Effective Combination of Two-Directional Synthesis and Rhenium(VII) Chemistry: Total Synthesis of meso Polyether Teurilene

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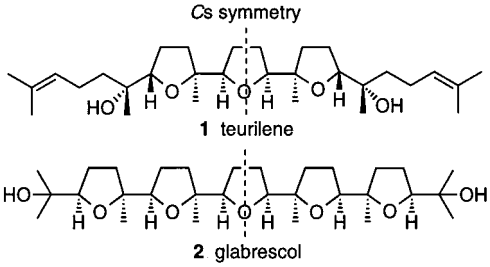
Abstract: The efficient total synthesis of the cytotoxic meso polyether teurilene (**1**), rarely occurring in nature, has been achieved through the effective combination of the concept of two-directional synthesis and the rapidly progressing rhenium(VII) chemistry. In the key rhenium(VII)-promoted syn oxidative cyclization reaction of the two-directional substrate **3**, trans-syn diastereoselectivity (steric control) has been observed in contrast to our previous observation of cis-syn diastereoselectivities (chelation control) for bishomoallylic tertiary alcohols possessing the neighboring tetrahydrofuran (THF) ring. This synthesis in only 10 steps from commercially available methyl tiglate is significantly shorter than the previous one requiring 25 steps as reported by Shirahama et al.

Introduction

The pursuit of efficiency is a lasting theme in organic synthesis since its beginning. One of the solutions to this profound problem in natural products synthesis is the concept of the two-directional synthesis.[1] This method offers the opportunity to reduce the total number of transformations required to complete a synthesis relative to the one-directional alternative. Recently, biologically active and structurally unique triterpene polyethers, rarely occurring in nature, which are thought to be biogenetically squalene-derived natural products, have been isolated from both marine and terrestrial plants. Among them is cytotoxic ($IC_{50} = 7.0\ \mu g/mL$ against KB cells)[2] teurilene (**1**), isolated from the red alga *Laurencia obtusa* by Kurosawa et al.[3] and from the wood of *Eurycoma longifolia* by Itokawa et al.[2] Another is glabrescol (**2**) extracted from the branches and wood of *Spathelia glabrescens* (Rutaceae) by Jacobs et al.[4] The stereostructures of **1** and **2** have been elucidated by X-ray crystallographic analysis and spectroscopic methods, respectively.



These unique polyethers **1** and **2** are achiral meso molecules due to *C*s symmetry despite possessing eight and ten asymmetric centers, respectively. Considering the recent active research studies on remarkable interactions (membrane transport and ion channel) of neutral oligotetrahydrofuranyl derivatives with metal cations in artificial systems as well as natural products,[5] these polyethers containing three or five tetrahydrofuran (THF) rings may be expected to exhibit ionophoric functions.[6] However, because these compounds are available only in restricted amounts from natural sources, the development of an efficient synthesis was desired.[7] The stereoselective construction of the THF rings[8] is the most important key event. Recent progress in rhenium(VII) chemistry[9] encouraged us to focus on hydroxy-directed syn oxidative cyclizations of acyclic bishomoallylic alcohols promoted by rhenium(VII) oxide[10] as the most efficient synthetic method for producing such THF skeletons.[11] In this

(1) For reviews, see the following: (a) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563. (b) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17. (c) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167−2213. For earlier examples, see the following: (d) Hoye, T. R.; Peck, D. R.; Trumper, P. K. *J. Am. Chem. Soc.* **1981**, *103*, 5618−5620. (e) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487−2489.

(2) Morita, H.; Kishi, E.; Takeya, K.; Itokawa, H.; Iitaka, Y. *Phytochemistry* **1993**, *34*, 765−771.

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(6) Morimoto, Y.; Iwai, T.; Yoshimura, T.; Kinoshita, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2005−2010.

(7) For the previous total synthesis of teurilene (**1**), see the following: (a) Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Chem. Lett.* **1988**, 645−646. (b) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5947−5948. (c) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *J. Org. Chem.* **1991**, *56*, 2299−2311. For synthetic approaches toward **1**, see the following: (d) Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855−2862. (e) Hoye, T. R.; Jenkins, S. A. *J. Am. Chem. Soc.* **1987**, *109*, 6196−6198. (f) Lindel, T.; Franck, B. *Tetrahedron Lett.* **1995**, *36*, 9465−9468.

(8) (a) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711−1754. (b) Koert, U. *Synthesis* **1995**, 115−132.

(9) For recent reviews, see the following: (a) Herrmann, W. A.; Kühn, F. E. *Acc. Chem. Res.* **1997**, *30*, 169−180. (b) Romao, C. C.; Kühn, F. E.; Herrmann, W. A. *Chem. Rev.* **1997**, *97*, 3197−3246.

