Natural Products Synthesis

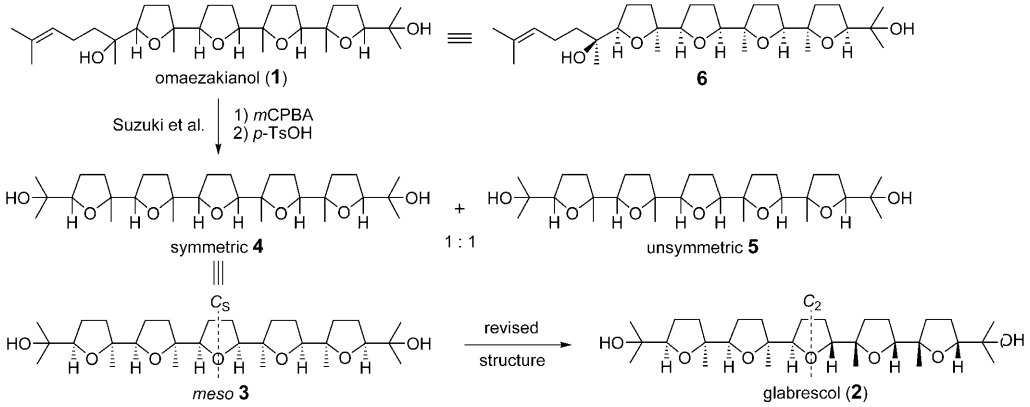
DOI: 10.1002/ange.200805857

Total Synthesis and Determination of the Absolute Configuration of (+)-Omaezakianol**

Yoshiki Morimoto, Tatsuya Okita, and Hitomi Kambara*

Omaezakianol (**1**), a member of the oxasqualenoid family of squalene-derived triterpene polyethers,[1] had been isolated from the red alga *Laurencia omaezakiana* Masuda (Enshusozo in Japanese) by Suzuki and co-workers in 1995 (Scheme 1).[2] Although the planar structure **1** had mainly been elucidated by NMR spectroscopic methods, the stereochemistry had remained unknown over a decade. Glabrescol (**2**), another oxasqualenoid, was isolated from the branches and wood of *Spathelia glabrescens* (Rutaceae) by Jacobs and co-workers in 1995.[3] The structure of glabrescol was proposed to correspond to the *meso* compound **3** based on spectroscopic data; however, the chemical syntheses of **3** by Kodama's,[4] Morimoto's,[5] and Corey's[6] groups, and of **2** by Morimoto's[5] and Corey's[7] groups revealed that the *meso* structure **3** originally proposed for glabrescol must be revised to the optically pure C_2-symmetric structure **2**. Recently, the spectral properties of synthetic *meso* compound **3** were found to be identical to those of a symmetric compound **4** derived from the natural omaezakianol (**1**). Thus, the relative configuration of omaezakianol was determined as shown by the structural formula **6**.[2] Herein, we report the first asymmetric total synthesis and determination of the absolute configuration of (+)-omaezakianol (**6**).

Our retrosynthetic analysis of omaezakianol (**6**) is depicted in Scheme 2. We envisaged that the right-hand three tetrahydrofuran (THF) rings in **6** would be constructed by sequential 5-*exo*-tet cascade oxacyclizations of triepoxy alcohol **7**.[6,8] The triepoxy alcohol **7** could be formed convergently by olefin cross-metathesis[9] between functionalized fragments **8** and **9** followed by hydrogenation. The desired THF derivative **8** could be constructed by the stereospecific and stereoselective oxacyclization of the diepoxy alcohol **10** under alkaline conditions originally developed by Hoye and Jenkins.[10] The required stereocenters in **9** and **10** would be introduced into commercially available *trans*,*trans*-farnesol by established methods of asymmetric oxidation.



Scheme 1. Historical relationship between omaezakianol (**1**) and glabrescol (**2**).

