Simple Enantioselective Total Synthesis of Glabrescol, a Chiral C_2-Symmetric Pentacyclic Oxasqualenoid

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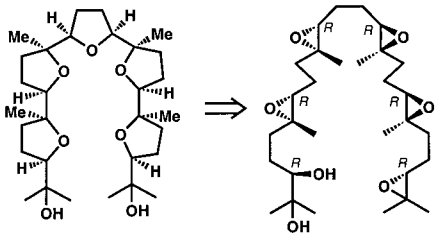
Glabrescol, the first pentacyclic member of the oxasqualenoid family which includes diverse and structurally novel members such as teurilene,[1,2] thyrsiferol (venustatriol)[3,4] longilene peroxide,[5] quassiol A,[6] and eurylene,[7] was originally assigned the novel C_S-symmetric structure **1**,[8] the origin of which could reasonably be explained as cascade pentacyclization of the precursor **2**. However,

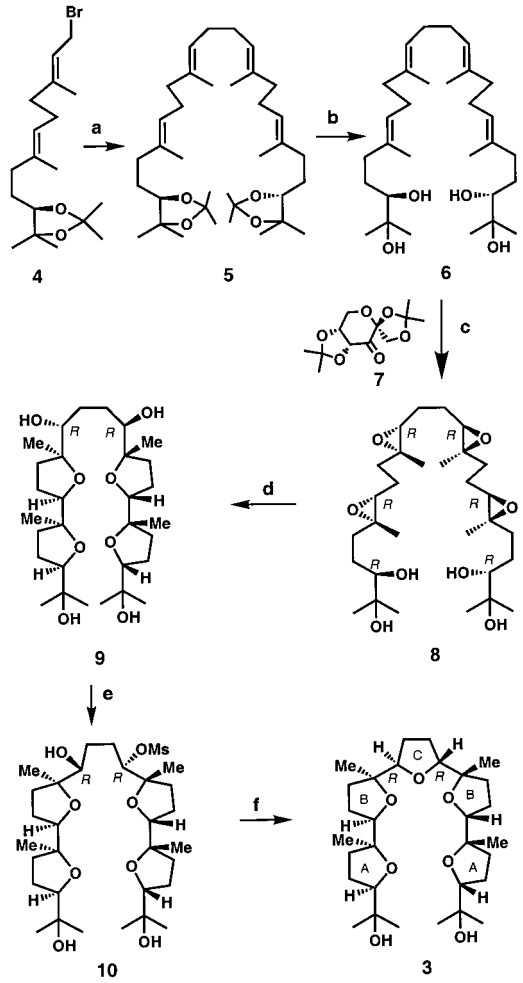


1 **2**

it was recently demonstrated by unequivocal synthesis of **1** that glabrescol did not possess this structure.[9] Furthermore, it was shown by synthesis of the three other C_S-symmetric diastereomers of **1** which could result from a similar cascade pentacyclization that none of these compounds correspond to glabrescol.[9] We surmised[9] that the true structure of glabrescol might be generated by a bidirectional pair of double cyclizations which could generate either a novel C_S-symmetric or a C_2-symmetric structure, either of which would be consistent with the reported[8] spectroscopic data for glabrescol. Although the reported lack of rotation of glabrescol would seem to indicate that it is C_S-symmetric, a C_2-symmetric structure would be possible if the optical rotation of such a structure were to be very small or if the reported optical rotation of glabrescol were to be in error. In this paper we describe an enantioselective total synthesis of the C_2-symmetric structure **3** and its identity with glabrescol. The synthesis is outlined in Scheme 1.[10]

The starting point for the synthesis was the bromo acetonide **4**,[11] which upon stirring with Rieke barium at −78 °C for 1 h gave the bis-acetonide **5**,[12] $[\alpha]^{23}_D$ +3.5 (*c* 1.5, MeOH) (56%). Ketal cleavage of **5** produced the chiral tetraol **6**, $[\alpha]^{23}_D$ +18.2

Scheme 1[a]



[a] Conditions: (a) Rieke barium, THF, −78 °C, 1 h (56%). (b) 3:1 HOAc−H_2O, 50 °C, 3 h (97%). (c) Oxone, ketone **7** (cat.), K_2CO_3, buffer pH 10.5, $(MeO)_2CH_2$−CH_3CN−H_2O, 0 °C, 1.5 h (66%). (d) Camphor-10-sulfonic acid (6 equiv), CH_2Cl_2, −94 °C, 3 h (44%). (e) CH_3SO_2Cl (5 equiv), C_5H_5N (10 equiv), DMAP (2 equiv), 0 °C for 1 h then 23 °C for 1 h (50% yield at 60% conversion). (f) 0.1 M NaOAc in HOAc at 40 °C for 12 h (65%).