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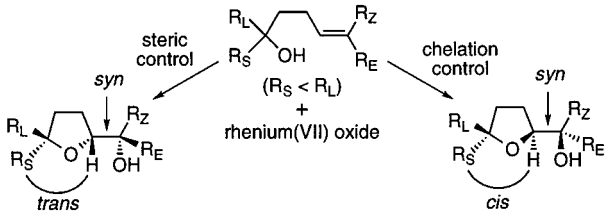
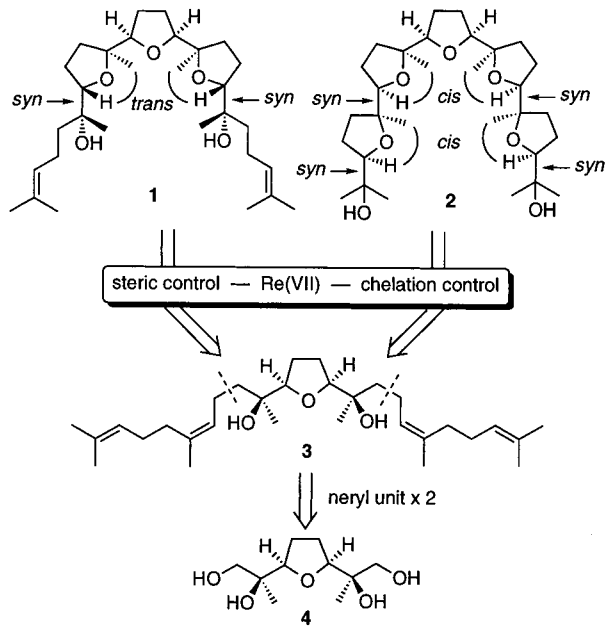
Scheme 1. The Rule for syn Oxidative Cyclizations of Bishomoallylic Tertiary Alcohols by Re(VII) Oxide



Scheme 2. Retrosynthetic Analysis of meso Polyethers **1** and **2**

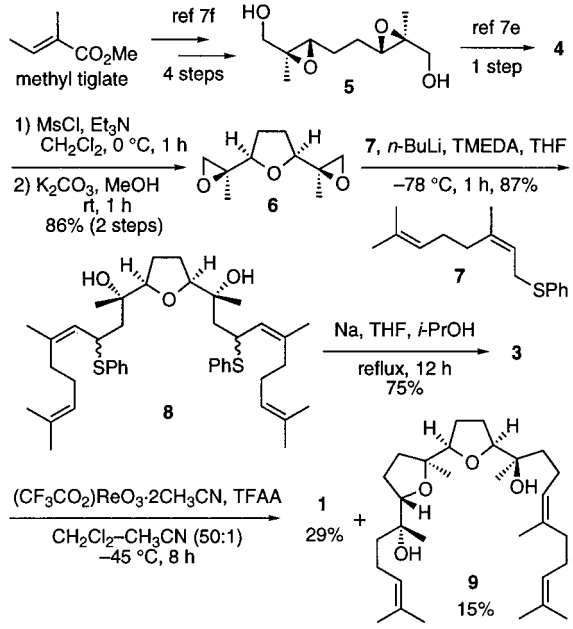


paper, we report the efficient total synthesis of meso polyether teurilene (**1**) through an effective combination of two-directional synthesis and rhenium(VII) chemistry.

Results and Discussion

Recently, we have developed steric (nonbonding) interaction-controlled trans and chelation-controlled cis highly diastereoselective cyclizations of bishomoallylic tertiary alcohols promoted by rhenium(VII) oxide (Scheme 1).[12] Our retrosynthetic analysis of both meso polyethers **1** and **2** takes their symmetry into consideration (Scheme 2). Except for the central cis 2,5-disubstituted THF ring common to these polyethers, the relative stereochemistry of both side THF rings, including the neighboring stereogenic centers, is trans-syn in the case of teurilene (**1**) and cis-syn in glabrescol (**2**). Therefore, if the Re(VII)-induced oxidative cyclizations of meso bishomoallylic diol **3** proceed in a two-directional manner, teurilene (**1**) will be produced under steric control and glabrescol (**2**) under chelation control. The meso bishomoallylic diol **3** will be in turn constructed from the known meso tetraol **4**[7e] by extending both side chains with double neryl units, still in the two-directional mode.

Scheme 3. Total Synthesis of Teurilene (**1**)



The meso tetraol **4** required for the two-directional substrate was conveniently prepared by subjecting bisglycidic alcohol **5**,[13] which was produced from commercially available methyl tiglate in four steps by Franck's method,[7f] to Hoye's procedure[7e] (Scheme 3). The mesylation of both primary hydroxyl groups in the tetraol **4** and subsequent basic treatment of the dimesylate afforded the desired meso bisepoxide **6**[14] in 86% yield in two steps. The lithiation of neryl sulfide **7**[15] and alkylation of the lithio derivative with the bisepoxide **6** were carried out in situ at −78 °C in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)[7c] to yield the bissulfide **8** having the total carbon framework as a mixture of diastereomeric sulfides. The bissulfide **8** was desulfurized under Bouvault-Blanc conditions[7c] to provide the expected diol **3**, contaminated with minor products thought to involve the endo-migrated (disubstituted) double bond. Although column chromatography on normal silica gel did not separate the desired diol **3** from the minor products, purification of the structurally homogeneous diol **3** could be performed by column chromatography on 10% silver nitrate-coated silica gel (benzene:ethyl acetate = 70:30) in 75% isolated yield.

With the requisite two-directional diol **3** in hand, we examined the crucial rhenium(VII)-promoted oxidative cyclization. The results are summarized in Table 1. The addition of trifluoroacetic anhydride (TFAA) was essential to induce any of the cyclizations.[12] Our standard reaction conditions (entry 1) using 8 equiv

(10) (a) Kennedy, R. M.; Tang, S. *Tetrahedron Lett.* **1992**, *33*, 3729−3732. (b) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299−5302. (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303−5306. (d) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 7823−7826. (e) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett.* **1994**, *35*, 5133−5136. (f) McDonald, F. E.; Towne, T. B. *J. Org. Chem.* **1995**, *60*, 5750−5751. (g) Towne, T. B.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022−6028. (h) McDonald, F. E.; Singhi, A. D. *Tetrahedron Lett.* **1997**, *38*, 7683−7686.

