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Biomimetic Epoxide-Opening Cascades of Oxasqualenoids Triggered by Hydrolysis of the Terminal Epoxide

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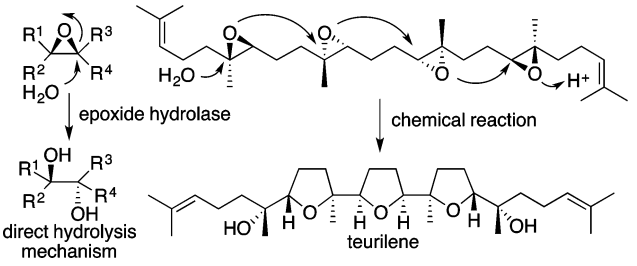
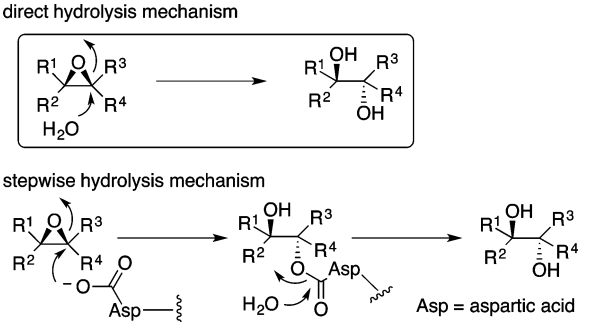
ABSTRACT



The biomimetic epoxide-opening cascades from squalene polyepoxides 4–6 to triterpene polyethers (oxasqualenoids) teurilene (1), glabrescol (2), and omaezakianol (3), respectively, were reproduced in a single event by chemical reaction. These cascades proceeded through the 5-*exo* tandem cyclization triggered by Brønsted acid-catalyzed hydrolysis of the terminal epoxide, mimicking the direct hydrolysis mechanism of epoxide hydrolases.

Organisms exquisitely produce biologically significant, complex, and diverse natural products. It is well-known that steroidal skeletons such as lanosterol are biosynthesized in a single event from 2,3-oxidosqualene via the protosterol cation by cyclases.[1] Such cascade cyclization is also invoked in neurotoxic ladderlike polyethers such as brevetoxin B as a biogenetic hypothesis.[2] The epoxide-opening cascade biogenesis was originally proposed for ionophoric polyether antibiotics as in the Cane–Celmer–Westley hypothesis in 1983,[3] and now it has been thought that it is universal for natural polyethers including marine toxins, acetogenins, and triterpenoids.[4] The epoxide-opening cascades have also attracted great interest of chemists from the viewpoint of chemical synthesis and have been utilized as a method to rapidly construct polyether frameworks.[5] However, the existence of enzymes catalyzing the epoxide-opening cascade reaction has been a puzzle for a long time.

Scheme 1. Two Mechanisms for Epoxide Hydrolases



Recently, direct experimental evidence on enzymatic epoxide-opening reactions was reported by Oikawa et al.[6]

(1) Christianson, D. W. *Chem. Rev.* **2006**, *106*, 3412.
(2) (a) Nakanishi, K. *Toxicon* **1985**, *23*, 473. (b) Yamazaki, M.; Izumikawa, M.; Tachibana, K.; Satake, M.; Itoh, Y.; Hashimoto, M. *J. Org. Chem.* **2012**, *77*, 4902.
(3) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.
(4) (a) Gallimore, A. G. *Nat. Prod. Rep.* **2009**, *26*, 266. (b) Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235.
(5) Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250.
(6) Shichijo, Y.; Migita, A.; Oguri, H.; Watanabe, M.; Tokiwano, T.; Watanabe, K.; Oikawa, H. *J. Am. Chem. Soc.* **2008**, *130*, 12230.