[*] Prof. Dr. Y. Morimoto, T. Okita, H. Kambara
Department of Chemistry, Graduate School of Science
Osaka City University
Sumiyoshi-ku, Osaka 558–8585 (Japan)
Fax: (+81) 6-6605-2522
E-mail: morimoto@sci.osaka-cu.ac.jp
Homepage: http://www.sci.osaka-cu.ac.jp/chem/org2/org2j.html

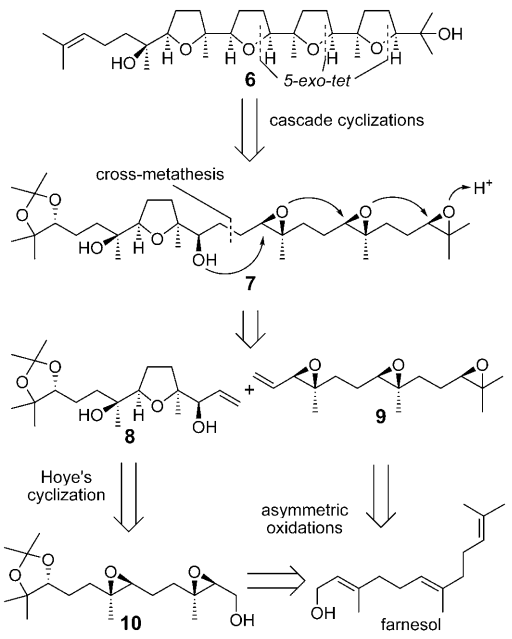
[**] We thank Dr. M. Suzuki, University Malaysia Sabah, for generously supplying us with copies of the spectra of natural omaezakianol. This research was supported by the Novartis Foundation (Japan) for the Promotion of Science, the Saneyoshi Scholarship Foundation, and Grants-in-Aid for Scientific Research on Basic Research (B) and (C) from the JSPS.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200805857.

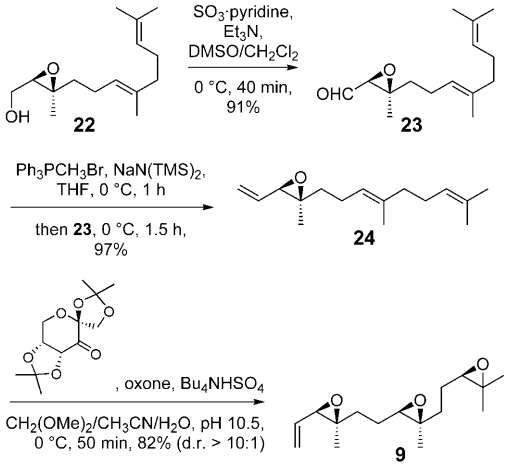
Protection of the known, nonracemic sample of diol **11** (>95% *ee*)[11] as an acetonide and subsequent deacetylation afforded allylic alcohol **13**[12] (Scheme 3). Katsuki–Sharpless asymmetric epoxidation[13] of **13** in the presence of (+)-diethyl L-tartrate (L-(+)-DET) provided epoxy alcohol **14**. Asymmetric epoxidation of the alkene **14** by the method of Shi and co-workers[14] with the chiral L ketone catalyst then gave diepoxy alcohol **10**. Treatment of the diepoxy alcohol **10** with 1M aqueous solution of sodium hydroxide and 1,4-dioxane (1:1) under reflux furnished the desired trihydroxy THF product **15** with high stereospecificity.[10] Selective *tert*-butyldimethylsilyl (TBDMS) protection of the primary hydroxy group in the triol **15**,[15] methoxymethyl (MOM) protection of the remaining hydroxy groups, cleavage of the silyl ether,

Parikh–Doering oxidation[16] of the alcohol **18**, and Wittig methylenation of the resulting aldehyde **19** afforded terminal alkene **20** in good overall yield. After removal of all protective groups in **20**, reprotection of only the vicinal diol provided the functionalized fragment **8**.

