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First Total Synthesis and Structural Confirmation of Fluvirucinine A_2 via an Iterative Ring Expansion Strategy

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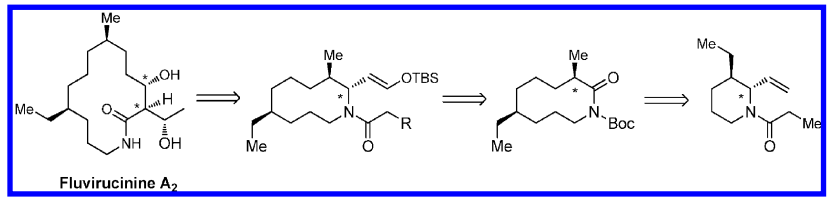
ABSTRACT



The first asymmetric total synthesis of fluvirucinine A_2 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 A_2 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 B_1, B_2, and B_3 from *Actinomadura vulgaris* in 1990.[2] The potent activities of fluvirucins against bacteria, fungi, and especially influenza[1a] 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 A_1 and A_2 has attracted attention due to the unique structural features of these molecules, which have promising antiviral activities (ID_{50}s of 4.3 and 4.6 μg/mL, respectively, against influenza virus) and low toxicity (Figure 1).[1a] Moreover, the structure of fluvirucinine A_2 has not been fully elucidated. We have been working toward the total synthesis of fluvirucinine A_2 (**1**), an aglycon of fluvirucin A_2. We report herein the first asymmetric total synthesis of fluvirucinines A_2 and its full structure.

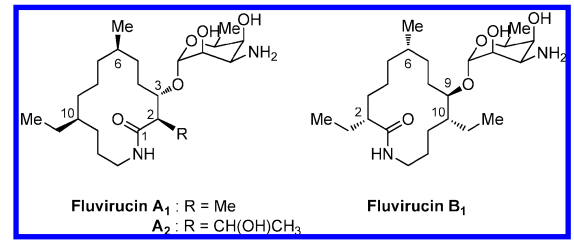


Figure 1. Structures of fluvirucins.

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(1) (a) Naruse, N.; Tenmyo, O.; Kawano, K.; Tomita, K.; Ohgusa, N.; Miyaki, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 733. (b) Naruse, N.; Tsuno, T.; Sawada, Y.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 741. (c) Naruse, N.; Konishi, M.; Oki, T.; Inouye, Y.; Kakisawa, H. *J. Antibiot.* **1991**, *44*, 756. (d) Tomita, K.; Oda, N.; Hoshino, Y.; Ohkusa, N.; Chikazawa, H. *J. Antibiot.* **1991**, *44*, 940.

(2) (a) Hegde, V. R.; Patel, M. G.; Gullo, V. P.; Ganguly, A. K.; Sarre, O.; Puar, M. S.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6403. (b) Hegde, V. R.; Patel, M.; Horan, A.; Gullo, V.; Marquez, J.; Gunnarsson, I.; Gentile, F.; Loebenberg, D.; King, A.; Puar, M.; Pramanik, B. *J. Antibiot.* **1992**, *45*, 624.

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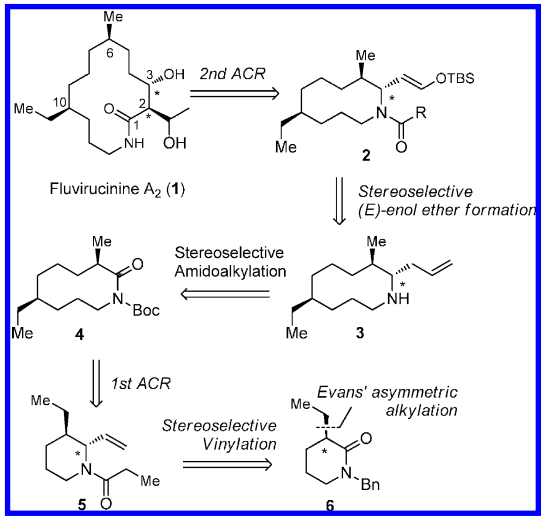
Since the Hoveyda group reported the first total synthesis of fluvirucinine B_1,[3a] inspirations of the synthetic community due to the unique structures and excellent biological activities of fluvirucins have led to notable endeavors to facilitate their total synthesis.[3,4a]

Since we reported the first asymmetric total synthesis of fluvirucinine A_1,[4a] we have been interested in iterative ring-expansion strategies (Scheme 1) as one of the most efficient

