Revised Structure of Squalene-Derived PentaTHF Polyether, Glabrescol, through Its Enantioselective Total Synthesis: Biogenetically Intriguing C_s vs C_2 Symmetric Relationships

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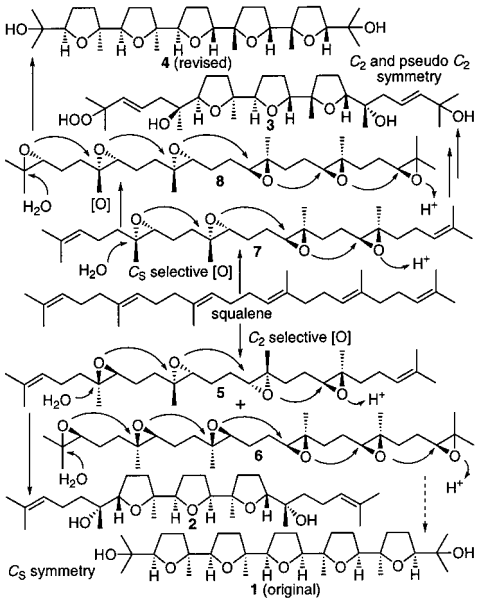
There are numerous examples of biologically active polycyclic natural products that are biosynthesized by sequential cascade cyclizations of acyclic precursors. Polycarbocyclic triterpenes such as steroids are derived from squalene precursors[1] and polyethers such as antibiotics,[2] marine toxins,[3] and acetogenins[4] are derived from polyepoxides. It is of great interest to consider the biogenesis[5] of the highly symmetric squalene-derived triterpene polyethers, glabrescol (**1**), teurilene (**2**), and longilene peroxide (**3**) (Scheme 1). Cytotoxic polyethers teurilene (**2**) and longilene peroxide (**3**) were isolated from the red alga *Laurencia obtusa* by Kurosawa et al.[6] and from the wood of *Eurycoma longifolia* by Itokawa et al.,[7] respectively, and their stereostructures were elucidated by X-ray crystallographic analysis. Glabrescol (**1**) was extracted from the branches and wood of *Spathelia glabrescens* by Jacobs et al., and the structure was proposed by spectroscopic methods.[8]

Considering the familiar examples of biogenesis discussed above,[1−4] these C_s symmetric (*meso*) polyethers **2** and **1** might be derived from C_2 symmetric (*d,l*) tetraepoxide **5** and hexaepoxide **6**, respectively, by sequential cascade cyclizations. On the other hand, the nearly C_2 symmetric polyether **3** could be obtained via the C_s symmetric tetraepoxide **7** in the same manner, except for the discriminating enantiotopic terminal epoxides. In this case, it may be invaluable to realize the complementary conservation of molecular symmetry between the biogenetic precursors and natural products (C_s vs C_2). Thus, the structurally symmetric arrays and the biogenetically unique features coupled with their biological activities have prompted a significant synthetic effort for these polyethers.[9] In this contribution, we report the first enantioselective total synthesis of glabrescol[10] and that the C_s symmetric stereostructure **1** originally proposed by Jacobs et al. must be revised to the optically pure C_2 symmetric **4**.

Our synthetic strategy for the proposed structure of glabrescol (**1**) is based on taking its intrinsic symmetry into consideration, and on the sequential hydroxy-directed *anti* oxidative cyclizations[9a,11] of acyclic bishomoallylic alcohols with vanadium catalyst and *tert*-butyl hydroperoxide (TBHP) to stereoselectively construct

Scheme 1. Complementary Conservation of Molecular Symmetry (C_s vs C_2) in Hypothetical Biogenesis



