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Enantioselective Synthesis of Cephalimysins B and C

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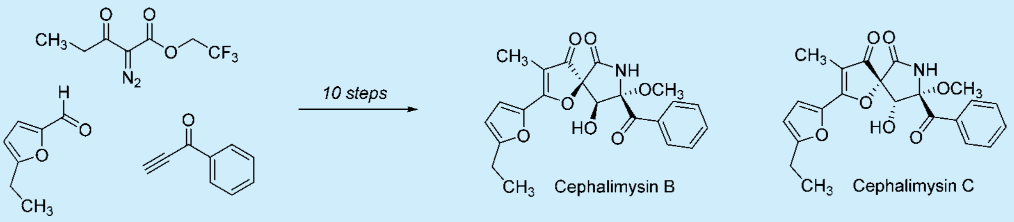
Supporting Information



ABSTRACT: The first synthesis of cephalimysins B and C is reported. The route features a Ni(II)−diamine-catalyzed enantioselective conjugate addition of a densely substituted 3(2*H*)-furanone and an efficient dihydroxylation−lactonization sequence as key steps in the assembly of the spirocyclic core. The fully synthetic strategy is amenable to analog preparation.

Cephalimysins B (**1**) and C (**2**) are secondary metabolites isolated from *Aspergillus sp.*[1] that belong to a small family of natural products named pseurotins (Figure 1). All members of the family share a densely substituted spirocyclic 3(2*H*)-furanone−γ-lactam core[2] but vary in terms of stereochemistry and appendage diversity. This relatively underexplored scaffold is understood to be a product of hybrid polyketide−nonribosomal peptide synthase biosynthetic machinery[3] and has been linked to a spectrum of biological effects. Examples include inhibition of angiogenesis,[4] inhibition of IgE production,[5] cytotoxicity toward certain cancer cell lines,[6] or antibacterial and antifungal activity.[7]

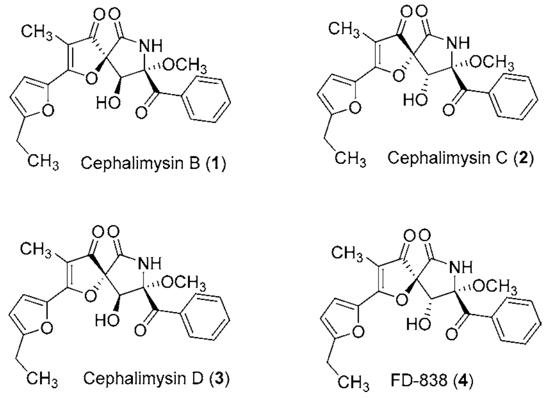
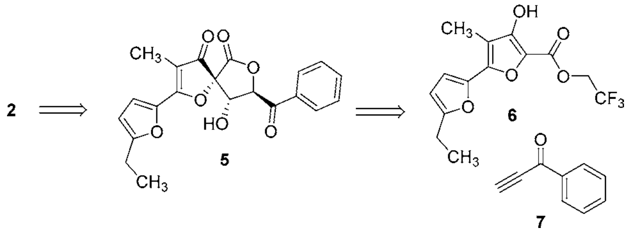


Figure 1. Stereoisomeric structures of cephalimysins B (**1**), C (**2**), D (**3**), and FD-838 (**4**).

Target-directed syntheses of several pseurotins were reported in the literature. Hayashi and co-workers used an aldol reaction approach to couple a functionalized γ-lactam with different aldehydes to access pseurotin A, azaspirene, synerazole, and FD-838 (**4**).[8] A similar disconnection was targeted by Tadano and colleagues in their synthesis of pseurotin A and azaspirene.[9] Enolate chemistry of a substituted γ-lactam featured also in the recent short synthesis of (±)-berkeleyamide D by Kuramochi and co-workers.[10] A distinct and concise strategy was disclosed by Rovis and colleagues, who utilized an enantioselective Stetter reaction to prepare three diastereomers of cephalimysin A.[11]

In most of these previous strategies, assembly of the γ-lactam preceded construction of the furanone ring.[12] Here, we describe a complementary approach that explores the chemical reactivity of a densely substituted 3(2*H*)-furanone intermediate. Key elements of our plan steered toward the synthesis of cephalimysin C (**2**) are summarized in Scheme 1. Spirocyclic γ-lactone **5** was recognized as a plausible precursor of the target γ-lactam. The lactone (**5**) can be disconnected into the furanone and the alkynyl ketone fragments (**6** and **7**, respectively). In the forward (synthetic) direction, a conjugate addition reaction between **6** and **7** followed by a dihydroxylation−lactonization sequence would form the γ-lactone

