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Diastereoselective Two-Directional Synthesis and Cation Transport Ability of the Central Tristetrahydrofuranyl Unit of *meso* Polyether Glabrescol as Naturally Occurring Podand

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Abstract

The diastereoselective synthesis of the central 2,5-linked tristetrahydrofuran (trisTHF) **6** of naturally occurring *meso* polyether, glabrescol (**5**), has been achieved in a two-directional manner by the vanadium(V)-catalyzed *anti* oxidative cyclizations of diol **14**. The trisTHF podand **6** and its stereoisomeric analogs **7** and **8** exhibited outstanding cation transport abilities for physiologically important Na^+ and K^+.

Keywords: Natural products; Plants; Cytotoxins; Complexation

Recently, biologically active and structurally unique triterpene polyethers, which are thought to be biogenetically squalene-derived natural products, have been isolated from both terrestrial and marine plants. Among them, our bioactive and synthetic interests are cytotoxic 14-deacetyl eurylene (**1**) [1], longilene peroxide (**2**) [2], teurilene (**3**) [1,3], and eurylene (**4**) [4] isolated from the wood of *Eurycoma longifolia* by Itokawa *et al.* and glabrescol (**5**) extracted from the branches and wood of *Spathelia glabrescens* (Rutaceae) by Jacobs *et al.* [5] (Figure 1). Based on their X-ray crystallographic analyses and NOE experiments in ^1H NMR spectra, it has been deduced that the polyethers **1–3** and **5** adopt the folded conformation in solution and **4** only the extended one. At that time, Itokawa *et al.* have proposed the very interesting relationship between the conformations and cytotoxicities of these polyethers **1–4**; i.e., **1–3** possessing the folded conformation exhibit prominent cytotoxic activities on KB cells, whereas **4** having the extended one does not (Table 1) [1]. Although the biological activity of glabrescol (**5**) has not been reported, we guess that **5** must also show some cytotoxicity due to its folded conformation. The mechanism of action for the cytotoxic activities of these natural polyethers, however, remains to be clarified.

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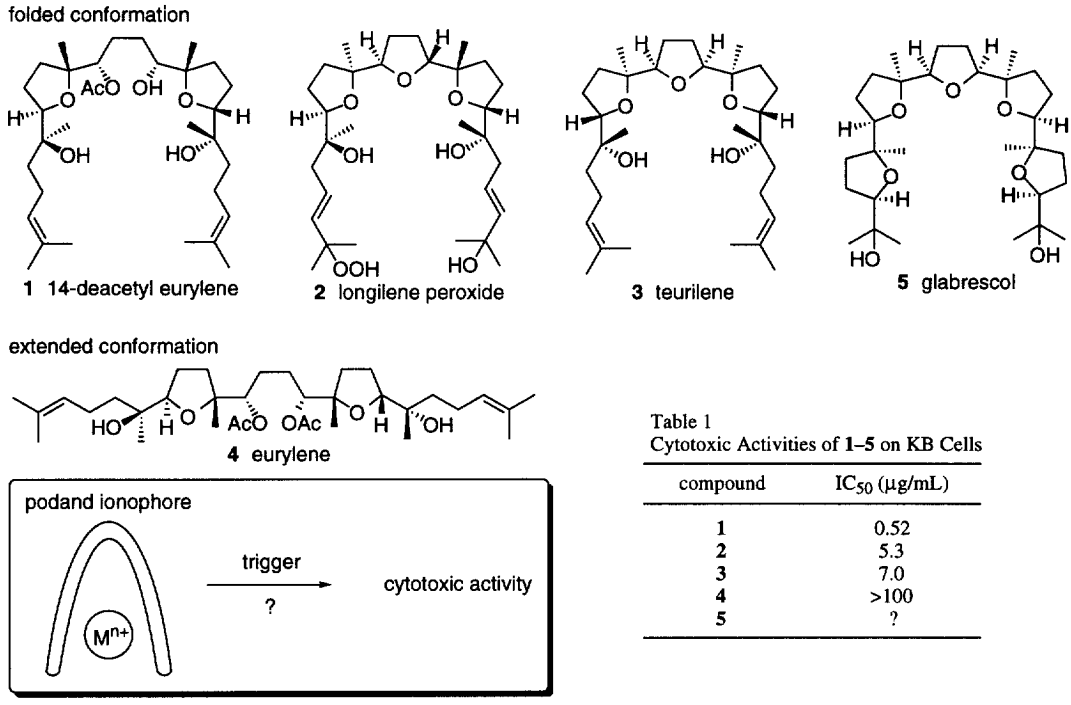


Table 1
Cytotoxic Activities of **1–5** on KB Cells

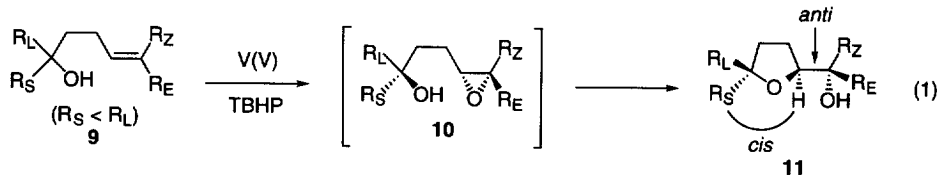
compound	IC_{50} (μg/mL)
1	0.52
2	5.3
3	7.0
4	>100
5	?