such THF rings via epoxides. In practice, our synthesis began with the readily available C_s symmetric diepoxide **9**[9b] corresponding to the central THF ring of **1** (Scheme 2). Attachment of geranyl side chains to **9** was carried out in 64% yield over two steps to afford tetraenediol **10**. Monoacetylation[12] of the diol **10** produced substrate **11**, and set the stage for the key sequential V-catalyzed *anti* oxidative cyclizations. The previous reaction conditions for the double cyclizations reported by Shirahama[9a] and McDonald[11] required AcOH in the reaction media to promote the in situ ring-opening of the epoxide intermediates into THF rings. Application of similar reaction conditions using AcOH to **11** for 4−5 h resulted in incomplete termination at the epoxide and monocyclized intermediates along with a small amount of dicyclized products. However, use of TFA instead of AcOH dramatically improved the results. Optimized conditions for the double cyclization of **11** (0.02 equiv $VO(acac)_2$, 2.5 equiv TBHP, 2 equiv TFA, CH_2Cl_2, room temperature, 30 min) provided the desired triTHF ether **12** as a major product in 28% yield over two steps, together with 23% of the other minor diastereomers. The treatment of **12** under similar conditions gave the original *meso* structure **1**[13] as the predominant product in 30% yield. Unfortunately, the ^1H and ^{13}C NMR spectra of our synthetic **1** were not identical with those of the natural glabrescol kindly provided by Jacobs.

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(1) For reviews, see: (a) Clayton, R. B. *Quart. Rev.* **1965**, *19*, 168−200. (b) Mulheirn, L. J.; Ramm, P. J. *Chem. Soc. Rev.* **1972**, *1*, 259−291.

(2) (a) Westley, J. W. In *Antibiotics IV. Biosynthesis*; Corcoran, J. W., Ed.; Springer-Verlag: New York, 1981; pp 41−73. (b) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594−3600.

(3) (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685−1698. (b) Garson, M. J. *Chem. Rev.* **1993**, *93*, 1699−1733. (c) Lee, M. S.; Qin, G.-W.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234−6241.

(4) (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (b) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 4017−4018.

(5) For the possible biogenesis of teurilene (**2**) and relevant polyethers, see: (a) Suzuki, M.; Matsuo, Y.; Takeda, S.; Suzuki, T. *Phytochemistry* **1993**, *33*, 651−656. (b) Matsuo, Y.; Suzuki, M.; Masuda, M. *Chem. Lett.* **1995**, 1043−1044.

(6) Suzuki, T.; Suzuki, M.; Furusaki, A.; Matsumoto, T.; Kato, A.; Imanaka, Y.; Kurosawa, E. *Tetrahedron Lett.* **1985**, *26*, 1329−1332.

(7) Morita, H.; Kishi, E.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Phytochemistry* **1993**, *34*, 765−771.

(8) Harding, W. W.; Lewis, P. A.; Jacobs, H.; McLean, S.; Reynolds, W. F.; Tay, L.-L.; Yang, J.-P. *Tetrahedron Lett.* **1995**, *36*, 9137−9140.

(9) For the total synthesis of teurilene (**2**), see: (a) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299−2311. (b) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792−6797. For the synthetic approaches for teurilene (**2**) and glabrescol (**1**), see: (c) Hoye, T. R.; Jenkins, S. A. *J. Am. Chem. Soc.* **1987**, *109*, 6196−6198. (d) Lindel, T.; Franck, B. *Tetrahedron Lett.* **1995**, *36*, 9465−9468. (e) Morimoto, Y.; Iwai, T.; Yoshimura, T.; Kinoshita, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2005−2010. After submission of our work, a paper by Corey and Xiong has independently appeared that reports the total synthesis of the original (incorrect) glabrescol (**1**) and three C_s-symmetric diastereomers: (f) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831−4832.

(10) Although there is no report on the biological activities of glabrescol, the vicinal pentaTHF linkage may be expected to exhibit ionophoric functions as well as cytotoxicities. See: (a) Schultz, W. J.; Etter, M. C.; Pocius, A. V.; Smith, S. *J. Am. Chem. Soc.* **1980**, *102*, 7981−7982. (b) Wagner, H.; Harms, K.; Koert, U.; Meder, S.; Boheim, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2643−2646.

(11) Towne, T. B.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022−6028.

(12) Although it was envisaged that the desirable pentaTHF **1** could be synthesized from the diol **10** in a single step by the two-directional and sequential oxidative cyclizations, direct oxidative cyclizations of the diol **10** unfortunately resulted in complex mixtures.

