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A Short Total Synthesis of (+)-Omaezakianol via an Epoxide-Initiated Cationic Cascade Reaction

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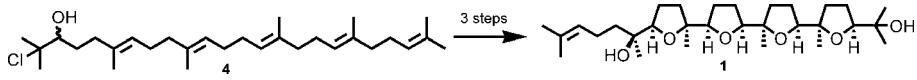
ABSTRACT



(+)-Omaezakianol was synthesized in only three steps from racemic chlorohydrin 4 by Shi epoxidation followed by cascade cyclization and reduction.

Natural products constitute a remarkably diverse and valuable collection of biologically active compounds.[1] However, they are often not available in amounts needed for study or development as biological reagents or medicines. In such instances, total chemical synthesis becomes indispensable to both research and further development. Often, nature uses cationic "cascade"-type polycyclization processes to produce topologically complex structures. As demonstrated many times over the past five decades, this strategy is also very useful in the design of short, simple, and aesthetically pleasing chemical syntheses.[2] Despite numerous elegant examples in the synthetic literature, much remains to be learned about the application of cascade-type chemistry for complex molecular synthesis. We report herein the use of an epoxide-initiated cationic cascade reaction[3,4] to achieve an efficient total synthesis of (+)-omaezakianol (**1**).

(+)-Omaezakianol (**1**), a member of the oxasqualenoid family[5] of squalene-derived triterpene polyethers, was recently isolated in milligram amounts from the red alga *Laurencia omaezakiana* Masuda.[6] These triterpene polyethers are believed to be biosynthesized from squalene via polyepoxide intermediates by cascade cyclizations.[5,7] Although there is no report on the biological activity on **1**, it is expected to have ionophoric functions as recent studies have shown that oligotetrahydrofuranyl derivatives have strong interactions with metal cations.[8] The cytotoxicities[9] exhibited by some members of this family may be linked to their ionophoric functions.[8a] The unique nonsymmetric structure with four *cis*-THF rings *anti* to each other combined with

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(1) For recent reviews, see: (a) Li, J. W.-H.; Vederas, J. C. *Science* **2009**, *325*, 161–165. (b) Rishton, G. M. *Am. J. Cardiol.* **2008**, *101*, 43D–49D. (c) Itokawa, H.; Morris-Natschke, S. L.; Akiyama, T.; Lee, K.-H. *J. Nat. Med.* **2008**, *62*, 263–280. (d) Baker, D. D.; Chu, M.; Oza, U.; Rajgarhia, V. *Nat. Prod. Rep.* **2007**, *24*, 1225–1244. (e) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329–8351. (f) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022–1037.

(2) Review: Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. J. *Angew. Chem., Int. Ed. Engl.* **2006**, *46*, 7134–7186.

(3) For previous work using epoxide-initiated cationic cascade reactions for the synthesis of squalene-derived triterpene polyethers, see: (a) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831–4832. (b) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328–9329.

(4) For a recent review, see: Vilotijevic, I.; Jamison, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250–5281.

(5) For reviews, see: (a) Connolly, J. D.; Hill, R. A. *Nat. Prod. Rep.* **2003**, *20*, 640–659. (b) Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235–246.

(6) Matsuo, Y.; Suzuki, M.; Masuda, M.; Iwai, T.; Morimoto, Y. *Helv. Chim. Acta* **2008**, *91*, 1261–1266.

(7) (a) Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855–2862. (b) Rudi, A.; Yosief, T.; Schleyer, M.; Kashman, Y. *Tetrahedron* **1999**, *55*, 5555–5566. (c) Kashman, Y.; Rudi, A. *Phytochem. Rev.* **2004**, *3*, 309–323.

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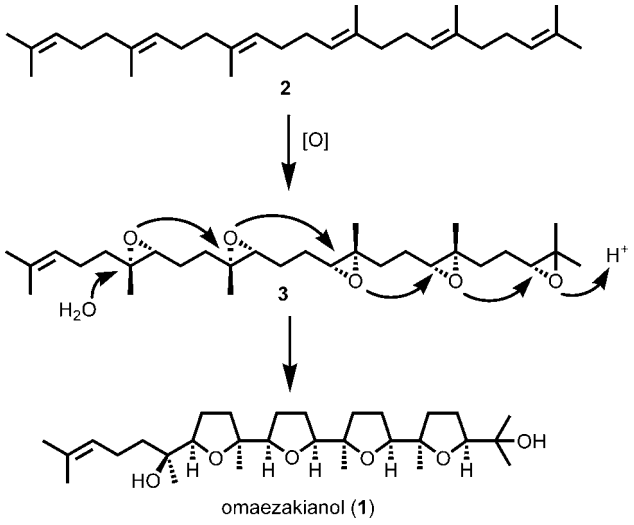
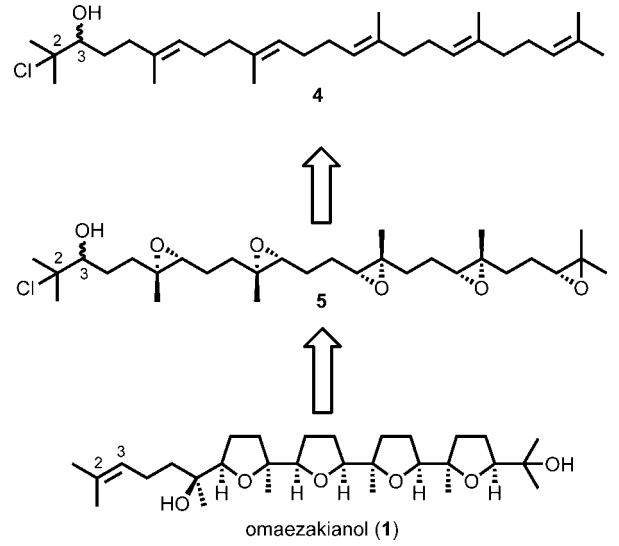
Scheme 1. Hypothetical Biogenesis of **1**



