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Synthesis of the core ring system of awajanomycin from *N*-Boc-3-methoxycarbonyl-2-pyridinone

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ABSTRACT

Awajanomycin, which was isolated from marine-derived fungus, possesses unique structural features and cytotoxic activity against A549 cells. Due to its unique structure, no total synthesis has yet been reported, and neither the relative stereochemistry nor the absolute configuration has been determined. We report the synthesis of the core ring system of awajanomycin, which includes: (i) regioselective addition of the acetate unit onto C4-position of *N*-Boc-3-methoxycarbonyl-2-pyridinone; (ii) stereoselective installation of a hydroxyl group on C3-position; and (iii) stereo- and regioselective epoxide-opening reaction by Me_3Al.

Because nitrogen-containing six-membered compounds are frequently found in natural products and many are known to possess valuable biological activities, they have long been of interest to organic and bio-organic chemists.[1] Utilization of nitrogen-containing six-membered heteroaromatic compounds seems to be a useful method to achieve stereoselective construction of functionalized piperidine ring systems because they are readily available. Reactions of pyridinium salts or dihydropyridine derivatives have been thoroughly investigated recently,[2] and the syntheses of many biologically active compounds have also been reported.[3] On the other hand, the utilization of the 2-pyridinone derivatives has been mainly carried out for the Diels–Alder reaction.[4] To the best of our knowledge, a few examples for the introduction of the allyl group to 2-pyridinone derivatives[5] and some literatures about the reactions of the related compounds and their applications to the organic synthesis also could be found.[6]

During our ongoing research to develop novel methods for the introduction of functional groups in heterocyclic compounds, we reported the regioselective addition of the acetate unit into 2-pyridinone derivatives in the presence of catalytic amounts of Lewis acid.[7] In particular, we successively carried out both the C4-selective functionalization of N-substituted-3-methoxycarbonyl-2-pyridinone derivatives **2a** and **2b** (Scheme 1A) and the introduction of an acetate unit into the C6-position of N-substituted-5-methoxycarbonyl-2-pyridinone derivative **5** (Scheme 1B).[8] In this Letter, we describe an application of this methodology to the synthesis of the core ring system of awajanomycin (**1**), which has anti-cancer activity.

Awajanomycin (**1**) was isolated in 2006 from extracts of the marine-derived fungus *Acremonium* sp. AWA16-1 by Jang et al., and reported to possess cytotoxic activity against A549 cells (IC_{50} = 27.5 μg/mL).[9] The structural features of awajanomycin (**1**) are: (i) a bicyclo[3.2.1]-ring system including a γ-lactone and a δ-lactam; (ii) four adjacent asymmetric centers (C1, C8, C5, and C4); (iii) a tertiary alcohol at the α-position of γ-lactone and δ-lactam (C1–OH); and (iv) an axially oriented C4-methyl group (Fig. 1).[10]

Due to its unique structure and difficulties in the stereo-controlled introduction of stereogenic centers, total synthesis of **1** is yet to be reported; in addition the absolute configuration and relative stereochemistry of the allylic alcohol of **1** have, so far, also not been determined.

The retrosynthetic analysis of **1** is shown in Scheme 2. In this convergent strategy, **1** could be synthesized from 1-decen-3-ol (**8**) and the core ring system **9** by a cross-metathesis reaction. The vinyl group of **9** could be prepared from the ethoxycarbonyl group of **10**, by sequential reduction of the ester and dehydration of the resultant alcohol. We designed two synthetic strategies to synthesize **10**. In first route, acetal **11a,** sulfide **11b,** or the sulfone **11c** was postulated as precursors to introduce the C6-methyl group. Epoxide **12** was envisioned as precursor to **10** in the second strategy. All these precursors **11a–c** and **12** could be obtained from the enamine **13**, which was projected to arise