Scheme 1. Retrosynthetic Analysis of Cephalimysin C (2)



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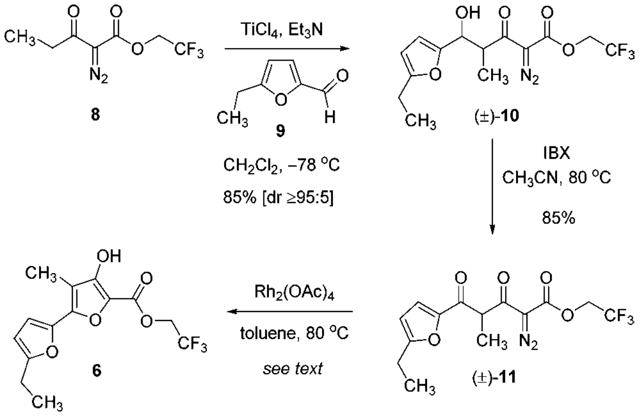
intermediate (**5**). Incorporation of an activated (trifluoroethyl) ester within the furanone was expected to facilitate the lactonization step.

In realizing the plan outlined above, we had to address uncertainties in the preparation and handling of the furanone fragment (**6**). Although 2-alkoxycarbonyl 3(2*H*)-furanones of similar substitution pattern are known,[13] they can suffer from limited stability that includes facile air oxidation.[14] We pursued rhodium(II)-catalyzed cyclization of diazo carbonyls[13e,15] as a mild method for construction of the furanone fragment, and the optimized sequence is shown in Scheme 2.

Scheme 2. Preparation of the Furanone Fragment (6)



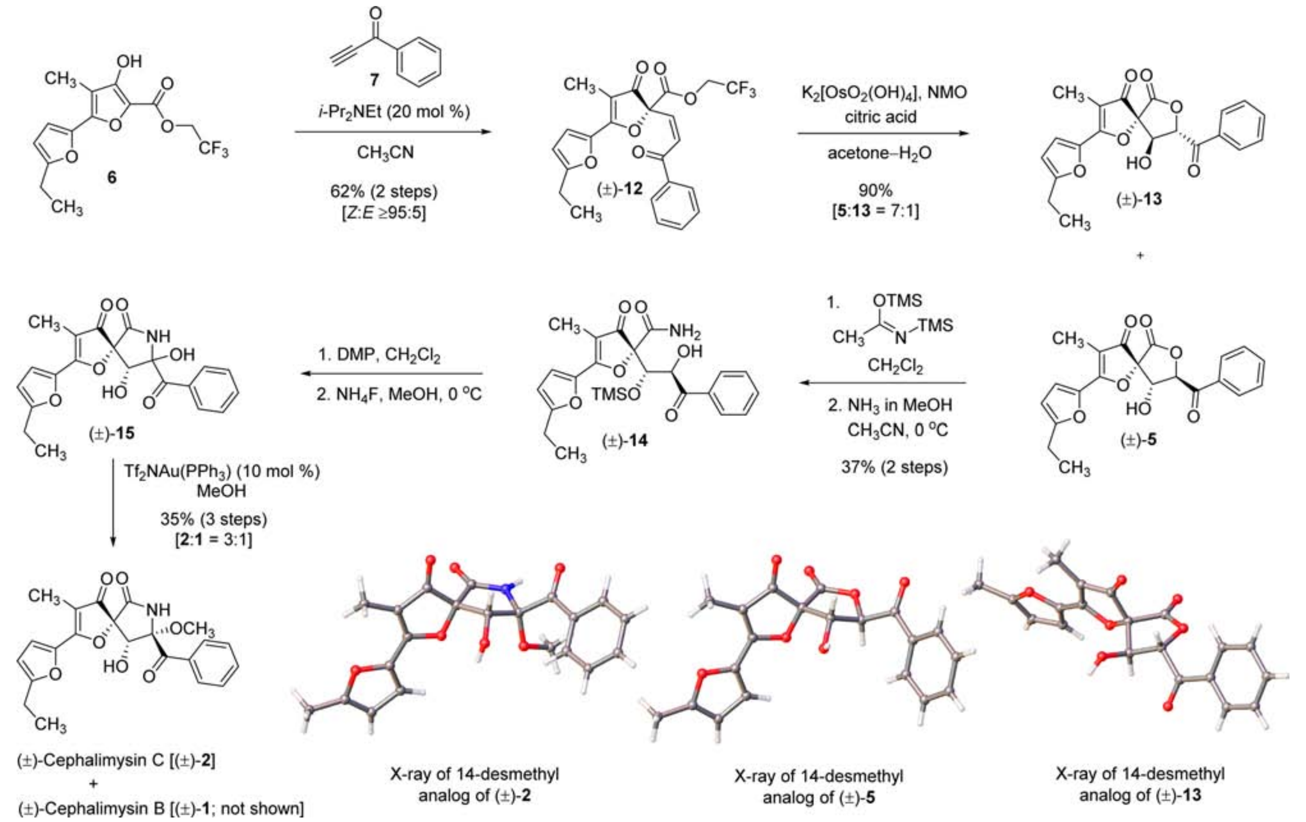
Titanium enolate generated from readily available α-diazo trifluoroethyl ester **8** (titanium(IV) chloride, −78 °C) underwent an aldol reaction with commercially available 5-ethylfurfural (**9**) to form adduct (±)-**10** (85% yield, dr ≥95:5; relative stereochemistry not determined).[16]