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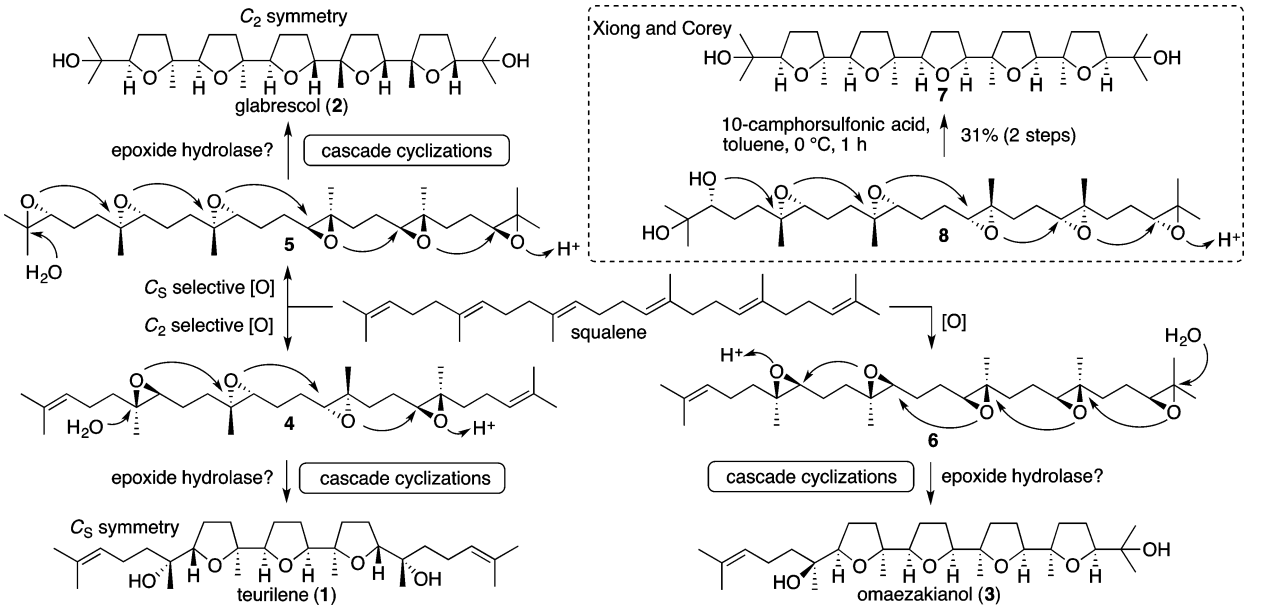
Scheme 2. Hypothetical Biogenesis of Some Oxasqualenoids **1**–**3** Based on Epoxide-Opening Cascades Triggered by Direct Hydrolysis of the Terminal Epoxide and Previous Work by Xiong and Corey[12]



Transformation of the prelasalocid diepoxide to lasalocid A was achieved by an epoxide hydrolase Lsd19 in the final stage of the biosynthesis. Lsd19 belongs to epoxide hydrolases, and the amino acid residues composing the active site are similar to those of epoxide hydrolases catalyzing the reaction that proceeds not with stepwise mechanism by way of covalent bond ester intermediates between substrates and the enzyme, but with a direct hydrolysis mechanism (Scheme 1).[7] In many examples of epoxide-opening cascades, it is almost always the case that intramolecular nucleophiles such as π-electrons, hydroxy and carboxy groups, and so on trigger the ring-opening of the neighboring epoxide. In this contribution, we report biomimetic and chemical epoxide-opening cascades triggered by an intermolecular nucleophilic attack of water to the terminal epoxide that mimics an intrinsic role of epoxide hydrolases catalyzing direct hydrolysis.