Figure 1. Relationship between the conformations and cytotoxicities of polyethers reported by Itokawa *et al.* and our hypothetical mechanism of action for their cytotoxicities.

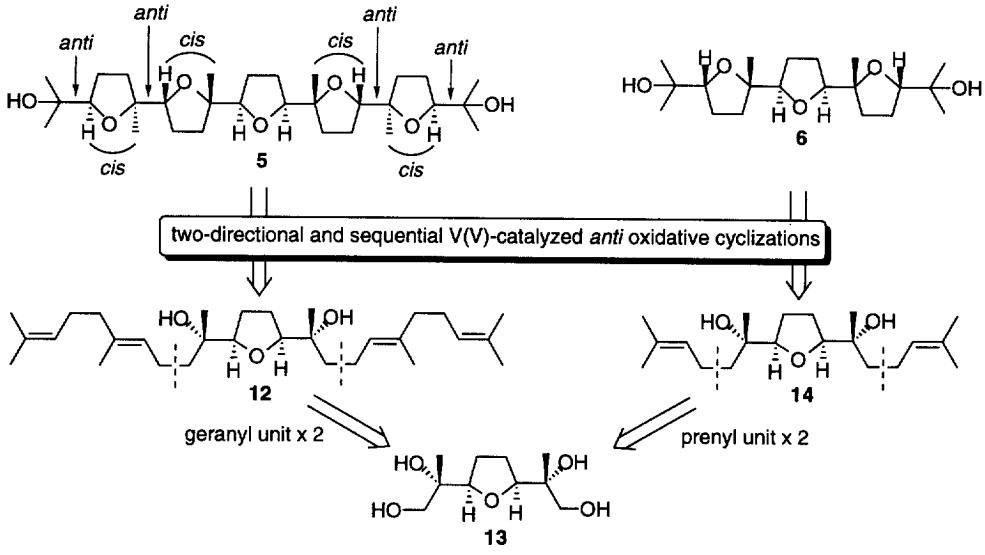
On the other hand, there are a variety of *Annonaceous* acetogenins structurally related to these polyethers, which possess a broad spectrum of important and potent biological activities [6–8]. It has been suggested that the biological activities of neutral acetogenins involving oligotetrahydrofuran rings might be attributed to their binding abilities with physiologically important divalent metal cations such as Ca^{2+} and Mg^{2+} [9–13].[1] In the same way, by thinking of the polyethers **1–3** as conformationally preorganized podand ionophores capable of complexing with physiologically important metal cations in biological systems, we also hypothesize that such an ionophoric interaction may be responsible for the occurrence of their cytotoxic activities (Figure 1). In this context, we have been interested in the cytotoxic activity unknown only for glabrescol (**5**) of these polyethers and its achiral *meso* structure despite having ten asymmetric centers, rarely occurring in nature, and planned its total synthesis[2] directed toward the clarification of its biological activity and ionophoric function. In this paper, we report the highly diastereoselctive two-directional synthesis [23,24] of the central 2,5-linked tristetrahydrofuranyl unit **6** of glabrescol (**5**) and its metal cation transport abilities including its stereoisomeric analogs **7** and **8**.

[1]Such interesting interactions of neutral oligotetrahydrofuranyl derivatives with metal cations have been reported in artificial systems as well as natural products [14–18].

[2]The total syntheses of teurilene (**3**) and (+)-eurylene (**4**) have already been reported by Shirahama *et al.* [19–22].

