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The Relative and Absolute Configuration of PF1140

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Abstract A potentially general approach for elucidating the absolute configuration of *N*-hydroxypyridone antibiotics has been developed. One member of this family of antibiotics, PF1140, was efficiently purified from a crude fungal extract following allylation of its *N*-hydroxyl group. Removal of the resultant allyl group permitted regeneration of the *N*-hydroxyl group as well as conversion into the corresponding pyridone derivative. The stereochemistry of PF1140 including the absolute configuration was established by X-ray crystallographic analysis of the *S*-2-methoxy-2-(1-naphthyl)propionic ester derivative.

Keywords antibiotics, PF1140, absolute configuration, *N*-hydroxypyridone

N-Hydroxypyridone antibiotics such as fusaricide (**1**) [1], pyridoxatins (**2**) [2, 3], leporin B (**3**) [4, 5] and cordypyridones A and B (**4**, **5**) [6] have been isolated from numerous fungi (Fig. 1). These compounds have cytotoxic and antifungal activities, and some may also act as free radical scavengers [2], small molecule modulators of erythropoietin gene expression [5], or anti-malarial drugs [6]. In 1996, an *N*-hydroxypyridone compound with an unspecified relative configuration, PF1140 (**6**), was isolated from *Eupenicillium* and shown to have broad antifungal activity [7]. The *N*-hydroxypyridone group exhibits remarkable affinity for iron(III) under physiological conditions, and thus these compounds are considered to be siderophores [8, 9]. Despite increased interest in *N*-hydroxypyridone antibiotics [10~12], their absolute configuration remains unknown; only the absolute configurations of a pair of cordypyridone atropisomers (**4**, **5**) [6], and of tolypocin [13], have been established to date. Interestingly, the absolute configuration of the cordypyridones is opposite to that of tolypocin; the configurations of the cordypyridone atropisomers were determined by X-ray crystallographic analysis (anomalous scattering methods) of *p*-bromobenzoylated derivatives [6], whereas the crystal structure of tolypocin was determined from an iron(III) tris-chelate complex [13]. During the course of our studies for elucidating of the stereochemistry of **6**, the polarity of the *N*-hydroxypyridone group of **6** hampered the chromatographic purification of **6** from crude extracts. Therefore, we investigated a simple, potentially general method for purifying *N*-hydroxypyridone antibiotics and for elucidating their absolute configuration. A synthetic approach to elucidate the stereochemistry and absolute configuration of **6** is described below.

As depicted in Scheme 1, elucidation of the stereochemistry of **6** by X-ray crystallography involved reduction of the *N*-hydroxypyridone group and subsequent covalent attachment of chiral auxiliaries, producing the crystallizable derivative **10**. Ethyl acetate extracts of *Eupenicillium* sp. PF1140 SL were fractionated on a Sephadex LH-20 column to afford crude **6** [7]. Since allylation of the *N*-hydroxyl group of **6** would generate a less polar derivative amenable to simple purification by silica gel chromatography, **6** was treated with allyl bromide and potassium carbonate in acetone to afford **7**, which was isolated using a silica gel column (eluent: hexane/EtOAc= 3/1). The reverse reaction, the palladium-catalyzed reduction of **7**, regenerated **6** in 97% yield. Exposure of **7** to excess lithium diisopropylamide (LDA) effected the deprotonation of the allyl ether, with subsequent loss of acrolein and net reduction of the *N*-hydroxypyridone group to afford **8** in 88% yield [14]. Condensation of **8** with **9** proceeded selectively at the carbonyl oxygen to afford **10** in

