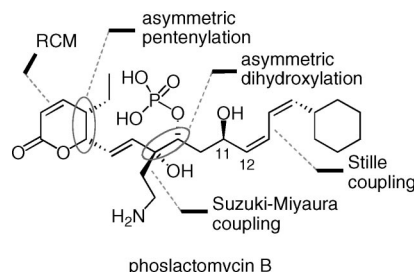


Asymmetric Total Synthesis of
(+)-Phoslactomycin BSetsuya Shibahara, Masataka Fujino, Yasumasa Tashiro, Keisuke Takahashi,
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ABSTRACT



(+)-Phoslactomycin B was synthesized by a highly enantio- and stereoselective approach involving asymmetric pentenylation, Suzuki–Miyaura coupling, ring-closing metathesis, asymmetric dihydroxylation, and Stille coupling. The synthetic method developed enables us to synthesize three other isomers concerning the C11-OH and Δ^{12} -double bond.

The soil bacteria species *Streptomyces* produce a series of structurally novel antifungal and antitumor antibiotics that include phoslactomycins A–F and I,¹ phosphazomycins C₁ and C₂,² leustroducsins A–C and H,^{1e,3} and fostriecin (Figure 1).⁴

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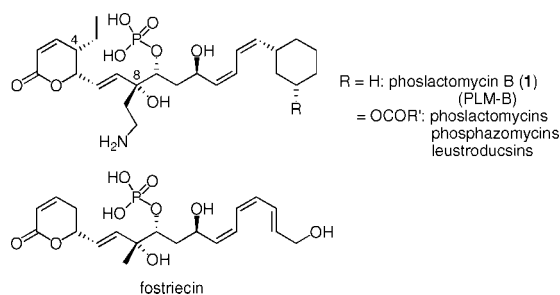
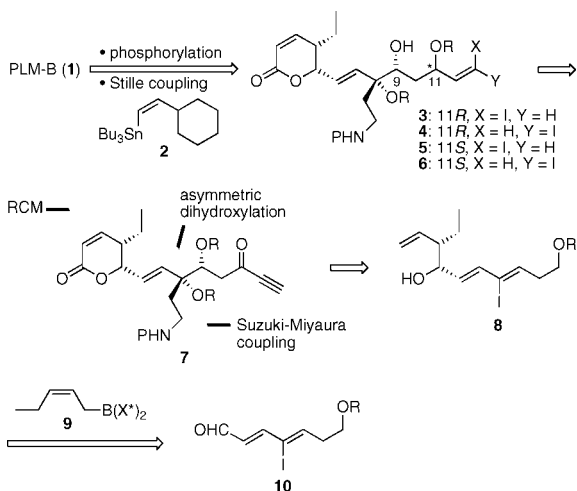


Figure 1. Related phosphate esters produced by *Streptomyces*.

These compounds are highly potent and selective inhibitors of protein serine/threonine phosphatase 2A (PP2A), which is proposed to be responsible for their antitumor activity.^{4–6} Due to their intriguing molecular architectures and the potential as a lead compound for anticancer drugs as well as the importance as a biological tool, this class of compounds has attracted much attention in the chemical and biological communities.⁷ Thus, there have been a number

of synthetic studies including formal and total syntheses of fostriecin,^{8,9} leustroducsin B,^{10,11} and phoslactomycin B.¹² However, apart from fostriecin, additional C4-ethyl, quaternary C8-aminoethyl, and cyclohexyl substituents in their structures hampers the development of an effective route to these natural products. Herein, we describe an efficient asymmetric synthesis of (+)-phoslactomycin B (**1**), which enables us to prepare various analogues required for biological testing as well.

Scheme 1. Retrosynthetic Analysis of Phoslactomycin B

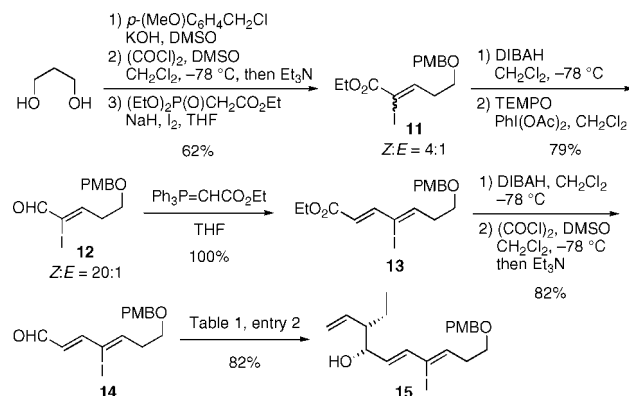


Our synthetic plan is illustrated in Scheme 1. Based on the methodology we have demonstrated in the total synthesis of fostriecin,^{9f} we envisaged ynone **7** as a precursor of