During the course of our and other chemical syntheses of some oxasqualenoids such as cytotoxic teurilene (**1**),[8] glabrescol (**2**),[9] and omaezakianol (**3**),[10] we became interested in the possibility of their epoxide-opening cascade biogenesis. The hypothetical biogenesis of **1**–**3**, isolated from marine and terrestrial plants,[11] is shown in Scheme 2. Considering the epoxide-opening cascade triggered by an intermolecular nucleophilic attack of water to the terminal epoxide that mimics an intrinsic role of epoxide hydrolases catalyzing direct hydrolysis, compounds **1** and **3** could stereospecifically be derived from chiral tetraepoxide **4**[8a,9a] and pentaepoxide **6**,[10b] respectively, in a single event with inversion of configuration upon regioselective opening of each epoxide. On the other hand, optically active glabrescol (**2**) could be provided from *meso* hexaepoxide **5** in the same manner, if the enantiotopic terminal epoxides were differentiated.[9a,c] Previously, Xiong and Corey reported the chemical epoxide-opening cascade of substrate **8** related to our hypothesis; however, it was from pentaepoxy diol **8** to non-natural pentaTHF compound **7** initiated by a nucleophilic attack of the intramolecular hydroxy group to the neighboring epoxide.[12] Although it has been unknown whether there are epoxide hydrolases catalyzing our hypothetical biogenesis triggered by direct hydrolysis or not, here we show that the biomimetic epoxide-opening cascades from squalene polyepoxides **4**–**6** to oxasqualenoids **1**–**3**, respectively, can be reproduced in a single event by chemical reaction.

The stereoselective syntheses of key substrates **4**–**6** are depicted in Scheme 3. Preparation of C_2 symmetric

(7) (a) Minami, A.; Migita, A.; Inada, D.; Hotta, K.; Watanabe, K.; Oguri, H.; Oikawa, H. *Org. Lett.* **2011**, *13*, 1638. (b) Hotta, K.; Chen, X.; Paton, R. S.; Minami, A.; Li, H.; Swaminathan, K.; Mathews, I. I.; Watanabe, K.; Oikawa, H.; Houk, K. N.; Kim, C.-Y. *Nature* **2012**, *483*, 355.

(8) (a) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299. (b) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792. (c) Rodríguez-López, J.; Crisóstomo, F. P.; Ortega, N.; López-Rodríguez, M.; Martín, V. S.; Martín, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 3659.

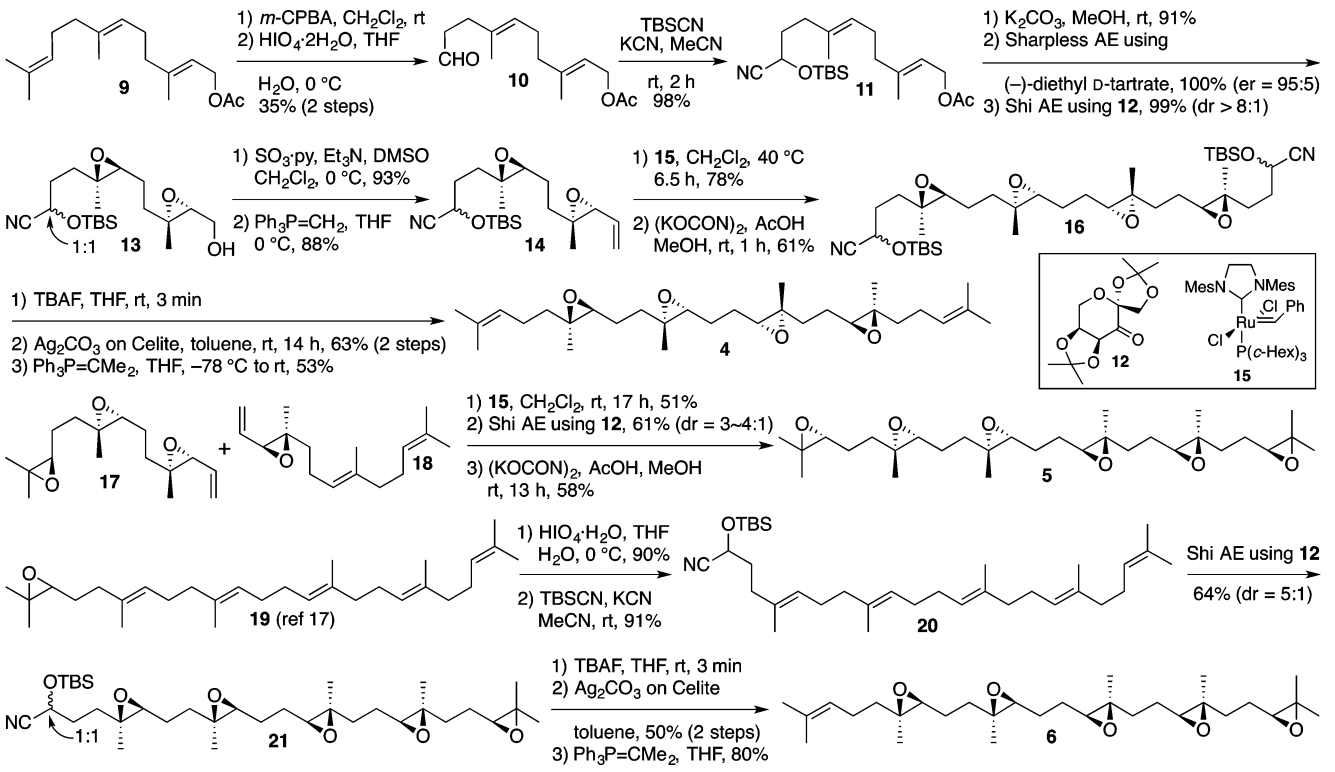
(9) (a) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **2000**, *122*, 7124. (b) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328. (c) Transformation to (−)-glabrescol (**2**) from a C_2 symmetric squalene hexaepoxide, diastereomeric to *meso* hexaepoxide **5**, by a base-promoted middle-to-terminal double epoxide-opening cascade is reported. See: Yang, P.; Li, P.-F.; Qu, J.; Tang, L.-F. *Org. Lett.* **2012**, *14*, 3932.

