

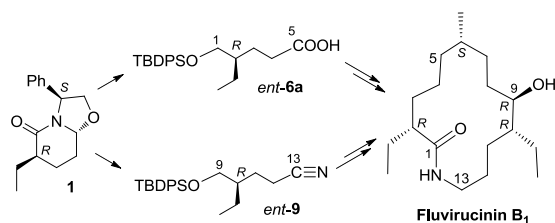
# Enantioselective Total Synthesis of Fluvirucinin B<sub>1</sub>

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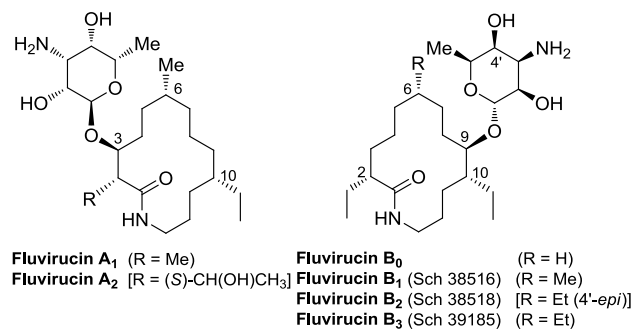
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Supporting Information Placeholder



**ABSTRACT:** A convergent synthesis of fluvirucinin B<sub>1</sub> 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 isolated<sup>1–3</sup> 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 (1*S*-hydroxyethyl in fluvirucin A<sub>2</sub>), C-6 (absent in some members), and C-10 positions (Figure 1). Fluvirucins possess important and varied biological activities, such as antifungal,<sup>1</sup> antibiotic,<sup>2</sup> antiviral,<sup>2</sup> and anthelmintic.<sup>3</sup> In particular, fluvirucin B<sub>1</sub> (Sch 38516) exhibits potent antifungal<sup>1a,c</sup> and anti-influenza virus<sup>2a</sup> activities,<sup>4</sup> the latter partially retained in the corresponding aglycon fluvirucin B<sub>1</sub>.<sup>2b</sup>

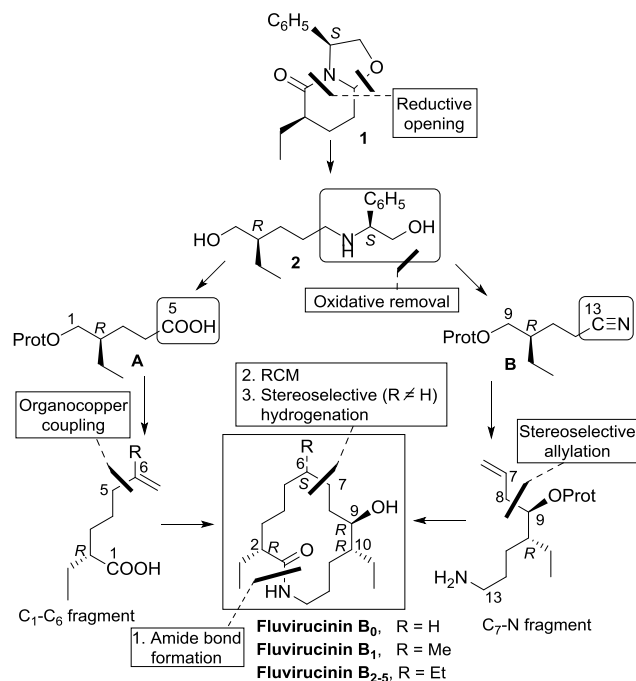


**Figure 1.** Representative fluvirucins.

Although only one total synthesis of a fluvirucin has been reported,<sup>5</sup> the synthesis of the macrolactam aglycons of fluvirucins, known as fluvirucinins, has received more attention.<sup>6–10</sup> A key point in the synthesis of fluvirucinins is the stereocon-

trolled 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 fluvirucin B<sub>0</sub>, *S*-Me in B<sub>1</sub>, *S*-Et in

**Scheme 1.** Unified Synthetic Strategy to Fluvirucinins B



B<sub>2-5</sub>), 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**.<sup>11</sup> Scheme 1 outlines our synthetic plan.