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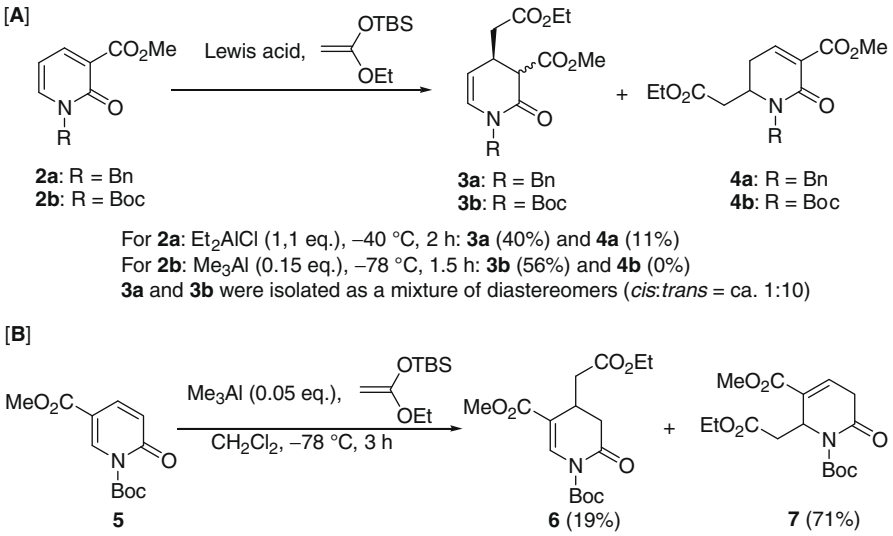


Scheme 1.

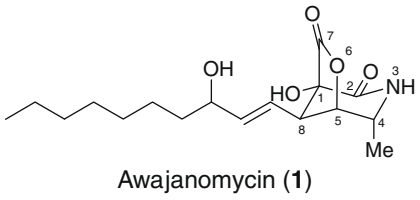
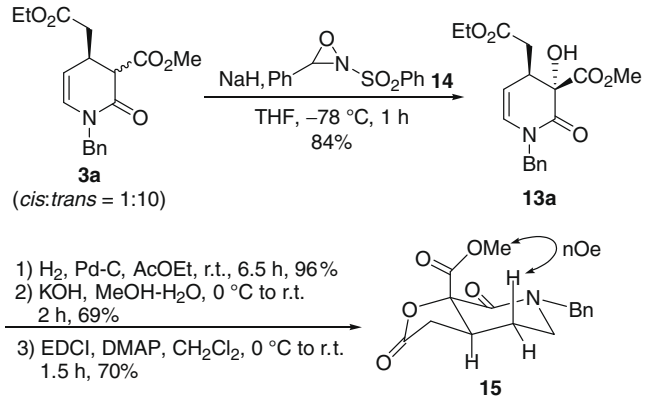


Figure 1.

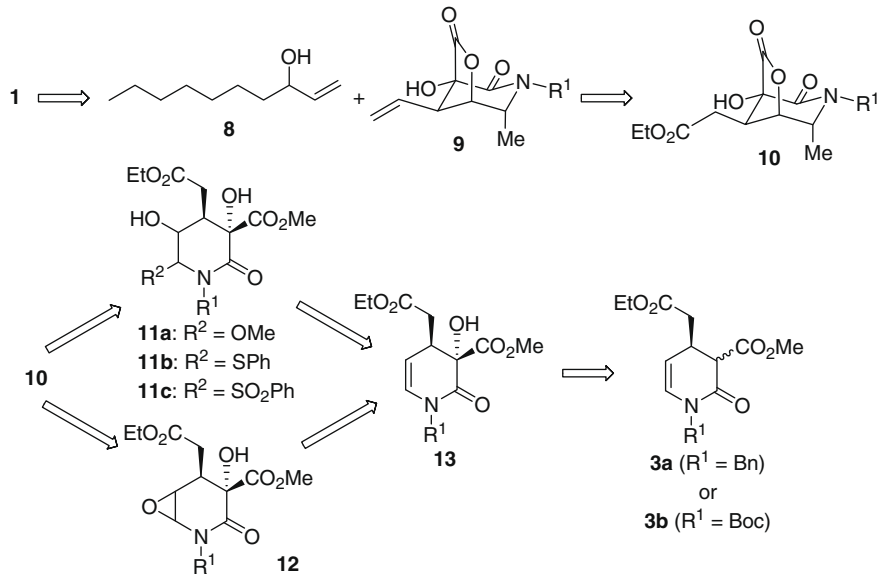
from the stereoselective hydroxylation reaction of either α-methoxycarbonyl-δ-lactam **3a** or **3b**.

We selected **3a**[7b,8] as the starting material for the first synthetic trial. Installation of the hydroxyl group was carried out using *N*-sulfonyloxaziridine **14**[11] in the presence of NaH, and afforded **13a** as a sole product in 84% yield. The stereochemistry of the hydroxyl group in **13a** was determined by nOe experiment on **15**, which was converted from **13a** by reduction of the double bond, selective hydrolysis of the ethyl ester, and lactone ring formation (Scheme 3).



Scheme 3.

With the desired **13a** in hand, the next task was functionalization of the enamine moiety. Fortunately, bicyclic acetal **16**[12] was



Scheme 2.