ORGANIC LETTERS

2012
Vol. 14, No. 15
3932–3935

Two Concise Enantioselective Total Syntheses of (−)-Glabrescol Implicate Alternative Biosynthetic Pathways Starting from Squalene

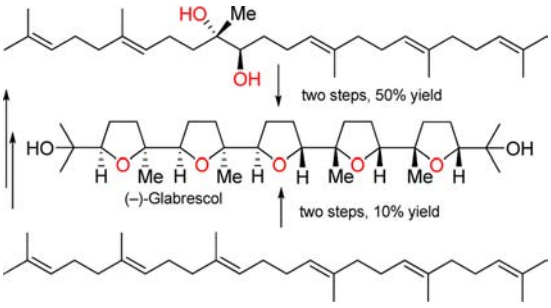
Peng Yang, Pei-Fang Li, Jin Qu,* and Liang-Fu Tang

State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, China

qujin@nankai.edu.cn

Received June 19, 2012

ABSTRACT



The C_2-symmetric (−)-glabrescol was synthesized in two steps from (10*S*,11*R*)-dihydroxy-10,11-dihydrosqualene or squalene with 50% or 10% overall yields, respectively. These highly efficient and biomimetic syntheses employed a base-promoted middle-to-terminal double epoxide-opening cascade, which constructs the five tetrahydrofuran rings in glabrescol in one operation.

In recent years, the groups of polyethers containing 2,5-linked tetrahydrofuran subunits, occurring in both terrestrial and marine plants, have attracted notable attention because of their special chemical structures and potential bioactivities.[1] (−)-Glabrescol, the first reported squalene-derived penta-tetrahydrofuran polyether, was extracted from the branches and wood of *Spathelia glabrescens* in 0.005% yield by Jacobs et al. in 1995.[2] It was originally assigned the C_s-symmetric structure **1** based on the observation that the optical rotation of this compound was zero (Scheme 1). In 2000, Corey's group[3a] and Kodama's group[3b] separately reported the total syntheses of this proposed structure but found that the NMR data of their synthetic compound **1** were different from those of the isolated natural product. The correct C_2-symmetric structure of (−)-glabrescol (**2**) was revealed in the same year through the enantioselective total synthesis by Morimoto et al.[4] They also reported that the optical rotation of the synthetic (−)-glabrescol was −22.4. Shortly after Morimoto's total synthesis, Corey and Xiong reported a biomimetic total synthesis of the revised C_2-symmetric (−)-glabrescol.[5] Their six-step total synthesis relies on the terminal-to-middle double cyclizations of a tetraol tetraepoxide to construct the key tetracycle intermediate. Herein, we report two concise biomimetic total syntheses of (−)-glabrescol (**2**) via base-promoted epoxide-opening cascade reactions.

(1) For reviews, see: (a) Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250–5281. (b) Connolly, J. D.; Hill, R. A. *Nat. Prod. Rep.* **2003**, *20*, 640–659. (c) Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235–246.

(2) 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.

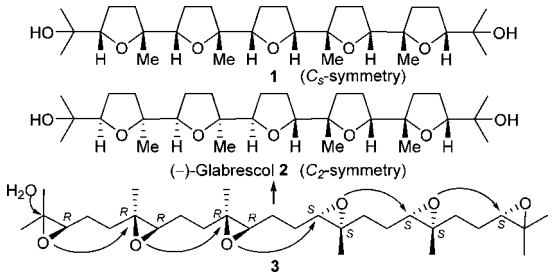
(3) (a) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831–4832. (b) Hioki, H.; Kanehara, C.; Ohnishi, Y.; Umemori, Y.; Sakai, H.; Yoshio, S.; Matsushita, M.; Kodama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2552–2554.