phoslactomycin B (**1**) to make our approach flexible. We expected that advanced intermediate **3** as well as its stereoisomers **4**, **5**, and **6** would each be available from **7** by the combination of stereoselective formation of the *E*- or *Z*-iodoenone and 9-OH directed anti- or syn-selective reduction. To access **7**, we envisaged the approach from alcohol **8** involving Suzuki–Miyaura coupling,¹³ ring-closing metathesis,¹⁴ and Sharpless asymmetric dihydroxylation¹⁵ as major transformations. In this synthetic plan, the first key issue to be addressed is, therefore, the enantio- and stereocontrolled construction of alcohol **8**. We envisaged that reaction of aldehyde **10** with chiral (*Z*)-2-pentenylborane or boronate **9** would proceed in the same fashion as Brown's or Roush's asymmetric crotylation^{16,17} to produce **8** in desired diastereo- and enantioselectivity, although such asymmetric pentenylation was unprecedented.

Our synthesis of **1** thus began with the enantio- and stereoselective preparation of alcohol **15** (Scheme 2). 1,3-

Scheme 2. Synthesis of Alcohol **15**



Propanediol was first converted to iodoalkene **11** as a 4:1 *Z/E*-mixture by a three-step sequence involving *p*-methoxybenzylation, Swern oxidation, and Horner–Emmons reaction using in situ generated triethyl iodophosphonoacetate.¹⁸ Upon DIBALH reduction followed by TEMPO oxidation, **11** afforded *Z*-aldehyde **12** in high geometrical purity (20:1), so that the moderate *Z/E*-selectivity of the iodolalkenylation step did not become a serious problem. It is important to note

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(10) Shimada, K.; Kabburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 4048–4049. The first synthesis was achieved in 0.07% overall yield in 47 steps exclusive of the manipulation on the cyclohexane ring.

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(12) Wang, Y.-G.; Takeyama, T.; Kobayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3320–3323. The first synthesis was achieved in 0.61% overall yield in 40 steps exclusive of the manipulation on the cyclohexane ring.

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that Dess–Martin and Swern oxidation conditions did not promote the above-mentioned isomerization effectively. Wittig reaction of **12** with $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ produced ester **13** stereoselectively, which was then subjected to DIBALH reduction and Swern oxidation to afford **14** in good yield.

The key asymmetric pentenylation of **14** was first examined following the procedures for asymmetric crotylation developed by Brown et al.¹⁶ (Table 1). When the reaction

Table 1. Asymmetric Pentenylation of **14**

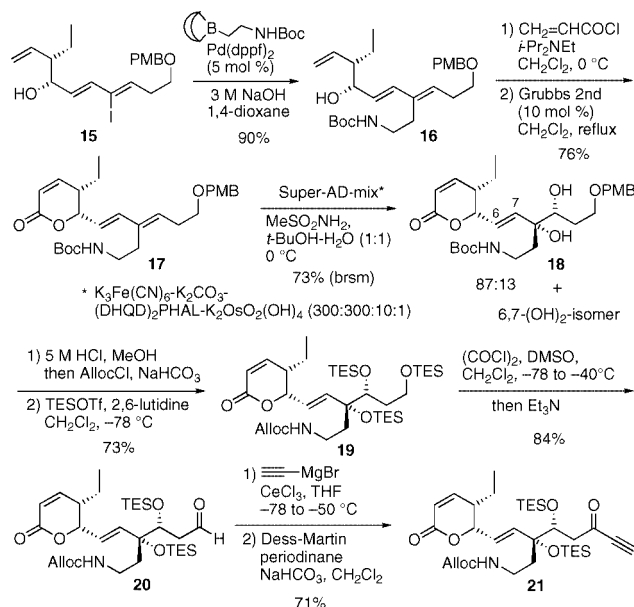
entry	method ^a	yield ^b (%)	syn/anti ^{c,d}	ee (%) (config) ^e
1	A	98	25/75	not determined
2	B	82	100/0	93 (<i>S,S</i>)
3	C	79	100/0	46 (<i>S,S</i>)

