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Stereoselective synthesis of spirofuranone-γ-lactam core of cephalimysin A

Wuxia Zhang [a,b,c], Wenhao Zhu [a,b,c], Dehai Xiao [b,*], Bo Wang [a,b,d,*]

[a] CAS Key Laboratory of High-Performance Synthetic Rubber and its Composite Materials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, Jilin 130022, China
[b] Key Laboratory of Green Chemistry and Process of Jilin Province, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, Jilin 130022, China
[c] University of Chinese Academy of Sciences, Beijing 100049, China
[d] University of Science and Technology of China, Hefei, Anhui 230026, China

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ABSTRACT

Cephalimysin A is a potent anticancer natural product and its structure remains to be fully elucidated. To solve the stereochemical issue, a stereoselective synthesis of its spirofuranone-γ-lactam core was performed in a cascade fashion. The absolute configuration of key spiro stereogenic center was introduced based on D-malic acid derived imide and confirmed by a stereospecific derivatization.

Introduction

Cephalimysin A (**1**, Fig. 1), exhibiting significant cytotoxic activity against P388 and HL-60 cell lines (IC_{50} = 15.0 nM and 9.5 nM, respectively), was isolated by Yamada and co-workers in 2007 from a strain of *Aspergillus fumigatus* originally separated from marine fish *Mugil cephalus* [1]. The core structure of cephalimysin A was deduced by 2D NMR as 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione that also was found in other natural products, such as azaspirene, FD-838, and pseurotin A isolated from different natural sources with diverse biological activities. The relative and absolute stereochemistry of cephalimysin A was originally assigned by chemical derivatization, but the C8 stereocenter was originally inferred as *8R*, and then revised as *8S* in 2010 by comparing the coupling constant of C9 methine proton with cephalimysin B, C, D, and FD-838 (Fig. 1, 9-OH oriented *trans* to 8-OMe, *J* = 4 Hz; *cis* to 8-OMe, *J* = 12 Hz) [2]. To date, several total syntheses of analogues except cephalimysin A itself were described in literatures [3] including the total synthesis of three diastereomers (*8-epi, 9-epi, 8,9-epi*) [4]. However, the exact stereochemistry of cephalimysin A still remains unconfirmed. Therefore, to solve this puzzle we engaged in total synthesis of this potent natural product, and herein disclose a strategy for rapid construction of the spiro furanone-γ-lactam core in all possible configurations.

Retrosynthetically, we envisioned the installation of benzoyl side-chain and configurationally modifiable aminal functionality of cephalimysin A to imide **6** in the end game (Scheme 1). The key spirobicycle of **6** was thus proposed to be generated diastereoselectively from β-ketoimide **7** by forming the C5-O bond avoiding the repulsion of vicinal 9-OPG. **7** could then be simply prepared from 1,3-dicarbonyl compound **8** and D-malic acid derived imide **9** [5].

Our synthesis commenced with Claisen condensation of known ester **10** [6] with methyl propionate **11** to afford β-ketoester **12** in 88% yield (Scheme 2). Ketal protection of the carbonyl of **12** gave ester **13**, which was then converted to aldehyde **14** via reduction/oxidation sequence. The key aldol reaction was conducted between the dianion of **9** [7] and aldehyde **14** to deliver diol **15** as an inconsequential mixture of diastereomers in moderate yield. Selective protection of the 9-hydroxyl with TBS afforded alcohol **16**. The concentration of substrates in this reaction was important for satisfied regioselectivity. Besides, the order of aldol and 9-hydroxyl protection must not be swapped, due to facile elimination of protected 9-hydroxyl of **9** to generate *N*-PMB-maleimide. Subsequent key spirofuranone-γ-lactam formation was achieved by a cascade reaction of **16** in the presence of Dess-Martin periodinane and $Sc(OTf)_3$ and resulted in **17** in 39% yield as diastereomers

* Corresponding authors at: Key Laboratory of Green Chemistry and Process of Jilin Province, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, Jilin 130022, China (B. Wang).
E-mail addresses: dhxiao@ciac.ac.cn (D. Xiao), wangbo@ciac.ac.cn (B. Wang).

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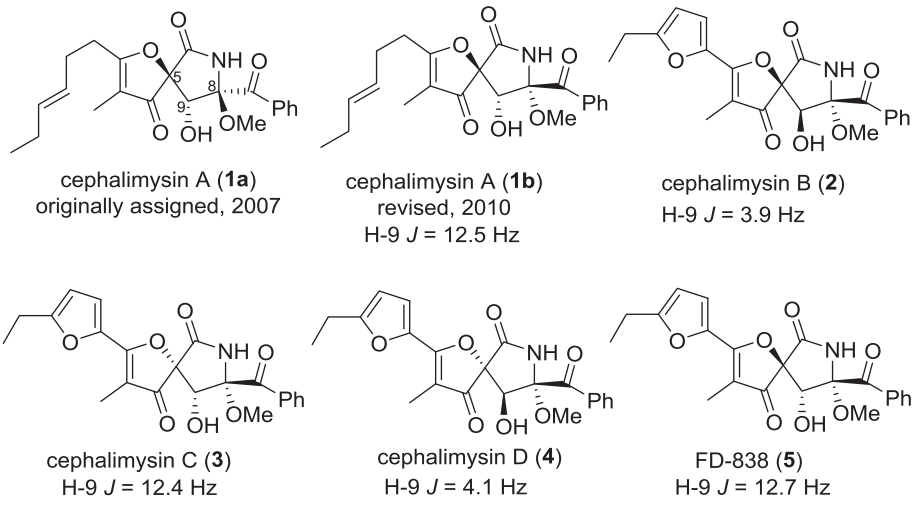
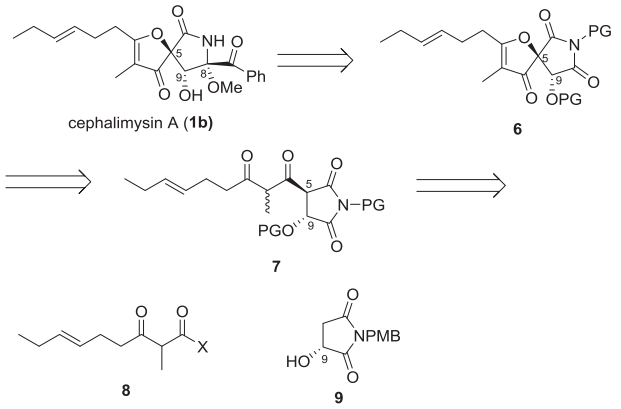