(11) For application of this Re(VII) protocol to natural products synthesis, see the following: (a) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Am. Chem. Soc.* **1995**, *117*, 1447−1448. (b) Sinha, S. C.; Sinha-Bagchi, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett.* **1995**, *36*, 9257−9260. (c) Sinha, S. C.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640−7641. (d) Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C.; Sinha, S. C. *Pure Appl. Chem.* **1997**, *69*, 423−430. (e) McDonald, F. E.; Schultz, C. C. *Tetrahedron* **1997**, *53*, 16435−16448. (f) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014−12015. (g) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 4017−4018.

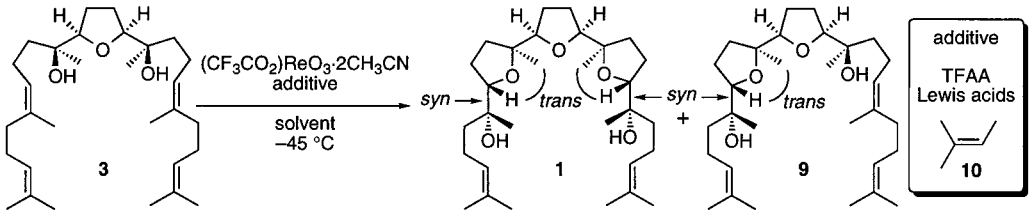
(12) Morimoto, Y.; Iwai, T. *J. Am. Chem. Soc.* **1998**, *120*, 1633−1634.

(13) The specific rotation of this bisglycidic alcohol **5** is $[\alpha]^{24}_{D}$ −22.3 (*c* 1.00, MeOH), lit. (ref 7f) $[\alpha]^{20}_{D}$ −20.0 (*c* 2.54, MeOH).

(14) All new compounds in this paper were satisfactorily characterized by ^{1}H and ^{13}C NMR, IR, MS, and HRMS spectra. See the Experimental Section.

(15) This neryl sulfide **7** was prepared from commercially available nerol in 97% yield (Ph_2S_2, *n*-Bu_3P, THF, rt, 2 h).

Table 1. trans-syn Diastereoselective Cyclizations of Two-Directional Substrate **3** by Re(VII) Oxide under a Variety of Conditions



entry	Re(VII) (equiv)	additive (equiv)	solvent	time (h)	yield (%)[a] 1	9	3
1	8	TFAA (10)	CH_2Cl_2	8	5.6	3.6	2.1
2	8	TFAA (10), BF_3·OEt_2 (1)	CH_2Cl_2	8	7.0	*b*	*b*
3	8	TFAA (10), La(OTf)$_3$ (1)	CH_2Cl_2	8	4.7	7.8	4.9
4	8	TFAA (10), **10** (10)	CH_2Cl_2	8	11	23	17
5	8	TFAA (10), BF_3·OEt_2 (2), **10** (10)	CH_2Cl_2	8	13	19	*b*
6	8	TFAA (10), La(OTf)$_3$ (1), **10** (10)	CH_2Cl_2	8	15	20	12
7	8	TFAA (10), $MgBr_2$·OEt_2 (1), **10** (10)	CH_2Cl_2	8	10	23	14
8	12	TFAA (15), La(OTf)$_3$ (1), **10** (10)	CH_2Cl_2	24	15	11	6.2
9	8	TFAA (10)	CH_2Cl_2/CH_3CN (10:1)	8	5.5	36	29
10	8	TFAA (10), **10** (10)	CH_2Cl_2/CH_3CN (10:1)	8	6.1	72	10
11	8	TFAA (10)	CH_2Cl_2/CH_3CN (20:1)	8	8.8	32	4.0
12	8	TFAA (10), La(OTf)$_3$ (1)	CH_2Cl_2/CH_3CN (20:1)	8	10	26	5.4
13	12	TFAA (15)	CH_2Cl_2/CH_3CN (10:1)	8	15	23	10
14	12	TFAA (15)	CH_2Cl_2/CH_3CN (20:1)	8	21	22	6.4
15	12	TFAA (15)	CH_2Cl_2/CH_3CN (10:1)	30	25	20	5.0
16	12	TFAA (15)	CH_2Cl_2/CH_3CN (20:1)	20	11	10	1.6
17	12	TFAA (15)	CH_2Cl_2/CH_3CN (50:1)	8	29	15	3.8
18	12	TFAA (15)	CH_2Cl_2/CH_3CN (50:1)	20	13	11	*b*
19	12	TFAA (15)	CH_2Cl_2/THF (10:1)	4	*b*	75	5.8
20	12	TFAA (15)	CH_2Cl_2/THF (10:1)	22	15	24	*b*

[a] Isolated yield. [b] Not detected.

of $(CF_3CO_2)ReO_3$·$2CH_3CN$[16] (i.e., 4 equiv of Re(VII) oxide for each bishomoallylic hydroxyl group)[12] provided the dicyclized product teurilene (**1**) in very low yield along with the monocyclized alcohol **9** as a byproduct (entry 1). The spectral (^{1}H and ^{13}C NMR, IR) and physical characteristics of the synthetic teurilene (**1**), mp 83.5−85 °C; $[\alpha]^{21}_D$ +0.2 (*c* 0.24, $CHCl_3$)[17] [lit.[3] mp 84−85 °C; $[\alpha]^{22}_D$ 0 (*c* 0.37, $CHCl_3$)], were identical to those reported.[3,7c] The trans-syn stereochemistry newly generated in the monocyclized product **9** was unambiguously established by converting **9** into **1** with the rhenium(VII) oxide reagent, albeit in low yield (ca. 15%). Thus, the Re(VII)-induced oxidative cyclization of the two-directional substrate **3** proceeded with trans-syn diastereoselectivity (vide infra) to achieve the teurilene synthesis, although the yield was low.