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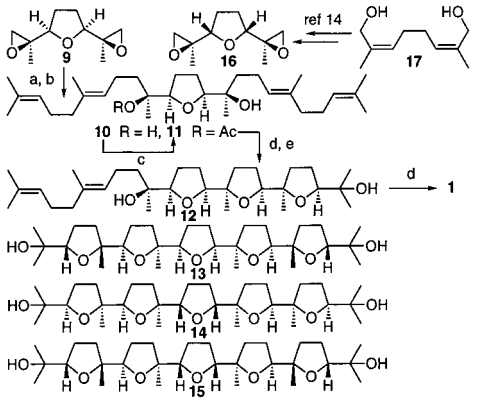
Scheme 2. Total Synthesis of Four Possible *meso* Structures **1** and **13**−**15**[a]

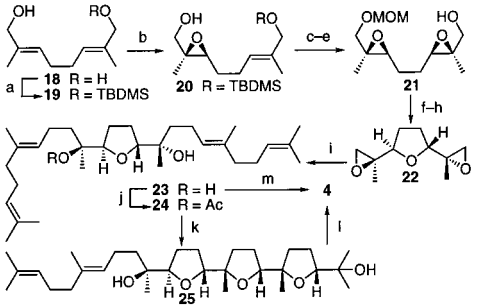


[a] Reaction conditions: (a) geranyl phenyl sulfide, BuLi, TMEDA, THF, −78 °C, 1 h; (b) Na, *i*-PrOH, THF, reflux, 64% (2 steps); (c) Ac_2O, Py, DMAP, CH_2Cl_2, rt, 24 h, 62%; (d) 0.02 equiv $VO(acac)_2$, 2.5 equiv TBHP, 2 equiv TFA, CH_2Cl_2, rt, 30 min; (e) $LiAlH_4$, THF, 0 °C, 1 h, 28% (2 steps).

Reviewing in detail the elucidation of the stereostructure of glabrescol,[8] it appeared to us that the assignments of the relative stereochemistries (*threo* or *erythro*) between each THF ring revealed an ambiguity.[13] Therefore, we decided to synthesize the three remaining possible *meso* structures **13**−**15** by utilizing the same synthetic strategy as that of **1**. Polyether **13** was prepared from the diepoxide **9** by the same sequence of reactions as shown in Scheme 2, except for the substitution of neryl phenyl sulfide for geranyl phenyl sulfide. On the other hand, **14** and **15** were derived from another *meso* diepoxide **16**,[14] diastereomeric to **9**, by attaching the geranyl and neryl side chains, respectively. Disappointingly, the ^1H and ^{13}C NMR spectra of our synthetic **13**−**15** were again inconsistent with those of the natural product.

Although Jacobs et al. proposed a *meso* structure for glabrescol based on the optical inactivity [lit.[8] $[\alpha]_D$ 0.0 (*c* 0.4, $CHCl_3$)] and the presence of fifteen signals in the ^{13}C NMR spectrum, the above results cannot support any *meso* structures for glabrescol. The other possibilities fulfilling the criteria are that glabrescol is C_2 symmetric and racemic or that glabrescol is C_2 symmetric and the value of the specific rotation is near zero. Thus, we embarked on the enantioselective total synthesis of the C_2 symmetric structure **4** possessing the same relative stereochemistry as that of longilene peroxide (**3**) (Scheme 3). The allylic alcohol **19**, prepared by monosilylation of the known diol **18**,[9d] was subjected to Sharpless asymmetric epoxidation[16] using L-DET to furnish the epoxy alcohol **20** in high optical purity. MOM protection, desilylation, and the second epoxidation using D-DET afforded the diepoxide **21**. The THF ring formation according to Hoye's procedure[9c] was followed by diepoxidation to provide the C_2 symmetric diepoxide **22** in high overall yield. Introduction of the geranyl side chains and monoacetylation yielded an alcohol **24**, whose double cyclizations under the optimized conditions gave triTHF **25** as a major product after deacetylation. Repeating the double cyclization on **25** produced predominantly the desired C_2 symmetric pentaTHF structure **4** in 40% yield. Fortunately, the

Scheme 3. Enantioselective Total Synthesis of C_2 Symmetric **4**[a]



