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# Asymmetric Total Synthesis of (−)-Awajanomycin

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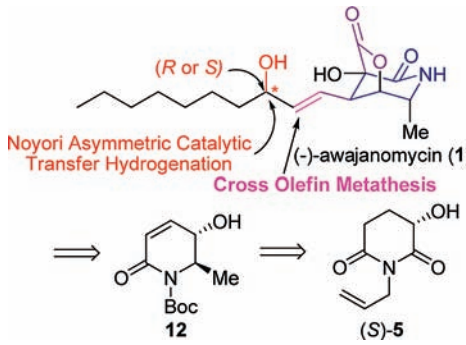
## ABSTRACT




**The first asymmetric total synthesis of the unnatural enantiomer of cytotoxic awajanomycin (1) is reported. The synthetic approach features first a convergent strategy using the cross-olefin metathesis reaction to link the lipid side chain 2 and the piperidinone core structure 3. The second feature of the synthesis resides on the construction of segment 3 from the building block 5 via a three-component tandem reaction on the mixed imide 12. Through this work, the stereochemistry at C-11 and the absolute configuration of awajanomycin were established as 3*R*,5*R*,6*S*,8*S*,11*S*.**

The marine natural product awajanomycin (**1**) (Figure 1) was isolated in 2006 from the marine-derived fungus *Acremonium* sp. AWA16-1, collected from sea mud off Awajishima Island in Japan.[1] Awajanomycin (**1**) exhibited cytotoxic activity against the A549 cells with an $IC_{50}$ value of 27.5 $\mu$g/mL. The stereochemistry at C-11 and the absolute configuration of the natural product remain unknown.

Awajanomycin (**1**) possesses a $\gamma$-lactone-$\delta$-lactam core structure with a fully substituted 2-piperidinone ring bearing four continuous chiral centers including an aza-quaternary carbon. While a racemic synthesis of the 2-piperidinone portion has been reported,[2] the total synthesis of awajanomycin (**1**) has not yet been achieved.

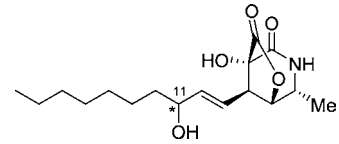



**Figure 1.** Awajanomycin (**1**).

As a continuation of our efforts in developing a 3-hydroxyglutarimide-based synthetic methodology,[3] we report

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(1) Jang, J.-H.; Kanoh, K.; Adachi, K.; Shizuri, Y. *J. Nat. Prod.* **2006**, *69*, 1358–1360.
(2) Hiroya, K.; Kawamoto, K.; Inamoto, K.; Sakamoto, T.; Doi, T. *Tetrahedron Lett.* **2009**, *50*, 2115–2118.

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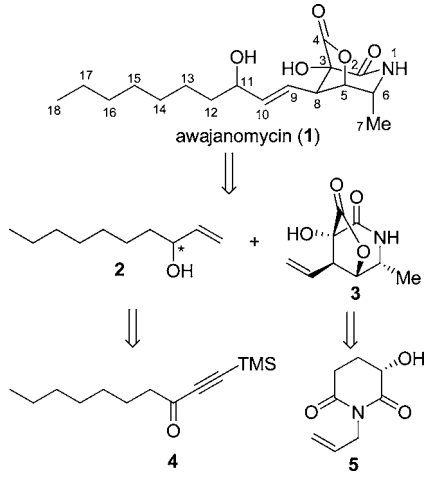
herein the first enantioselective total synthesis of (−)-awajanomycin (**1**), which allowed the determination of both the C-11 stereochemistry and the establishment of the absolute configuration of this natural product.

Our retrosynthetic analysis of **1** is displayed in Scheme 1. The basic strategy was to connect the lipid side chain **2** with the piperidinone moiety **3** by cross-olefin metathesis.[4] The

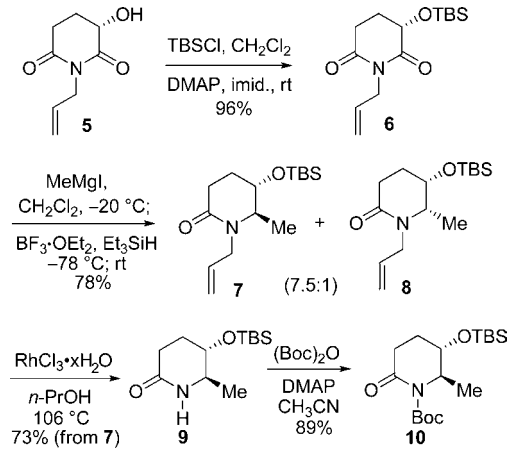
**Scheme 1.** Retrosynthetic Analysis of Awajanomycin (**1**)




allylic alcohol **2** could be prepared by catalytic asymmetric transfer hydrogenation[5] of ketone **4**. The piperidinone segment **3** was envisioned to be synthesized from the piperidinone building block **5**.[6]