In model studies, we have found that the addition of Lewis acids results in better yields of a dicyclized product; therefore, the effect of Lewis acids was examined (entries 2 and 3). For substrate **3**, however, the yields of **1** were not improved. The material balances other than **1** and **9** in entries 1−3 were the recovered starting diol **3** (yields shown in Table 1) and a large amount of unidentifiable complex mixture (ca. 30−50 wt %) which was much more polar than tricyclic ether teurilene (**1**). Because it was deduced from the ^{1}H NMR spectra of the unidentifiable polar products that the double bonds had been consumed during the reaction, 2-methyl-2-butene (**10**) was added to the reaction system as a scavenger, improving the yields of **1** slightly (entries 4−8). The uses of various solvents capable of ligating to rhenium[16] were investigated at length (entires 9−20). Optimal reaction conditions involved treating diol **3** with 12 equiv of $(CF_3CO_2)ReO_3$·$2CH_3CN$ and 15 equiv of trifluoroacetic anhydride in a mixed solvent system (dichloromethane/acetonitrile = 50:1) at −45 °C for 8 h to diastereoselectively give teurilene (**1**) under steric control (Schemes 1 and 2) in 29% yield (entry 17 and Scheme 3).

It is worthwhile noting that only the trans-syn diastereoselectivity (steric control) has been obtained in the Re(VII)-induced oxidative cyclization of the two-directional substrate **3**, because we have previously observed that the Re(VII)-promoted cyclizations of bishomoallylic tertiary alcohols possessing a neighboring THF ring give rise to the cis-syn diastereoselectivity (chelation control), due to the intramolecular coordination of the THF ring to rhenium (Scheme 1).[12,18] However, this result might be rationalized as follows by considering the characteristics in the two-directional substrate **3** (i.e., the neighboring THF ring is a cis 2,5-disubstituted one for both hydroxyl groups). Because an excess of rhenium reagent was used, a bisalkoxyrhenium like **A** or **B** could be generated as a reaction intermediate (Figure 1). At that time, chelation control model **B**, wherein the coordination of the THF ring to one rhenium encounters a significant steric repulsion with the second alkoxyrhenium moiety, appears to be more disfavored than steric control model **A** without such steric hindrance. These results are also consistent with the rule reported by Sinha et al. that if the vicinal oxygen functions formed in the first cyclization have an erythro relationship, the next cyclization produces a trans THF ring.[19]

(16) (a) Herrmann, W. A.; Thiel, W. R.; Kühn, F. E.; Fischer, R. W.; Kleine, M.; Herdtweck, E.; Scherer, W.; Mink, J. *Inorg. Chem.* **1993**, *32*, 5188−5194. (b) Edwards, P.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1984**, 2695−2702.

(17) The residual optical rotation of synthetic **1** is an experimental error, and neither **3** nor **9** shows a rotation.

(18) This chelation effect on the neighboring THF ring has also been observed in secondary alcohols (refs 10g and 11f).

(19) More recently, Sinha et al. have reported rules of stereoselectivity in tandem oxidative polycyclization reaction of bishomoallylic secondary alcohols with rhenium(VII) oxides. See the following: Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076−9077.

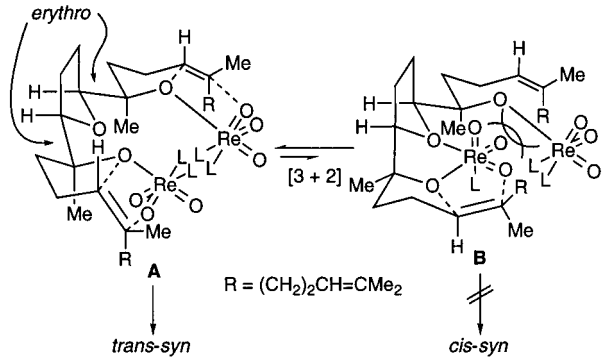
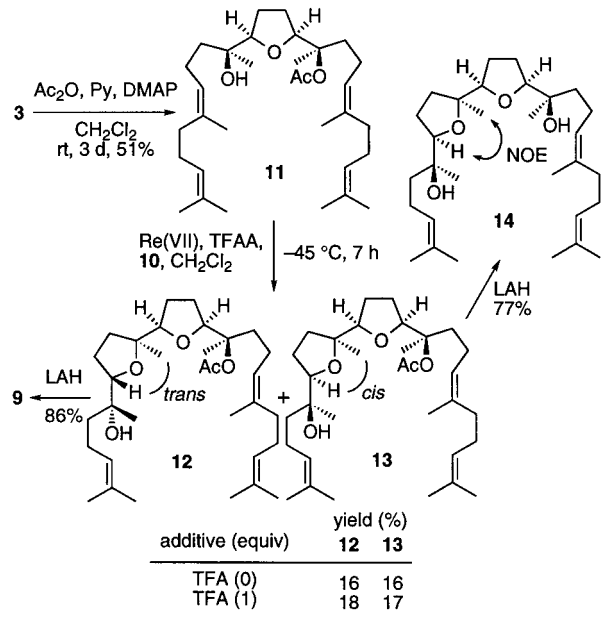


Figure 1. Plausible bisalkoxyrhenium intermediate leading to the trans-syn diastereoselectivity.