(4) (a) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **2000**, *122*, 7124–7125. (b) Morimoto, Y.; Kinoshita, T.; Iwai, T. *Chirallity* **2002**, *14*, 578–586. (c) Morimoto, Y.; Takaishi, M.; Iwai, T.; Kinoshita, T.; Jacobs, H. *Tetrahedron Lett.* **2002**, *43*, 5849–5852. (d) Morimoto, Y.; Iwai, T.; Nishikawa, Y.; Kinoshita, T. *Tetrahedron: Asymmetry* **2002**, *13*, 2641–2647. (e) Morimoto, Y. *Org. Biomol. Chem.* **2008**, *6*, 1709–1719. (f) Morimoto, Y. *Asahi Garasu Zaidan Josei Kenkyu Seika Hokoku*, 2011.

(5) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328–9329.

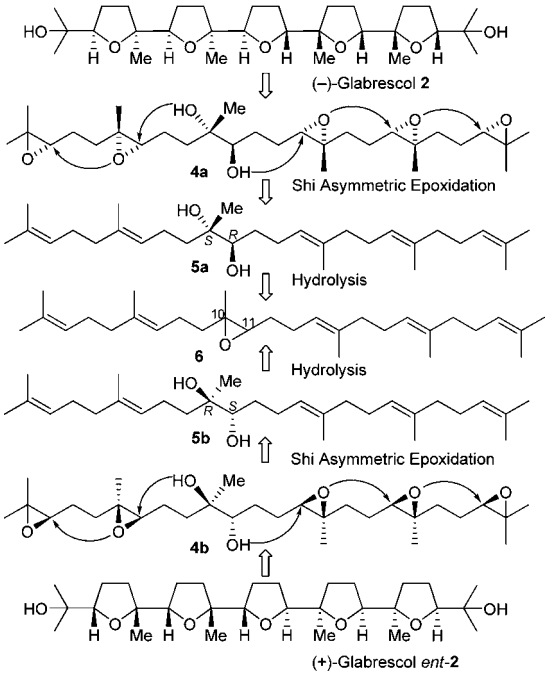
10.1021/ol3016836 © 2012 American Chemical Society
Published on Web 07/20/2012

Scheme 1. Originally Proposed C_s-Symmetric Glabrescol (**1**) and the Correct C_2-Symmetric (−)-Glabrescol (**2**) and Its Proposed Biogenesis



It was proposed that (−)-glabrescol (**2**) is biosynthesized in a single step from the *meso* hexaepoxide (**3**) derived from squalene (Scheme 1). The nucleophilic attack of water at the terminal epoxide of **3** initiates an all-*exo* left-to-right unidirectional epoxide-opening cascade and constructs the five tetrahydrofuran rings in one step.[2,4] Mimicking this biogenetic pathway meets two challenges: (1) the regio- and stereoselective epoxidation of squalene to generate a hexaepoxide, in which the configurations of the right three epoxides are opposite to those of the left three epoxides; (2) the unidirectional cascade epoxide-opening cyclization from the correct terminus of the polyepoxide precursor (the cascade proceeds in the opposite direction giving *ent*-glabrescol). The feasibility of this biogenetic pathway has recently been tested by Morimoto's group. The unidirectional left-to-right or right-to-left epoxide-opening cascades of *meso* hexaepoxide **3** proceeded in the presence of a catalytic amount of TfOH, but as was expected, the reaction gave (±)-glabrescol in 8% yield.[4f] However, by applying a bidirectional epoxide-opening strategy, it is possible to design a cascade utilizing a homochiral polyepoxide precursor. Inspired by the previous successful utilizations of cascade epoxide-opening cyclizations in the total synthesis of polyether natural products,[4−6] we considered that the C_2-symmetric (−)-glabrescol was possibly generated from the cascade epoxide opening of 10,11-dihydroxypentaepoxide (**4a**). The two middle hydroxyl groups of **4a** may initiate the middle-to-terminal double epoxide-opening cascades and produce the penta-THF structure in one step (Scheme 2). **4a** (with all *S*,*S*-epoxides) and **4b** (with all *R*,*R*-epoxides) could be synthesized from

