Natural Products Synthesis

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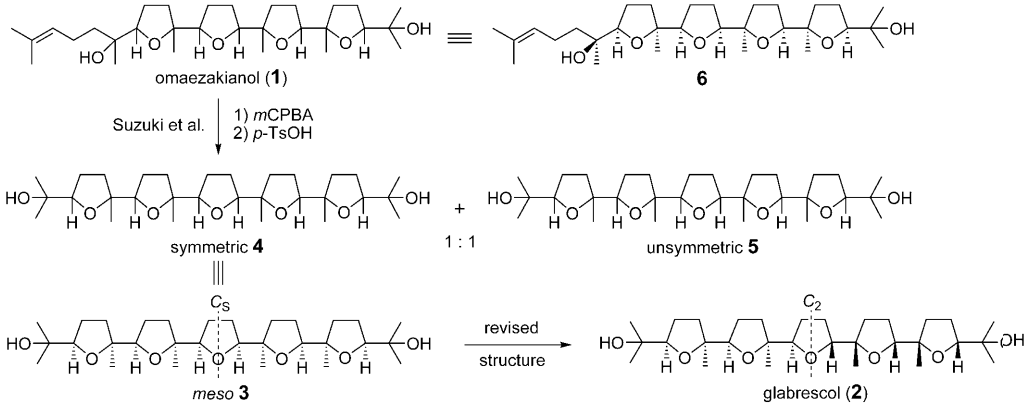
Total Synthesis and Determination of the Absolute Configuration of (+)-Omaezakianol**

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

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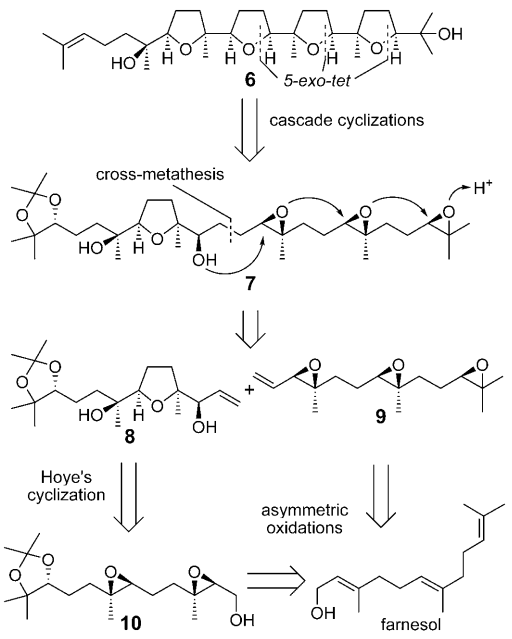
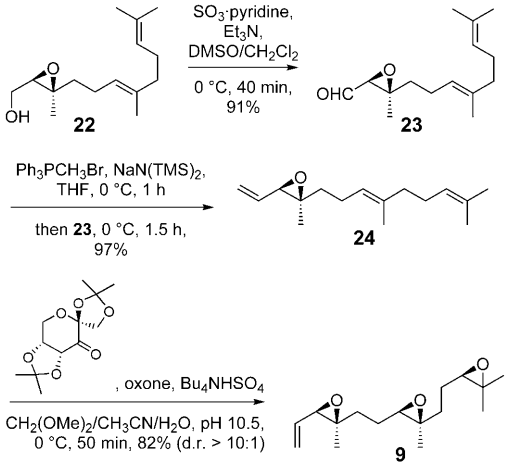
Protection of the known, nonracemic sample of diol **11** (>95% *ee*)[11] as an acetonide and subsequent deacetylation afforded allylic alcohol **13**[12] (Scheme 3). Katsuki–Sharpless asymmetric epoxidation[13] of **13** in the presence of (+)-diethyl L-tartrate (L-(+)-DET) provided epoxy alcohol **14**. 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**.