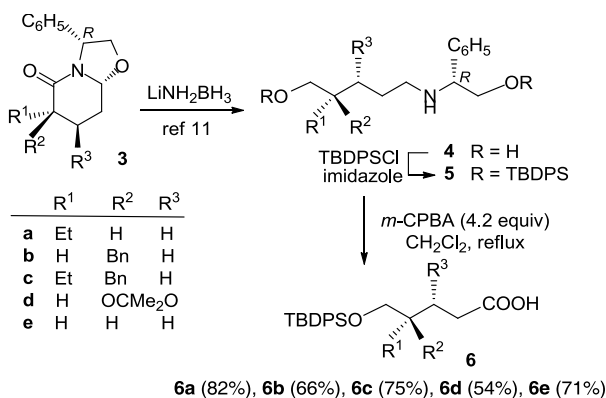
Amino diol **2** would be converted to a 5-hydroxypentanoic acid derivative **A** by oxidative removal of the phenylglycinol moiety and then to the C<sub>1</sub>–C<sub>6</sub> fragment of fluvirucinins **B** by copper-catalyzed coupling of the corresponding iodide with an appropriately substituted (R = 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 C<sub>7</sub>–N fragment of fluvirucinins **B** after the incorporation of the C-9 stereogenic center by a stereoselective allylation 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*-chloroperbenzoic acid,<sup>12</sup> 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 CH<sub>2</sub>Cl<sub>2</sub> 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,<sup>11</sup> the above oxidative procedure opens a general synthetic entry to enantiopure 5-hydroxypentanoic acid derivatives.

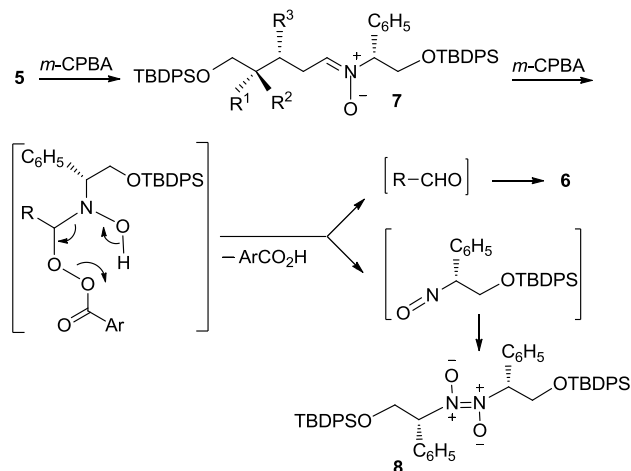
The formation of carboxylic acids **6** can be accounted for by considering the generation of the nonconjugated nitrones **7**<sup>13</sup> and their *m*-CPBA-promoted oxidative cleavage<sup>14</sup> with subsequent oxidation of the resulting aldehyde. The oxidative cleavage also produces a nitroso derivative, which was isolated as the corresponding nitroso dimer **8** (Scheme 3).

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



In support of this mechanism, nitron **7e**, prepared by Na<sub>2</sub>WO<sub>4</sub>/hydrogen peroxide–urea oxidation<sup>13b</sup> 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).

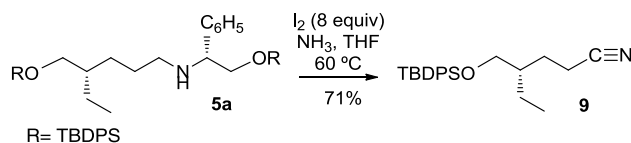
**Scheme 3. Proposed Mechanism for the *m*-CPBA-Promoted Oxidation of Secondary Amines **5****



On the other hand, the generation of a 5-hydroxypentanenitrile 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.<sup>15</sup> 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.

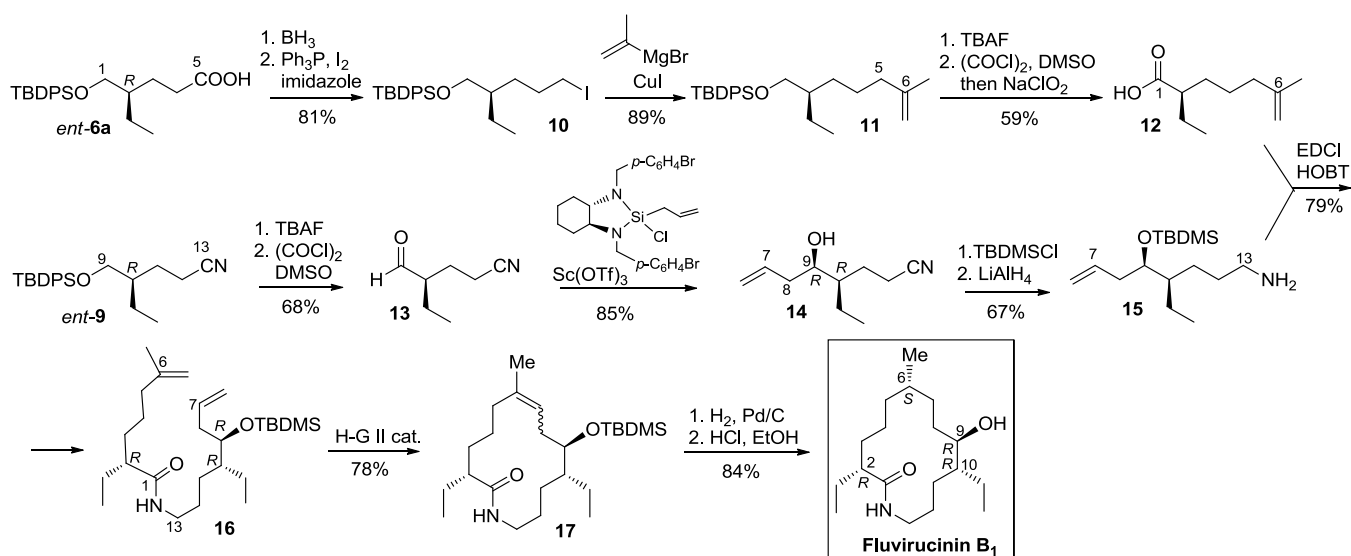
**Scheme 4. Oxidation of Secondary Amine **5a** to Nitrile **9****



