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Total Synthesis and Stereochemistry of the Antitumor Antibiotic PD 113,271

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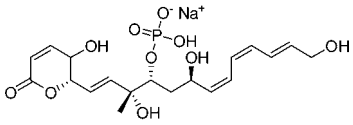
ABSTRACT



A total synthesis of PD 113,271, an antitumor fostriecin analogue isolated from *Streptomyces pulveraceus*, was achieved by the chiral pool approach starting with D-galactose and L-tartaric acid. The synthesis of PD 113,271 led to unambiguous assignment of the relative and absolute stereochemistry of its stereocenters.

PD 113,271 (**1**), which is a 4-hydroxy analogue of fostriecin (CI-920, **2**), was isolated in 1983 by Tunac and co-workers from a fermentation broth of *Streptomyces pulveraceus* subsp. *fostreus* ATCC 31906 (Figure 1).[1,2] Compound **1** exhibits excellent cytotoxic activity against a mouse leukemia (L1210, IC_{50} = 1.8 μM) and a human ileocecal carcinoma (HCT-8, IC_{50} = 9.0 μM) in vitro, and it also exhibits potent antitumor activity against L1210 and P388 leukemia in vivo.[3] It has been reported that PD 113,271 inhibits the enzyme topoisomerase II with an MIC of 12.5 μM in an in vitro assay.[4] There have been several reports of total synthesis of fostriecin (**2**) as well as many biological studies on **2**, including descriptions of its mechanism of action.[5−7] However, little is known about PD 113,271 (**1**). Since there are neither synthetic nor degradation studies reported for **1**, the complete relative and absolute configurations of **1** have not

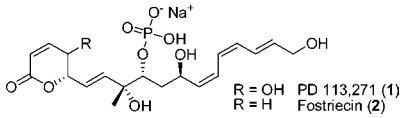


Figure 1. Structures of PD 113,271 (**1**) and fostriecin (**2**).

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yet been established.[1c,2,8] To confirm the configurations and examine the structure activity relationships, total synthesis of **1** is required. Herein we report the synthesis of PD 113,-271 and establish that its stereochemistry is 4*S*,5*S*,8*R*,9*R*,-11*R* in **1**.

In planning the synthesis, we drew from knowledge of the structurally related natural products fostriecin (**2**),[2,5,6,8] phomalactone (**3**),[9] and 4-*epi*-phomalactone (**4**),[10] whose absolute and relative configurations have been determined by NMR spectroscopy, degradation studies, and total synthesis (Figure 2). Since **1** should be synthesized via biosyn-

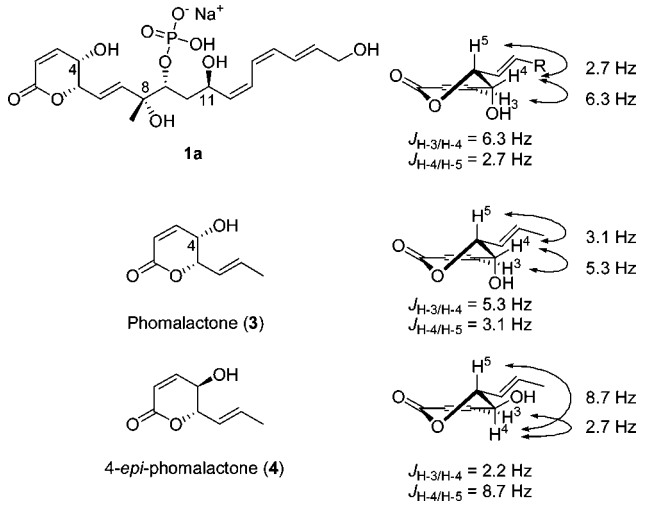

Figure 2. Speculations about the absolute configuration of PD 113,271 (**1**) based on the NMR data for phomalactone (**3**) and 4-*epi*-phomalactone (**4**).

thetic pathways that are similar to **2**, the absolute configurations at C5, C8, C9, and C11 of **1** might be *S*, *R*, *R*, and *R*, respectively, the same as the stereochemistry of **2**. The *syn* relationship between C4 and C5 of **1** was deduced based on the reported coupling constants ($J_{H-3/H-4}$ = 6.3 Hz, $J_{H-4/H-5}$ = 2.7 Hz) of **1**,[1c] which are similar to those of **3** ($J_{H-3/H-4}$ = 5.3 Hz, $J_{H-4/H-5}$ = 3.1 Hz, 4,5-*syn*) versus those of **4** ($J_{H-3/H-4}$ = 2.7 Hz, $J_{H-4/H-5}$ = 8.7 Hz, 4,5-*anti*). Thus we deduced that the absolute configuration at C4 might be *S*.