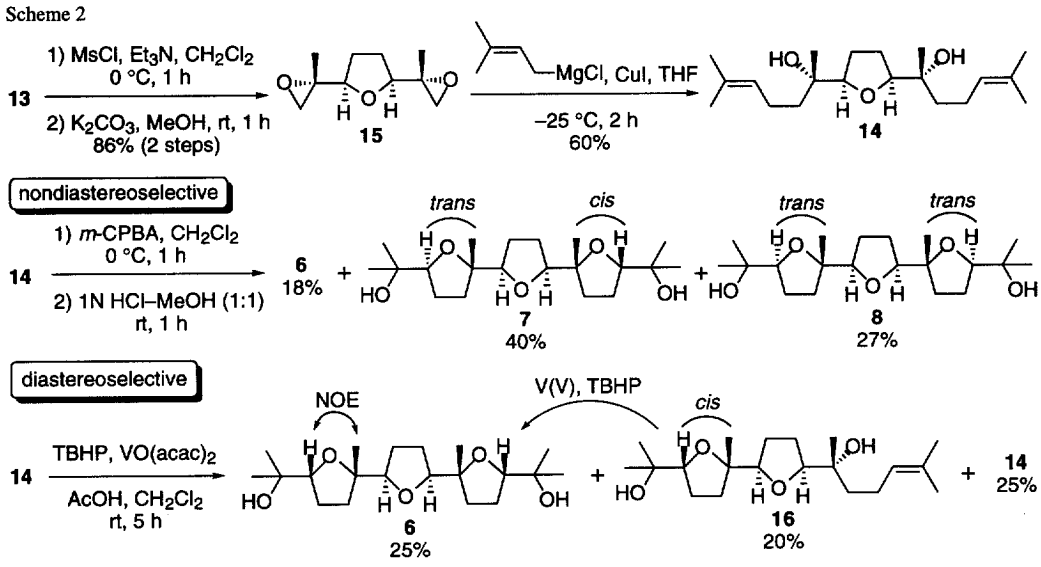


Scheme 1. Retrosynthetic analysis of *meso* glabrescol (**5**) and its central trisTHF unit **6**.



Our synthetic strategy toward glabrescol (**5**) is as follows. Since the stereoselective construction of the tetrahydrofuran (THF) rings [25,26] is the key point to achieve the efficient synthesis of **5**, we chose hydroxy-directed *anti* oxidative cyclizations of acyclic bishomoallylic alcohols with vanadium(V) and *tert*-butyl hydroperoxide (TBHP) as the most efficient synthetic method for producing such THF skeletons. It has already been found that the vanadium(V)-catalyzed *anti* oxidative cyclizations of bishomoallylic tertiary alcohols such as the type **9** predominantly give *cis-anti* THF ring **11** via epoxy intermediate **10** as shown in equation 1 [21,27–29]. Based on the rule, we propose the retrosynthetic analysis of *meso* glabrescol (**5**) by taking its symmetrical property into consideration (Scheme 1). Except for the central *cis* 2,5-disubstituted THF ring of **5**, the relative stereochemistry of the remaining four THF rings including the neighboring stereogenic centers is all *cis-anti*. Therefore, if the V(V)-catalyzed oxidative cyclizations of *meso* bishomoallylic diol **12** proceed in a two-directional and sequential mode, glabrescol (**5**) will be produced in a single step. The *meso* bishomoallylic diol **12** will be in turn constructed from the known *meso* tetraol **13** [30] by extending both side chains with double geranyl units, still in the two-directional manner. We explored the possibility for the two-directional synthesis in diol **14** with shorter side chains as the primary stage.

Scheme 2



The preparation of diol **14** required as the two-directional substrate was begun by mesylation of both primary hydroxyl groups in the known tetraol **13** [30] and subsequent basic treatment of the dimesylate to afford bisepoxide **15**[3] in 86% yield (2 steps) (Scheme 2). The alkylation of bisepoxide **15** with prenylmagnesium chloride [31] was carried out in the presence of a catalytic amount of copper(I) iodide at –25 °C for 2 h to yield the desired diol **14**. In the face of the two-directional strategy, we preliminarily prepared three possible stereoisomers **6–8**[4] as authentic samples in a nondiastereoselective manner by subjecting diol **14** to *m*-CPBA oxidation followed by acid treatment. The stereochemistries of these compounds **6–8** could easily be determined on the basis of the *meso* properties in **6** and **8** (10 peaks in their ^{13}C NMR spectra) and the observation of NOE as shown in *cis* **6**. The key cyclizations of diol **14** with 3 equiv of TBHP, 0.1 equiv of $VO(acac)_2$, and 1.7 equiv of AcOH in CH_2Cl_2 successfully proceeded in the two-directional mode at room temperature for 5 h to diastereoselectively give the favorable *cis-cis* **6** in 25% yield along with monocyclized *cis* **16**

[3]All new compounds in this paper were satisfactorily characterized by ^1H and ^{13}C NMR, IR, MS, and HRMS spectra.

