8.566(2) Å, $\alpha = 91.696(2)$, $\beta = 96.988(4)$, $\gamma = 99.278(4)^\circ$, $V = 2968$ Å^3, $Z = 1$, $\rho_{calcd} = 1.02$ g cm^{-3}, $\mu_{Mo} = 4.51$ cm^{-1}, $\theta_{max} = 27.5^\circ$, 11695 measured reflections, $R_1 = 0.098$ for 4134 data [$I > 3\sigma(I)$], $wR_2 = 0.119$ for all measured data.

[14] N. Yoshida, N. Aratani, A. Osuka, *Chem. Commun.* **2000**, 197.

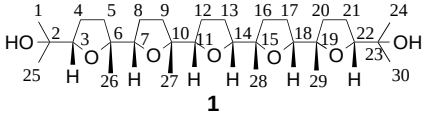
[15] T. X. Lü, J. R. Reimers, M. J. Crossley, N. S. Hush, *J. Phys. Chem.* **1994**, *98*, 11878; J. R. Reimers, T. X. Lü, M. J. Crossley, N. S. Hush, *Chem. Phys. Lett.* **1996**, *256*, 353; N. S. Hush, J. R. Reimers, L. E. Hall, L. A. Johnston, M. J. Crossley, *Ann. N.Y. Acad. Sci.* **1998**, *852*, 1; J. R. Reimers, L. E. Hall, M. J. Crossley, N. S. Hush, *J. Phys. Chem.* **1999**, *103*, 4385.

[16] Redox potentials versus $AgClO_4$/Ag were measured by cyclic voltammetry in $CHCl_3$.

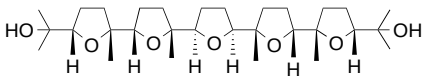
What Is the Structure of Glabrescol? Stereoselective Synthesis of Reported Glabrescol**

Hideaki Hioki, Chie Kanehara, Yumiko Ohnishi, Yukiko Umemori, Hitoshi Sakai, Suzuyo Yoshio, Masayuki Matsushita, and Mitsuaki Kodama*

Glabrescol is a triterpene isolated as a minor constituent of the branches and trunk of *Spathelia glabrescens*. Based on extensive NMR spectra analysis, as well as the symmetrical nature of the molecule, Jacobs et al. proposed a *meso*-type structure **1** containing five continuously linked tetrahydrofuran rings.[1] The novel structural features prompted us to attempt the synthesis of glabrescol.[2, 3] Furthermore, we expected that the synthesis would make it possible to examine the biological activity, including the ionophore-like character which has not yet been reported on. Herein, we describe the stereoselective synthesis of **1** and one of its diastereomers **2**,



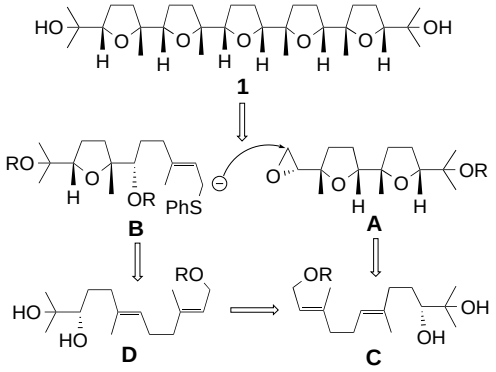
1



2

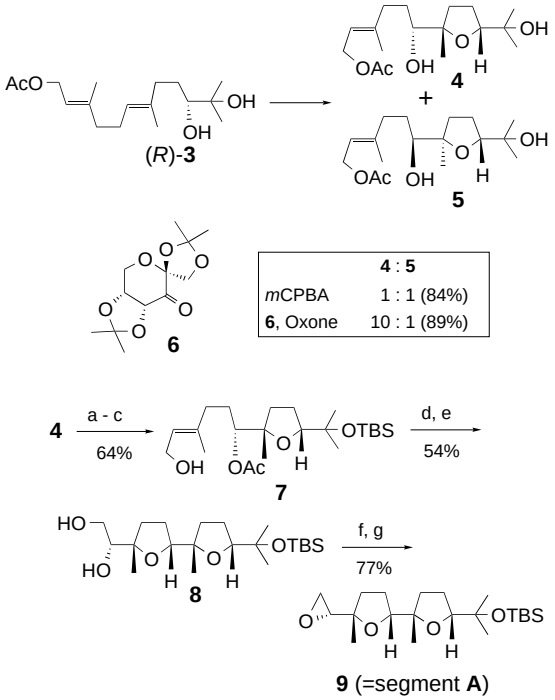
using a baker's yeast reduction as the chirality induction method.[4] Comparison of NMR spectra, however, revealed that neither compound was identical to the natural product.