Scheme 2. Synthetic Strategy



the interesting biogenesis and potential biological activity made it an interesting target for total synthesis. Recently, Morimoto and co-workers reported the first total synthesis of this compound and established its absolute configuration.[10] The synthesis was accomplished in 24 steps from farnesol. In this paper, we describe a total synthesis of **1** which requires only six steps from squalene via a biomimetic epoxide-opening cascade reaction.

Our synthetic strategy was inspired by the hypothetical biosynthethic pathway of **1**, which involves a regioselective asymmetric epoxidation of five out of six double bonds of squalene (**2**) followed by a subsequent cascade cyclization of the pentaepoxide **3** to give **1** (Scheme 1). Mimicking this biogenesis through the chemical synthesis presents two challenges: regioselective asymmetric pentaepoxidation of squalene (**2**) and unidirectional cascade cyclization of the pentaepoxide **3**. Our approach relied on squalene-derived chlorohydrin **4** as the key intermediate (Scheme 2). We expected the chlorohydrin group in **4** to serve not only as a masking group for the terminal double bond to achieve regioselective pentaepoxidation but also as the initiating group (3-hydroxyl group)[3,4] for the epoxide-opening cascade cyclization. Since the chlorohydrin moiety in **4** serves as a masking group for the olefin in **1**, the chirality at the 3-position is of no consequence and the racemic mixture can be used.

As outlined in Scheme 3, the synthesis started with (±)-2,3-oxidosqualene (**6**), which was easily prepared in two steps from squalene (**2**) by a reported procedure.[11] Treatment of epoxide **6** with HCl in ether gave a 1:1 mixture of chlorohydrin **4**[12] and its regioisomer **7** in 92% yield. The mixture was easily separated by flash column chromatography, and compound **7** could be converted back to epoxide **6** in 94% yield by treatment with potassium carbonate in methanol. Asymmetric epoxidation of **4** with Shi catalyst **8**[13] (3 equiv, 60 mol % per double bond) gave pentaepoxide **5**. Without purification, compound **5** was treated with camphorsulfonic acid (CSA) in acetone to induce an epoxide-opening cascade cyclization which afforded the pentacyclic compound **9** in 21% overall yield from **4** after chromatographic purification on silica gel column.[3a] Since racemic **4** was used, **9** was obtained as a 1:1 mixture of two diastereomers as shown by the ^{1}H NMR spectrum.[14] Reduction of this diastereomeric mixture **9** with sodium in refluxing ether generated the terminal double bond and opened the tethered

(8) (a) Morimoto, Y.; Iwai, T.; Yoshimura, T.; Kinoshita, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2005–2010. (b) Bellenie, B. R.; Goodman, J. M. *Tetrahedron Lett.* **2001**, *42*, 7477–7479. (c) Tsukube, H.; Takagi, K.; Higashiyama, T.; Iwachido, T.; Hayama, N. *Inorg. Chem.* **1994**, *33*, 2984–2987. (d) Schultz, W. J.; Etter, M. C.; Pocius, A. V.; Smith, S. *J. Am. Chem. Soc.* **1980**, *102*, 7981–7982. (e) Wagner, H.; Harms, K.; Koert, U.; Meder, S.; Boheim, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2643–2646.

(9) (a) Suzuki, T.; Suzuki, M.; Furusaki, A.; Matsumoto, T.; Kato, A.; Imanaka, Y.; Kurosawa, E. *Tetrahedron Lett.* **1985**, *26*, 1329–1332. (b) Morita, H.; Kishi, E.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Phytochemistry* **1993**, *34*, 765–771.

(10) Morimoto, Y.; Okita, T.; Kambara, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2538–2541.

(11) (a) Ceruti, M.; Balliano, G.; Viola, F.; Cattel, L.; Gerst, N.; Schuber, F. *Eur. J. Med. Chem.* **1987**, *22*, 199–208. (b) van Tamelen, E. E.; Curphey, T. J. *Tetrahedron Lett.* **1962**, *3*, 121–124. (c) van Tamelen, E. E.; Sharpless, K. B. *Tetrahedron Lett.* **1967**, *8*, 2655–2659.