Scheme 2. Retrosynthetic Analysis of (−)-Glabrescol (**2**) and (+)-Glabrescol (*ent*-**2**)



diol **5a** and **5b** respectively using the Shi asymmetric epoxidation.[7] Equal amounts of **5a** and **5b** could be obtained from the racemic 10,11-oxidosqualene (**6**) via hydrolysis and resolution. Therefore, according to this strategy, both (−)-glabrescol and *ent*-glabrescol can be synthesized from the same starting material **6**. It should be mentioned that both enantiomers of 10,11-oxidosqualene are natural products and, more specifically, the (10*R*,11*R*)-oxidosqualene was suggested as the biogenetic precursor of several natural polyethers.[8]

This strategy was first tested with the synthesis of (+)-glabrescol (*ent*-**2**) (Scheme 3). (10*R*,11*S*)-Dihydroxy-10,11-dihydrosqualene (**5b**) was prepared from the racemic 10,11-oxidosqualene **6** by hydrolysis and resolution using the reported methods.[9] Shi asymmetric epoxidation of **5b** with the ketone **7** derived from the inexpensive D-fructose[7] gave a mixture of pentaepoxide **4b**, tetraepoxide **8**, and a small amount of other diastereomers in 90% yield. Compounds **4b** and **8** were inseparable by flash column chromatography, and their ratio varied depending on the silica gel chromatography and the storage conditions. The existence of the central THF ring in compound **8** was judged from the characteristic signals in the ^{1}H and ^{13}C NMR spectra of the mixture of **4b** and **8**. The peak at 3.87 ppm in the ^{1}H NMR spectrum (in $CDCl_3$) suggests the existence of a THF structure. There is only one ^{13}C signal at 86.2 ppm

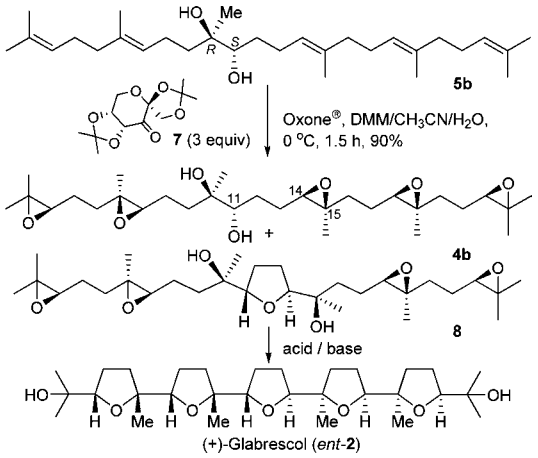
(6) (a) Xiong, Z.; Busch, R.; Corey, E. J. *Org. Lett.* **2010**, *12*, 1512–1514. (b) Morimoto, Y.; Okita, T.; Kambara, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2538–2541. (c) Marshall, J. A.; Hann, R. K. *J. Org. Chem.* **2008**, *73*, 6753–6757. (d) Morimoto, Y.; Yata, H.; Nishikawa, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6481–6484. (e) Morimoto, Y.; Okita, T.; Takaishi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 1132–1135. (f) Marshall, J. A.; Mikowski, A. M. *Org. Lett.* **2006**, *8*, 4375–4378. (g) Morimoto, Y.; Nishikawa, Y.; Takaishi, M. *J. Am. Chem. Soc.* **2005**, *127*, 5806–5807. (h) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448–3467. (i) Lindel, T.; Franck, B. *Tetrahedron Lett.* **1995**, *36*, 9465–9468. (j) Koert, U.; Wagner, H.; Stein, M. *Tetrahedron Lett.* **1994**, *35*, 7629–7632. (k) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691–1694.

(7) (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235. (b) Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 5377–5379.

(8) (a) Kigoshi, H.; Ojika, M.; Shizuri, Y.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1982**, *23*, 5413–5414. (b) Napoli, L.; De; Fattorusso, E.; Magno, S.; Mayol, L. *Phytochemistry* **1982**, *21*, 782–784.

(9) (a) Abad, J. L.; Casas, J.; Sánchez-Baeza, F.; Messeguer, A. *J. Org. Chem.* **1995**, *60*, 3648–3656. (b) Abad, J. L.; Camp, F. *Tetrahedron* **2004**, *60*, 11519–11525.