The retrosynthetic analysis for **1** is illustrated in Scheme 1. Thus, compound **1** is constructed by coupling the 15-carbon segments **A** and **B**, followed by stereoselective oxygenation and tetrahydrofuran (THF) ring formation. Segments **A** and **B** can be prepared from the common (*R*)-diol **C**, obtained by baker's yeast reduction, through asymmetric oxidation.



Scheme 1. Retrosynthetic analysis of the reported glabrescol (**1**).

Segment **A** was synthesized according to Scheme 2. (*R*)-**3**[5] was first treated with *m*CPBA to yield diastereomeric THF derivatives **4** and **5** in a 1:1 ratio.[6] When the same transformation was performed using the epoxidation mediated by



9 (=segment **A**)

Scheme 2. Synthesis of segment **A**. a) Ac_2O, Et_3N, DMAP; b) TBSOTf, 2,6-lutidine; c) LiOH, MeOH; d) Ti(O*i*Pr)$_4$, (−)-DET, *t*BuOOH, 4 Å molecular sieves; e) 1M NaOH, MeOH; f) TsCl, Et_3N, DMAP; g) K_2CO_3, MeOH. *m*CPBA = *meta*-chloroperoxybenzoic acid, DMAP = 4-dimethylaminopyridine, TBS = *tert*-butyldimethylsilyl, Tf = triflate = trifluoromethanesulfonyl, (−)-DET = (−)-diethyl tartrate, Ts = tosyl = toluene-4-sulfonyl.

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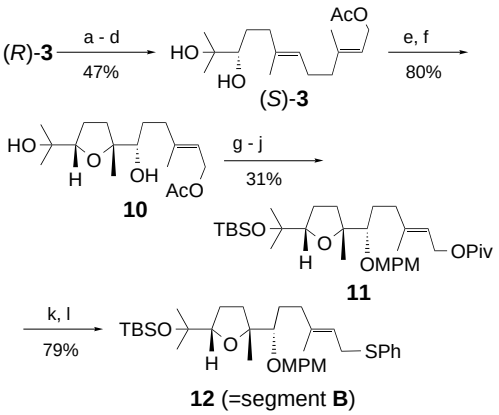
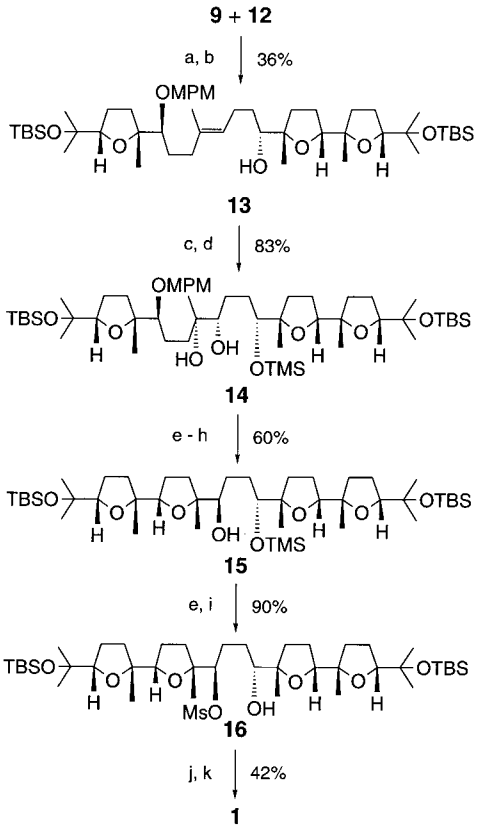
ketone (**6**), developed by Shi,[7] the ratio was increased to 10:1, favoring the desired *cis* derivative **4**. After protection of the two hydroxyl groups in **4** with acetyl and TBS groups, the terminal acetate was selectively hydrolyzed. The resulting allylic alcohol **7** was subjected to asymmetric epoxidation using (−)-DET.[8] Hydrolysis of the acetyl group in the product caused a concomitant THF ring formation to afford diol **8** as the major product (87.5 % *de*). Conversion of the diol in **8** to an epoxide completed the synthesis of segment **A** (**9**).[9]