(10) (a) Morimoto, Y.; Okita, T.; Kambara, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2538. (b) Xiong, Z.; Busch, R.; Corey, E. J. *Org. Lett.* **2010**, *12*, 1512.

(11) (a) Suzuki, T.; Suzuki, M.; Furusaki, A.; Matsumoto, T.; Kato, A.; Imanaka, Y.; Kurosawa, E. *Tetrahedron Lett.* **1985**, *26*, 1329. (b) Morita, H.; Kishi, E.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Phytochemistry* **1993**, *34*, 765. (c) Harding, W. W.; Lewis, P. A.; Jacobs, H.; McLean, S.; Reynolds, W. F.; Tay, L.-L.; Yang, J.-P. *Tetrahedron Lett.* **1995**, *36*, 9137. (d) Matsuo, Y.; Suzuki, M.; Masuda, M.; Iwai, T.; Morimoto, Y. *Helv. Chim. Acta* **2008**, *91*, 1261.

(12) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831.

Scheme 3. Stereoselective Syntheses of Squalene Polyepoxides **4**–**6**



tetraepoxide **4** began with epoxidation of commercially available *trans*,*trans*-farnesyl acetate (**9**). Hydrolysis of the terminal epoxide followed by oxidative cleavage of the resulting vicinal diol afforded aldehyde **10**. After closely examining protective groups of the aldehyde, we found a TBS ether of cyanohydrin[13] was suitable for the latter conversion. Deacetylation and subsequent Sharpless asymmetric epoxidation (AE) of the resultant allylic alcohol provided an epoxy alcohol as a 1:1 mixture at the cyanohydrin moiety. AE of the remaining alkene with Shi's L-ketone **12**[14] then gave diepoxy alcohol **13**. Parikh–Doering oxidation of the alcohol **13** and Wittig methylenation of the resulting aldehyde furnished alkene **14**. The dimerization of **14** was carried out in 78% yield by olefin metathesis with the Grubbs catalyst **15**, and diimide reduction of the product provided tetraepoxide **16**. The TBS ether **16** was subjected to desilylation with TBAF to immediately afford a labile cyanohydrin, which upon treatment with Fétizon's reagent (Ag_2CO_3 on Celite) in toluene regenerated the aldehyde functionality. The Wittig olefination of the dialdehyde with an excess of $Ph_3P{=}CMe_2$ gave the requisite tetraepoxide **4**.[15]

The cross-metathesis[16] of known monoepoxy triene **18**[12] with triepoxy alkene **17**[10a] in the presence of the Grubbs catalyst **15** afforded the metathesis product. Shi AE of the triene proceeded in a chemoselective manner at the trisubstituted alkenes to provide a hexaepoxy alkene, diimide reduction of which furnished *meso* hexaepoxide **5**. Pentaepoxide **6** was prepared from easily available squalene monoepoxide **19**[17] by the same methodology as that of **4** using the TBS ether of cyanohydrin. The exhaustive epoxidation[10b,12] of pentaene **20** was achieved with a large excess of Shi's L-ketone **12** to afford pentaepoxide **21** in 64% yield. Regeneration of the terminal trisubstituted alkene was carried out by the aforementioned method, providing the squalene pentaepoxide **6**.