Acidic workup (acetic acid) was employed to prevent undesired post-aldol lactonization (δ-lactone formation) that was observed under basic conditions. Oxidation of the aldol adduct [(±)-**10**] with 2-iodoxybenzoic acid in acetonitrile[17] (1.5 equiv, 80 °C) proceeded smoothly, and the α-diazo 1,3-dicarbonyl [(±)-**11**] was isolated in 85% yield after simple filtration. Brief exposure of (±)-**11** to catalytic quantities (0.25 mol %) of rhodium(II) acetate dimer as a suspension in preheated toluene (80 °C, 20 min) led to the clean formation of furanone **6** (≥95% conversion by ^{1}H NMR analysis). To assess its chemical stability, we analyzed the solution of **6** in $CDCl_3$ by ^{1}H NMR and found that the cyclization product gradually decomposed on the order of hours (see Supporting Information (SI) for the time-course experiment).

The spiro carbon atom of cephalimysins B (**1**) and C (**2**) was established in the planned conjugate addition (Scheme 3). Reaction between freshly prepared furanone **6** and alkynyl ketone **7** was initially examined in the presence of *N,N*-diisopropylethylamine (0.2 equiv) in acetonitrile. Under these conditions, a racemic *C*-alkenylation product (enone (±)-**12**) formed selectively as the *Z*-isomer (*Z*:*E* ≥95:5) in 62% isolated yield (two steps from (±)-**11**). The product was stereochemically stable when kept neat but underwent slow *Z* → *E* isomerization in $CDCl_3$ solution.[18]

To achieve clean dihydroxylation of the electron-poor enone [(±)-**12**], we used a citric acid modified Upjohn protocol described by Sharpless and co-workers.[19] Under these conditions, the *in situ* lactonization of intermediate diols led to a mixture of two diastereomeric γ-lactones [(±)-**5**:(±)-**13** = 7:1, 90% combined yield]. The use of an activated ester was

Scheme 3. Synthesis of Racemic Cephalimysins B [(±)-1] and C [(±)-2]

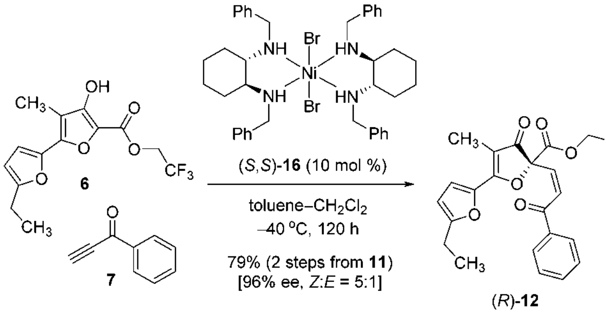


required for the spontaneous lactonization, where the trifluoroethyl ester was superior due to the straightforward product isolation (no chromatography required).[20] The relative stereochemistry of the separable γ-lactones was assigned by comparative analysis with the 14-desmethyl analogs, for which we had determined X-ray crystal structures (Scheme 3, bottom). In an attempt to access a complementary stereochemistry found in cephalimysin D (**3**) and FD-838 (**4**), we also studied dihydroxylation of the *E*-isomer of enone (±)-**12** (see SI). The major γ-lactone obtained in this experiment converged, later in the synthesis, with the *Z*-isomer-derived major lactone (±)-**5**, indicating that the osmium reagent approached preferentially from the same π-face regardless of the enone stereochemistry.