For the synthesis of segment **B**, (*R*)-**3** was first converted into (*S*)-**3** in 4 steps through an epoxide, as shown in Scheme 3. Epoxidation of (*S*)-**3** using *ent*-**6** as the chiral



Scheme 3. Synthesis of segment **B**. a) MsCl, pyridine; b) K_2CO_3, MeOH; c) Ac_2O, pyridine; d) $HClO_4$, aq. THF; e) *ent*-**6**, oxone; f) SiO_2; g) 1 M NaOH, MeOH; h) PivCl, pyridine; i) MPMCl, NaH, DMF; j) TBSOTf; k) DIBAH; l) PhSSPh, Bu_3P. Ms = mesyl = methanesulfonyl, Piv = pivaloyl, MPM = *para*-methoxyphenylmethyl, DIBAH = diisobutylaluminum hydride.



Scheme 4. Completion of the synthesis of reported glabrescol (**1**). a) *n*BuLi, DABCO, THF; b) Na, *n*BuOH; c) TMSCl, imidazole; d) AD-mix-α; e) MsCl, Et_3N; f) K_2CO_3; g) DDQ; h) SiO_2; i) 1.2 M HCl; j) NaH; k) nBu_4NF. DABCO = 1,4-diazabicyclo[2.2.2]octane, TMS = trimethylsilyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

catalyst,[7] followed by treatment with SiO_2, yielded the THF derivative **10** in almost the same diastereomeric selectivity as with (*R*)-**3**. The acetyl group was then changed into a pivaloyl group and the two hydroxyl groups were protected as the *p*-methoxybenzyl and TBS ethers. Finally, the pivaloyl group was reductively removed and the resulting hydroxyl group was converted into a sulfide moiety using Hata's procedure[10] to produce segment **B** (**12**).[11]

The two segments were then coupled together (Scheme 4). Reaction of the lithium anion of **12** with the epoxide **9** in the presence of DABCO ($-78 \rightarrow 0\,^{\circ}C$) afforded the desired coupling product in a rather low yield, due to the instability of **12** under the coupling conditions; the coupling product was then desulfurized with Na and *n*BuOH to give the alcohol **13**. Protection of the hydroxyl group in **13** as the TMS ether and oxidation of the double bond with AD-mix-α afforded the diol **14** in 83 % yield.[12, 13] The diol in **14** was converted to an epoxide through the mesylate derivative and the MPM group was removed. Treatment of the product with SiO_2 resulted in the formation of a fourth THF ring yielding the alcohol **15**. The hydroxyl group in **15** was mesylated and the TMS group was removed to produce **16**, which was treated with NaH to yield the compound with five THF rings. Although THF ring formation is generally easily accessed, the yield of the product was unexpectedly low because of the formation of substantial amounts of the elimination product. Finally, the TBS groups were removed to achieve complete synthesis of **1**.

