CL-140618 Received: June 24, 2014 | Accepted: July 22, 2014 | Web Released: October 5, 2014

Biomimetic Total Synthesis of (−)-Neroplofurol and (+)-Ekeberin D_4 Triggered by Hydrolysis of Terminal Epoxides

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To accumulate the chemical basis of epoxide-opening cascade biogenesis, chemical syntheses of sesqui- and triterpenoids were performed. The biomimetic total syntheses of (−)-neroplofurol (**1**) and (+)-ekeberin D_4 (**2**) were accomplished by protic acid-catalyzed hydrolysis of the terminal epoxide from nerolidol diepoxide **3** and squalene tetraepoxide **4** through single and double 5-*exo* cyclizations in intermediates **5** and **6**, respectively. This chemical reaction mimics the direct hydrolysis mechanism of epoxide hydrolases, enzymes that catalyze an epoxide-opening reaction to finally produce vicinal diols.

Recently, the epoxide-opening cascade biogenesis of natural polyethers,[1] known as the Cane–Celmer–Westley hypothesis,[2] has progressively been evidenced experimentally. An epoxide hydrolase Lsd19 found by Oikawa and co-workers has realized transformation of the prelasalocid diepoxide to lasalocid A in the final stage of the biosynthesis.[3] The amino acid residues constituting the active site of Lsd19 resemble those of epoxide hydrolases catalyzing direct hydrolysis (Figure 1).[4] The epoxide-opening cascades have also been utilized by synthetic chemists as a method to rapidly construct polyether frameworks.[5] In these examples of epoxide-opening cascades, however, it is almost always the case that the first epoxide-opening is initiated by an intramolecular nucleophilic attack to the neighboring epoxide.[6] Recently, Qu's[7] and our[8] groups reported epoxide-opening cascades triggered by an intermolecular nucleophilic attack of water to the epoxide under basic and acidic conditions, respectively, that mimics the intrinsic role of epoxide hydrolases catalyzing direct hydrolysis. To understand the biogenetic mechanism of epoxide-opening cascades in the absence of intramolecular nucleophiles, we think that it might be important to accumulate the chemical basis. In this contribution, we show a further two examples of the chemical epoxide-opening cascade mimicking the direct hydrolysis mechanism of epoxide hydrolases.

(−)-Neroplofurol (**1**), a nerolidol sesquiterpene bearing one THF ring, was isolated from anti-TB active fractions of the inner stem bark of *Oplopanax horridus*, an abundant deciduous shrub found along the Northern Pacific coast of North America, by Pauli and co-workers (Figure 1).[9] The molecular structure and relative configuration of **1** were elucidated on the basis of spectroscopic studies. The absolute configuration was determined by Huo and co-workers through the total synthesis of (+)-neroplofurol, enantiomeric to natural neroplofurol.[10] (+)-Ekeberin D_4 (**2**) was isolated from the stem bark of *Ekebergia capensis*, a tree widely distributed in Kenya, by Miyase and co-workers (Figure 1).[11] Ekeberin D_4 (**2**) exhibits antiplasmodial activity against FRC-3 with $IC_{50} = 40\,\mu M$, and the triterpenoid structure possesses C_2 symmetry and two THF ring moieties with the same relative configuration as that of **1**. Based on the epoxide-opening cascade mimicking the direct hydrolysis mechanism of epoxide hydrolases,

