Simple Total Synthesis of the Pentacyclic C_s-Symmetric Structure Attributed to the Squalenoid Glabrescol and Three C_s-Symmetric Diastereomers Compel Structural Revision

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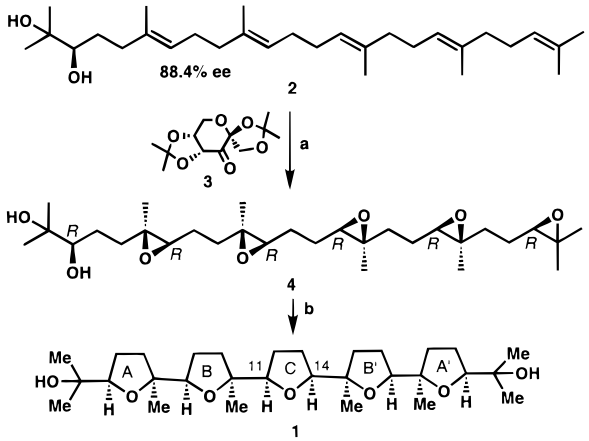
The hexaisoprenoid squalene occupies a unique place in chemistry and biology because of its extraordinary versatility as the biosynthetic parent of a huge number of steroids and triterpenoids. Recently, yet another class of squalenoids, the polycyclic oxasqualenoids, has emerged as natural offspring of squalene which are produced by new types of cascade polycyclization. An especially intriguing member of this class is glabrescol, a novel squalenoid which has been isolated from the Caribbean plant *Spathelia glabrescens* (0.005% yield) and assigned the pentaoxacyclic structure **1** on the basis of physicochemical and spectroscopic data, including HMQC, COSY, NOESY, and HMBC NMR analysis.[1] A central plane of symmetry in the structure of glabrescol was indicated by the absence of optical activity, the occurrence of only 15 signals in the ^{13}C NMR spectrum, and a 2-fold simplification in the ^1H NMR spectrum. Described herein is a stereoselective synthesis of structure **1** in just two steps (Scheme 1) from the known (*R*)-2,3-dihydroxy-2,3-dihydrosqualene (**2**), which is available by Sharpless enantioselective dihydroxylation of squalene using the Noe-Lin catalyst (16/1 enantioselectivity).[2]

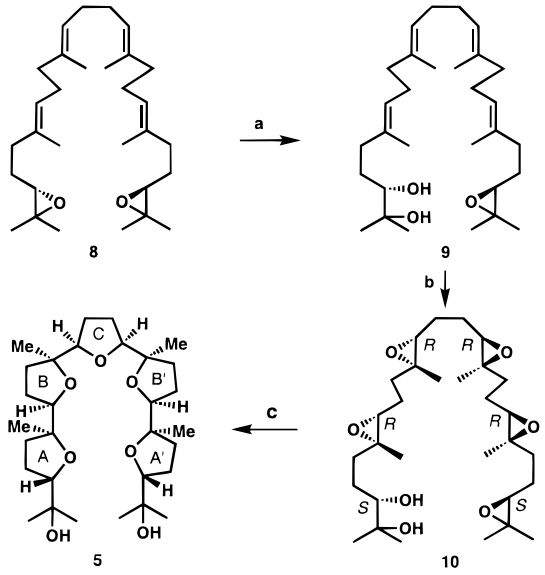
Epoxidation of each of the trisubstituted double bonds could be achieved with remarkable enantioselection using the Shi chiraldioxirane derived from ketone **3**[3] in pH 10.5 $H_2O-CH_3CN-(CH_3O)_2CH_2$ (DMM) which produced the pentaepoxide **4** (80% estimated purity by ^1H NMR analysis) along with several minor diastereomers that together totaled ∼20% of the total reaction product.[4] The chromatographic separation of the diastereomeric mixture was difficult but catalyst **3** could be separated from the mixture by column chromatography on silica gel (**3** was eluted before **4** and recovered in good yield for reuse). Treatment of **4** and diastereomers with a 3 mM solution of camphor-10-sulfonic acid (CSA) in toluene at 0 °C for 1 h and subsequent purification by column chromatography on silica gel using 25−50% ethyl acetate in hexane for elution provided pure **1** in 31% overall yield from **2**. The spectroscopic and physicochemical data were distinctly different from reported data[1] and from measurements performed in these laboratories with a small sample (∼0.5 mg) of authentic glabrescol.[5] The structure of this synthetic product, predicted to be **1** on the basis that the conversion of **4** to **1** involves inversion of configuration during each of the five epoxide displacements which lead to formation of the five tetrahydrofuran rings of **1**, was confirmed independently. Reaction of synthetic **1** with excess *p*-bromobenzoyl chloride and 4-(dimethylamino)-pyridine in CH_2Cl_2 at 23 °C for 60 h produced a crystalline bis-*p*-bromobenzoate derivative, mp 142−143 °C, which was shown by single-crystal X-ray diffraction to correspond to **1**.[6] Thus, if the tetrahydrofuran rings of structure **1** are designated as ABCB′A′ (reading **1** from left to right), the H and methyl substituents at carbons 2 and 5 are A(cis), B(cis) and C(cis). Since the proposal of structure **1** for glabrescol[1] is untenable, we embarked on the synthesis of the three other possible meso diastereomers of **1** that could result from the pentacyclization of various 2,3-dihydroxy-6,7-, 10,11-, 14,15-, 18,19-, 22,23-pentaepoxides of all *E*-squalene. The structures of these three C_s-symmetric (meso) diastereomers of **1** are expressed by formulas **5**, **6**, and **7** in Schemes 2−4.