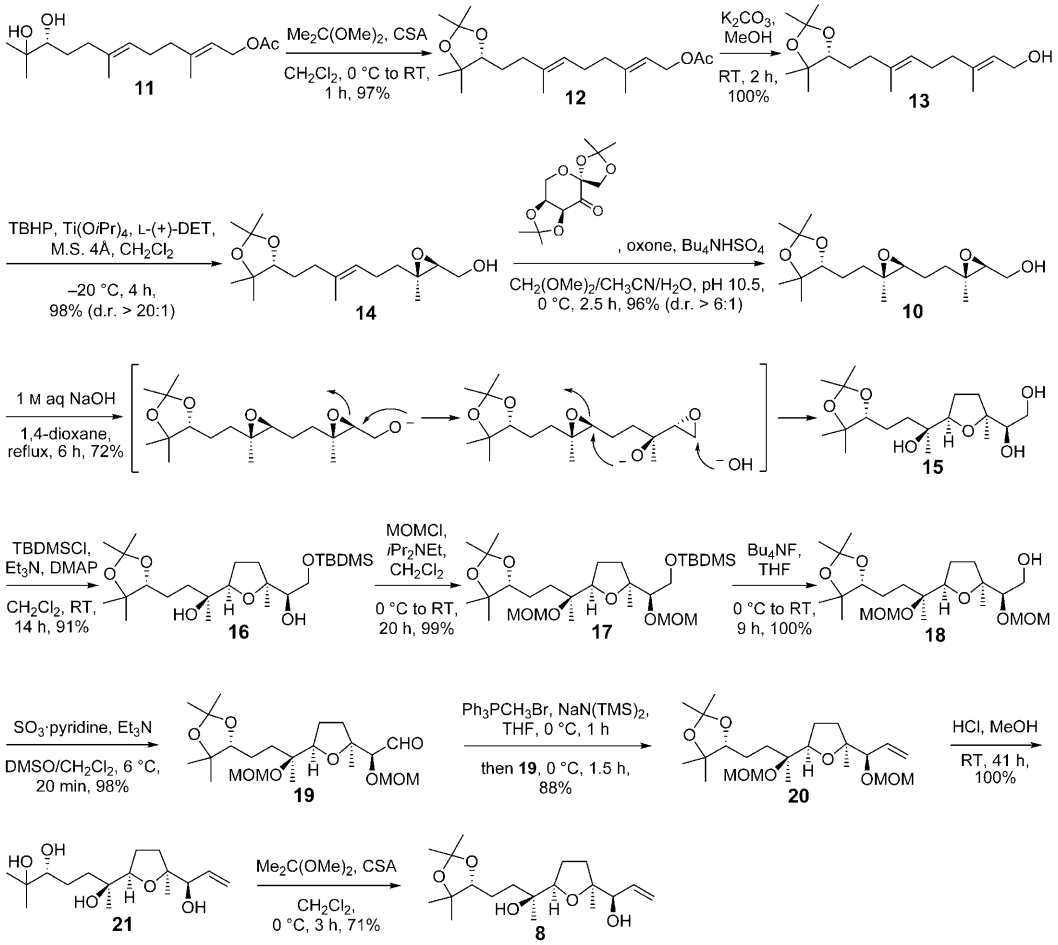
Preparation of the triepoxy alkene **9**, the reaction partner for the cross-metathesis with olefin **8**, was carried out in three steps from the known optically active epoxy alcohol **22** (92% *ee*)[17] (Scheme 4). Parikh–Doering oxidation of the



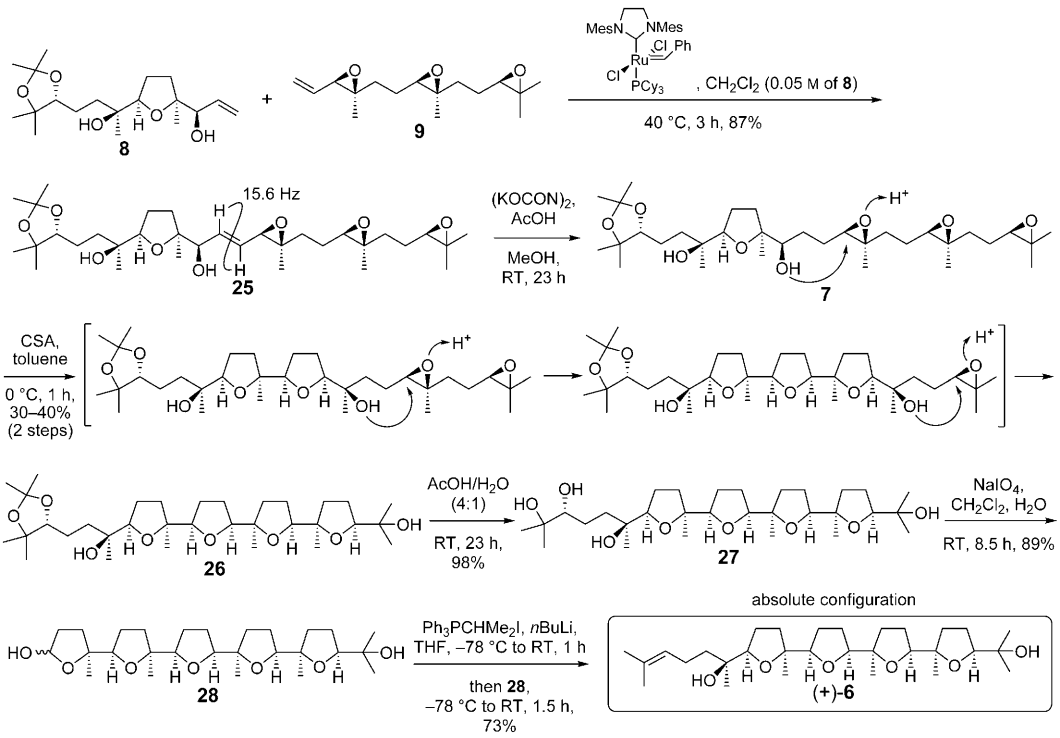
Scheme 2. Retrosynthetic analysis of omaezakianol (**6**).



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.

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