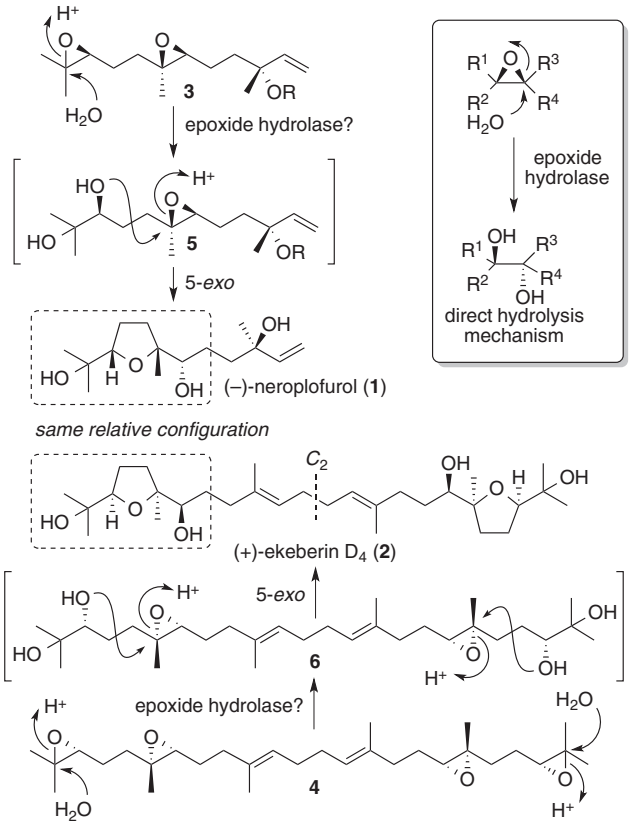

Figure 1. Hypothetical biogenesis of (−)-neroplofurol (**1**) and (+)-ekeberin D_4 (**2**) based on epoxide-opening cascades triggered by direct hydrolysis of the terminal epoxide.

we envisioned that **1** and **2** could biogenetically be derived by hydrolysis of the terminal epoxide from nerolidol diepoxide **3** and squalene tetraepoxide **4** via single and double 5-*exo* cyclizations in intermediates **5** and **6**, respectively. We attempted the biomimetic synthesis of **1** and **2** along this line.

Iodination of the known optically active epoxy alcohol **7** (er = 95.5:4.5)[12] followed by zinc reduction of the resulting iodide furnished (3*R*,6*E*)-nerolidol (**8**) in 88% yield over two steps (Figure 2). After triethylsilyl (TES) protection of the tertiary alcohol, triene **9** was subjected to Shi asymmetric epoxidation with a chiral L-ketone catalyst to afford the required diepoxide **3** (R = TES) in an approximately 5:1 dr.[13] Treatment of **3** (R = TES) under our previous epoxide-opening cascade conditions[8] (0.3 equiv of TfOH, THF/H_2O (9:1), 0 °C, 42 h) gave the desired (−)-neroplofurol (**1**) in 29% yield along with many other complex mixtures.[14]

The spectral data (^1H and ^{13}C NMR) and optical rotation of synthetic **1**, $[\alpha]_D^{25}$ −23.4 (*c* 0.026, MeOH), were consistent with those reported for the natural product, lit.,[9] $[\alpha]_D^{25}$ −23.7 (*c* 0.013,

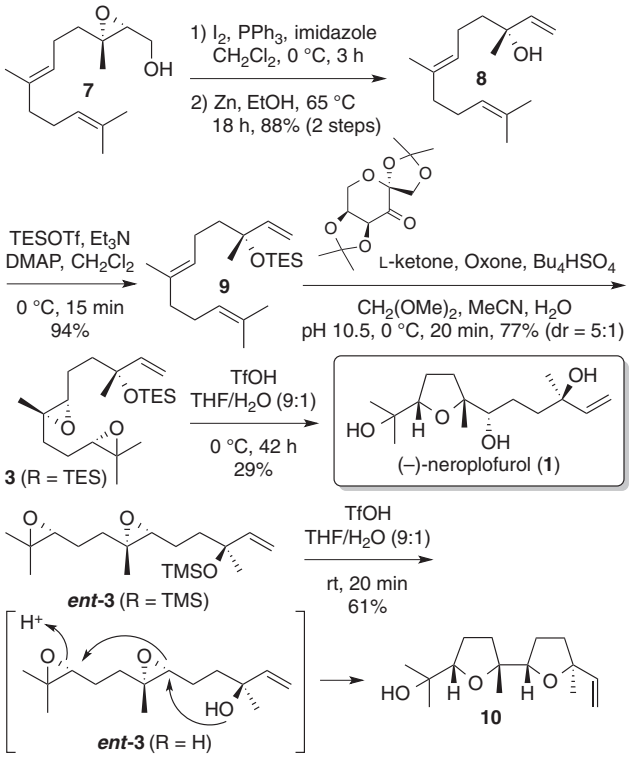

Figure 2. Biomimetic total synthesis of (−)-neroplofurol (**1**).

MeOH). To successfully obtain (−)-**1** in the last reaction, the hydrolysis of the terminal epoxide to generate **5** (R = TES) should occur prior to desilylation; this is because when diepoxide ***ent*-3** (R = TMS),[15] enantiomeric to **3** (R = TMS), was exposed to the cyclization conditions, compound **10** reported by Marshall and Hann[17] was produced in 61% yield, indicating that deprotection of the TMS group has occurred prior to the epoxide-opening.