Scheme 3. Synthesis of (+)-Glabrescol (*ent*-**2**)



which indicated that a C_2-symmetric THF ring was formed, and this judgment was further supported by the fact that only one signal appeared at 72.9 ppm which belonged to the carbons of the tertiary alcohol. Compound **8** was likely formed through the opening of the 14,15-epoxide of **4b** by the hydroxyl group at C_{11}. The diastereoselectivity of the Shi asymmetric epoxidation was very high (*dr* value >9:1 and the ee value of the epoxidation of each double bond >97%).[3a,10] Both **4b** and **8** could afford *ent*-**2** in the next step, so the mixture of **4b** and **8** was used in the following studies.[11] Treatment of the above mixture with camphor-10-sulfonic acid (CSA)[3a,5,6a,12] in toluene at 0 °C for 2 h provided the desired pentacyclic product *ent*-**2** in 44% isolated yield (entry 1, Table 1).[13] The NMR, LRMS (EI), and HRMS data match very well with the literature data,[2,4,5] whereas the optical rotation of *ent*-**2**, $[\alpha]_D^{25}$ = +21.3 (c = 0.3, $CHCl_3$), is of the opposite sense to that of the synthetic (−)-glabrescol ($[\alpha]_D^{25}$ = −22.4 (*c* = 1.27, $CHCl_3$) reported by Morimoto[4] or $[\alpha]_D^{23}$ = −25.2 (*c* = 0.3, $CHCl_3$) reported by Corey[5]). The CD spectrum of *ent*-**2** showed the opposite absorption pattern compared with (−)-glabrescol measured by Morimoto's group. Under acidic conditions, the epoxide-opening cascade may proceed at various levels depending on which epoxides in the polyepoxide precursor have been activated, and thus the cascade reactions give rather complex products.[1a] We envisioned that activation of the hydroxyl group might impart better control over the progress of the cascade and make the reaction cleaner. When the mixture of **4b** and **8** was treated with 16 equiv of NaOH in the mixed solvent of H_2O and 1,4-dioxane (v/v = 1:1)[14] at reflux temperature, *ent*-**2** was formed in 55% yield (entry 2, Table 1). The cascade cyclization was also tested with other bases and solvent systems. The highest yield (90%, entry 7) of *ent*-**2** was obtained by treating the mixture of **4b** and **8** with 3 equiv of NaOH in methanol at 60 °C.

Table 1. Epoxide-Opening Cascade Reaction Operated under Acidic or Basic Conditions[a]

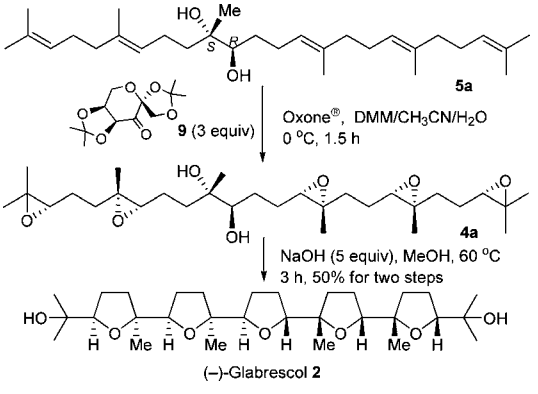
4b, **8** $\xrightarrow{\text{conditions}}$ (+)-Glabresol (*ent*-**2**)

entry	reagent (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1	CSA (0.6)	toluene	0	2	44
2	NaOH (16)	H_2O/1,4-dioxane v/v = 1:1	100	0.5	55
3	KOH (8)	H_2O/1,4-dioxane v/v = 1:2	100	1	80
4	K_2CO_3 (10)	MeOH	60	1.5	61
5	NaOH (10)	MeOH	60	0.8	85
6	NaOH (5)	MeOH	60	2	87
7	NaOH (3)	MeOH	60	3	90
8	KOH (3)	MeOH	60	3	87
9	NaOH (3)	EtOH	60	2	65
10	NaOH (3)	H_2O	60	13	45