The ^1H and ^{13}C NMR spectra of synthetic compound **1** were compared to those of the natural glabrescol. The chemical shifts and splitting patterns were very similar to each other in the ^1H NMR spectrum, but there was a large difference in the chemical shift of the signal assigned to H-11(14) (shown in bold figures in Table 1).[14] In the ^{13}C NMR spectrum, a large difference was observed in the chemical shifts of C-10(15), C-11(14), and C-12(13). Therefore, it was concluded that the structure of glabrescol is not **1**. As the differences in the NMR spectra suggested that the stereochemistry around the central part is incorrect, we attempted the synthesis of diastereomer **2** as the possible structure of the natural product. The synthetic route was almost the same as for the synthesis of **1** (Scheme 5). Comparison of the ^1H and ^{13}C NMR spectra revealed that **2** was also not identical to natural glabrescol. The difference in the chemical shifts in the signals for **2** was even larger than in the case of **1**.

In summary, we have achieved the stereoselective synthesis of two *meso* compounds corresponding to glabrescol. Neither of them, however, were identical to the natural product and the correct structure of glabrescol remains to be clarified.

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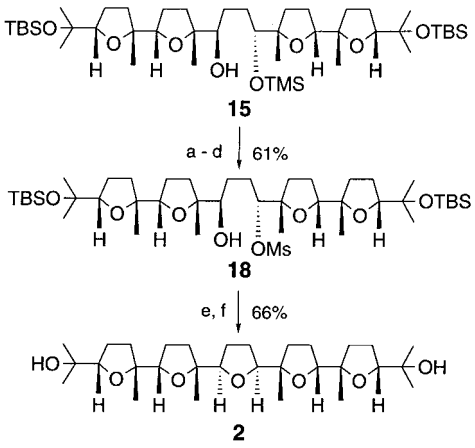
Table 1. Comparison of ^{1}H and ^{13}C NMR chemical shifts of natural and synthetic compounds.[a]

Compound	NMR nucleus	Chemical shift[b] at positions: 1, 30	2, 23	3, 22	4, 21	5, 20	6, 19	7, 18	8, 17	9, 16	10, 15	11, 14	12, 13	24, 25	26, 29	27, 28
natural glabrescol	^{1}H	1.05		3.79	1.80 2.08	1.39 2.23		3.97	1.48 1.72	1.53 1.96		**3.83**	1.60 1.92	1.27	1.09	1.11
	^{13}C	25.38	71.57	85.74	26.62	31.14	85.60	84.17	29.01	34.75	**85.27**	**85.01**	**28.23**	28.28	25.16	22.11
1	^{1}H	1.05		3.78	1.80 2.06	1.37 2.22		3.97	1.46 1.69	1.51 2.02		**3.70**	1.54 1.80	1.28	1.09	1.10
	^{13}C	25.26	71.57	85.59	26.48	30.88	85.49	84.20	28.98	34.52	**84.48**	**83.93**	**27.01**	28.11	24.98	22.48
2	^{1}H	1.04		3.79	1.80 2.05	1.38 2.17		3.96	1.42 1.73	1.49 2.01		3.63	1.61 1.79	1.27	1.10	1.20
	^{13}C	25.29	71.50	85.62	26.51	31.02	85.24	83.52	29.11	33.72	83.54	84.22	26.13	28.04	25.06	24.34

[a] NMR spectra were measured in $CDCl_3$:C_6D_6 (7:3). [b] Chemical shifts quoted in ppm.



Scheme 5. Synthesis of **2**. a) Ac_2O, Et_3N; b) HCl; c) MsCl, Et_3N; d) DIBAH; e) NaH; f) *n*-Bu_4NF.

[1] W. W. Harding, P. A. Lewis, H. Jacobs, S. McLean, W. F. Reynolds, L.-L. Tay, J.-P. Yang, *Tetrahedron Lett*. **1995**, *36*, 9137.

[2] For the synthetic studies of glabrescol, see: Y. Morimoto, T. Iwai, T. Yoshimura, T. Kinoshita, *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2005.

[3] For the stereoselective synthesis of *trans-threo*-penta(tetrahydrofuran), see: a) U. Koert, M. Stein, K. Harms, *Angew. Chem.* **1994**, *106*, 1238; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1180; b) U. Koert, M. Stein, H. Wagner, *Chem. Eur. J.* **1997**, *3*, 1170.