Our retrosynthetic analysis of **1a** is outlined in Figure 3. In this strategy, two unstable units, phosphate monoester and

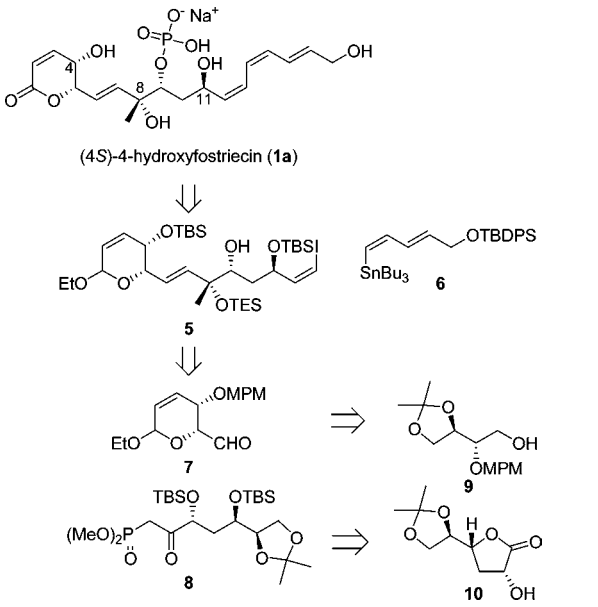

Figure 3. Retrosynthetic analysis of (4*S*)-4-hydroxyfostriecin (**1a**).

triene, should be introduced at the late stages of the synthesis. Further disconnection of the α,β-unsaturated lactone **5** at the C6−C7 bond would lead to an aldehyde **7** and a ketophosphonate **8**. The aldehyde **7** would be derived from alcohol **9**, prepared from L-tartaric acid according to a published method.[11] The ketophosphonate **8** would be prepared from the optically active lactone **10**, which is derived from D-galactose.[12]

Synthesis of the aldehyde **7** is outlined in Scheme 1. The alcohol **9**, which can be readily produced in three steps from dimethyl L-tartrate,[11] was oxidized by a Swern oxidation[13] to give the corresponding aldehyde. Without any further purification, the aldehyde was directly subjected to the *Z*-selective Horner−Emmons reaction[14] to produce the unsaturated ester **11** in 93% yield from **9**. Next was a DIBAL reduction of ester **10** (98% yield) and oxidation of the corresponding allylic alcohol with MnO_2, followed by treatment of the resulting aldehyde with CSA in EtOH to provide **12** (69% yield in two steps). A Swern oxidation of **12** furnished aldehyde **7** with a 97% yield.

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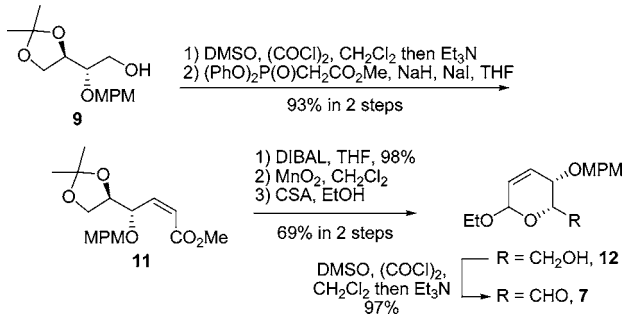
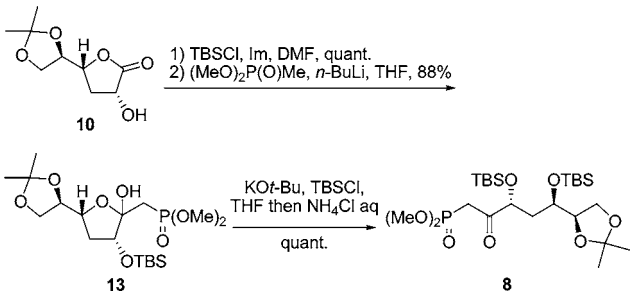
Scheme 1. Synthesis of the Aldehyde **7** from **9**