[a] The reaction was conducted with 0.1 mmol of substrate in the indicated solvent at the indicated temperature. [b] Isolated yield.[13]

The optimized reaction protocol of base-promoted cascade epoxide-opening was then applied to the synthesis of the natural (−)-glabrescol (Scheme 4). Shi asymmetric epoxidation of (10*S*,11*R*)-dihydroxy-10,11-dihydrosqualene **5a** with the ketone **9** derived from L-fructose[7] gave pentaepoxide **4a**. Without further purification, the crude product was subsequently treated with 5 equiv of NaOH in

Scheme 4. Synthesis of (−)-Glabrescol (**2**)



(10) In the Shi asymmetric epoxidation of the (*S*)-(+)-α-methoxy-α-(phenyl)-acetate of **4b**, the purity of the designed pentaepoxide product was >90% determined by ^{1}H NMR, indicating that the *dr* value was >9:1 and the *ee* value of each epoxide formation was >97%; see SI.

(11) The (*S*)-(+)-α-methoxy-α-(phenyl)-acetate of **4b** could also afford *ent*-**2** under identical reaction conditions; see SI.

(12) (a) Paterson, I.; Boddy, I.; Mason, I. *Tetrahedron Lett*. **1987**, *28*, 5205–5208. (b) Paterson, I.; Boddy, I. *Tetrahedron Lett*. **1988**, *29*, 5301–5304. (c) Paterson, I.; Craw, P. A. *Tetrahedron Lett*. **1989**, *30*, 5799–5802.

(13) The yield was corrected for the diastereomeric purity of **4b** and **8** in the starting material. The total purity of **4b** and **8** as the products of the Shi asymmetric epoxidation in different runs ranged from 70% to 90% determined by ^{1}H NMR.

(14) (a) Hoye, T. R.; Witowski, N. E. *J. Am. Chem. Soc*. **1992**, *114*, 7291–7292. (b) Hoye, T. R.; Jenkins, S. A. *J. Am. Chem. Soc*. **1987**, *109*, 6196–6198. (c) Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855–2862. (d) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc*. **1985**, *107*, 5312–5313.

methanol at 60 °C.[15] The above two-step reaction afforded **2** in 50% isolated yield. The ^{1}H and ^{13}C NMR, IR, CD, LRMS (EI), HRMS, and the optical rotation ($[\alpha]_D^{25}$ = −20.6 (c = 0.3, $CHCl_3$)) of **2** match those of the natural and synthetic (−)-glabrescol.[2,4,5]