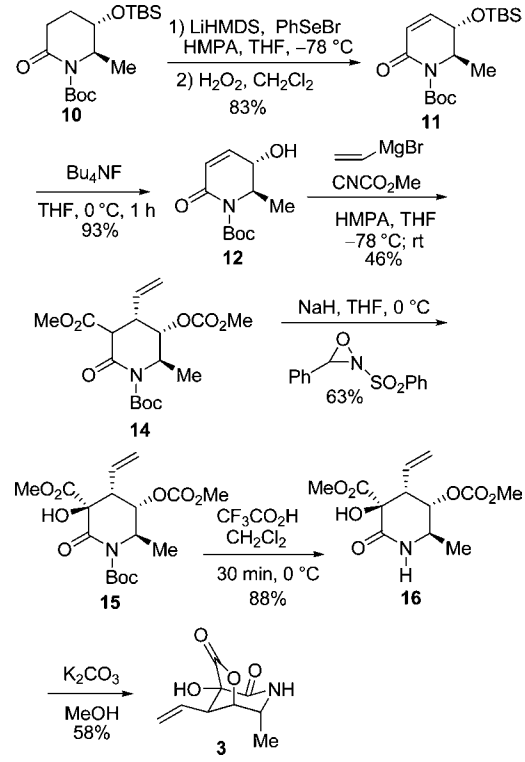
The synthesis of segment **3** started from the known building block **5** (Scheme 2). *O*-Protection (TBSCl, DMAP, imid., $CH_2Cl_2$, rt, overnight) of **5** followed by stepwise reductive methylation of the resultant **6** (MeMgI, $CH_2Cl_2$, −20 °C; $BF_3{\cdot}OEt_2$, $Et_3SiH$, −78 °C ∼ rt) produced regioselectively lactam **7** and its diastereomer **8** in 7.5:1 ratio with 78% combined yield. $RhCl_3{\cdot}xH_2O$-catalyzed *N*-deallylation[7] of **7** was run in refluxing *n*-propanol for 2−3 h, affording lactam **9** in 73% yield. Treatment of lactam **9** with di-*tert*-butyl dicarbonate [$(Boc)_2O$] and a catalytic amount of DMAP in acetonitrile[8] afforded mixed imide **10** in 89% yield.

**Scheme 2.** Synthesis of Mixed Imide **10**




The mixed imide **10** was then converted to α,β-unsaturated lactam **11** by Reich's method.[9] Thus, successive treatment of compound **10** with LiHMDS and PhSeBr, followed by oxidation of the resultant α-phenylselenide with a 30% hydrogen peroxide solution and *in situ* elimination of the resultant selenoxide, gave compound **11** in 83% yield (Scheme 3). To perform a *cis*-diastereoselective vinylation[10]

**Scheme 3.** Synthesis of Segment **3**




at C-4, α,β-unsaturated lactam **11** was desilylated to give the requisite lactam **12** in 93% yield. With the hydroxyl lactam **12** in hand, a one-pot three-component reaction was attempted. Thus, compound **12** was treated with vinyl magnesium bromide in THF at −78 °C then at rt. The resultant enolate intermediate **13** (not shown) was trapped with the Mander reagent[11] (CNCOOMe) (HMPA:**12** = 5:1 molar ratio) at −78 °C, and the reaction was allowed to run at rt. In such a manner, the concomitantly *O*-methoxycarbonylated product **14** was obtained in 46% yield as a 8.3:1 diastereomeric mixture. The stereochemistry of **14** was determined by NOESY experiments. Upon successive treatment of the diastereomeric mixture of compound **14** with sodium hydride and the Davis' oxaziridine[12] in THF at 0 °C, compound **15** was formed in 63% yield as a single diastereomer. Treatment of compound **15** with trifluoroacetic acid in $CH_2Cl_2$ at 0 °C for 30 min provided lactam **16** in

88% yield. The stereochemistry of **16** was first determined by NOESY experiments and finally confirmed by a single-crystal X-ray diffraction analysis (Figure 2). Treatment of

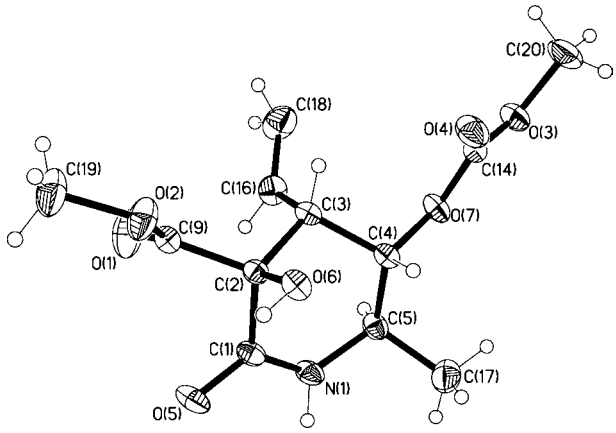
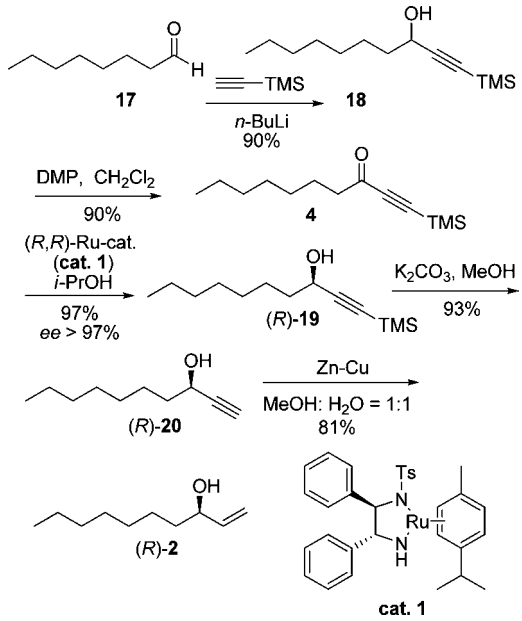



