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Total synthesis and determination of the absolute configuration of FD-838, a naturally occurring azaspirobicyclic product

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ABSTRACT

The first asymmetric total synthesis of FD-838, a naturally occurring azaspirobicyclic product, has been accomplished allowing determination of its absolute stereochemistry.

Pseurotins,[1] synerazol,[2] and azaspirene[3] are natural products possessing a unique azaspirocyclic framework, such as the 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione ring system (Fig. 1). The pseurotins are a small family of secondary microbial metabolites isolated from a culture broth of *Pseudeurotium ovalis* (strain S2269/F) in 1976 by Bloch et al.[1a] Pseurotin A was reported to inhibit chitin synthase by Sterner and co-workers in 1993,[1e] and was also found to induce cell differentiation of PC12 cells by Komagata et al. in 1995.[1f] The structure of pseurotin A, including its absolute stereochemistry, has been unambiguously determined by a single-crystal X-ray analysis of its 12,13-dibromo derivative.[1b] Synerazol, an antifungal antibiotic isolated by Ando and co-workers in 1991 from the culture broth of *Aspergillus fumigatus* SANK 10588, is active against *Candida albicans* and other fungi, showing marked synergistic activity with azole-type antifungal agents.[2] Azaspirene, isolated from the fungus *Neosartorya* sp. by Kakeya and co-workers was found not only to inhibit the endothelial migration induced by vascular endothelial growth factor,[3] but also to exhibit antiangiogenic effects by blocking Raf-1 activation.[4] These compounds possess the same highly oxygenated azaspiro core structure with different side chains. Because of its unique structure and interesting biological properties, there have been several attempts at its total synthesis.[5] Our group has accomplished the first enantioselective total synthesis of pseurotin A,[6] F2,[6] synerazol,[7] and azaspirene,[8] in which the aldol chemistry of a chiral benzylidene lactam with an appropriate aldehyde, followed by successive oxidation and dehydration, creates the key azaspiro structure (Eq. 1). By these syntheses, the absolute configurations of synerazol[9] and azaspirene have been determined. Tadano and co-workers also reported the total syntheses of pseurotin A, F2, and azaspirene from D-glucose.[10]

FD-838, isolated from *A. fumigatus fresenius* F-838 by Mizoue and co-workers of Taisho pharmaceutical company in 1985, is reported to induce the differentiation of leukemia in cultures and to inhibit the growth of certain Gram-positive bacteria and fungi.[11] Recently, Rovis and Orellana reported the synthesis of the spirobicyclic core of FD-838 via the asymmetric Stetter reaction.[12] Its total synthesis has not been accomplished, and its absolute configuration has been unknown, with its optical rotation being reported to be zero ($[\alpha]_D^{26}$ 0 (*c* 0.1, MeOH)).[10] As the fungus no longer produces FD-838, chemical synthesis is the only way to obtain this molecule. Despite the interesting biological properties, biological investigations cannot be performed because of lack of supply of FD-838.

Despite the structural similarity of FD-838, pseurotin A, synerazol, and azaspirene, the reported biological properties of these natural products are rather different, as described above. Systematic comparison of the biological properties of these natural products and their derivatives is highly desirable, and a sufficient quantity of not only the natural products but also several