[a] Reaction conditions: (a) TBDMSCl, imidazole, CH_2Cl_2, rt, 1 h, 55%; (b) TBHP, $Ti(O\textit{i}\text{-}Pr)_4$, L-DET, MS 4A, CH_2Cl_2, −20 °C, 4 h, 86% (98% ee); (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C—rt, 17 h, 96%; (d) Bu_4NF, THF, 0 °C, 1 h, 98%; (e) TBHP, $Ti(O\textit{i}\text{-}Pr)_4$, D-DET, MS 4A, CH_2Cl_2, −25 °C, 4 h, then citric acid, Bu_3P, 85%; (f) 1 M aq NaOH, 1,4-dioxane, reflux, 1 h, then acidified by HCl (pH 2), reflux, 10 min, 88%; (g) MsCl, Py, CH_2Cl_2, 0 °C to rt, 1 h; (h) K_2CO_3, MeOH, rt, 15 min, 75% (2 steps); (i) a, b in Scheme 2, 65% (2 steps); (j) c in Scheme 2, 50%; (k) d, e in Scheme 2, 26% (2 steps); (l) d in Scheme 2, 40%; (m) 0.05 equiv $VO(acac)_2$, 5 equiv TBHP, 2 equiv TFA, CH_2Cl_2, rt, 30 min, 18%.

spectral characteristics (^1H and ^{13}C NMR, IR, MS, and HRMS) including the CD spectrum ($\Delta\epsilon_{190} = +3.45$ in CH_3CN) of the synthetic **4**, $[\alpha]^{25}_D$ −22.4 (*c* 1.27, $CHCl_3$), were identical to those of the natural glabrescol ($\Delta\epsilon_{190} = +3.03$ in CH_3CN).[17] Thus, the correct stereostructure of glabrescol must be revised from the C_s symmetric **1** to the C_2 symmetric **4** with the indicated absolute configuration.

Can glabrescol (**4**) be constructed in a single step from tetraenediol **23** by a two-directional double cyclization? Such a cyclization would produce four THF rings and six stereogenic centers. It has, indeed, been found that the double cyclizations of **23** by our protocol in the presence of TFA can proceed in a two-directional manner to provide **4** as a major diastereomer in 18% yield along with fifteen other minor diastereomers in 61% combined yield based on the HPLC analysis (Scheme 3).

In conclusion, we have accomplished the total synthesis of the four possible *meso* structures **1** and **13**−**15** and one optically active C_2 symmetric **4** of glabrescol through the key one- and two-directional double cyclizations utilizing $VO(acac)_2$, TBHP, and TFA, and revised the structural formula **1** proposed by Jacobs et al.[8] to **4**. These results may imply that the C_2 symmetric glabrescol (**4**) is biogenetically produced by the enantiodifferentiated cascade cyclizations (enzymatic participation?) of the C_s symmetric hexaepoxide precursor **8** as shown in Scheme 1, and it would be interesting to determine the absolute configuration of longilene peroxide (**3**), which possesses the same relative stereochemistry. The biological activities of the synthetic glabrescol (**4**) and application of this synthetic strategy to **3** are currently under investigation.

Acknowledgment. We thank Dr. H. Jacobs (University of the West Indies) for generously supplying an authentic sample and copies of the ^1H and ^{13}C NMR, MS, and HRMS spectra of natural glabrescol. We are grateful to Professor I. Kinoshita and Dr. Y. Usuki (Osaka City University) for the CD measurements, HPLC analysis, and valuable discussions. This research was supported by the Naito Foundation and the SUNBOR GRANT (Suntory Institute for Bioorganic Research).

Supporting Information Available: Characterization data for **1**, **13**−**15**, **18**−**25**, and **4**, experimental procedures for synthesis of **4**, ^1H and ^{13}C NMR spectra of synthetic **4**, and CD spectra of synthetic and natural **4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The relative stereochemistry between the 2- and 5-positions within each THF ring, except for the central THF ring, in the pentaTHF ethers **1**, **13**−**15**, **4**, and natural glabrescol generously supplied by Jacobs was determined by the presence of NOEs observed between the oxymethine proton and the methyl group in a relationship *cis* to that proton in their NOE spectra. See the Supporting Information.

(14) Diepoxide **16** was prepared in 30% overall yield from the known diol **17** (ref 15) by the following sequence of reactions: (1) Sharpless asymmetric epoxidation (ref 9d); (2) 1 M aq NaOH−1,4-dioxane, reflux, 2 h; (3) MsCl, Py; (4) K_2CO_3, MeOH.

(15) Bhalerao, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 5311−5313.

(16) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(17) Since an authentic sample generously supplied by Jacobs was too small to obtain a constant $[\alpha]_D$ value, we employed the CD spectrum to determine the absolute configuration of glabrescol. The incompatibility of $[\alpha]_D$ between Jacobs et al. (ref 8) and us is not clear at present.