Fig. 1. Cephalimysin A and its family members.

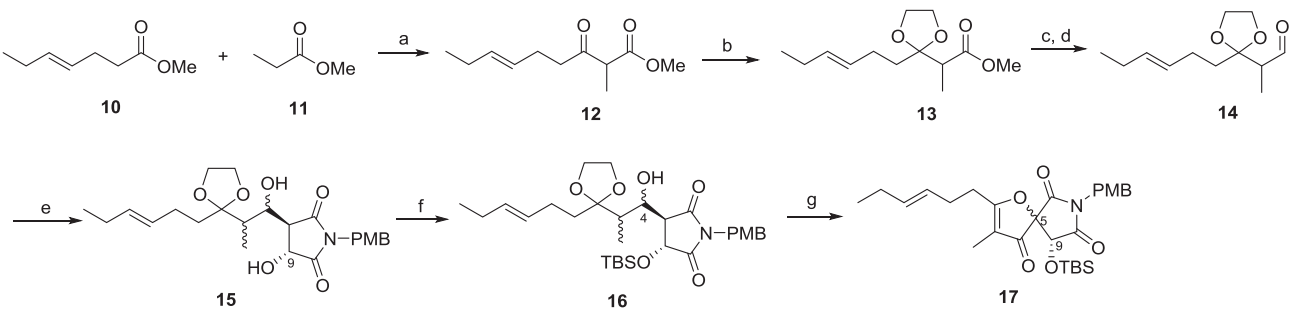


Scheme 1. Retrosynthetic analysis of cephalimysin A.

(*dr* = 4:1). In this process, the 4-hydroxyl was presumably oxidized to a carbonyl. The β-ketoimide obtained was then further oxidized in a locked conformation by chelating with scandium and a 5-hydroxyl was attached from the less hindered face in dominant. The following transketalization between this tertiary 5-hydroxyl and ketal in the sidechain delivered the desired spirocycle. In the absence of Lewis acid, C-5 hydroxylation was detectable in prolonged reaction, when **16** was treated with DMP, but enolization facilitated by Lewis acid coordination of the 1,3-dicarbonyl accelerated C4 oxidation. Among the Lewis acids screened [$Cu(OTf)_2$, $LiClO_4$, $Sc(OTf)_3$, $Ni(ClO_4)_2$, $Ni(acac)_2$], $Sc(OTf)_3$ turned out to be the best catalyst for both enolization and succeeded transketalization. The diastereomeric **17** obtained were then separated by preparative HPLC. We assigned, based on assumed mechanism, the C5-O and C9-O bonds in the major isomer of **17** to be *trans*, but it was not confirmed by NMR due to highly substituted nature of the spirobicycle.

A multistep detour was employed to prove our stereochemical assignment (Scheme 3). Alcohol **16** was oxidized to β-ketoimide **18** using 1.2 equiv of DMP in 91% yield. Then **18** was oxidized with magnesium monoperoxyphthalate (MMPP) in MeOH to afford an inseparable 1:1 mixture of 5-hydroxyl ketoimide **19**. Removal of TBS protecting group of **19** delivered diol **20a** and **20b**, which were separated by flash column chromatography. To determine the absolute configuration at C5 stereogenic center, **20a** and **20b** were treated with triphosgene respectively. The untouched **20a** was proved to be a 5,9-*trans*-diol; while cyclic carbonate **22** obtained from **20b** indicated its *cis* orientation of the 5,9-dihydroxyl. Therefore, **20a** and **20b** were reprotected with TBS, and forced to cyclize under basic condition (PPTS, pyridine) [8] respectively. The former produced spirobicycle **23a**, which was identical in spectroscopic properties to the major diastereomer of **17** obtained by one-step cascade reaction of **16**, and was also in consistence with proposed spirofuranone-γ-lactam core structure of cephalimysin A.

The final installation of the benzoyl side-chain and aminal functionality to **23a** proved to be problematic (Scheme 4). To differentiate the two carbonyl groups of the malic imide, the TBS was cleaved to give **24** with free 9-hydroxyl, which was assumed as a steric and electronic bias for regio and facial selective attack to adjacent carbonyl. Albeit a series of benzoyl anion equivalent



Scheme 2. Reagents and conditions: (a) LDA, **11**, THF, −78 °C, then **10**, 88%; (b) ethylene glycol, cat. PTSA, benzene, Dean-Stark trap, reflux, 86%; (c) $LiAlH_4$, Et_2O, 0 °C; (d) DMP, CH_2Cl_2, 0 °C, 92% for 2 steps; (e) **9**, NaHMDS, THF, −78 °C, then **14**, 58%; (f) TBSCl, imid., DMF, 97%; (g) DMP, $Sc(OTf)_3$, CH_3CN, 39% (*dr* = 4:1).

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