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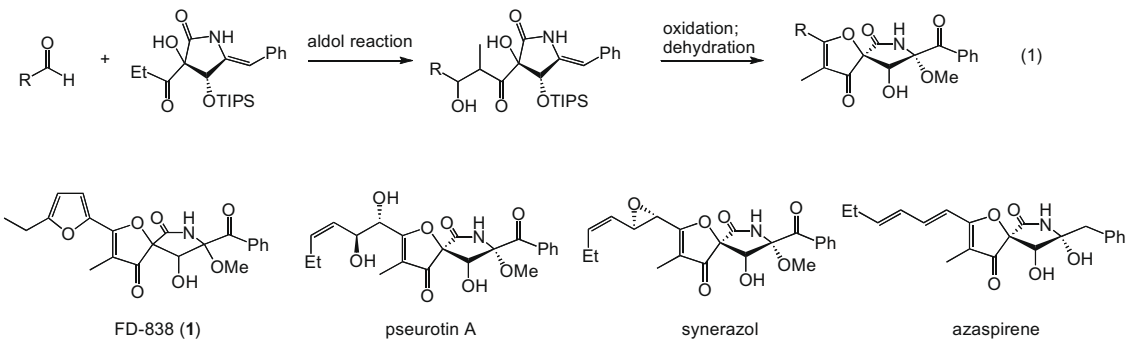
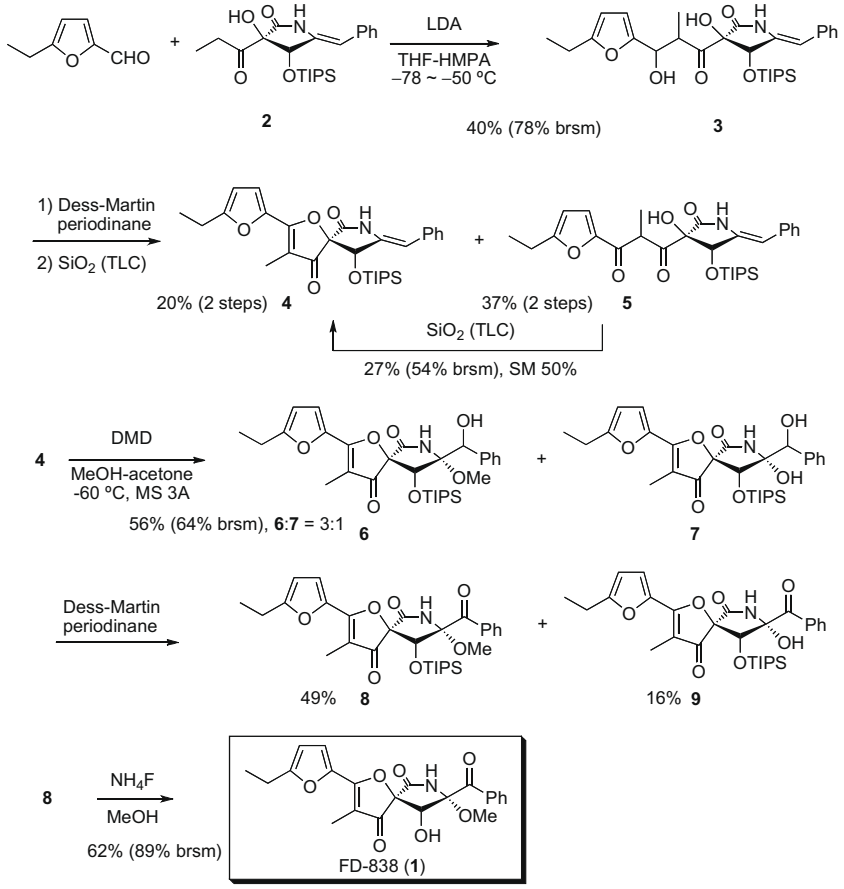


Figure 1. FD-838 (**1**), pseurotin A, synerazol, and azaspirene.

derivatives is required for such biological studies. Because we had established a synthetic method for the latter three natural products, we began to investigate the total synthesis of FD-838. In this communication we report the first total synthesis of FD-838 along with the determination of its absolute configuration.

Because we have already established the synthesis of the azaspirocyclic framework, the same synthetic strategy would be applicable to the synthesis of FD-838. The aldol reaction between 5-ethyl-2-formylfuran and the functionalized benzylidene lactam **2**, which was a key intermediate for other azaspiro compounds prepared from methyl pentenoate via Sharpless dihydroxylation as a key step, was examined.[6–8] The lithium enolate of **2** reacted with 5-ethyl-2-formylfuran, affording the desired aldol product **3** (mixture of four diastereomers, 1:1:3:3.5) in 40% yield with recovery of the lactam **2** in 49% yield (78% yield based on the recovered starting material (br sm)). Oxidation of the alcohol **3** with Dess–Martin periodinane (DMP)[13] in CH_2Cl_2 in the presence of $NaHCO_3$ afforded the 1,3-diketone **5**. When 1,3-diketone **5** was treated with silica gel on TLC, cyclization followed by dehydration proceeded because of the acidity of the silica gel to produce azaspiro derivative **4** in 20% yield with recovery of 1,3-diketone **5** in 37% yield over two steps. Recovered 1,3-diketone **5** was further transformed into azaspiro derivative **4** in 27% yield (54% br sm) by the same reaction conditions. Oxidation of the benzylidene moiety with dimethyldioxirane (DMD)[14] in MeOH afforded a mixture of methoxy derivative **6** and hydroxy derivative **7** in 56% yield (single diastereomers at the benzylic alcohol position), the mixture of which was treated with DMP in CH_2Cl_2 to provide benzoylated methoxy **8** and hydroxy **9** derivatives in 49% and 16% yields, respectively, which can be separated by TLC. Removal of the TIPS group with NH_4F in MeOH afforded FD-838 (**1**) in 62% yield (89%, br sm). Synthetic FD-838 exhibited identical properties to those of the natural substance (^{1}H NMR, ^{13}C NMR, IR).



Scheme 1. The synthesis of FD-838.

Because the optical rotation of natural FD-838 was reported to be zero using MeOH as a solvent,[11] the optical rotation was measured in other solvents, such as $CHCl_3$. The optical rotations of natural FD-838 and synthetic FD-838 show large negative values (synthetic FD-838: $[\alpha]_D^{26}$ −41.9 (*c* 0.4, $CHCl_3$), natural FD-838: $[\alpha]_D^{26}$ −32.4 (*c* 0.7, $CHCl_3$)), indicating that both compounds have the same absolute configuration.[15] Thus, the absolute configuration is determined, as shown in Scheme 1.

In summary, we have accomplished the first asymmetric total synthesis of FD-838 along with the determination of its absolute configuration.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.154.

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