Scheme 4



The bisalkoxyrhenium intermediate **A** might be responsible for the trans diastereoselectivity of THF rings, especially in the first oxidative cyclization, from the following control experiments. When monohydroxyalkene substrate **11** prepared by monoacetylation of **3** was subjected to the Re(VII)-induced cyclization (4 equiv of $(CF_3CO_2)ReO_3 \cdot 2CH_3CN$, 5 equiv of TFAA, and 10 equiv of **10** in CH_2Cl_2, −45 °C, 7 h) in the absence or presence of trifluoroacetic acid (TFA) as an additive, the high trans diastereoselectivity of THF rings was not observed (trans **12**/cis **13** = ca. 1:1) in contrast to the two-directional substrate **3** (Scheme 4). The trans stereochemistry of **12** was chemically correlated to the trans-syn product **9** by deacetylation ($LiAlH_4$ in THF, 0 °C, 30 min, 86% yield). The cis stereochemistry of **13** could be determined by the presence of NOE shown in **14** after the deacetylation of **13**, because of signal overlapping of oxymethine protons in the cyclized product **13**.

These facts suggest that coordination of the neighboring THF ring to rhenium (chelation control) partially occurred in a monoalkoxyrhenium intermediate generated from the alcohol **11** and trifluoroacetyl perrhenate. The concentrations of TFA in the reaction media hardly affect the diastereoselectivity;[10g] therefore, the observation of the cis product **13** does not appear to be due to the difference (1 or 2 equiv) of TFA generated in the reactions but due to that of the alkoxyrhenium intermediates (bisalkoxyrhenium vs monoalkoxyrhenium). Furthermore, because only trans THF rings were also produced in the experiments of relatively high mass balance (entries 10 and 19 in Table 1), the first cyclization of the two-directional substrate **3** proceeds with trans-syn diastereoselectivity (steric control in Scheme 1). On the other hand, it seems that we cannot apparently claim trans diastereoselectivity in the second cyclization, because of the relatively low material balances of the isolatable and identifiable products. However, if a cis THF ring had been formed in the second cyclizations of **3**, we could have isolated a tricyclic ether product involving the cis THF ring such as **13** in addition to teurilene (**1**).

Another possibility for the observed trans THF ring formation is that intermolecular coordination of the acetonitrile cosolvent to rhenium[16] predominates over the intramolecular coordination of the THF ring. The latter case, however, appears to be ruled out, because trans-syn products were obtained with similar material balances even in the absence of acetonitrile (entries 1−8 in Table 1).

In summary, we have accomplished the efficient total synthesis of meso polyether teurilene (**1**) in only 10 steps by effectively combining the concept of two-directional synthesis with the rapidly progressive rhenium(VII) chemistry. This synthesis proceeded in 6.1% overall yield in 10 steps from commercially available methyl tiglate and was significantly more efficient than the previous one (0.67% overall yield in 25 steps).[7c] Application of this two-directional strategy to another target, glabrescol (**2**), and the ionophoric activities of **1** are currently under investigation in our laboratory.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were recorded in deuteriochloroform on JEOL model JNM-LA 300 (300 MHz) and 400 (400 MHz) spectrometers. ^{13}C NMR spectra were measured in deuteriochloroform on JEOL model JNM-LA 300 (75 MHz) and 400 (100 MHz) spectrometers. Infrared (IR) spectra were recorded on a JASCO A-102 spectrophotometer. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Low- and high- (EI, CI, and FAB) resolution mass spectra were determined on JEOL model AX-500 and SX-102 spectrometers. Analytical thin-layer chromatography was carried out by precoated silica gel (Merck TLC plates Silica gel 60 F_{254}). The silica gel used for column chromatographies was Merck Silica gel 60 (70−230 mesh). All reactions were performed in oven-dried glassware. Tetrahydrofuran (THF) was distilled over sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), 2-propanol (*i*-PrOH), acetonitrile (CH_3CN), and pyridine (Py) were distilled over calcium hydride. Methanol (MeOH) was distilled over magnesium.

(2*R,5*S**)-2-[(2*S**)-2-Methyl-2-oxiranyl]-5-[(2*R**)-2-methyl-2-oxiranyl]tetrahydrofuran (6).** To a solution of tetraol **4**[7e] (4.14 g, 18.8 mmol) and 6.50 mL (47.0 mmol) of triethylamine in 120 mL of dichloromethane at 0 °C under a nitrogen atmosphere was slowly added a solution of methanesulfonyl chloride (3.06 mL, 39.5 mmol) dissolved in 30 mL of dichloromethane. The mixture was stirred at the same temperature for 1 h. Water (80 mL) was added to the solution, and the dichloromethane layer was separated. The aqueous layer was extracted with ethyl acetate (80 mL × 3). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford the dimesylate which was taken to the next step without further purification.

To a solution of the above dimesylate in 130 mL of methanol was added potassium carbonate (6.50 g, 47.0 mmol), and the mixture was stirred under a nitrogen atmosphere at room temperature for 1 h. After the solvent was evaporated in vacuo, 80 mL of water was added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate (80 mL × 3). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/ethyl acetate = 60:40) on 100 g of silica gel to furnish bisepoxide **6** (2.97 g, 85.7% yield from tetraol **4**) as a colorless oil: R_f = 0.25 (hexane/ethyl acetate = 70:30); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (2H, ddd, J =

6.7, 4.8, 1.6 Hz), 2.78 (2H, d, J = 4.8 Hz), 2.62 (2H, d, J = 5.0 Hz), 2.00−1.72 (4H, m), 1.36 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.5, 57.0, 52.5, 27.0, 17.3; IR (neat) 2980, 1450, 1350, 1235, 1170, 1060, 995, 965, 900, 845, 805, 715 cm^{-1}; EI-MS *m*/*z* (relative intensity) 184 (M^+, 5.0), 154 (46), 127 (40), 97 (85), 57 (77), 55 (100); EI−HRMS calcd for $C_{10}H_{16}O_3$ (M^+) 184.1099, found 184.1084.