[4]These compounds **6–8** were characterized as follows: **6**, mp 77–80 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95–3.87 (2H, m), 3.86–3.78 (2H, m), 2.11–2.00 (4H, m), 1.97–1.81 (4H, m), 1.61–1.46 (4H, m), 1.25 (6H, s), 1.15 (6H, s), 1.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.1, 84.7, 84.1, 71.0, 31.2, 27.7, 27.5, 25.8, 25.4, 23.8; IR (nujol) 3450, 3355, 1450, 1366, 1065 cm^{-1}; FAB-MS *m/z* (relative intensity) 357 [$(M + H)^+$, 6.0]; FAB-HRMS calcd for $C_{20}H_{37}O_5$ [$(M + H)^+$] 357.2641, found 357.2642. **7**, ^1H NMR (300 MHz, $CDCl_3$) δ 3.94–3.78 (4H, m), 2.24–1.45 (12H, m), 1.24 (3H, s), 1.18 (6H, s), 1.17 (3H, s), 1.12 (3H, s), 1.07 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.2, 85.4, 85.3, 84.9, 84.8, 83.8, 71.5, 70.5, 34.9, 31.3, 28.0, 27.9, 27.6, 26.6, 26.50, 26.47, 25.04, 24.99, 23.7, 23.5; IR (neat) 3470, 1459, 1370, 1065 cm^{-1}; EI-MS *m/z* (relative intensity) 338 [$(M - H_2O)^+$, 4.2]; EI-HRMS calcd for $C_{20}H_{34}O_4$ [$(M - H_2O)^+$] 338.2457, found 338.2444. **8**, ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (2H, br t, J = 5.0 Hz), 3.81 (2H, dd, J = 8.5, 7.1 Hz), 2.20 (2H, br s), 2.07 (2H, dt, J = 10.3, 9.4 Hz), 1.90–1.79 (6H, m), 1.71–1.59 (4H, m), 1.21 (6H, s), 1.19 (6H, s), 1.11 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.1, 85.1, 84.7, 70.5, 33.5, 27.6, 27.2, 26.3, 24.2, 24.0; IR (neat) 3470, 1460, 1370, 1070 cm^{-1}; CI-MS *m/z* (relative intensity) 357 [$(M + H)^+$, 10]; CI-HRMS calcd for $C_{20}H_{37}O_5$ [$(M + H)^+$] 357.2641, found 357.2615.

Table 2
Competitive Cation Transtport Properties of TrisTHF Podands **6–8**[a]

trisTHF	transport rate × 10^9 mol/h					
	Li^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Ba^{2+}
6	0.8	8.3	4.6	<3.8	<3.8	13.1
7	1.0	9.2	10.6	<3.8	<3.8	<3.8
8	1.2	21.8	15.6	<3.8	<3.8	<3.8

[a]Conditions: monovalent $LiClO_4$, $NaClO_4$, $KClO_4$ (0.50 mmol, each) in H_2O (5 mL) / carrier (0.0372 mmol) in CH_2Cl_2 (12 mL) / H_2O (5 mL); divalent $Mg(ClO_4)_2$, $Ca(ClO_4)_2$, $Ba(ClO_4)_2$ (0.50 mmol, each) in H_2O (5 mL) / carrier (0.0372 mmol) in CH_2Cl_2 (12 mL) / H_2O (5 mL).

and the recovered **14**.[5] These results imply the validity of our two-directional and sequential strategy toward glabrescol (**5**), though the key reaction needs to be optimized.

Since it is worthwhile examining whether there is in fact some interaction between the trisTHF podands **6–8** thus obtained and metal cations or not, cation transport experiments were performed using perchlorates of alkali and alkali earth metals (Table 2). In the case of monovalent cations, all these trisTHF podands **6–8** exhibited approximately 10 times higher transport rates of Na^+ and K^+ cations important in biological systems than Li^+ cation. In addition, *trans-trans* **8** corresponding to teurilene (**3**) possessing cytotoxic activity showed approximately 3 times higher transport rates of Na^+ and K^+ cations than *cis-cis* **6** corresponding to glabrescol (**5**). In the case of divalent cations, *cis-cis* **6** only indicated the outstanding transport ability for Ba^{2+}. These facts appear to be very interesting to prove our hypothesis on the mechanism of action for the cytotoxicities of these polyethers (Figure 1).

In summary, we have accomplished the diastereoselective two-directional synthesis of the central trisTHF unit **6** of glabrescol (**5**) through the vanadium methodology and revealed ionophoric activities of the trisTHF podands **6–8** for physiologically important metal cations. Application of this two-directional and sequential strategy to glabrescol (**5**) and more detailed ionophoric properties of these podands are under investigation in our laboratory.

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[5]The longer reaction time in this cyclization resulted in lowering the yields of cyclized products, though the starting material **14** was completely consumed. The *cis* stereochemistry newly generated in the monocyclized product **16** has unambiguously been confirmed by the conversion of **16** into **6** using the repeated vanadium methodology.

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