Scheme 1[a]



[a] (a) Oxone, **3**, MeCN−DMM−H_2O (pH 10.5), 0 °C, 1.5 h. (b) CSA, toluene, 0 °C, 1 h, 31% (two steps).

Scheme 2[a]



[a] (a) $HClO_4$, THF−H_2O, 0 °C. (b) **3**, Oxone, as for **4**. (c) CSA, C_7H_8, 0 °C.

The synthesis of **5**, the A(trans), B(cis), C(cis) pentacycle, is outlined in Scheme 2. The (*S*,*S*)-epoxide **8** is available from *E*,*E*-farnesyl acetate by the sequence: (1) enantioselective dihydroxylation of the terminal double bond using the Noe-Lin catalyst,[2] (2) reaction with $MeSO_2Cl-C_5H_5N$ to form the secondary mesylate, (3) treatment with K_2CO_3−MeOH to form (*S*)-10,11-epoxyfarnesol, (4) primary mesylate formation with $MeSO_2Cl-Et_3N$ and in situ conversion to (*S*)-10,11-epoxyfarnesyl bromide

(1) Harding, W. W.; Lewis, P. A.; Jacobs, H.; McLean, S.; Reynolds, W. F.; Tay, L.-L.; Yang, J.-P. *Tetrahedron Lett.* **1995**, *36*, 9137.
(2) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741.
(3) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.
(4) The enantioselectivity of the epoxidation of each double bond in the conversion of **2** to **4** can be estimated as >20:1.
(5) Generously provided by Dr. Helen Jacobs, University of the West Indies.
(6) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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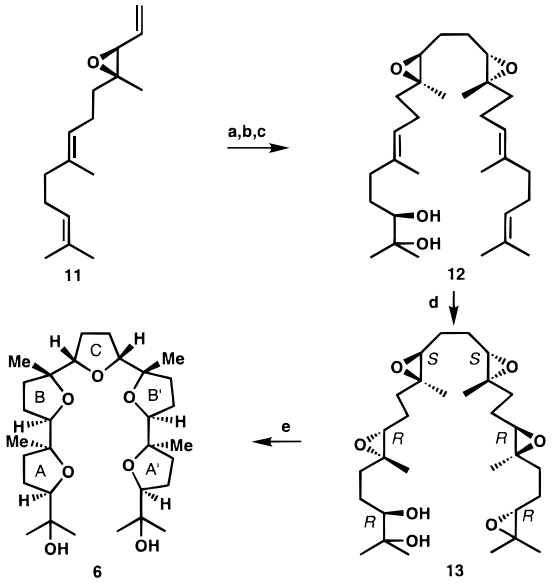
Scheme 3[a]



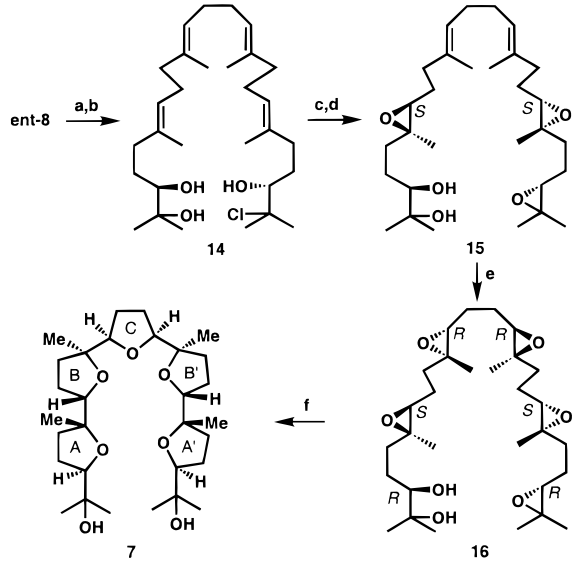
[a] (a) $(Cy_3P)_2RuCl_2$(=CHPh), CH_2Cl_2, 23 °C. (b) $KO_2CN{=}NCO_2K$, HOAc, CH_2Cl_2, 23 °C. (c) Noe-Lin (ref 2). (d) **3**, Oxone, as for **4**. (e) CSA, C_7H_8, 0 °C.