Neryl Phenyl Sulfide (7). To a solution of nerol (2.29 g, 14.9 mmol) and diphenyl disulfide (4.54 g, 20.8 mmol) dissolved in 60 mL of tetrahydrofuran was added dropwise 5.13 mL (20.8 mmol) of tributylphosphine, and the mixture was stirred under a nitrogen atmosphere at room temperature for 2 h. To the reaction mixture was added 50 mL of 1 M aqueous sodium hydroxide solution, and the aqueous layer was extracted with ether (50 mL × 3). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 96:4) on 170 g of silica gel to provide sulfide **7** (3.56 g, 97.2% yield) as a colorless oil: R_f = 0.28 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (2H, m), 7.29−7.24 (2H, m), 7.16 (1H, tt, J = 7.2, 1.5 Hz), 5.32 (1H, dt, J = 1.3, 7.7 Hz), 5.13−5.06 (1H, m), 3.55 (2H, dd, J = 7.8, 0.7 Hz), 2.08−1.99 (4H, m), 1.72 (3H, d, J = 1.0 Hz), 1.68 (3H, s), 1.60 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 137.0, 132.0, 129.4, 128.7, 125.8, 123.9, 119.8, 31.92, 31.87, 26.5, 25.7, 23.4, 17.7; IR (neat) 2990, 2940, 1585, 1480, 1440, 1375, 1220, 1090, 1025, 835, 735, 690 cm^{-1}; EI-MS *m*/*z* (relative intensity) 246 (M^+, 16), 137 (53), 110 (29), 69 (100); EI−HRMS calcd for $C_{16}H_{22}S$ (M^+) 246.1443, found 246.1432.

(2*R,5*S**)-2-[(4*Z*,1*S**)-1-Hydroxy-1,5,9-trimethyl-4,8-decadienyl]-5-[(4*Z*,1*R**)-1-hydroxy-1,5,9-trimethyl-4,8-decadienyl]tetrahydrofuran (3).** To a solution of bisepoxide **6** (2.06 g, 11.2 mmol), sulfide **7** (8.25 g, 33.5 mmol), and 10 mL (66.3 mmol) of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine dissolved in 100 mL of tetrahydrofuran was added dropwise 27.7 mL (44.7 mmol) of butyllithium (1.6 M in hexane) under a nitrogen atmosphere at −78 °C, and the mixture was stirred at the same temperature for 1 h. To the reaction mixture was added 100 mL of water, and the aqueous layer was extracted with ether (100 mL × 3). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/ethyl acetate = 85:15) on 180 g of silica gel to yield bissulfide **8** (6.60 g, 87.2% yield) as a mixture of diastereomeric sulfides.

The bissulfide **8** (6.60 g, 9.75 mmol) was dissolved in a mixture of tetrahydrofuran (100 mL) and 2-propanol (50 mL) under a nitrogen atmosphere. Metallic sodium (5.0 g, 0.217 mol) was added to the boiling solution under reflux, and the resulting mixture was stirred under reflux for 12 h. After the mixture was cooled to room temperature, 150 mL of water was added to the solution and the mixture was extracted with ether (150 mL × 3). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 85:15) on 180 g of silica gel to give crude product. Further purification of the crude product was carried out by column chromatography (benzene/ethyl acetate = 70:30) on 180 g of 10% silver nitrate-coated silica gel to provide diol **3** (3.27 g, 75.1% yield) as a colorless oil: R_f = 0.33 (benzene/ethyl acetate = 70:30 on 10% silver nitrate-coated TLC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15−5.07 (4H, m), 3.77 (2H, br t, J = 5.0 Hz), 2.25−1.75 (18H, m), 1.68 (12H, s), 1.61 (6H, s), 1.49 (2H, ddd, J = 13.7, 10.9, 5.7 Hz), 1.37 (2H, ddd, J = 13.4, 11.0, 5.7 Hz), 1.27 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 131.6, 125.1, 124.2, 85.1, 73.8, 38.6, 31.9, 26.5, 25.7, 24.1, 23.4, 22.0, 17.6; IR (neat) 3400, 2980, 2940, 1450, 1370, 1235, 1135, 1080, 985, 825 cm^{-1}; EI-MS *m*/*z* (relative intensity) 460 (M^+, 1.0), 442 (7.0), 425 (2.1), 378 (10), 292 (24), 195 (27), 177 (44), 136 (50), 109 (63), 69 (100); EI−HRMS calcd for $C_{30}H_{52}O_3$ (M^+) 460.3917, found 460.3914.

Teurilene (1). To a solution of rhenium(VII) oxide (357 mg, 0.738 mmol) dissolved in 4 mL of acetonitrile was added dropwise 0.104 mL (0.738 mmol) of trifluoroacetic anhydride, and the solution was stirred under a nitrogen atmosphere at room temperature for 30 min. The solution was cooled to 0 °C and concentrated in vacuo to give trifluoroacetyl perrhenate as a solid.

To a solution of the above trifluoroacetyl perrhenate dissolved in 3 mL of dichloromethane were sequentially added 0.262 mL (1.85 mmol) of trifluoroacetic anhydride and 0.1 mL of acetonitrile, and the solution was cooled to −45 °C under a nitrogen atmosphere. To the solution was added diol **3** (56.6 mg, 0.123 mmol) dissolved in 2 mL of dichloromethane, and the solution was stirred at −45 °C for 8 h. To the solution was added 5 mL of 1 M aqueous sodium hydroperoxide, and the mixture was allowed to warm to room temperature. After being stirred for 30 min, the resulting mixture was filtered through a pad of Celite. The filtrates were poured into 15 mL of water and extracted with dichloromethane (15 mL × 3). The extracts were washed with 30 mL of brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 85:15) on 6 g of silica gel to afford diol **3** (2.2 mg, 3.8% yield) as a colorless oil, monocyclized alcohol **9** (8.8 mg, 15.0% yield) as a colorless oil, and teurilene (**1**) (17.6 mg, 29.0% yield) as a white solid.

