Enantioselective Total Synthesis of Fluvirucinin B₁

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Supporting Information Placeholder

**ABSTRACT:** A convergent synthesis of fluvirucinin B₁ from acid ent-6a and nitrile ent-9, involving an organocopper coupling, a stereoselective allylation, a ring-closing metathesis reaction, and a stereoselective hydrogenation as the key steps, is reported. The starting building blocks have been prepared in a straightforward manner from a common phenylglycinol-derived lactam 1. An unprecedented regioselective oxidation of phenylglycinol-derived secondary amines 5 to carboxylic acids 6 has been developed.

Fluvirucins are 14-membered macrocyclic lactams isolated1,3 from the fermentation broth of actinomycete strains. They are glycosides characterized by the presence of an aminosugar moiety (L-mycosamine, its 4-epimer, or an N-substituted derivative) attached at the C-3 or C-9 positions of the core lactam nucleus through a hydroxy group. They also incorporate a methyl or ethyl substituent at the C-2 (1S-hydroxyethyl in fluvirucin A₂), C-6 (absent in some members), and C-10 positions (Figure 1). Fluvirucins possess important and varied biological activities, such as antifungal,1 antibacterial,7 antiviral,2 and anthelmintic.1 In particular, fluvirucin B₁ (Sch 38516) exhibits potent antifungal1a,c and anti-influenza virus2a activities,4 the latter partially retained in the corresponding aglycon fluvirucinin B₁.2b

Figure 1. Representative fluvirucins.

Although only one total synthesis of a fluvirucin has been reported,3 the synthesis of the macrolactam aglycons of fluvirucins, known as fluvirucinins, has received more attention.5-10 A key point in the synthesis of fluvirucinins is the stereoselective assembly of the stereocenters on the macrocyclic ring. Taking into account that all fluvirucinins B possess the same substitution and stereochemical patterns at the C-2 (R-Et), C-9 (S-OH), and C-10 (R-Et) positions, differing only in the C-6 substituent (none in fluvirucinin B₀, S-Me in B₁, S-Et in

Scheme 1. Unified Synthetic Strategy to Fluvirucinins B
B₂(OH)₃), we envisaged a unified synthetic strategy to these macro-
lactams in which the C-2 and C-10 ethyl substituents would come from a common enantiopure amino diol 2, easily accessible by reductive opening of oxazolopiperidone lactam 1. Scheme 1 outlines our synthetic plan.

Amino diol 2 would be converted to a 5-hydroxypentanoic acid derivative A by oxidative removal of the phenylglycinol moiety and then to the C₇-C₉ fragment of fluvirucinins B by copper-catalyzed coupling of the corresponding iodide with an appropriately substituted (R = H, Me or Et) alkenyl Grignard reagent. In turn, the secondary amino group of amino diol 2 would be oxidized to a cyano group, and the resulting 5-
hydroxypentanenitrile B would be converted to the C₇-N fragment of fluvirucinins B after the incorporation of the C-9 stereogenic center by a stereoselective alkylation of an aldehyde. Linkage of the two fragments by an amidation reaction, followed by a ring-closing metathesis and stereoselective hydrogenation of the resultant alkene would complete the synthesis of the target fluvirucinins B. The success of our synthetic plan would rely on the development of efficient procedures for the oxidative removal of the phenylglycinol moiety present in amino diol 2 to afford 5-hydroxypentanoic acid and 5-hydroxypentanenitrile derivatives.

The conversion of a secondary amine to a carboxylic acid is a challenging, unprecedented transformation. Taking into account that primary amines are oxidized to nitro derivatives by treatment with m-chloroperoxybenzoic acid, we decided to study this oxidation using a set of phenylglycinol-derived secondary amines structurally related to 2.

To our delight, treatment of the O-protected amino diols 5a–d with an excess of m-CPBA (4.2 equiv) in refluxing CH₂Cl₂ directly afforded the corresponding carboxylic acids 6a–d, bearing a variety of substituents (ethyl, benzyl, isopropylidenedioxy) in good yields (Scheme 2). Considering that amino diols 4 are available with virtually any type of substitution pattern, the above oxidative procedure opens a general synthetic entry to enantiopure 5-hydroxypentanoic acid derivatives.

The formation of carboxylic acids 6 can be accounted for by considering the generation of the nonconjugated nitrones 7 by oxidative cleavage of the phenylglycinol moiety of the starting O-protected amino diol was successfully accomplished in a single step using molecular iodine in aqueous ammonia. In this way, secondary amine 5a was converted to nitrile 9 in 71% yield (Scheme 4).