^a Method A: (*Z*)-2-pentenyl bromide, Mg, Et₂O, −20 °C, then (+)-(Ipc)₂BOMe, −78 °C to rt, then **14**, toluene, −78 °C. Method B: (*Z*)-2-pentene, *t*-BuOK, *n*-BuLi, THF, −78 °C, then (+)-(Ipc)₂BOMe, BF₃·Et₂O, **14**, THF, −78 to −50 °C. Method C: (*Z*)-2-pentene, *t*-BuOK, *n*-BuLi, THF, −78 °C, then B(O-*i*-Pr)₃, then 1 M HCl, D-DIPT, then **14**, toluene, −78 °C. ^b Isolated yield. ^c Determined by ¹H NMR analysis of the product. ^d Determined by NOE analysis of **17** and its C4-epimer. ^e Determined by ¹H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters as well as HPLC analysis of **17** using a chiral column.

was conducted using the pentenylborane reagent prepared from 2-pentenylmagnesium bromide and (+)-(Ipc)₂BOMe, a 1:3 syn/anti-mixture was unexpectedly obtained although the yield was almost quantitative (entry 1). This result suggests that a partial isomerization would take place during the preparation of the Grignard reagent from (*Z*)-2-pentenyl bromide. However, to our delight, the use of the reagent prepared from 2-pentenylpotassium and (+)-(Ipc)₂BOMe allowed highly diastereo- and enantioselective pentenylation to give (*S,S*)-syn-isomer **15** in 100% de and 93% ee in 82% yield (entry 2). In the reaction employing the (*Z*)-2-pentenylboronate following Roush's protocol,¹⁷ the enantioselectivity was unsatisfactorily low, although the diastereoselectivity was perfect (entry 3).

Assembly of ynone **21**, a pivotal intermediate, was achieved from **15** in completely stereoselective fashion as illustrated in Scheme 3. Suzuki–Miyaura coupling¹⁹ of **15** with 9-(*N*-Boc-aminoethyl)-9-BBN prepared from *tert*-butyl vinylcarbamate effectively introduced the C8-aminoethyl appendage to give amino alcohol **16**. After acryloylation of **16**, the resulting acrylate was subjected to ring-closing metathesis²⁰ using the second generation Grubbs' catalyst in boiling CH₂Cl₂ to afford unsaturated lactone **17** cleanly. Upon reaction of **17** with Super-AD-mix^{21,22} using (DHQD)₂-PHAL as a chiral ligand in aqueous *t*-BuOH at 0 °C, highly diastereoselective dihydroxylation occurred preferentially at the Δ⁸-double bond to give diol **18** and its 6,7-dihydroxy isomer in a ratio of 87:13. However, very high regioselectivity was not observed in this case unlike the similar dihydroxylation in our previous synthesis of fostriecin.^{9f} Interestingly, diol **18** was found to be enantiomerically pure despite the use of **17** (93% ee) as a starting material,

Scheme 3. Synthesis of Ynone **21**



suggesting the concomitant kinetic resolution²³ of **17** during the dihydroxylation reaction. Successive acidic hydrolysis followed by allyloxycarbonylation in the same flask converted **18** to the triol which was silylated to give tri-TES ether **19** in good yield. Exposure of **19** to Swern oxidation conditions²⁴ allowed the direct production of aldehyde **20** via selective cleavage of the primary triethylsilyl ether group. Aldehyde **20** thus obtained was then converted to ynone **21** by ethynylation followed by Dess–Martin oxidation.

According to the procedure we have previously established,^{9f} **21** was converted to advanced intermediate **25** and three other isomers **26**, **27**, and **28** (Scheme 4).

Thus, treatment²⁵ of **21** with 2 equiv of NaI and 1.1 equiv of acetic acid in acetone at room temperature produced a chromatographically easily separable 92:8 *Z/E*-mixture of **22** and **23** in nearly quantitative yield. When this reaction was conducted using NaI (2 equiv) in acetic acid, thermodynamically more stable *E*-isomer **23** was obtained exclusively. After selective desilylation of **22**, reduction of aldol **24** with Me₄NB(OAc)₃H proceeded with excellent anti-selectivity²⁶ to afford 11*R*-diol **25** almost quantitatively. On the other hand, NaBH₄ reduction of **24** in the presence of Et₃B²⁷ gave

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(22) Dihydroxylation employing AD-mix-β turned out to be unsatisfactory in terms of reproducibility.