After investigating the epoxide-opening cascades of polyepoxides **4**–**6** under various reaction conditions (Brønsted and Lewis acid catalysts, solvent, temperature, time, and so forth), we found that TfOH (0.2–0.3 equiv) in THF/H_2O (9:1) at rt for 10 min to 24 h afforded the best yields in the reactions (Scheme 4). Thus, optically active tetraepoxide **4** and pentaepoxide **6** could be converted into *meso* teurilene (**1**) and (+)-omaezakianol (**3**) in 28 and 33% yields, respectively. On the other hand, *meso* hexaepoxide **5** was transformed into (±)-glabrescol (**2**) in less than 10% yield.[18] Respective ^1H and ^{13}C NMR spectra of the

(13) Yamamoto, K.; Watanabe, N.; Matsuda, H.; Oohara, K.; Araya, T.; Hashimoto, M.; Miyairi, K.; Okazaki, I.; Saito, M.; Shimizu, T.; Kato, H.; Okuno, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4932.

(14) (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 5377.

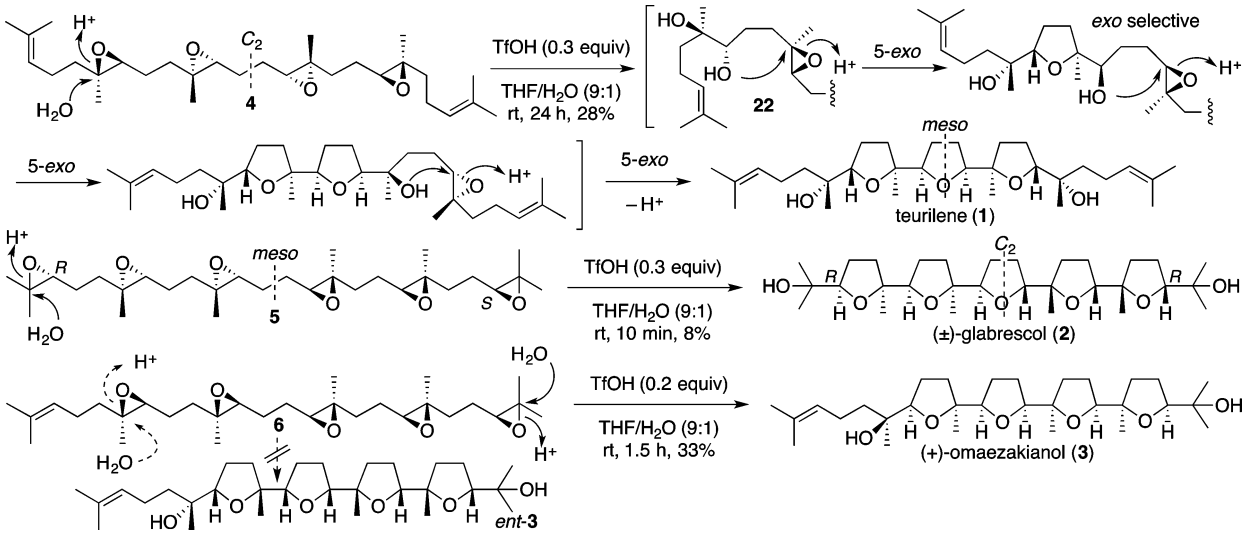
(15) A synthesis of **4** by the other method is reported. See:Ujihara, K. Ph.D. Dissertation, The University of Tokyo, Tokyo, Japan, 2004.

(16) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(17) van Tamelen, E. E.; Curphey, T. J. *Tetrahedron Lett.* **1962**, *3*, 121.