**Figure 2.** X-ray structure of compound **16**.

compound **16** with $K_2CO_3$ in methanol afforded the key segment **3** in 58% yield. Thus, starting from glutarimide derivative **5**, segment **3** was synthesized in 10 steps with an overall yield of 4.9%.

With the synthesis of segment **3** secured, we next turned our attention to the synthesis of the chiral lipid side chain **2** (Scheme 4). Because the stereochemistry of the chiral

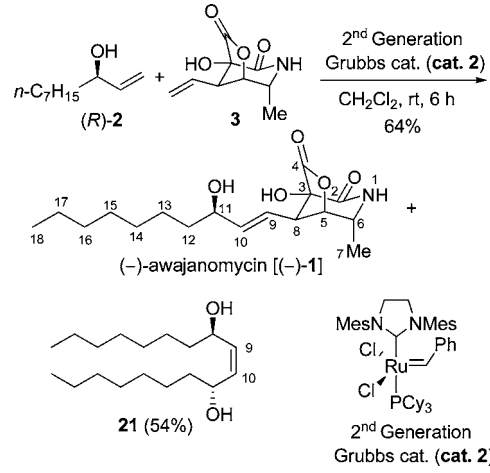
**Scheme 4.** Synthesis of Segment (*R*)-**2**




center at C-11 is unknown, we decided to synthesize the *R*-enantiomer of **2**. The required ketone **4** was synthesized from *n*-octanal **17** by reaction with lithium (trimethylsilyl)acetylenide, followed by Dess−Martin oxidation.[13] Heating a mixture of ketone **4** and (*R*,*R*)-Ru catalyst (**cat. 1**) in *iso*-propanol[5] led to the formation of allylic alcohol **19** in 97% yield. The enantiomeric excess of compound **19** was determined to be 97.9% by chiral HPLC analysis of its *O*-benzyloyl derivative. Treatment of **19** with $K_2CO_3$ in methanol gave the desilylated product **20** in 93% yield that was subjected to Zn−Cu-catalyzed partial hydrogenation[14] to give the desired segment (*R*)-**2** {$[\alpha]_D^{20}$ −8.2 (*c* 1.1, $CHCl_3$); lit.[15] $[\alpha]_D^{25}$ −14.9 (neat)} in 81% yield.

Now the stage was set for the key cross-olefin metathesis reaction (Scheme 5). In the presence of the Grubbs second

**Scheme 5.** Total Synthesis of (−)-Awajanomycin (**1**)




catalyst (**cat. 2**),[16] the coupling of segment (*R*)-**2** with segment **3** was run at rt for 6 h in $CH_2Cl_2$ to give the desired product **1** in 64% yield (based on **3**), along with a homocoupling product (**21**) {*Z*, $J_{9,10}$ < 4 Hz, $[\alpha]_D^{20}$ −7.7 (*c* 1.0, $CHCl_3$)} in 54% yield (based on *R*-**2**). The $^1H$ and $^{13}C$ NMR spectral data of the synthetic product (**1**) are in agreement with those of the natural product.[1] Comparing the optical rotation data of the synthetic compound {$[\alpha]_D^{20}$ −70.5 (*c*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0.21, $CH_3OH$)} with natural awajanomycin (**1**) {$[\alpha]_D^{25}$ +78 (*c* 0.1, $CH_3OH$)} allowed the conclusion that our synthetic compound **1** is the enantiomer of the natural awajanomycin. Through the total synthesis of (−)-**1**, we were able to conclude that the stereochemistry at C-11 of awajanomycin was *S*, and the absolute configuration of the natural awajanomycin is 3*R*,5*R*,6S,8*S*,11*S*.

In summary, we have developed the first enantioselective synthesis of (−)-awajanomycin (**1**) in 16 steps with an overall yield of 1.9% starting from the building block **5** and *n*-octanal **17**. Through this work, the stereochemistry at C-11 of awajanomycin was determined as *S*, and the absolute configuration of the natural product was established as 3*R*,5*R*,6*S*,8*S*,11*S*.

**Acknowledgment.** The authors are grateful to the NSF of China (20832005), the NFFTBS (No. J0630429), and the National Basic Research Program (973 Program) of China (Grant No. 2010CB833206) for financial support.

**Supporting Information Available:** Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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