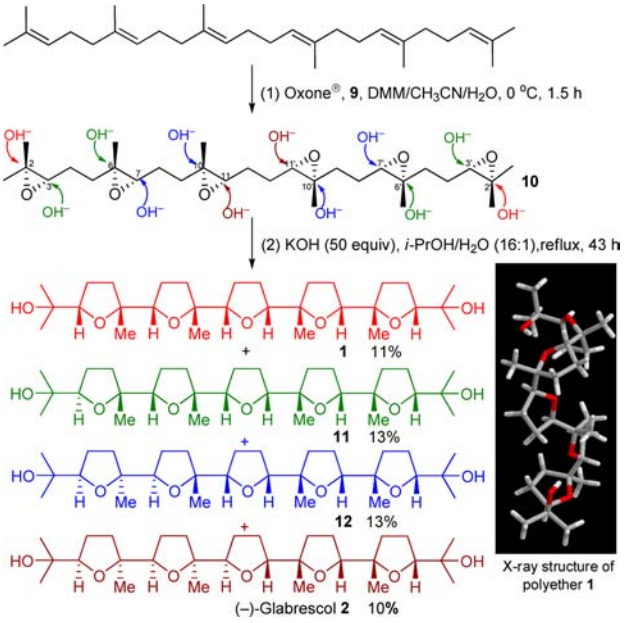
Although the middle-to-terminal epoxide-opening cascade of pentaepoxide **4a** proceeds with very high efficiency, its precursor **5a** needs to be synthesized from squalene over four steps. We further expected that the base-promoted regioselective hydrolysis of hexaepoxide **10** would lead to pentaepoxide **4a** and the *in situ* generated **4a** would further cyclize under the same basic condition to give (−)-glabrescol. In homochiral hexaepoxide **10**, there are 12 possible initiating sites for the single hydrolysis reaction and the attack of OH^- at any site would trigger an epoxide-opening cascade and lead to one penta-tetrahydrofuran polyether product (Scheme 5). However, we found that theoretically only four penta-tetrahydrofuran polyethers would be formed through these 12 possible attacking modes. To test this hypothesis, the all *S,S*-hexaepoxide **10** was synthesized from squalene using the Shi asymmetric epoxidation. The crude hexaepoxide was then treated with 50 equiv of KOH in the mixed solvent of H_2O and *i*-PrOH (v/v = 1:16) at reflux temperature. The reaction rate was relatively slow, but all of hexaepoxide **10** was consumed in 43 h. The diastereomeric mixture could be clearly separated by repeating column chromatography using chloroform/acetone (v/v = 9:1) as the eluent. Analysis of the reaction products showed that all four penta-tetrahydrofuran polyethers were formed as was expected (total yield 47%). The characteristic data of the diastereomer with an 11% yield corresponds to those of the *meso* polyether **1**. X-ray crystal analysis of this compound revealed that it adopts an interesting coiled conformation in which the two terminal hydroxy groups each form two intramolecular hydrogen bonds with the THF ether oxygen atoms close to it and next to it.[16] The NMR data of polyether **11**, obtained in 13% yield, match very well with those of the reported penta-tetrahydrofuran polyether derived from (+)-omaezakianol.[17] The opposite optical rotation value of polyether **11** confirmed its absolute stereochemistry. Polyether **12** has not been reported before, and its structure was determined by the combined use of ^{1}H−^{1}H COSY, HSQC, HMBC, and NOESY spectra. Its relative stereochemistry was further checked by the middle-to-terminal epoxide-opening cascade of all *R,R*-pentaepoxide of **5a**, which was expected to afford *ent*-**12** as the only cyclization product (see Supporting Information (SI)). The NMR spectra of the fourth isomer with a 10% yield was determined to be (−)-glabrescol (**2**). The optical purity of

(15) The reaction was very slow with 3 equiv of NaOH due to the existence of the unseparated ketone **9**.

(16) CCDC number: 876022; see SI. The crystal structure of the bis-*p*-bromobenzoate of compound **1** displays a linear conformation since both of the two terminal hydroxy groups are protected; see ref 3a.

(17) Matsuo, Y.; Suzuki, M.; Masuda, M.; Iwai, T.; Morimoto, Y. *Helv. Chim. Acta* **2008**, *91*, 1261–1266.

Scheme 5. Synthesis of (−)-Glabrescol (**2**) from Squalene



(−)-glabrescol prepared via this synthetic route was equal to that synthesized from pentaepoxide **4a**. Although the regioselectivity of the epoxide-opening cascades is not good, this synthetic route for (−)-glabrescol is still very attractive since it starts from the readily available and inexpensive squalene.

In conclusion, two concise total syntheses of (−)-glabrescol (**2**) have been achieved in 50% yield starting from (10*S*,11*R*)-dihydroxy-10,11-dihydrosqualene (2% overall yield from squalene, the first route) or 10% overall yield from squalene (the second route) respectively. The key feature of our synthetic strategy is the base-promoted middle-to-terminal double epoxide-opening cascade, which constructs the five tetrahydrofuran rings of the C_2-symmetric glabrescol in one operation. The epoxide-opening cascade cyclization is generally accepted as the biogenetic pathway of squalene-derived polyethers. Therefore these syntheses implicated two possible biogenetic pathways of (−)-glabrescol.

Acknowledgment. This work was financially supported by the NSFC (21072098), Program for New Century Excellent Talents in University, and the 111 Project (B06005). We thank Prof. Wei-Dong Li and Prof. Qi-Lin Zhou at Nankai University for helpful discussions.

Supporting Information Available. Experimental procedures and characterization data for all compounds, crystal structure of **1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.