Next, we turned our attention to the biomimetic total synthesis of (+)-ekeberin D_4 (**2**). Squalene tetraepoxide **4**[15,16] reported by McDonald et al. was treated under the cyclization conditions and a large number of spots were observed on the TLC (Figure 3). However, since we have already synthesized (+)-ekeberin D_4 (**2**) by another method,[18] we assumed that synthetic **2** could be isolated from the complex mixtures, albeit in only 6% yield.[14,19] The spectral data (^{1}H and ^{13}C NMR) and optical rotation of synthetic **2**, $[\alpha]_D^{27}$ +5.94 (*c* 0.245, $CHCl_3$), were identical to those reported for the natural and another synthetic product, lit.,[11] $[\alpha]_D$ +8.00 (*c* 0.420, $CHCl_3$); another synthetic:[18] $[\alpha]_D^{27}$ +7.80 (*c* 0.19, $CHCl_3$). However, when we performed derivatization of synthetic **2** to diMTPA esters, we noticed that **2** was not a single isomer but a 2:1 mixture. We guessed that *meso*-compound **11** was present as an impurity in **2**, by comparing the ^{1}H NMR data of a 2:1 mixture of synthetic (*R*)-MTPA-**2** and (*R*)-MTPA-**11**, respectively, with those of (*R*)- and (*S*)-MTPA-**2** derived from the natural product by Miyase et al.[11] We confirmed that the impurity was **11** through independently synthesizing (*R*)-MTPA-**2** and (*R*)-MTPA-**11** as a single diastereomer by another method.[18,21]

Although it was found from these results that the production of (+)-ekeberin D_4 (**2**) could be reproduced by an intermolecular nucleophilic attack of water to both terminal epoxides of **4**, it was envisaged that regioselectivity would be considerably low compared to that of other squalene polyepoxides.[8] Therefore, if the hypothetical intermediate **6**, an immediate product obtained after hydrolysis of both terminal epoxides, could only be generated, the yield of **2** would be improved. To demonstrate this, we attempted the synthesis of the hypothetical intermediate tetraol **6** and its conversion to (+)-ekeberin D_4 (**2**).

The known diol **12**[22] with a high optical purity (er = 97.5:2.5) was protected as diTBS ether **13**, which was subjected to Shi epoxidation using D-ketone to afford monoepoxide **14** in a regio- and diastereoselective manner (Figure 4).[16,18] Deacetylation of **14** and bromination of the resulting allylic alcohol produced unstable allylic bromide **15**, which was substituted with sodium benzenesulfinate to yield allylic sulfone **16**. Alkylation of a lithio derivative of **16** with **15** followed by reductive desulfonylation[23] of **17** resulted in dimerization in a good yield. Desilylation of tetraTBS ether **18** with TBAF in refluxing THF in the presence of AcOH generated the hypothetical biogenetic intermediate **6**, which was exposed to the same cyclization conditions as those in Figure 3 to furnish the desired (+)-ekeberin D_4 (**2**) in 63% yield over two steps. The spectral characteristics (^{1}H and ^{13}C NMR) of synthetic (+)-ekeberin D_4 (**2**), $[\alpha]_D^{30}$ +8.22 (*c* 0.19, $CHCl_3$), from **6** were consistent with those of the natural and another synthetic product.

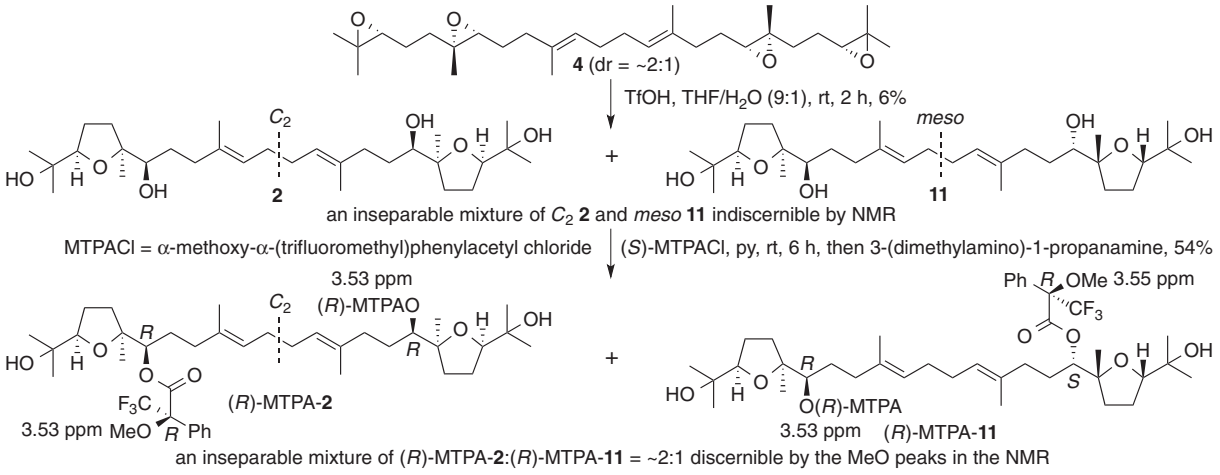

Figure 3. Biomimetic total synthesis of (+)-ekeberin D_4 (**2**).