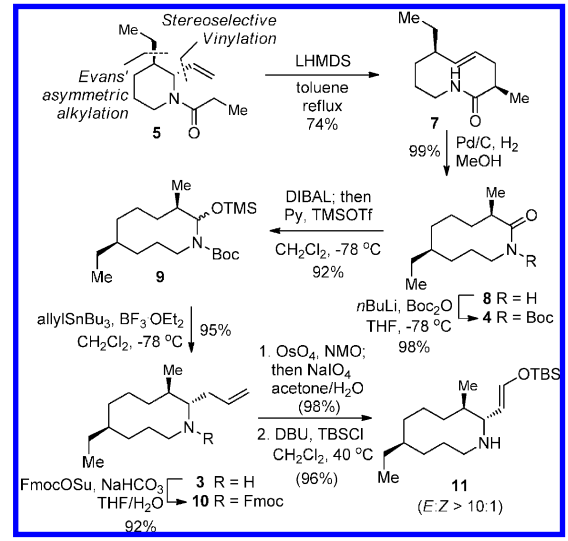
Scheme 1. Retrosynthesis of Fluvirucinine A_2



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 distal asymmetric induction, and (3) entropic and enthalpic advantages.[5] As shown in Scheme 1, our unique strategy takes full advantage of the initially introduced C10 chiral center to control the relative stereochemistries of the remaining remote stereogenic centers (C2, C3, and C6) through a highly ordered ring expansion via an aza-Claisen rearrangement (ACR). In particular, the second ACR (**2** → **1**) seems to offer an attractive alternative to the conventional asymmetric amide aldol reaction for elaboration of C2 and C3 stereogenic centers.

Shown in Scheme 2, our synthesis commenced with preparation of the 10-membered lactam **4** from lactam **6** by

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



the first ACR as reported.[4a] Amide enolate induced aza-Claisen rearrangement of **5**, prepared from lactam **6** via direct stereoselective vinylation, afforded the ring-expanded lactam **7** as a sole product possessing the second requisite stereogenic center corresponding to C6 of fluvirucinine A_2. The 10-membered lactam **4** was obtained by olefin hydrogenation of **7** and subsequent Boc-protection. Taking advantage of our recent protocol via an *N*,*O*-acetal TMS ether,[6] we could further provide the requisite allylazacycle **3**, in spite of the ring-opening propensity of medium or macrolactams. 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 BF_3OEt_2 treatment of *N*,*O*-acetal TMS ether **9**, highly stereoselective amidoalkylation 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 (TBSCl, DBU, CH_2Cl_2, reflux)[7,4c] 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

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(4) (a) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem.* **1999**, *111*, 3753; *Angew. Chem., Int. Ed.* **1999**, *38*, 3545. (b) Suh, Y.-G.; Lee, J.-Y.; Kim, S.-A.; Jung, J.-K. *Synth. Commun.* **1996**, *26*, 1675. (c) Paek, S.-M.; Kim, N.-J.; Shin, D.; Jung, J.-K.; Jung, J.-W.; Chang, D.-J.; Moon, H.; Suh, Y.-G. *Chem.—Eur. J. [Online]* http://dx.doi.org/10.1002/chem.200902591 (accessed Mar 18, 2010).

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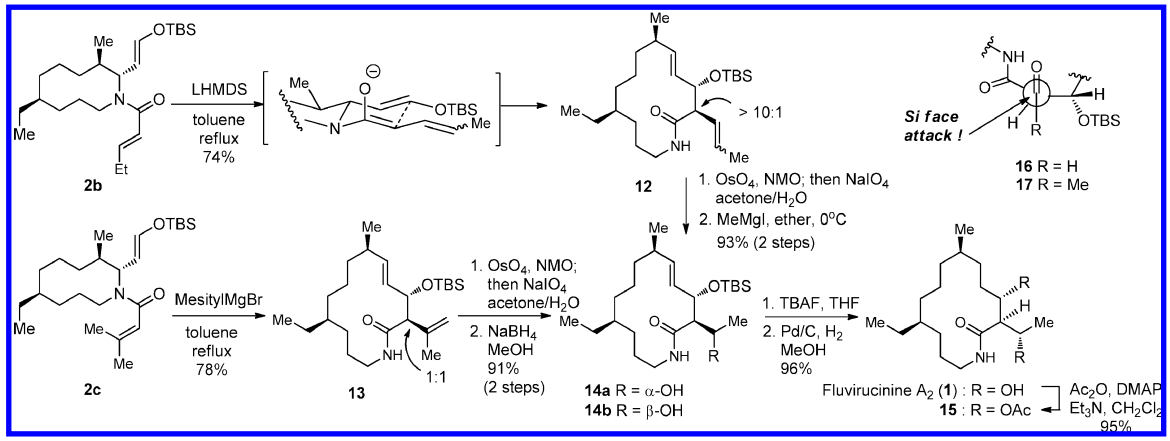
(6) (a) Suh, Y.-G.; Kim, S.-H.; Jung, J.-K.; Shin, D.-Y. *Tetrahedron Lett.* **2002**, *43*, 3165. (b) Suh, Y.-G.; Shin, D.-Y.; Jung, J.-K.; Kim, S.-H. *Chem. Commun.* **2002**, 1064. (c) Shin, D.-Y.; Jung, J.-K.; Seo, S.-Y.; Lee, Y.-S.; Paek, S.-M.; Chung, Y. K.; Shin, D. M.; Suh, Y.-G. *Org. Lett.* **2003**, *5*, 3635. (d) Jung, J.-W.; Shin, D.-Y.; Seo, S.-Y.; Kim, S.-H.; Paek, S.-M.; Jung, J.-K.; Suh, Y.-G. *Tetrahedron Lett.* **2005**, *46*, 573.

