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

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Herbarumin III (1) isolated from the fermentation broth and mycelium of the fungus \textit{Phoma herbarum} displays significant phytotoxic effects against seedlings of \textit{A. hypochoeridiacus}. 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 stereocontrol of \textit{syn}-1,3-diol unit are two major issues in the total synthesis of herbarumin III (1). In the previous total synthesis of 1, the 10-membered lactone ring was synthesized by ring-closing metathesis (RCM) reaction and Yamaguchi’s lactonization method. Asymmetric synthesis of the \textit{syn}-1,3-diol moiety have been achieved using chiral pool methods, chemoenzymatic method, and asymmetric allylation/Sharpless epoxidation method. 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 \textit{syn}-1,3-diol moiety.

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

The starting epoxide 7 is prepared from (–)-8 that we have prepared previously by using Jacobsen’s hydrolytic kinetic resolution (HKR) method. Removal of double bond in 8 by catalytic hydrogenation followed by treatment with dimethylsulfonium methylide yields the \textit{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-toluenesulfonate) in dichloromethane gives 10.

\begin{figure}
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\includegraphics[width=\textwidth]{Scheme_1}
\caption{Retroynthetic analysis for herbarumin III (1).}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_2}
\caption{Asymmetric synthesis of RCM precursor 12.}
\end{figure}


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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 reaction7 as shown in Scheme 3. Treatment of compound 12 with 5 mol % Grubbs’ catalyst 13 under high dilution conditions (0.001 M in CH2Cl2) 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 nucleophile epoxide opening reaction.

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References

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.