(*c* 1.2, $CHCl_3$) (97%), which has been isolated previously from various natural sources.[13,14] Epoxidation of **6** using the Shi chiral dioxirane from ketone **7**[15] afforded tetraepoxide **8**, $[\alpha]^{23}_D$ +38.1 (*c* 1.3, EtOH), in 66% yield (estimated diastereomeric purity ca. 80% by ^{1}H NMR analysis) with an estimated *R*/*S* selectivity at each double bond of >20:1.[9] Exposure of **8** to camphor-10-sulfonic acid in CH_2Cl_2 at −94 °C effected bidirectional tetracyclization to **9**, which was isolated in pure condition by column chromatography on silica gel in 44% yield; $[\alpha]^{23}_D$ −6.1 (*c* 0.2, $CHCl_3$). Tetraol **9** could be selectively converted to the monomesylate **10** (at 60% conversion) despite an unusual lack of reactivity

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(10) After the submission of this manuscript (July 7, 2000) a paper appeared in which syntheses of **1** and **3** were reported by other, more lengthy routes; see: Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **2000**, *122*, 7124.
(11) (a) This compound was prepared in four steps and 58% overall yield from *E*,*E*-farnesyl acetate by the following sequence: (1) position and enantioselective terminal dihydroxylation (as described by: Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741), (2) bis-acetonide formation (2,2-dimethoxypropane, 0.01 equiv of *p*-TsOH at 23 °C for 2 h), (3) deacetylation (K_2CO_3, MeOH, at 23 °C for 2 h), and (4) mesylate formation (1.3 equiv each of CH_3SO_2Cl and Et_3N in THF, at −45 °C for 45 min) and in situ displacement of mesylate by addition of 5 equiv of LiBr, and reaction at 0 °C for 1 h. (b) See also: Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999.
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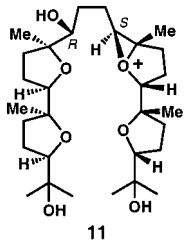
of the two secondary (neopentyl type) hydroxyl groups of **9**; for **10**; $[\alpha]^{23}_D$ +10.0 (*c* 0.2, $CHCl_3$).[16] Because of the extreme steric shielding at the backside of the mesyloxy carbon subunit of **10**, we anticipated that solvolysis of **10** in HOAc, a good ionizing solvent, would occur via nucleophilic participation of the vicinal tetrahydrofuran oxygen, forming the intermediate oxonium ion **11** (with inversion), which would then undergo a second internal



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backside displacement by the secondary hydroxyl to generate a new tetrahydrofuran ring. The resulting product would correspond to overall ring closure of **10** with retention of configuration and, more specifically, would therefore be the C_2-symmetric chiral product **3**. We were pleased to find that the major product from the acetolysis of **10** was indeed **3**, as was clear from its optical activity and the 2-fold simplification of the ^{1}H and ^{13}C NMR spectra, due to C_2-symmetry. The 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, IR, and high-resolution mass spectra were identical with those reported and measured by us for an authentic sample of glabrescol.[17] In addition the chromatographic mobilities measured for synthetic **3** and natural glabrescol were identical in several different solvent systems. Finally, the optical rotation of **3**, $[\alpha]^{23}_D$ −25.2 (*c* 0.3, $CHCl_3$), compares well with a recently determined sample of natural glabrescol, $[\alpha]_D$ about −28.[18,19] On the basis of all these data, as well as previous synthetic work,[9] it is clear that glabrescol possesses the C_2-symmetric structure **3** and not a C_S-symmetric alternative.[20]

The success of the bidirectional double cyclization of tetraol tetraepoxide **8** to the tetracycle **9**, a key feature in the synthesis outlined in Scheme 1, can be ascribed to a considerably faster rate of closure of rings A and B relative to ring C. Consequently, the bidirectional formation of rings A/B and A′/B′ occurs rather than a unidirectional formation of an A/B/C/B′ tetracycle. Of course, in the case of the pentacyclization of **2** to form **1**,[9] the unidirectional cyclization cascade is favored because there is a single initiating secondary hydroxyl function.

This study suggests a number of interesting questions for further research, for example: (1) Will the C_S-symmetric pentatetrahydrofuran oxasqualenoids previously synthesized[9] make their appearance in due course as natural products? (2) Does the biosynthetic route to glabrescol involve cyclizations analogous to those used for the synthetic construction described herein? (3) Do glabrescol and the other pentatetrahydrofurans display significant bioactivity?

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Supporting Information Available: Experimental procedures for the synthesis of **3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) R_f values measured for compounds **3** and **5**−**10** using silica gel TLC plates with the indicated elution solvent were as follows: **5**, 0.30 (5:1 hex−Et_2O); **6**, 0.15 (1:1 hex−EtOAc); **8**, 0.24 (10:1 EtOAc−EtOH); **9**, 0.26 (1:2 hex−EtOAc); **10**, 0.19 (1:2 hex−EtOAc); **3**, 0.37 (1:2 hex−EtOAc).

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(16) The two secondary hydroxyl groups of **9** are very resistant to S_N2 substitution reactions, e.g., Mitsunobu-type displacement or reaction with Ph_3P-Br_2.

(17) Kindly provided by Dr. Helen Jacobs, University of the West Indies.

(18) Personal communication to E.J.C. from Dr. Helen Jacobs, May 3, 2000. We are indebted to Dr. Jacobs for this information and for her generous assistance in this research.

(19) Additional values for the optical rotation of synthetic **3** as a function of wavelength (Hg lines): −26.1 at 578 nm, −28.1 at 546 nm, −38.7 at 436 nm, and −43.2 at 365 nm (*c* 0.3, $CHCl_3$).

(20) Measurement of the ^{1}H−^{1}H NOESY spectrum of synthetic **3** by us confirmed the cis arrangement of the H and CH_3 substituents at C(2) and C(5) of the two equivalent A rings and also the two equivalent B rings, as required by that structure.