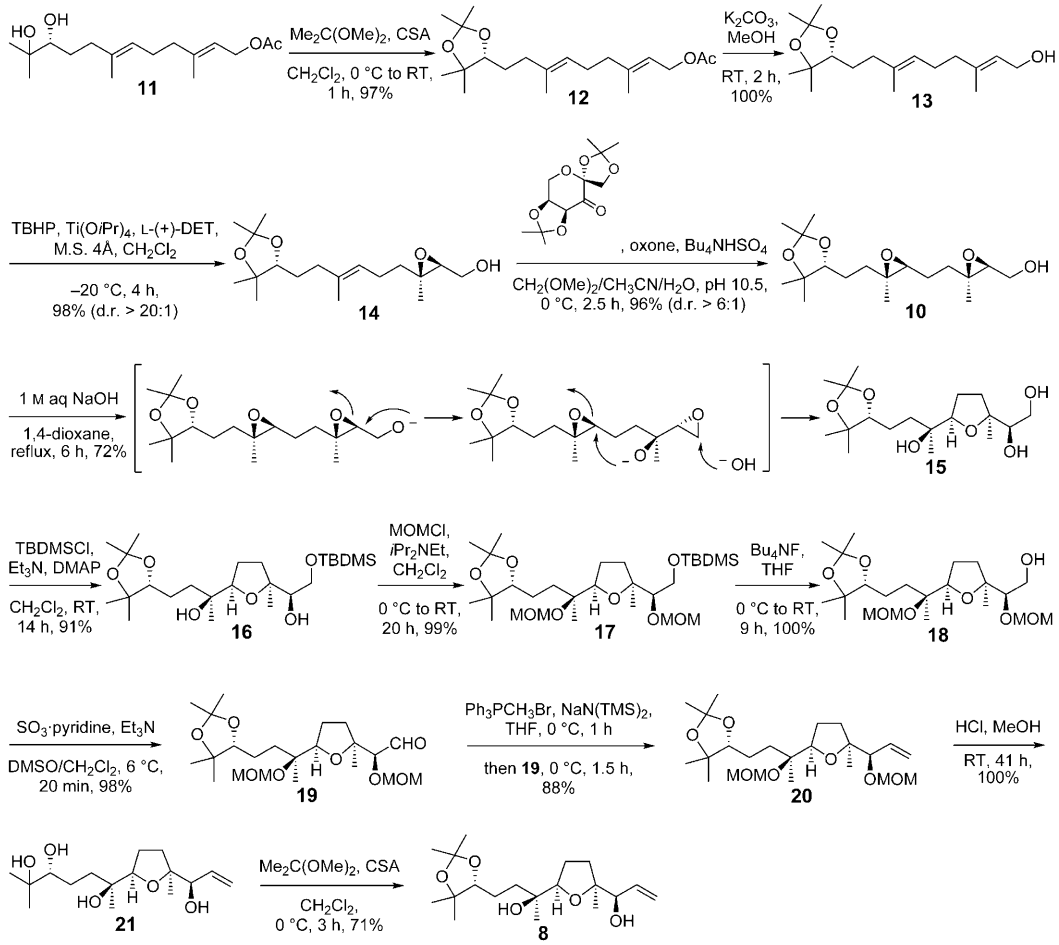
Preparation of the triepoxy alkene **9**, the reaction partner for the cross-metathesis with olefin **8**, was carried out in three steps from the known optically active epoxy alcohol **22** (92% *ee*)[17] (Scheme 4). Parikh–Doering oxidation of the