The synthesis of ketophosphonate **8** is outlined in Scheme 2. TBS protection of an optically active lactone **10**, produced

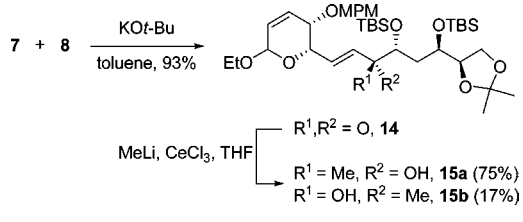
Scheme 2. Synthesis of the Phosphonate **8** from the Lactone **10**



in five steps from D-galactose,[12] then addition of dimethyl methylphosphonate to the lactone, followed by TBS protection[15] of the hemiketal **13** produced the ketophosphonate **8** with an 88% yield in three steps.

A Horner−Emmons reaction of ketophosphonate **8** with aldehyde **7** yielded enone **14**. Addition of MeLi to enone **14** in the presence of $CeCl_3$[5a,16] gave the desired (8*R*)-alcohol **15a** and the undesired (8*S*)-alcohol **15b** in 75% and 17% yields, respectively (Scheme 3). The major diastereomer **15a**

Scheme 3. Synthesis of the C1−C12 Fragment of PD 113,271



is derived from a Felkin−Anh addition mechanism. The relative configuration of C8 and C9 was determined by NOESY experiments of the corresponding acetonide derivative (see the Supporting Information).

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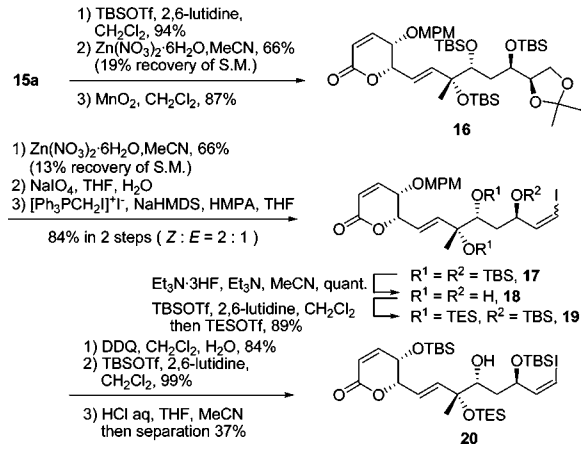
Protection of **15a** as a TBS ether, then deprotection of the ethyl acetal followed by MnO_2 oxidation of the resulting hemiacetal furnished lactone **16** with a 54% yield in three steps (Scheme 4). After deprotection of the acetonide **16**,

Scheme 4. Synthesis of the C1−C13 Fragment of PD 113,271



the resulting diol was oxidized with sodium periodate to give an aldehyde, which was subsequently converted into the vinyl iodide **17** by a Wittig reaction[17] as an inseparable mixture (*E*:*Z* = 2:1) with a 58% yield in three steps. Deprotection of the TBS ether with in situ generated $Et_3N{\cdot}2HF$[18] in acetonitrile afforded triol **18**. TBS protection of the C11 hydroxyl group and sequential TES protection (C8 and C9) of two hydroxyl groups afforded vinyl iodide **19** with an 89% yield in two steps. Deprotection of the MPM ether with DDQ,[19] TBS protection of the C4 hydroxy group, and selective removal of the C8 TES group followed by separation of the *Z*-isomer by silica gel column chromatography furnished the vinyl iodide **20** with a 31% yield in three steps.