This transformation involves the initial generation of an imine and its reaction with ammonia to form an aminal, which decomposes to a primary amine and an imine. Subsequent oxidation and hydrolytic steps lead to the nitrile and (tert-butyldiphenylsilyloxy)methyl phenyl ketone, regardless of the regioselectivity of the initial oxidation.

Scheme 2. Oxidative Removal of the Chiral Inductor. Access to Enantiopure O-Protected 5-Hydroxypentanoic Acids

In support of this mechanism, nitrone 7e, prepared by Na₂WO₄/hydrogen peroxide–urea oxidation of the simple secondary amine 5e, was converted to hydroxypentanoic acid derivative 6e (45% from 5e) and dimer 8 by treatment with m-CPBA (2.5 equiv).

Scheme 3. Proposed Mechanism for the m-CPBA-Promoted Oxidation of Secondary Amines 5

Scheme 4. Oxidation of Secondary Amine 5a to Nitrile 9

Having developed straightforward procedures for the conversion of secondary amines 5 to functionalized carboxylic acids 6 and nitrile 9, to evaluate the feasibility of the unified strategy outlined in Scheme 1, we undertook the synthesis of fluvirucinin B₁. To achieve the required 2R and 10R configuration characteristic of fluvirucinins B, we started from the (S)-phenylglycinol-derived secondary amine ent-4a (= 2), which was converted, as in the above (R)-phenylglycinol series, to hydroxy acid ent-6a (A; Prot = TBDPS) and hydroxy nitrile ent-9 (B; Prot = TBDPS).

Scheme 5 outlines the synthesis of fluvirucinin B₁. The C₁–C₆ fragment (compound 12) was prepared from carboxylic acid ent-6a, which was converted, via an alcohol, to iodide 10.
Scheme 5. Total Synthesis of Fluvirucinin B1\textsuperscript{a}

A subsequent cross-coupling with 2-propenylmagnesium bromide in the presence of a catalytic amount of Cul\textsuperscript{16} (bond formed C5–C6) provided the protected alcohol 11, which was desilylated and oxidized to carboxylic acid 12 (23% overall yield from 1).

On the other hand, after the protected hydroxy nitrile \textit{ent}-9 was converted to aldehyde 13, a stereoselective alkylation using the (S,S)-Leighton reagent\textsuperscript{17} installed the C-9 stereogenic center to give homoallylic \textit{syn} alcohol 14\textsuperscript{18} (bond formed C8–C9). Protection of the hydroxy group of 14, followed by reduction of the cyano group, afforded amine 15 (the C7-N fragment of fluvirucinins B) in 21% overall yield from 1.

Coupling of the two fragments, carboxylic acid 12 and amine 15, took place in excellent yield to give amide 16. A subsequent ring-closing metathesis reaction (bond formed C6–C7), followed by stereoselective catalytic hydrogenation of the resulting 1:2:1 mixture of trisubstituted olefins 17, generated the C-6 stereocenter of the macrocycle,\textsuperscript{19} leading to the O-protected fluvirucinin derivative 18. The NMR data of our silyl derivative 18 matched those reported in the literature,\textsuperscript{5b,9b} and its mp and absolute rotation were consistent with those previously reported.\textsuperscript{9b} Additionally, the absolute configuration of 18 was unambiguously established by X-ray crystallographic analysis\textsuperscript{20} (Figure 2). A final removal of the silyl protecting group completed the synthesis of fluvirucinin B\textsubscript{1}, whose NMR data and [\(\alpha\)] value are reported for the first time (see the Supporting Information).

The convergent enantioselective synthesis of fluvirucinin B\textsubscript{1} herein reported consists of 12 linear synthetic steps from phenylglycinol-derived lactam 1\textsuperscript{21} in the longest linear sequence. The overall yield was 11%, which compares advantageously with previous syntheses\textsuperscript{9} of this aglycon. The synthesis also features an unprecedented oxidation of phenylglycinol-derived secondary amines 5 to diversely substituted enantiopure 5-hydroxypentanoic acid derivatives 6. By using an appropriate alkenyl Grignard reagent in the assembly of the C1–C6 fragment, the strategy we have developed could be applied to the synthesis of fluvirucinins B\textsubscript{0} and B\textsubscript{2–5}.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website.

- Experimental procedures, product characterizations, and \(^1\)H and \(^{13}\)C NMR spectra (PDF)
- Crystallographic data for compound 18 (CIF)

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**Notes**

The authors declare no competing financial interest.
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