[4] For our examples of natural product synthesis using baker's yeast reduction, see: a) M. Kodama, S. Yoshio, T. Tabata, Y. Deguchi, Y. Sekiya, Y. Fukuyama, *Tetrahedron Lett*. **1997**, *38*, 4627; b) H. Hioki, H. Ooi, Y. Mimura, S. Yoshio, M. Kodama, *Synlett* **1998**, 729.

[5] M. Kodama, H. Minami, Y. Mima, Y. Fukuyama, *Tetrahedron Lett*. **1990**, *31*, 4025. The optical purity was determined to be 98% *ee* by liquid chromatographic analysis using a chiral column.

[6] The stereochemistry of **4** and **5** was determined by a modified Mosher's method. See Ref. [4a].

[7] Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc*. **1997**, *119*, 11224.

[8] The stereochemistry of the Sharpless asymmetric epoxidation has been unambiguously established. See: a) M. G. Finn, K. B. Sharpless, *Asymmetric Synthesis* (Ed.: J. D. Morrison), Academic Press, New York, **1985**, Chap. 8, p. 247; b) T. Katsuki, V. S. Martin, *Org. React*. **1996**, *48*, 1.

[9] Compound **9**: $[\alpha]_D^{19}$ +7.69 (c = 1.09, $CHCl_3$); ^{1}H NMR: δ = 0.07 (3H, s), 0.08 (3H, s), 0.85 (9H, s), 1.16 (3H, s), 1.18 (3H, s), 1.18 (3H, s), 1.19 (3H, s), 1.53–1.66 (2H, m), 1.79–1.97 (6H, m), 2.69–2.74 (2H, m), 3.03 (1H, dd, J = 3.9, 3.0 Hz), 3.71 (1H, dd, J = 7.2, 7.2 Hz), 3.92 (1H, dd, J = 7.0, 7.0 Hz).

[10] I. Nagawa, T. Hata, *Tetrahedron Lett*. **1975**, 1409.

[11] Compound **12**: $[\alpha]_D^{25.5}$ −4.19 (c = 1.8, $CHCl_3$); ^{1}H NMR: δ = 0.08 (6H, s), 0.86 (9H, s), 1.12 (3H, s), 1.14 (3H, s), 1.22(3H, s), 1.57 (3H, br.s), 1.20–2.40 (8H, m), 3.21 (1H, dd, J = 8.8, 2.5 Hz), 3.54 (2H, d, J = 7.4 Hz), 3.74 (1H, t, J = 7.0 Hz), 3.80 (3H, s), 4.47 (1H, d, J = 11.0 Hz), 4.59 (1H, d, J = 11.0 Hz), 5.31 (1H, br.t, J = 7.7 Hz), 6.86 (2H, d, J = 8.8 Hz), 7.16–7.36 (7H, m).

[12] The stereochemistry of diol **14** was based on the empirical rule. See: a) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, X.-L. Zhang, *J. Org. Chem*. **1992**, *57*, 2768; b) H. Becker, S. B. King, M. Taniguchi, K. P. M. Vanhessche, K. B. Sharpless, *J. Org. Chem*. **1995**, *60*, 3940.

[13] The AD-mix-α oxidation afforded **14** and its diastereomer in the ratio of 5.2:1.

[14] No difference was observed in ^{1}H and ^{13}C NMR spectra of **1** when they were recorded at the lower concentration.

Beneficial Effect of *ortho*-Methoxy Groups in the Asymmetric Ring Opening of *meso* Epoxides with Silicon Tetrachloride Catalyzed by Chiral *ortho*-Methoxyphenyldiazaphosphonamide Lewis Bases**

Jean Michel Brunel, Olivier Legrand, Sébastien Reymond, and Gérard Buono*

The asymmetrization of suitable *meso* compounds is an attractive approach to the synthesis of complex molecules and often greatly simplifies their preparation.[1] Numerous procedures to effect asymmetrization have been developed, including the deprotonation,[2] protonation,[3] esterification,[4] hydrolysis,[5] and ring cleavage of *meso* carboxylic anhydrides.[6]

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