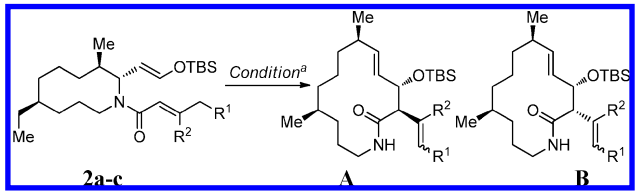
(7) Taniguchi, Y.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn. 30.* **1981**, *54*, 3229.

Scheme 3. Completion of Fluvirucinine A_2 Synthesis via Vinylogous Amide Enolate Induced ACR



for production of the 14-membered lactam with the desired C2-stereochemistry.[8] 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 A_2 (**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.[1b]

Table 1. Vinylogous Amide Enolate-Induced ACR



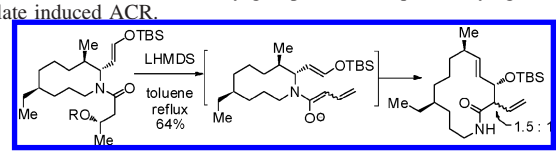
substrate	R^1	R^2	base	yield[b] (%)	dr[c] (**A**:**B**)
2a	H	H	LHMDS	64	1.5:1
2b	Me	H	LHMDS	74	>10:1
2c	H	Me	mesitylMgBr[4c]	78	1:1

[a] All reactions were conducted in toluene at 130 °C. [b] Isolated yields. [c] Determined by isolation yield of each isomer.

Synthesis of *epi*-fluvirucinine A_2 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.[9] However, $NaBH_4$ reduction of the methyl ketone prepared by selective oxidative olefin cleavage of the correct diastereomer interestingly resulted in exclusive formation of the stereoisomer **14b**.[10] Thus, we were finally able to synthesize *epi*-fluvirucinine A_2 from **14b** by analogy to the synthesis of fluvirucinine A_2 (**1**).[11]

In conclusion, we have accomplished the first asymmetric total synthesis of fluvirucinine A_2 as well confirmed its

(8) Attempted lactam ring expansion of a precursor possessing β-hydroxyl amide in hand under the standard ACR conditions gave the vinyl-substituted product as a 1.5:1 diastereomeric mixture, possibly via initial elimination of the labile alkoxy group and subsequent vinylogous amide enolate induced ACR.



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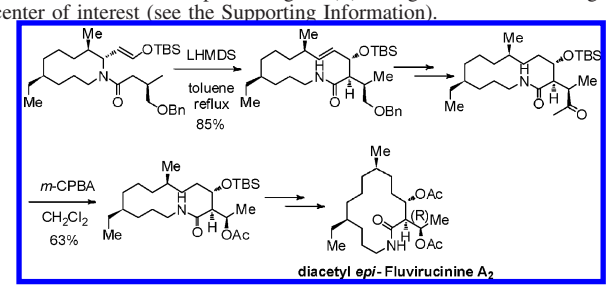
(10) For a mechanism on the 2-alkyl-3-oxo-amide reduction with borohydride species: (a) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 4643. (b) Bartoli, G.; Bosco, M.; Marcantoni, E.; Melchiorre, P.; Rinaldi, S.; Sambri, L. *Synlett* **2004**, *1*, 73.

(11) To provide solid evidence for the structures of the synthetic fluvirucinines, an alternate synthesis employing Baeyer−Villiger oxidation was also undertaken. Spectral data for the synthetic *epi*-fluvirucinine A_2 prepared via vinylogous amide enolate induced ACR (Scheme 3) were identical to the data for the *epi*-fluvirucinine A_2 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.

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