First Total Synthesis and Structural Confirmation of Fluvirucinine A₂ via an Iterative Ring Expansion Strategy

Yong-Sil Lee,† Jong-Wha Jung,† Seok-Ho Kim,† Jae-Kyung Jung,‡ Seung-Mann Paek,† Nam-Jung Kim,† Dong-Jo Chang,† Jeeyeon Lee,† and Young-Ger Suh*,†

College of Pharmacy, Seoul National University, 599 Gwanakro, Gwanak-gu, Seoul 151-742, Korea, and College of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea

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ABSTRACT

The first asymmetric total synthesis of fluvirucinine A₂ has been accomplished. A key feature of the synthesis is an iterative lactam ring expansion to provide rapid access to the 14-membered lactam skeleton and three stereogenic centers. The excellent remote control of the three stereogenic centers relied on stereoselective amidoalkylation followed by an amide-enolate-induced aza-Claisen rearrangement. In addition, the structure of fluvirucinine A₂ has been completely elucidated by our total synthesis.

Fluvirucins were isolated from fermentation broths of actinomycete isolates in 1991 by the scientists of Bristol-Myers Squibb.¹ Scientists at Schering-Plough also independently isolated fluvirucin B₁, B₂, and B₃ from Actinomadura vulgaris in 1990.² The potent activities of fluvirucins against bacteria, fungi, and especially influenza¹ᵃ as well as structural features of this novel class of macrolactams have attracted interests in the past two decades. In particular, the synthesis of fluvirucin A₁ and A₂ has attracted attention due to the unique structural features of these molecules, which have promising antiviral activities (ID₅₀ of 4.3 and 4.6 μg/mL, respectively, against influenza virus) and low toxicity (Figure 1).¹ᵃ Moreover, the structure of fluvirucinine A₂ has not been fully elucidated. We have been working toward the total synthesis of fluvirucinine A₂ (I), an aglycon of fluvirucin A₂. We report herein the first asymmetric total synthesis of fluvirucinines A₂ and its full structure.

Figure 1. Structures of fluvirucins.

¹ Seoul National University.
² Chungbuk National University.

Since the Hoveyda group reported the first total synthesis of fluvirucinine B1,3a inspirations of the synthetic community due to the unique structures and excellent biological activities of fluvirucins have led to notable endeavors to facilitate their total synthesis.3,4a

Since we reported the first asymmetric total synthesis of fluvirucinine A1,4a we have been interested in iterative ring-expansion strategies (Scheme 1) as one of the most efficient approaches to the synthesis of macrolactam alkaloids. This prominent ring-expansion strategy would provide (1) rapid access to a variety of functionalized macrolactam skeletons without an extra cyclization step, (2) concomitant stereoselective elaborations of the requisite stereogenic centers by a metric amide aldol reaction for elaboration of C2 and C3 to offer an attractive alternative to the conventional asymmetric vinylation, afforded the ring-expanded lactam 4 by olefin hydrogenation of 7 and subsequent Boc-protection. Taking advantage of our recent protocol via an N,O-acetal TMS ether,5 we could further provide the requisite allylazacycle 3, in spite of the ring-opening propensity of medium or macro lactams. The Boc-protected lactam 4 was partially reduced with DIBAL-H, and then the resulting N,O-acetal was trapped with subsequent addition of Py and TMSOTf to give the N,O-acetal TMS ether 9. Upon BF3-OEt2 treatment of N,O-acetal TMS ether 9, highly stereoselective amidalkylation was achieved at a low temperature, and prolonged stirring at room temperature allowed subsequent Boc-deprotection to give the allylazacycle 3, with no detectable stereoisomer in high yield. Expecting a chairlike transition state during the second ACR, stereoselective (E)-enol ether formation was required to facilitate the introduction of newly generated stereochemistry at C3 as desired. Fortunately, silylation of the aldehyde, obtained by oxidative cleavage of the corresponding α-allylazacycle 10, under mild conditions (TBSOTf, DBU, CH2Cl2, reflux)5c resulted in the highly stereoselective formation of the desired (E)-enol TMS ether 11 in an excellent yield, along with a negligible amount of the corresponding (Z)-enol TMS ether (>10:1).

With a reliable protocol established for the synthesis of functionalized macrolactams, we turned our attention to the second ACR. A variety of ACR precursors were investigated

The first ACR as reported,4a Amide enolate inducedaza-Claisen rearrangement of 5, prepared from lactam 6 by direct stereoselective vinylation, afforded the ring-expanded lactam 7 as a sole product possessing the second requisite stereo-}

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**Scheme 1. Retrosynthesis of Fluvirucine A2**

**Scheme 2. Stereoselective Synthesis of (E)-Enol TBS Ether 12**

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for production of the 14-membered lactam with the desired C2-stereochemistry. Notably, stereoselectivity for the ACR of 2 was quite substituent-dependent and the ACR precursor 2b turned out to be best in terms of diastereoselectivity (>10:1) and yield as shown in Table 1. Both the ethyl substituent and the (E)-olefin geometry of the acyl side chain seemed to enhance the stereoselectivity probably by inducing a more favorable chairlike transition state for the ACR. It is noteworthy that vinylogous amide enolate-induced ACR has not been reported to the best of our knowledge. As anticipated, LHMDS treatment of 2b in toluene effectively furnished the desired intermediate 12. Selective olefin cleavage of 12 followed by stereoselective Grignard addition to the resulting aldehyde furnished alcohol 14a with the correct stereochemistry (>20:1) probably by the Felkin–Ahn rule. Total synthesis of fluvirucinine A2 (1) was finally completed by TBS deprotection of 14a and hydrogenation of the remaining olefin. The structure of the synthetic 1 was confirmed by its conversion into diacetate 15, which exhibited spectral data identical to those of the reported diacetate.

Synthesis of epi-fluvirucinine A2 could also be achieved from 2c. The β-methyl substituent of the vinylogous amide enolate of 2c seemed deleterious to stereoselectivity in ACR, which led to a 1:1 diastereomeric mixture of macrolactam 13. The absence of diastereoselectivity is likely due to nonselective formation of the (Z)-enolate. However, NaBH4 reduction of the methyl ketone prepared by selective oxidative olefin cleavage of the correct diastereomer interestingly resulted in exclusive formation of the stereoisomer 14b. Thus, we were finally able to synthesize epi-fluvirucinine A2 from 14b by analogy to the synthesis of fluvirucinine A2 (1).

In conclusion, we have accomplished the first asymmetric total synthesis of fluvirucinine A2 as well confirmed its structure by its conversion into diacetate identical to the data for the epi-fluvirucinine A2 synthesized from the 14-membered macrolactam possessing the (R)-configuration at the stereogenic center of interest (see the Supporting Information).
structure. In particular, the excellent remote stereocontrol by our approach attests to the efficiency and synthetic versatility of our iterative ring-expansion strategy. The first and highly stereo- and regioselective amide enolate-induced vinylogous ACR was also reported. Further synthetic applications of our strategy and detailed investigation into the vinylogous amide enolate-induced ACR are currently underway.

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Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.