Communication

Asymmetric Total Synthesis of Herbarumin III: Introduction of the *syn*-1,3-Diol Moiety from an Optically Pure Hydroxy Epoxide Resolved by HKR

Jieun Lee, Young-Hee Jung, and Jinsung Tae*

Department of Chemistry and Center for Bioactive Molecular Hybrids (CBMH), Yonsei University, Seoul 120-749, Korea
**E-mail: jstae@yonsei.ac.kr*
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Herbarumin III (**1**) isolated from the fermentation broth and mycelium of the fungus *Phoma herbarum* displays significant phytotoxic effects against seedlings of *A. hypochondriacus*.[1] The herbarumin macrolides (**1-3**, Figure 1) interact with bovin-brain calmodulin and inhibit the activation of the calmodulin-dependent enzyme cAMP phosphodiesterase. Construction of the 10-membered lactone ring and the streocontrol of *syn*-1,3-diol unit are two major issues in the total synthesis of herbarumin III (**1**). In the previous total synthesis of **1**,[2] the 10-membered lactone ring was synthesized by ring-closing metathesis (RCM) reaction[2a,2b,2d,2e] and Yamaguchi's lactonization method.[2c] Asymmetric synthesis of the *syn*-1,3-diol moiety have been achieved using chiral pool methods,[2a,2b,2d] chemoenzymatic method.[2c] and asymmetric allylation/Sharpless epoxidation method.[2e] Herein, we would like to report an asymmetric total synthesis of herbarumin III (**1**) starting from an enantiomerically pure hydroxy epoxide generated by using Jacobsen's hydrolytic kinetic resolution (HKR) method to install the *syn*-1,3-diol moiety.

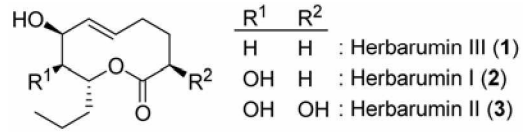
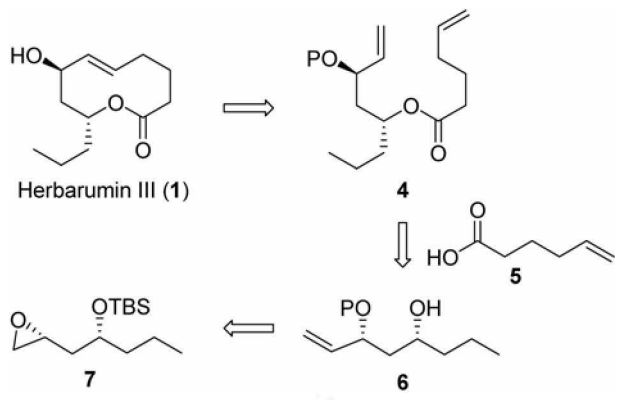


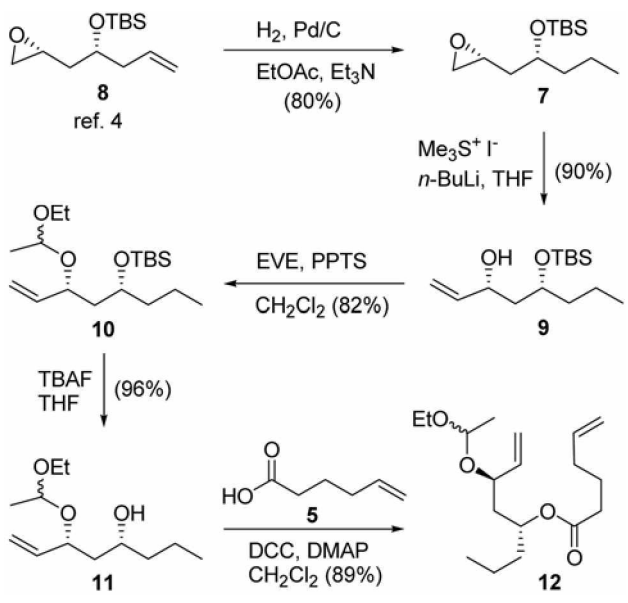
Figure 1

Retrosynthetically (Scheme 1), the macrolactone ring of **1** could be constructed by RCM reaction[3] at the final stage and the corresponding diene **4** would be prepared from alcohol **6** and 5-hexenoic acid (**5**). The *syn*-1,3-diol moiety of **6** could be introduced by using a nucleophilic epoxide opening reaction of epoxide **7**.