A Stille coupling reaction[20] of the vinyl iodide **20** with the known stannane derivative **6**,[21] followed by phosphorylation[22] of the resulting alcohol, gave **21** (Scheme 5). Deprotection of the allyl ester and deprotection of the silyl ether with in situ generated $Et_3N{\cdot}2HF$[18] in acetonitrile provided **1a** as a sodium salt with a 92% yield in two steps. ^1H and ^{13}C NMR spectral data for **1a** were in good agreement with those reported for natural PD 113,271(**1**).[1c,2]

Unfortunately, the optical rotation of natural PD 113,271 (**1**) has not been reported and the authentic sample of natural PD 113,271 (**1**) is no longer available. To confirm the

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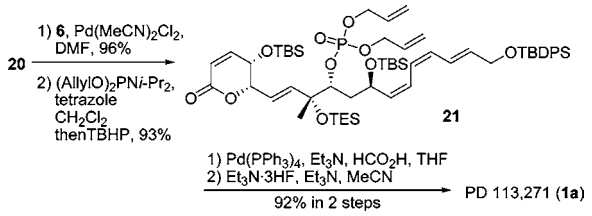
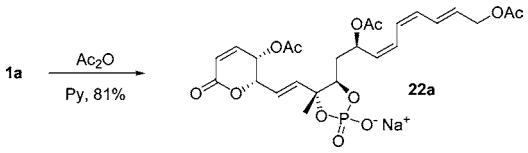
Scheme 5. Total Synthesis of PD 113,271



absolute configuration of **1**, synthetic **1a** was converted into PD 116,251 by acetylation according to the reported procedure,[2b] and the spectral data for synthetic PD 116,251 (**22a**) were compared with those of the authentic natural PD 116,251 sample (Scheme 6). ^{1}H NMR data for our synthetic

Scheme 6. Acetylation of **1a**



22a were in excellent agreement with those of the natural sample. However, the ^{31}P chemical shift of PD 116,251 was observed at 14.5 ppm, which is characteristic of a five-membered phosphate (10−15 ppm) against phosphate monoester (−1 to 6 ppm),[23] indicating that PD 116,251 contains a cyclic phosphate. Furthermore, the molecular formula of **22a**, $C_{25}H_{30}O_{12}NaP$, was established by HRESIMS (calculated for $C_{25}H_{30}O_{12}Na_2P$ ($[M + Na]^+$) to be 599.1264, observed value 599.1258). Although the proposed structure of PD 116,251 is phosphate monoester as depicted in **22**, the structure and the absolute configuration of PD 116,251 were determined to be those shown in **22a** (Figure 4). The formation of a cyclic phosphate might occur during the

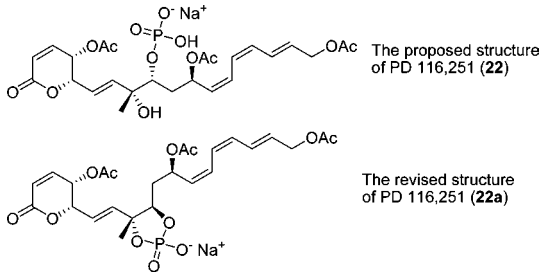


Figure 4. The proposed and revised structure of PD 116,251.

acetylating step.[24] The optical rotation of our synthetic PD 116,251 ($[\alpha]^{24}_D$ +28 (*c* 0.02 in H_2O)) was identical with that of the authentic one ($[\alpha]^{23}_D$ +29 (*c* 0.04 in H_2O)). Thus we confirmed the structural and stereochemical assignments (4*S*,5*S*,8*R*,9*R*,11*R*) of **1**.

In summary, we have accomplished the first total synthesis of PD 113,271 from readily available starting materials using a chiral pool approach, thereby establishing its relative and absolute stereochemistry. The natural product was obtained in a 23-step sequence with an overall yield of 2.9%, starting from the known and easily accessible alcohol **9**. Further synthetic studies to improve the synthetic efficiency as well as biological studies are currently ongoing. Our synthesis and structural determination of **1** now open up opportunities to develop new tools for biological studies and to design new drugs to treat or prevent cancer.

Acknowledgment. We are especially indebted to Pfizer Inc. for providing us the authentic sample of PD 116,251. We gratefully acknowledge Prof. Imanishi and Dr. Miyashita of Osaka University for giving us helpful advice. We thank Prof. Soai and Dr. Kawasaki of Tokyo University of Science for giving us technical support for high-resolution NMR examination.

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

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