(23) This phenomenon was also proved by the enantiomeric purity of the recovered **17** (59% ee).

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21 $\xrightarrow[\text{acetone}]{\text{NaI (2 equiv), AcOH (1.1 equiv)}}$ 22 (22:23 = 92:8) (98%)

22 $\xrightarrow[\text{AcOH}]{\text{AcOH-THF-H}_2\text{O (3:3:1)}}$ 24 (89%)

24 $\xrightarrow[\text{AcOH, MeCN, -10 } ^\circ\text{C}]{\text{Me}_4\text{NBH(OAc)}_3}$ 25 (96%)

25 $\xrightarrow[\text{THF-MeOH (6:1), -78 } ^\circ\text{C}]{\text{NaBH}_4, \text{Et}_3\text{B}}$ 26 (74%)

26 $\xrightarrow[\text{MeCN-THF (4:1)}]{\text{Pd(MeCN)}_2\text{Cl}_2 (30 \text{ mol } \%), \text{Bu}_3\text{Sn-2}}$ 29 (81% brsm)

29 $\xrightarrow[\text{CH}_2\text{Cl}_2, 0 } ^\circ\text{C}]{\text{1) TBSOTf, 2,6-lutidine, CH}_2\text{Cl}_2, -78 } ^\circ\text{C}; \text{2) (CH}_2=\text{CHCH}_2\text{O)}_2\text{PN(i-Pr)}_2, \text{1H-tetrazole, CH}_2\text{Cl}_2, \text{then 30\% H}_2\text{O}_2, 0 } ^\circ\text{C}}$ 30 (89%)

30 $\xrightarrow[\text{H}_2\text{O-MeCN (4:1:2:20)}]{\text{47\% HF-pyridine-}}$ 31: R = TES; 32: R = H (51%)

31 $\xrightarrow[\text{H}_2\text{O, CH}_2\text{Cl}_2, 0 } ^\circ\text{C}]{\text{n-Bu}_3\text{SnH, PdCl}_2(\text{PPh}_3)_2 (5 \text{ mol } \%)}$ 32 (73%)

32 $\rightarrow$ PLM-B (1)

Having secured reliable routes to attain **25** and all of its isomers including the C11 stereocenter and Δ^{12} -double bond, we then moved on to the final stage toward the total synthesis of phoslactomycin B (**1**). In this particular case, Stille coupling²⁸ of **25** with stannane **2**²⁹ was low yielding under various conditions. However, we eventually found a reliable method which gave **29** with good reproducibility. Namely, when **25** was reacted with **2** in the presence of 0.3 equiv of Pd(MeCN)₂Cl₂ in MeCN–THF (4:1) at room temperature for 1 h, **29** was obtained in 46% yield along with the clean recovery of **25** (43%). After separation, the recovered **25** was again subjected to the above-mentioned coupling conditions. As a result of this sequence, **29** was obtained in >60% yield. Upon selective silylation of the C11-OH and phosphorylation of the C9-OH, **29** afforded phosphate **30** in good yield. Finally, desilylation of **30** using HF–pyridine–H₂O–MeCN³⁰ followed by Pd(0)-catalyzed deallylation¹²

In conclusion, we have accomplished a total synthesis of (+)-phoslactomycin B from 1,3-propanediol in 26 steps in 1.3% overall yield. The synthetic method developed is flexible and of potential value for the preparation of various analogues. The synthesis of stereoisomers of **1** from **26**, **27**, and **28** is currently under investigation.

Acknowledgment. This work was partly supported by Grant-in-Aid for Scientific Research of Japan Society for the Promotion of Science (JSPS) and The Ministry of Education, Culture, Sports, Science and Technology (MEXT). We thank Professor Yuichi Kobayashi (Tokyo Institute of Technology) for the ^1H and ^{13}C NMR spectra of phoslactomycin B.

Supporting Information Available: Experimental details for all new compounds and ^1H and ^{13}C NMR spectra for **1**, **2**, and **11–32**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(30) Exposure of **30** to the desilylation conditions over 3 h caused appreciable decomposition of **32**. The optimal procedure to obtain **32** involves a 2 h reaction of **30** and another 2 h reaction of **31** formed together with **32** in the first desilylation (see the Supporting Information).