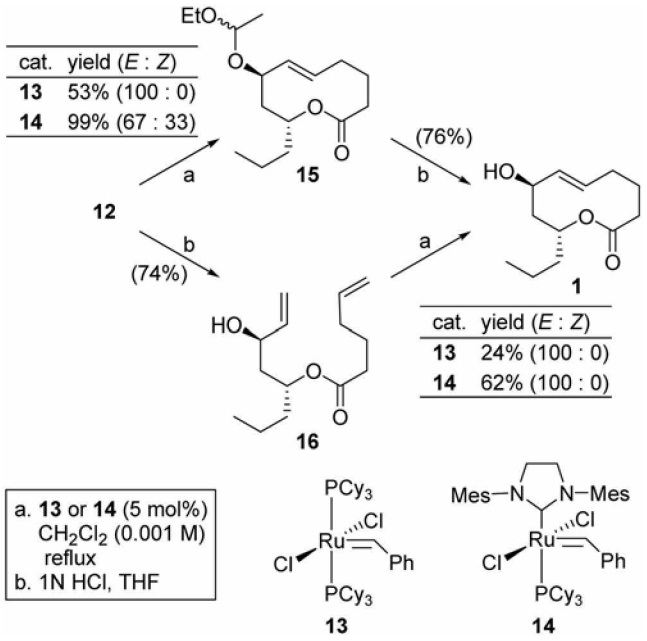
The starting epoxide **7** is prepared from (–)-**8** that we have prepared previously[4] by using Jacobsen's hydrolytic kinetic resolution (HKR) method.[5] Removal of double bond in **8** by catalytic hydrogenation followed by treatment with dimethylsulfonium methylide[6] yields the *syn*-1,3-diol moiety **9** in good yield (Scheme 2). Protection of the allylic alcohol using ethyl vinyl ether (EVE) in the presence of PPTS (pyridinium *para*-toulenesulfonate) in dichloromethane gives **10**



Scheme 1. Retrosynthetic analysis for herbarumin III (**1**).



Scheme 2. Asymmetric synthesis of RCM precursor **12**.



Scheme 3. Completion of total synthesis of herbarumin III (1).

in 82% yield. Subsequent deprotection of the TBDMS (*tert*-butyldimethylsilyl) ether in **10** using TBAF (tetrabutylammonium fluoride) in THF affords alcohol **11** which is then coupled with 5-hexenoic acid (**5**) using DCC and DMAP in dichloromethane to give the RCM precursor **12** in good yield (89%).

With the diene **12** in hand, we next investigated ring-closing metathesis mediated macrolactonization reaction[7] as shown in Scheme 3. Treatment of compound **12** with 5 mol % Grubbs' catalyst **13** under high dilution conditions (0.001 M in CH_2Cl_2) produces **15** in 53% (*E*/Z = 100:0).[8] Under the same conditions, the second generation Grubbs' catalyst **14** yields **15** in 99% yield as an alkene mixture (*E*/Z = 67:33).[9] On the other hand, the cyclization reactions of alcohol **16** with either **13** or **14** produce only herbarumin III (**1**) in 24% and 62% respectively. Overall, the 2nd generation Grubbs' catalyst **14** is better for the cyclization reactions (99% for **12** and 62% for **16**). Spectral data for **1** are consistent with those reported in the literature.[1]

In conclusion, an asymmetric total synthesis of herbarumin III has been accomplished by employing a 7-step sequence starting from an enantiomerically pure hydroxy epoxide generated by using Jacobsen's hydrolytic kinetic resolution (HKR) method. The macrolactone ring was constructed by employing a RCM reaction and the *syn*-1,3-diol moiety was introduced by using a nucleophilic epoxide opening reaction.

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8. The (*E*:*Z*) ratios were determined after conversion to herbarumin (1). The coupling constants between the vinyl protons are J = 16.0 Hz for **15**, J = 16.0 Hz for **1**, and J = 11.3 Hz for (*Z*)-isomer of **1**.
9. The RCM dimerization product is not observed for this ethoxy ethyl protected alcohol substrate **15**.