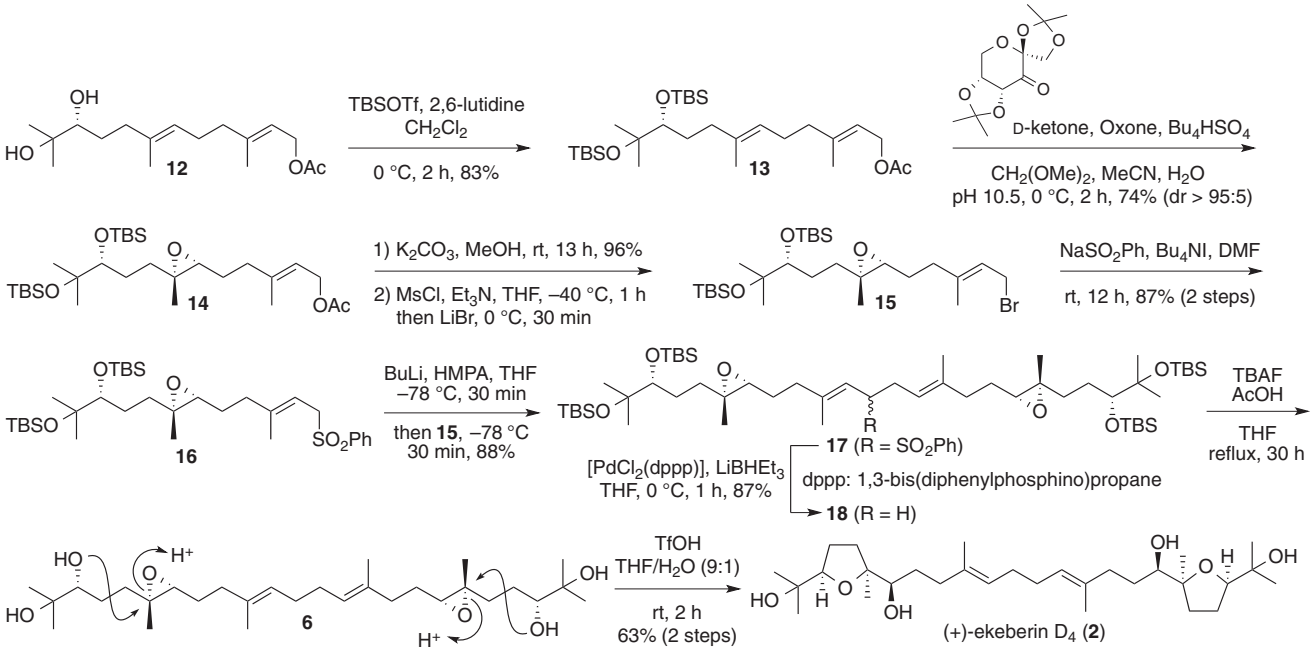

Figure 4. Synthesis of hypothetical intermediate tetraol **6** and its conversion to (+)-ekeberin D_4 (**2**).

In conclusion, we have achieved biomimetic epoxide-opening cascades of (−)-neroplofurol (**1**) and (+)-ekeberin D_4 (**2**) through single and double 5-*exo* cyclizations, respectively, triggered by triflic acid-catalyzed hydrolysis of terminal epoxides. In the case of squalene polyepoxide precursors, **4** and other substrates,[8] it was found that the yields of the cascade reaction were of a wide range depending on the number, position, and configuration of the epoxides. It would be significant to understand the biogenetic mechanism so that the epoxide-opening cascade mimicking the direct hydrolysis mechanism of epoxide hydrolases could chemically be reproduced. Improvement of the reaction efficiency is under investigation.

We are grateful to Prof. T. Miyase for generously providing the ^{1}H NMR spectrum of natural (+)-ekeberin D_4. This work was financially supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science and the Asahi Glass Foundation.

Supporting Information is available electronically on J-STAGE.

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