(18) In these reactions starting materials **4**–**6** were completely consumed, and many products other than **1**–**3** were also observed; however, we could not isolate identifiable ones.

Scheme 4. Epoxide-Opening Cascades of Squalene Polyepoxides **4**–**6** to Oxasqualenoids **1**–**3**, Respectively, Triggered by Hydrolysis of the Terminal Epoxide



synthetic compounds **1**–**3** were identical to those of previously reported natural and synthetic ones.[8−10,11a,11c,11d]

On the basis of the cascade cyclizations of similar substrates reported by Corey[10b,12] and McDonald,[19] we discuss mechanistic aspects on the epoxide-opening cascades of polyepoxides **4**–**6**. In the transformation from tetraepoxide **4** to teurilene (**1**), the first step would be initiated by hydrolysis of the terminal epoxide, to which water seems more accessible, with inversion of configuration at the more substituted epoxide carbon to afford diol intermediate **22** (Scheme 4). The type of 2,5-linked polyTHF such as **1** could be formed from the diol **22** via the kinetically favored 5-*exo*[20] cascade cyclizations similar to those of **8** in Scheme 2.[10b,12] Such an intramolecular attack of the neighboring epoxide oxygen to the less substituted carbon of the terminal epoxide as shown in **4** of Scheme 2 should not be the first step, because under acidic conditions the intramolecular attack occurs at the more substituted carbon of the terminal epoxide, and subsequently, polyepoxide substrates such as **4** undergo 6-*endo*[20] cascade cyclizations to ladderlike fused polycyclic ethers via an epoxonium ion intermediate proposed by McDonald et al.[19] Whichever terminal epoxide is hydrolyzed, only *meso* teurilene (**1**) is produced due to C_2 symmetric **4**. Similarly, the racemic glabrescol (±)-**2** was obtained from the *meso* hexaepoxide **5** in low yield along with many other complex mixtures.[9c] In the initial hydrolysis of pentaepoxide **6**, the right and left terminal epoxides need to be precisely differentiated because if the epoxide-opening cascade were initiated from the left terminal epoxide, an undesired compound ***ent*-3**, antipodal to the natural **3**, would be formed. Practically, the initial hydrolysis took place at the right terminal epoxide which was thought to be less hindered, because the optical rotation of the synthetic (+)-omaezakianol (**3**), $[\alpha]^{29}_{D}$ +18.1 (*c* 0.20, $CHCl_3$), was in good agreement with those of the natural product, $[\alpha]^{20}_{D}$ +15.8 (*c* 0.59, $CHCl_3$),[11d] and other synthetic (+)-**3**'s, $[\alpha]^{29}_{D}$ +17.7 (*c* 0.57, $CHCl_3$)[10a] and $[\alpha]^{23}_{D}$ +17.1 (*c* 1.0, $CHCl_3$).[10b] Without the aforementioned epoxide-opening cascade mechanism initiated by hydrolysis of the terminal epoxide, the stereochemical relationship between substrates **4**–**6** and products **1**–**3**, respectively, could not reasonably be explained.

In conclusion, we have realized the biomimetic and chemical epoxide-opening cascades of squalene polyepoxides **4**–**6** to oxasqualenoids **1**–**3**, respectively, through the 5-*exo* cascade cyclizations triggered by the protic acid-catalyzed hydrolysis of the terminal epoxide. Because epoxide hydrolase Lsd19 is responsible for the epoxide-opening reaction in the final polyether formation of lasalocid A,[6,7] some epoxide hydrolases with a direct hydrolysis mechanism might also be implicated in the enzymatic epoxide-opening cascades of squalene polyepoxides **4**–**6**. In particular, to generate the optically active glabrescol (**2**) from *meso* hexaepoxide **5** enzymatic participation would be so essential that the (*R*)-epoxide of the two enantiotopic terminal ones has to be selectively hydrolyzed (Scheme 4). Details of the reaction mechanism and the possibility of the epoxide hydrolase-triggered epoxide-opening cascades are under investigation.

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Supporting Information Available. Full experimental details and spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodrîguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515.

(20) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

The authors declare no competing financial interest.