Trimethylsilylation of the 7:1 mixture of (±)-**5** and (±)-**13** with excess *N*,*O*-bis(trimethylsilyl)acetamide, followed by treatment with 7 M ammonia solution in methanol at 0 °C, provided primary amide (±)-**14** (single diastereomer, 37% yield over two steps).[21] Oxidation of the revealed secondary alcohol using Dess–Martin periodinane[22] gave a 1,2-diketone (^{13}C NMR analysis), which underwent an intramolecular cyclization to hydroxy spirolactam (±)-**15** upon cleavage of the trimethylsilyl ether (ammonium fluoride in methanol). Because (±)-**15** displayed limited stability during silica-gel chromatography, the crude material was processed forward. Introduction of the methoxy group was accomplished under mild conditions using a novel procedure. Treatment of (±)-**15** with a gold(I) triflimide–triphenylphosphine complex (10 mol %) in methanol (23 °C, 1 h) gave racemic cephalimysin C [(±)-**2**] in a 3:1 mixture with cephalimysin B [(±)-**1**] in a combined yield of 35% over three steps.[23] Spectral data for (±)-**1** and (±)-**2** were in full agreement with the literature,[1] and the structures were cemented further by an X-ray crystal structure of 14-desmethylcephalimysin C (Scheme 3, bottom) prepared by the same route.

The natural products cephalimysins B (**1**) and C (**2**) were previously assigned opposite configuration at the spiro carbon.[1] To control the absolute stereochemistry at this position, we examined several chiral amine-containing catalysts in the conjugate addition process described above. Promising levels of enantioselectivity were observed with the Ni(II)–diamine complex described by Evans and Seidel (Scheme 4).[24] The optimized reaction conditions (10 mol % of (*S*,*S*)-**16**, toluene–dichloromethane, −40 °C, 120 h) afforded the addition product [(*R*)-**12**] in 96% ee (79% over two steps, *Z*/*E* = 5:1). For reproducible results, it was essential to reach high conversion, otherwise a background reaction occurred during the purification process and eroded the enantiomeric purity of the product.[25] Examined cinchona alkaloids, and their thiourea or squaric acid derivatives, also catalyzed the reaction but with significantly diminished enantioselectivities (≤35% ee). To our knowledge, the Ni(II)–diamine catalyst was not described in conjugate additions with alkynones or enones previously.

Scheme 4. Enantioselective Conjugate Addition of Furanone 6



The six-step sequence described in Scheme 3 converted enone (*R*)-**12** (96% ee) to cephalimysin C (**2**, 96% ee; see SI). An analogous sequence starting from the enantiomeric enone [(*S*)-**12**, 94% ee] gave *ent*-cephalimysin C (*ent*-**2**, 90% ee; see SI). Importantly, the (*S*)-enone also provided cephalimysin B (**1**; see SI), an observation consistent with the reported opposite configuration of the spiro carbon atom of cephalimysins B (**1**) and C (**2**).[1]

There are only a few reports in which systematic structural modifications (primarily semisynthesis and precursor-directed biosynthesis derived) were examined in the context of biological activity of pseurotins.[5,26] The concise and modular route to cephalimysins B (**1**) and C (**2**) described herein has an exciting potential in this area. By a simple variation of the furanone or the alkynyl ketone components, we were able to rapidly access numerous spirocyclic analogs with a selection depicted in Figure 2.

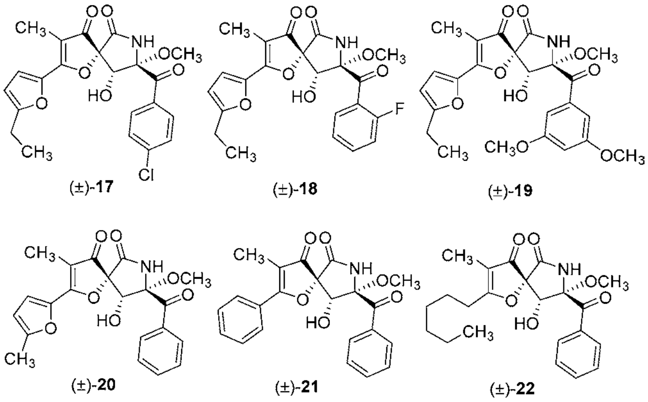


Figure 2. Selection of spirocyclic analogs prepared.

In summary, we have completed the first synthesis of cephalimysins B (**1**) and C (**2**), which proceeded in 12 steps from 3-oxopentanoic acid. Our strategy made use of Ni(II)–diamine-catalyzed enantioselective conjugate addition of a reactive 3(2*H*)-furanone intermediate and featured an efficient dihydroxylation–lactonization sequence. The work lends support to the previously assigned structures of the natural products cephalimysins B (**1**) and C (**2**). Importantly, our route is amenable to analog synthesis and is envisioned to aid the mapping of the biological activity of molecules featuring the underexplored spirocyclic scaffold of pseurotins.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03373.

Detailed experimental procedures and spectroscopic data for all new compounds (PDF)

Crystallographic data (CIF, CIF, CIF)

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Notes

The authors declare no competing financial interest.

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