(LiBr−THF), and (5) coupling to form **8** by means of Rieke barium.[7,8] Controlled acidic hydrolysis of the diepoxide **8** using 1 equiv of $HClO_4$ in 5:1 THF−H_2O at 0 °C for 10 min afforded 46% conversion to the mono-1,2-glycol epoxide **9** (92% yield based on recovered starting material). Epoxidation of **9** using Oxone and a catalytic amount of the Shi reagent **3** gave the pentaepoxide **10** of ∼80% purity. Cascade cyclization of the mixture of **10** and diastereomers (∼20%) afforded as major product the pentacyclic ether **5** which differed from glabrescol and **1**.

The synthesis of the A(cis), B(trans), C(cis) diastereomer **6** was carried out as summarized in Scheme 3. The epoxy triene **11** was prepared from *E*,*E*-farnesol by the sequence: (1) epoxidation with (*R*,*R*)-diisopropyl tartrate, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4A MS in CH_2Cl_2;[9] (2) Swern oxidation; and (3) reaction with methylenetriphenylphosphorane in THF. Exposure of **11** to 10 mol % of the Grubbs Ru catalyst[10] in CH_2Cl_2 at 23 °C for 36 h provided the C_{30}-coupled pentaene with the *E*-arrangement at the central olefinic linkage (∼50% yield). Selective reduction of this central *E*-double bond with diimide[11] (generated from excess potassium azodicarboxylate and acetic acid in CH_2Cl_2) produced a symmetrical tetraene which was dihydroxylated using 5 mol % of the Noe-Lin catalyst-OsO_4 in aqueous *tert*-butyl alcohol[2] (stopped at .∼ 70% conversion) to afford diol **12** (50% yield based on recovered starting tetraene). Epoxidation of **12** using the chiral ketone **3** and Oxone produced the pentaepoxide **13** which upon acid-catalyzed cyclization and silica gel chromatography gave the pentacyclic product **6**. The spectroscopic properties of **6** confirmed its C_s symmetry and also its non-identity with **1**, **5**, and glabrescol.

The synthesis of the A(trans), B(trans), C(cis) diastereomer **7**, outlined in Scheme 4, started with the enantiomer of **8** (analogously prepared) which was converted to **14** in two steps: (1)

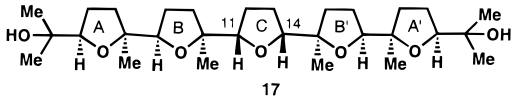
Scheme 4[a]



[a] (a) 1 equiv $HClO_4$ in 5:1 THF−H_2O at 0 °C for 10 min. (b) Dry HCl on silica gel, C_7H_8 at −78 °C for 45 min. (c) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, 2,6-di-*t*-Bu-pyridine at 23 °C for 8 h. (d) K_2CO_3-MeOH at 23 °C for 2 h. (e) **3**, Oxone, as for **4**. (f) CSA, C_7H_8, 0 °C.

controlled $HClO_4$−H_2O-catalyzed hydration of one oxirane function to generate an epoxy diol (∼70% yield at 50% conversion, cf. **8** → **9**) and (2) reaction of the remaining oxirane function with dry HCl on silica gel in toluene suspension at −78 °C for 45 min to form the chlorohydrin **14** (60% yield). Hydroxyl-directed bis-epoxidation of **14** with *tert*-butyl hydroperoxide−$VO(acac)_2$ [12] in CH_2Cl_2 gave, after base-catalyzed conversion of chlorohydrin to epoxide, the triepoxide **15**. Diastereoselective epoxidation of the remaining two double bonds of **15** generated the pentaepoxide **16**, which upon acid-catalyzed cascade cyclization gave **7**, shown by spectroscopic analysis to be C_s symmetric and distinctly different from glabrescol, **1**, **5**, and **6**.

Although structures **1** and **5**−**7** can be ruled out for glabrescol, there are other C_s-symmetric structures (e.g., **17**) which might be formed from all *E*-squalene via a meso hexaepoxide using a different mode of cyclization: two double cyclizations (generating rings A, B, A′ and B′) and subsequent closure of ring C with double inversion. The surmise that glabrescol may be a structure such as **17** is being tested.



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Supporting Information Available: Supplemental procedures for the synthesis of **1**. Characterization data for compounds **1** and **5**−**7** (PDF). A crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Alternatively, the (*S*,*S*)-diepoxide **8** can be obtained from a mixture of isomeric epoxides by preparative HPLC separation on a Chiral Technologies Chiralpak AS column.

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