(12) The preparation of (*S*)-**4** (69% ee) has been reported in two steps with 46% yield from racemic **6**; see: Raina, S.; Singh, V. K. *Tetrahedron* **1995**, *51*, 2467–2476.

(13) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.

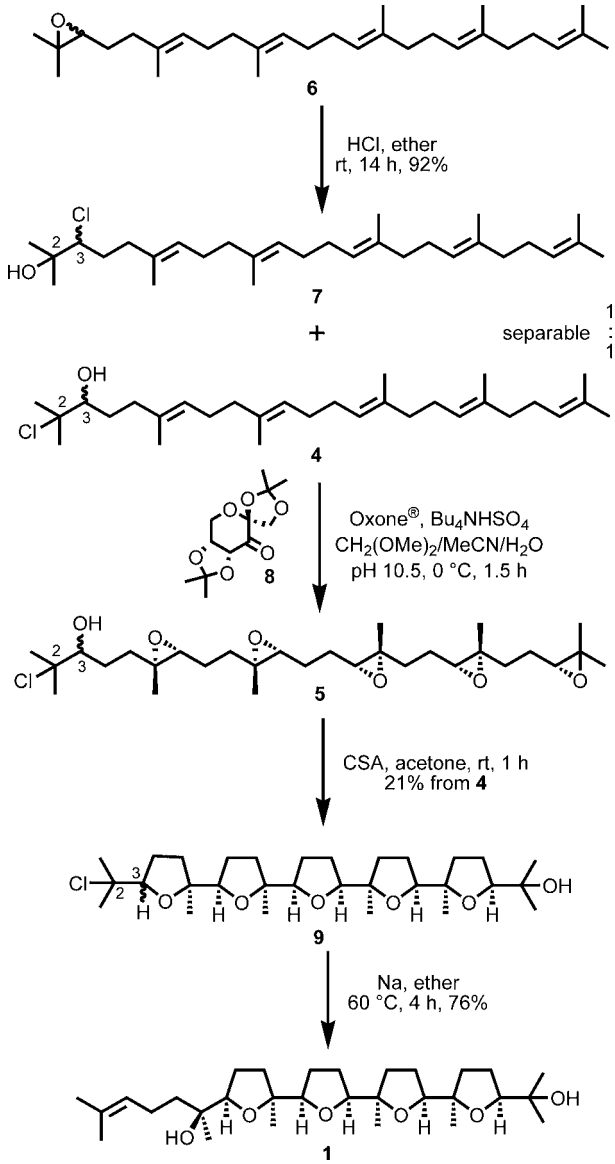
(14) The 1HNMR of the diastereomeric mixture of **9** shows two sets of two singlets of the two methyl groups attached to C-2 with 1:1 integration ratio indicating the diastereomeric ratio is 1:1.

(15) (a) Bromidge, S. M.; Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1725–1730. (b) Chen, B.; Ko, R. Y. Y.; Yuen, M. S. M.; Cheng, K.-F.; Chu, P. *J. Org. Chem.* **2003**, *68*, 4195–4205. (c) Geng, Z.; Chen, B.; Chiu, P. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 6197–6201.

(16) Suzuki, M.; Matsuo, Y.; Takeda, S.; Suzuki, T. *Phytochemistry* **1993**, *33*, 651–656.

(17) Morimoto, Y.; Okita, T.; Takaishi, M.; Tanaka, T. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 1132–1135.

Scheme 3. Total Synthesis of (+)-Omaezakianol (**1**)



THF ring to give the natural product (+)-omaezakianol (**1**) in 76% yield.[15] The HRMS and ^{1}H and ^{13}C NMR of **1** match very well with those reported[6,10] for (+)-omaezakianol. In addition, the optical rotation of our synthetic **1** ($[\alpha]^{23}_{D} = +17.1$ ($c = 1.0$, $CHCl_3$)) is also in agreement with that of the natural product **1** ($[\alpha]^{20}_{D} = +15.8$ ($c = 0.57$, $CHCl_3$))[6] and that of synthetic **1** by Morimoto and co-workers ($[\alpha]^{29}_{D} = +17.7$ ($c = 0.59$, $CHCl_3$)).[10]

In summary, we have developed a short and efficient total synthesis of tetracyclic oxasqualenoid (+)-omaezakianol (**1**) in only six steps from squalene via a biomimetic epoxide-opening cascade reaction. The key feature of the synthesis is the use of a chlorohydrin function to mask the terminal olefin, which allows the utilization of the Shi asymmetric epoxidation as well as an epoxide-opening cascade reaction to construct rapidly the four THF-ring subunits with the required stereochemistry in both regio- and stereoselective fashion. This synthetic strategy resulted in a simple total synthesis of (+)-omaezakianol (**1**) and provided another example of the power of cascade reactions for the efficient synthesis of a complex natural product. This strategy could also find application for the total synthesis of other natural products in the oxasqualenoid family with an olefinic or olefin-derived terminal group such as, for example, intricatetraol.[16,17]

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Supporting Information Available: Experimental details for the synthesis and characterization data of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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