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 fluvirucinins **B**. To achieve the required 2*R* and 10*R* 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 fluvirucinins **B**. The C<sub>1</sub>–C<sub>6</sub> 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 B<sub>1</sub><sup>a</sup>



<sup>a</sup> The carbon numbering of the intermediates corresponds to that of fluvirucinin B<sub>1</sub>

A subsequent cross-coupling with 2-propenylmagnesium bromide in the presence of a catalytic amount of CuI<sup>16</sup> (bond formed C<sub>5</sub>–C<sub>6</sub>) 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 *ent*-**9** was converted to aldehyde **13**, a stereoselective allylation using the (*S,S*)-Leighton reagent<sup>17</sup> installed the C-9 stereogenic center to give homoallylic *syn* alcohol **14**<sup>18</sup> (bond formed C<sub>8</sub>–C<sub>9</sub>). Protection of the hydroxy group of **14**, followed by reduction of the cyano group, afforded amine **15** (the C<sub>7</sub>–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 C<sub>6</sub>–C<sub>7</sub>), followed by stereoselective catalytic hydrogenation of the resulting 1.2:1 mixture of trisubstituted olefins **17**, generated the C-6 stereocenter of the macrocycle,<sup>19</sup> leading to the *O*-protected fluvirucinin derivative **18**. The NMR data of our silyl derivative **18** matched those reported in the literature,<sup>5b,9b</sup>

and its mp and absolute rotation were consistent with those previously reported.<sup>9b</sup> Additionally, the absolute configuration of **18** was unambiguously established by X-ray crystallographic analysis<sup>20</sup> (Figure 2). A final removal of the silyl protecting group completed the synthesis of fluvirucinin B<sub>1</sub>, whose NMR data and [α] value are reported for the first time (see the Supporting Information).

The convergent enantioselective synthesis of fluvirucinin B<sub>1</sub> herein reported consists of 12 linear synthetic steps from phenylglycinol-derived lactam **1**<sup>21</sup> in the longest linear sequence. The overall yield was 11%, which compares advantageously with previous syntheses<sup>9</sup> 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 C<sub>1</sub>–C<sub>6</sub> fragment, the strategy we have developed could be applied to the synthesis of fluvirucinins B<sub>0</sub> and B<sub>2–5</sub>.

## ASSOCIATED CONTENT

### Supporting Information

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

Experimental procedures, product characterizations, and <sup>1</sup>H and <sup>13</sup>C NMR spectra (PDF)

Crystallographic data for compound **18** (CIF)

## AUTHOR INFORMATION

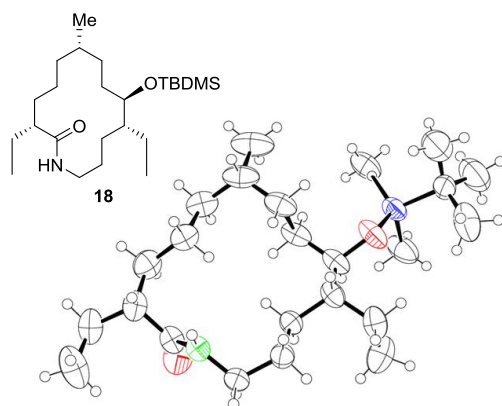
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### Notes

The authors declare no competing financial interest.



**Figure 2.** X-ray crystal structure of the fluvirucinin B<sub>1</sub> precursor **18**.

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- (18) Minor amounts (dr = 9:1) of the *anti* adduct were detected by NMR. Purification of amine **15** afforded a single diastereoisomer.
- (19) A similar remote macrocyclic stereocontrol in the synthesis of fluvirucinins was first observed by Hoveyda<sup>5</sup> in the hydrogenation of related macrocyclic olefins bearing a trisubstituted C<sub>5</sub>-C<sub>6</sub> (instead of C<sub>6</sub>-C<sub>7</sub>) double bond.
- (20) CCDC 1440667 contains the supplementary crystallographic data for compound **18**. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
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