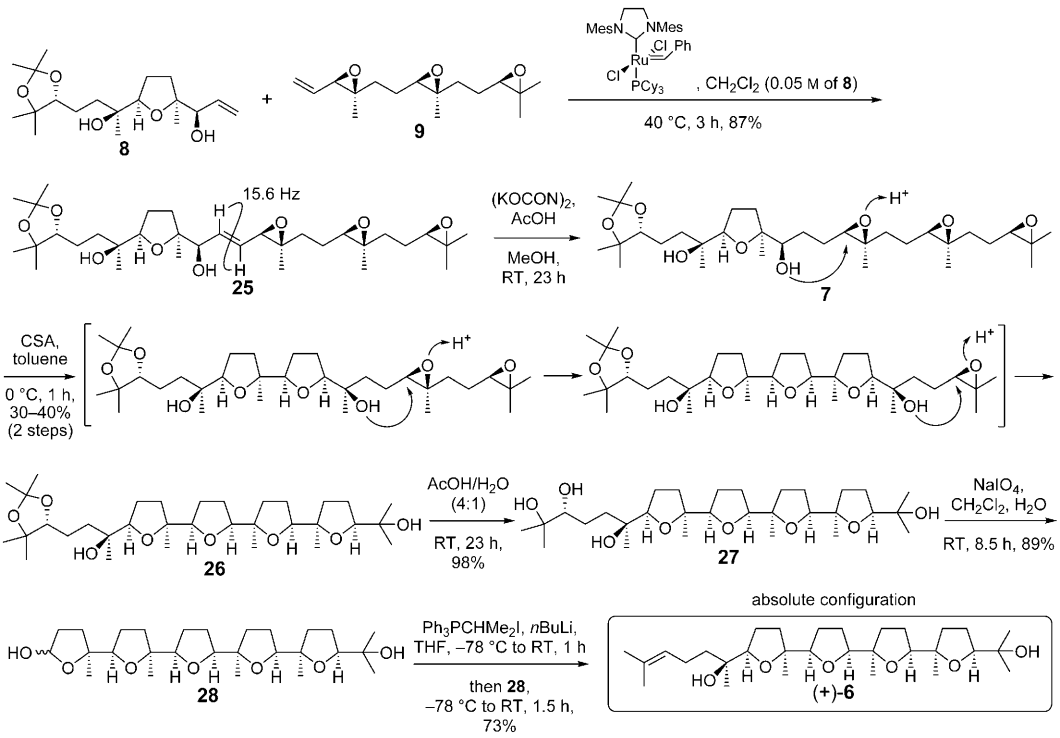
Scheme 2. Retrosynthetic analysis of omaezakianol (**6**).



Scheme 4. Synthesis of triepoxide **9**.



Scheme 3. Synthesis of diol **8**. CSA = (±)-10-camphorsulfonic acid, TBHP = *tert*-butyl hydroperoxide, DMAP = 4-dimethylaminopyridine, M.S. = molecular sieves, TMS = trimethylsilyl.



Scheme 5. Completion of the synthesis of (+)-omaezakianol (**6**). Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.

alcohol **22** and Wittig olefination of the resulting aldehyde **23** furnished triene **24**. Shi asymmetric epoxidation[14a] of the triene **24** proceeded in a chemoselective manner[8,10c] at the trisubstituted double bonds to give the requisite triepoxy alkene **9** in 82% yield.

The cross-metathesis of the alkene **8** with 4.7 equiv of triepoxy alkene **9** in the presence of the Grubbs second-generation catalyst (0.1 equiv) provided *trans* alkene **25** in 87% yield (Scheme 5).[9] Diimide reduction of the alkene **25** yielded the triepoxy alcohol **7**, which was treated with (±)-10-camphorsulfonic acid (CSA) in toluene to afford the 5-*exo*-tet cascade cyclization product **26**.[6,8] Deprotection of the acetonide group in diol **26** and subsequent oxidative cleavage of the resultant vicinal diol with sodium metaperiodate provided hemiacetal **28**. The Wittig olefination of the hemiacetal **28** with an excess of isopropylidene triphenylphosphorane gave the target compound **6**. The NMR, IR, and mass spectra of the synthetic compound **6** were identical with those of the natural product.[2] Fortunately, the optical rotation of the synthetic compound **6** ($[\alpha]_D^{29} = +17.7\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.57\ \mathrm{g\,cm^{-3}}$, $CHCl_3$)) was also in good agreement with that of the natural product ($[\alpha]_D^{20} = +15.8\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.59\ \mathrm{g\,cm^{-3}}$, $CHCl_3$)).[2] Thus, we found that the unknown absolute configuration of (+)-omaezakianol is represented by the structural formula **6**.