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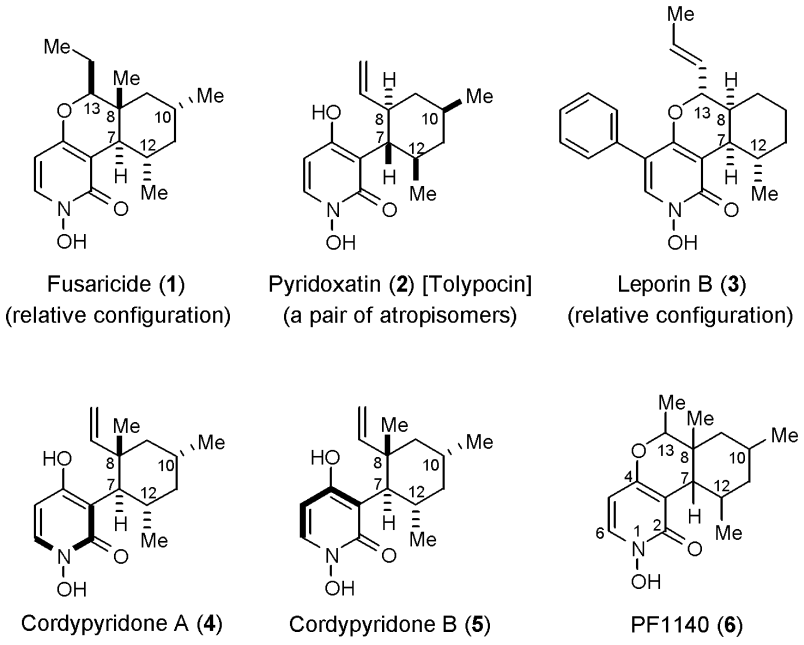
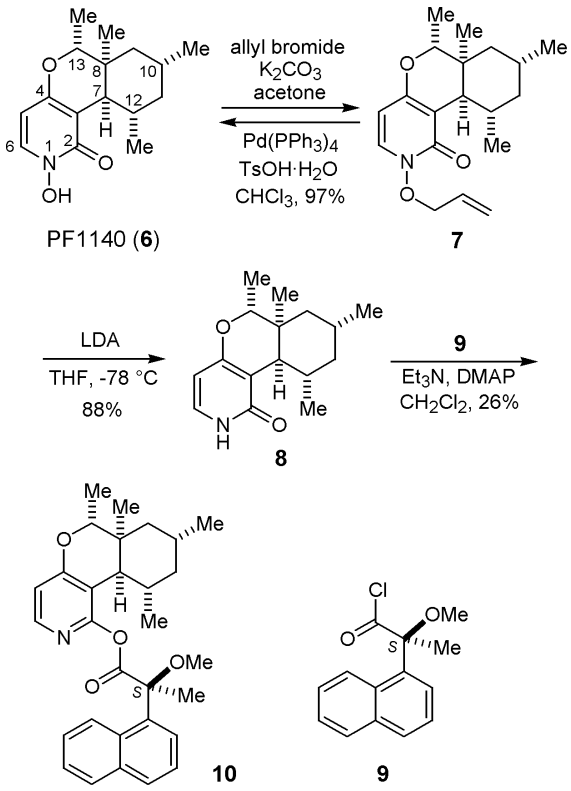


Fig. 1 Structures of *N*-hydroxypyridone antibiotics.



Scheme 1 Isolation of the allylated derivative **7** and conversion into **10**.

26% yield, along with recovered **8** (30%) [15]. Recrystallization of **10** from hexane–$CHCl_3$ provided single crystals suitable for X-ray analysis.

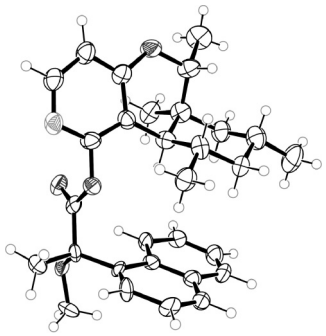
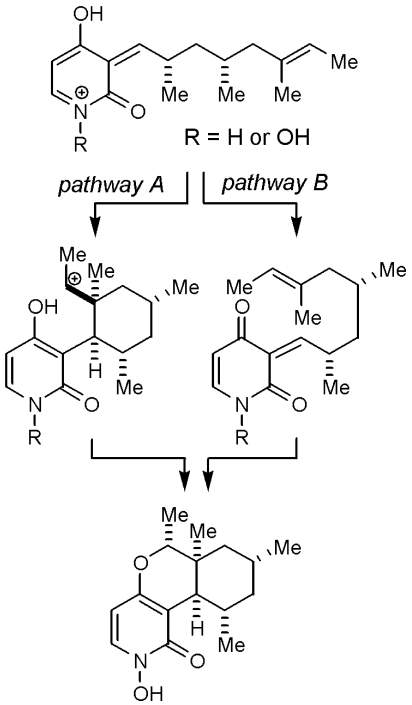


Fig. 2 ORTEP drawing of the X-ray structure of **10**.

In contrast to most reported congeners, which are in the 1,2-*trans* configuration (Fig. 1) at C7-C8, crystallographic analysis of **10** showed a 1,2-*cis* relationship (Fig. 2). To our knowledge, several leporins (including **3**) are the only other *N*-hydroxypyridone antibiotics with this relative configuration [4]. Apart from the C8 and C13 stereocenters, the absolute configuration of **6** is consistent with that of the cordypyridones [6].

Based on the above stereochemical assignments, we hypothesize that the biosynthesis of **6**, with its *cis*-fused carbocyclic skeleton, involves either a stepwise cyclization (pathway A) or a hetero Diels-Alder reaction (pathway B), as illustrated in Scheme 2. The approach described above will be widely applicable to the isolation and determination of the absolute configurations of *N*-hydroxypyridone antibiotics, and to the synthesis of their unnatural analogues. Investigations into the biosynthetic pathway of **6**



Scheme 2 Proposed biosynthetic pathways to PF1140 (**6**).

are currently underway in our laboratory.

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