Diol 3. R_f = 0.58 (hexane/ethyl acetate = 70:30). Characterization data have already been described above.

Monocyclized Alcohol 9. R_f = 0.45 (hexane/ethyl acetate = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16−5.06 (3H, m), 3.97−3.90 (1H, m), 3.87−3.75 (2H, m), 2.15−1.75 (18H, m), 1.68 (9H, s), 1.61 (6H, s), 1.55−1.43 (2H, m), 1.38−1.20 (2H, m), 1.30 (3H, s), 1.25 (3H, s), 1.22 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 131.6, 131.5, 125.3, 124.5, 124.3, 87.4, 85.5, 85.2, 84.9, 73.6, 72.0, 38.5, 37.4, 34.3, 31.9, 26.8, 26.6, 25.71, 25.70, 25.66, 25.4, 25.3, 24.5, 24.3, 23.4, 22.2, 22.1, 17.63, 17.60; IR (neat) 3470, 2995, 2950, 2890, 1450, 1375, 1077 cm^{-1}; EI-MS *m*/*z* (relative intensity) 476 (M^+, 1.9), 458 (8.0), 440 (6.0), 211 (100), 193 (68), 175 (54), 135 (74), 69 (94); EI−HRMS calcd for $C_{30}H_{52}O_4$ (M^+) 476.3866, found 476.3883.

Synthetic Teurilene (1). R_f = 0.33 (hexane/ethyl acetate = 70:30); mp 83.5−85 °C (recrystallized from diisopropyl ether); $[\alpha]^{21}_D$ +0.2 (*c* 0.24, $CHCl_3$);[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (2H, br t, J = 6.9 Hz), 3.87 (2H, br t, J = 5.1 Hz), 3.83 (2H, dd, J = 9.8, 5.9 Hz), 2.17−1.55 (18H, m), 1.68 (6H, s), 1.61 (6H, s), 1.49 (2H, ddd, J = 13.5, 11.6, 5.0 Hz), 1.33 (2H, ddd, J = 13.4, 11.6, 5.3 Hz), 1.20 (6H, s), 1.18 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.5, 124.6, 86.7, 85.3, 84.5, 72.2, 37.4, 33.5, 27.3, 25.8, 25.7, 24.5, 24.2, 22.2, 17.6; IR ($CHCl_3$) 3550, 2980, 2940, 2870, 1450, 1370, 1070 cm^{-1}; EI-MS *m*/*z* (relative intensity) 492 (M^+, 1.1), 474 (7.8), 459 (9.6), 405 (11), 392 (12), 347 (33), 211 (100), 193 (54), 69 (49); EI−HRMS calcd for $C_{30}H_{52}O_5$ (M^+) 492.3814, found 492.3832.

Monoacetate 11. To a solution of meso diol **3** (503 mg, 1.09 mmol) and 4-(dimethylamino)pyridine (40 mg, 0.328 mmol) dissolved in 5 mL of dichloromethane were successively added pyridine (0.53 mL, 6.55 mmol) and acetic anhydride (0.41 mL, 4.73 mmol), and the mixture was stirred under a nitrogen atmosphere at room temperature for 3 days. To the reaction mixture was added 30 mL of 1 M aqueous hydrochloric acid, and the aqueous layer was extracted with dichloromethane (20 mL × 3). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 90:10) on 30 g of silica gel to afford monoacetate **11** (277 mg, 50.6% yield) as a colorless oil: R_f = 0.48 (hexane/ethyl acetate = 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17−5.04 (4H, m), 4.15−4.08 (1H, m), 3.76−3.67 (1H, m), 2.30−1.20 (20H, m), 1.98 (3H, s), 1.69 (9H, s), 1.67 (3H, s), 1.61 (6H, s), 1.50 (3H, s), 1.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 135.5, 135.3, 131.51, 131.50, 125.2, 124.5, 124.3, 124.2, 85.2, 85.1, 82.1, 73.0, 38.1, 36.2, 31.89, 31.87, 26.54, 26.51, 26.0, 25.7, 25.3, 24.2, 23.34, 23.30, 22.3, 22.2, 21.9, 20.1, 17.6; IR (neat) 3540, 2970, 2925, 1727, 1436, 1361, 1238, 1065, 1010, 820 cm^{-1}; EI-MS *m*/*z* (relative intensity) 502 (M^+, 4.0), 442 (19), 424 (6.0), 373 (6.0), 305 (20), 292 (25), 177 (25), 142 (36), 109 (40), 81 (43), 69 (100); EI−HRMS calcd for $C_{32}H_{54}O_4$ (M^+) 502.4022, found 502.4018.

Oxidative Cyclization of Monoacetate 11. To a solution of rhenium(VII) oxide (130 mg, 0.268 mmol) dissolved in 3 mL of acetonitrile was added dropwise 0.04 mL (0.268 mmol) of trifluoroacetic anhydride, and the solution was stirred under a nitrogen atmosphere at room temperature for 30 min. The solution was cooled to 0 °C and concentrated in vacuo to give trifluoroacetyl perrhenate as a solid.