In conclusion, we have accomplished the first asymmetric total synthesis of the marine tetracyclic oxasqualenoid (+)-omaezakianol (**6**). Our synthesis features a convergent olefin cross-metathesis between functionalized fragments **8** and **9** and cascade oxacyclizations of triepoxy alcohol **7**. The total synthesis resulted in the determination of the absolute configuration of omaezakianol (**6**), which is difficult to determine by other means.[5d] Further contributions to structure elucidation by chemical synthesis are in progress.

Received: December 2, 2008
Published online: February 26, 2009

Keywords: asymmetric synthesis · structure elucidation · terpenoids · total synthesis

[1] For a review, see: J. J. Fernández, M. L. Souto, M. Norte, *Nat. Prod. Rep.* **2000**, *17*, 235–246.
[2] Y. Matsuo, M. Suzuki, M. Masuda, T. Iwai, Y. Morimoto, *Helv. Chim. Acta* **2008**, *91*, 1261–1266.
[3] W. W. Harding, P. A. Lewis, H. Jacobs, S. McLean, W. F. Reynolds, L.-L. Tay, J.-P. Yang, *Tetrahedron Lett.* **1995**, *36*, 9137–9140.
[4] H. Hioki, C. Kanehara, Y. Ohnishi, Y. Umemori, H. Sakai, S. Yoshio, M. Matsushita, M. Kodama, *Angew. Chem.* **2000**, *112*, 2652–2654; *Angew. Chem. Int. Ed.* **2000**, *39*, 2552–2554.
[5] a) Y. Morimoto, T. Iwai, T. Kinoshita, *J. Am. Chem. Soc.* **2000**, *122*, 7124–7125; b) Y. Morimoto, T. Kinoshita, T. Iwai, *Chirality* **2002**, *14*, 578–586; c) Y. Morimoto, T. Iwai, T. Kinoshita, *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 1112–1122; d) Y. Morimoto, *Org. Biomol. Chem.* **2008**, *6*, 1709–1719.
[6] Z. Xiong, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 4831–4832.
[7] Z. Xiong, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 9328–9329.
[8] Y. Morimoto, H. Yata, Y. Nishikawa, *Angew. Chem.* **2007**, *119*, 6601–6604; *Angew. Chem. Int. Ed.* **2007**, *46*, 6481–6484.
[9] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
[10] a) T. R. Hoye, S. A. Jenkins, *J. Am. Chem. Soc.* **1987**, *109*, 6196–6198; b) Y. Morimoto, T. Iwai, Y. Nishikawa, T. Kinoshita, *Tetrahedron: Asymmetry* **2002**, *13*, 2641–2647; c) Y. Morimoto, Y. Nishikawa, M. Takaishi, *J. Am. Chem. Soc.* **2005**, *127*, 5806–

5807; d) Y. Morimoto, T. Okita, M. Takaishi, T. Tanaka, *Angew. Chem.* **2007**, *119*, 1150 – 1153; *Angew. Chem. Int. Ed.* **2007**, *46*, 1132 – 1135.
[11] G. Vidari, A. Dapiaggi, G. Zanoni, L. Garlaschelli, *Tetrahedron Lett.* **1993**, *34*, 6485 – 6488.
[12] All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, and by low- and high-resolution mass spectrometry (see the Supporting Information).
[13] Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765 – 5780.
[14] a) Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224 – 11235; b) M.-X. Zhao, Y. Shi, *J. Org. Chem.* **2006**, *71*, 5377 – 5379.
[15] S. K. Chaudhary, O. Hernandez, *Tetrahedron Lett.* **1979**, *20*, 99 – 102.
[16] J. R. Parikh, W. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505 – 5507.
[17] H. Kigoshi, M. Ojika, Y. Shizuri, H. Niwa, K. Yamada, *Tetrahedron* **1986**, *42*, 3789 – 3792.

