A stereocontrolled 1,4-addition of an alkenyl moiety was chosen for the introduction of the C16 stereocenter (scheme 4). Among the various methods for asymmetric

Scheme 4. Synthesis of the C14−C21 Fragment



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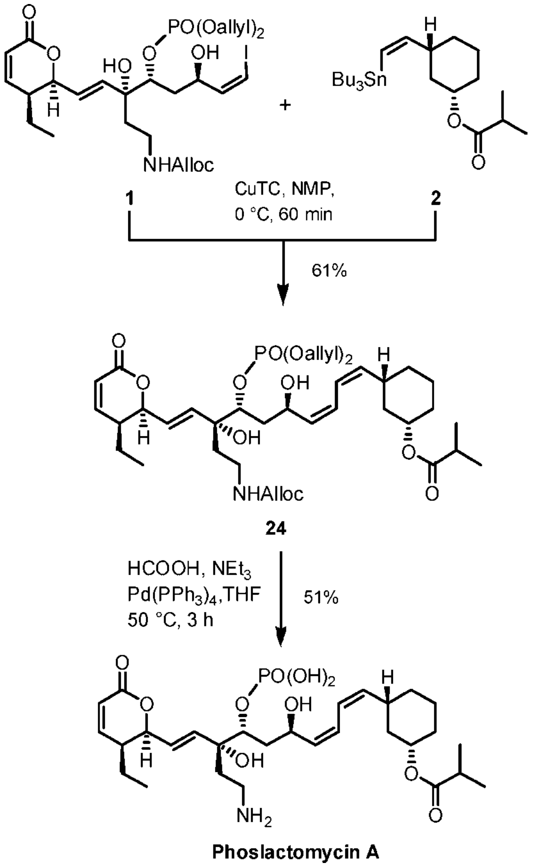
1,4-addition, the Rh-mediated addition of alkenylboronic acids developed by Hayashi stands out in terms of catalyst loading and enantioselectivity.[18] The addition of the *E*-styrylboronic acid to cyclohexenone **4** gave the ketone **21** with very good yield and enantioselectivity. The subsequent $NaBH_4$ reduction followed by TBS protection delivered the alkene **22**. A 7:1 diastereoselectivity in favor of the cis-disubstituted cyclohexane was observed for the reduction step. After ozonolysis of the double bond, the resulting aldehyde was subjected to a *Z*-selective Stork−Zhao olefination. The resulting *Z*-alkenyl iodide was transformed via iodine−lithium exchange into the desired *Z*-alkenylstannane. Removal of the TBS group led to the alcohol **23**, which was esterified to the desired building block **2**.

With both fragments in hand, we turned our attention to the final coupling (Scheme 5). A priori, a Pd-catalyzed Stille reaction[19] or a Cu-mediated Liebeskind coupling[20] are suitable to link an alkenyl iodide with an alkenylstannane. In order to prevent side reactions of the Pd(0) catalyst with the allyl phosphate, we chose Cu(I) thiophene carboxylate CuTC as reagent of choice. The reaction of the C1−C13 alkenyl iodide **1** with the C13−C21 alkenylstannane **2** delivered the desired *Z*,*Z*-diene **24** in 61% yield. After simultaneous removal of the phosphate and amine protective groups with $Pd(PPh_3)_4/HCOOH$[4a] and subsequent RP-HPLC purification, phoslactomycin A was obtained. The spectra and analytical data of the synthetic sample corresponded to those reported for the natural material.[1]

In conclusion, we have reported the first total synthesis of phoslactomycin A. The convergent approach used a CuTC coupling of a C1−C13 fragment alkenyl iodide with a C14−C21 alkenylstannane. The C8,C9 stereocenters were established by an asymmetric dihydroxylation, the C4,C5 centers were formed in an Evans−aldol reaction, and the C16 center was formed by an asymmetric 1,4-addition. The present and the previous[4−6] phoslactomycin syntheses applied protective-group tactics to a synthetic problem with a very high density of different functional groups.

Scheme 5. Final Coupling and Deprotection



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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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