To a solution of the above trifluoroacetyl perrhenate dissolved in 4 mL of dichloromethane was added 0.09 mL (0.671 mmol) of tri-

fluoroacetic anhydride, and the solution was cooled to −45 °C under a nitrogen atmosphere. To the solution were sequentially added monoacetate **11** (67.5 mg, 0.134 mmol) dissolved in 1 mL of dichloromethane and 2-methyl-2-butene (**10**) (0.16 mL, 1.34 mmol), and the solution was stirred at −45 °C for 7 h. To the solution was added 5 mL of 1 M aqueous sodium hydroperoxide, and the mixture was allowed to warm to room temperature. After being stirred for 30 min, the resulting mixture was poured into 10 mL of water and extracted with dichloromethane (10 mL × 3). The extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 94:6 → 92:8) on 6.5 g of silica gel to yield cis cyclized alcohol **13** (11.1 mg, 16.0% yield) as a colorless oil and trans cyclized alcohol **12** (10.8 mg, 15.6% yield) as a colorless oil.

***cis* Cyclized Alcohol 13.** R_f = 0.48 (hexane/ethyl acetate = 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16−5.05 (3H, m), 4.22 (1H, t, J = 7.1 Hz), 3.91−3.82 (2H, m), 3.05 (1H, br s), 2.18−1.20 (20H, m), 1.97 (3H, s), 1.68 (3H, s), 1.67 (6H, s), 1.61 (6H, s), 1.45 (3H, s), 1.21 (3H, s), 1.16 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 135.3, 131.4, 131.2, 124.79, 124.75, 124.3, 84.83, 84.75, 84.7, 81.6, 73.0, 38.3, 35.8, 31.9, 31.8, 27.6, 26.6, 26.1, 25.8, 25.7, 25.6, 24.54, 24.48, 23.3, 22.3, 22.2, 22.1, 19.8, 17.60, 17.57; IR (neat) 3490, 2960, 2920, 2875, 1729, 1440, 1362, 1240, 1070, 1020, 825, 732 cm^{-1}; CI-MS *m*/*z* (relative intensity) 518 (M^+, 1.6), 458 (13), 441 (16), 332 (30), 321 (18), 263 (51), 211 (100), 182 (43), 109 (40), 69 (86); CI−HRMS calcd for $C_{32}H_{54}O_5$ (M^+) 518.3971, found 518.3952.

***trans* Cyclized Alcohol 12.** R_f = 0.41 (hexane/ethyl acetate = 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16−5.05 (3H, m), 4.21 (1H, t, J = 7.1 Hz), 3.85−3.76 (2H, m), 2.17−1.20 (20H, m), 1.96 (3H, s), 1.68 (6H, s), 1.67 (3H, s), 1.61 (6H, s), 1.44 (3H, s), 1.19 (3H, s), 1.16 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 135.3, 131.4, 124.8, 124.6, 124.3, 86.5, 85.21, 85.19, 84.1, 81.5, 72.2, 37.4, 36.1, 33.7, 31.9, 27.1, 26.6, 26.0, 25.8, 25.7, 25.6, 24.3, 23.9, 23.3, 22.21, 22.15, 22.1, 19.5, 17.6; IR (neat) 3510, 2975, 2930, 2875, 1730, 1444, 1363, 1242, 1075, 1020, 897, 828, 730 cm^{-1}; CI-MS *m*/*z* (relative intensity) 518 (M^+, 6.0), 501 (9.0), 459 (30), 441 (40), 331 (15), 263 (30), 211 (100), 193 (31), 69 (42); CI−HRMS calcd for $C_{32}H_{54}O_5$ (M^+) 518.3971, found 518.3982.

Diol 14. To a solution of cis cyclized alcohol **13** (56.0 mg, 0.108 mmol) in 1 mL of tetrahydrofuran was added dropwise 0.43 mL (0.430 mmol) of lithium aluminum hydride (1 M in tetrahydrofuran) under a nitrogen atmosphere at 0 °C, and the solution was stirred at the same temperature for 30 min. To the reaction mixture were successively added a small amount of methanol and 10 mL of 1 M aqueous sodium hydroxide, and the mixture was extracted with ether (10 mL × 3). The ethereal layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was subjected to column chromatography (hexane/ethyl acetate = 90:10) on 6.5 g of silica gel to provide diol **14** (39.4 mg, 76.5% yield) as a colorless oil: R_f = 0.31 (hexane/ethyl acetate = 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17−5.05 (3H, m), 3.93 (1H, t, J = 7.2 Hz), 3.85 (1H, t, J = 7.0 Hz), 3.75 (1H, t, J = 7.1 Hz), 2.14−1.19 (20H, m), 1.68 (9H, s), 1.61 (6H, s), 1.25 (3H, s), 1.24 (3H, s), 1.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 131.5, 131.4, 125.2, 124.6, 124.3, 85.5, 84.8, 84.7, 84.6, 73.1, 73.0, 38.4, 38.2, 32.6, 31.9, 27.2, 26.6, 26.0, 25.7, 25.6, 25.3, 25.0, 24.7, 24.4, 23.4, 22.2, 21.9, 17.6; IR (neat) 3480, 2990, 2945, 2880, 1450, 1375, 1342, 1077, 985, 832, 735 cm^{-1}; FAB-MS *m*/*z* (relative intensity) 475 [$(M - H)^+$, 62], 459 (6.0), 323 (14), 209 (17), 148 (62), 104 (60); FAB−HRMS calcd for $C_{30}H_{51}O_4$ [$(M - H)^+$] 475.3787, found 475.3779.

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Supporting Information Available: Characterization data for **4** and **5** and the ^{1}H and ^{13}C NMR spectra of synthetic **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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