Articles

Total Synthesis of the *meso*-Triterpene Polyether Teurilene

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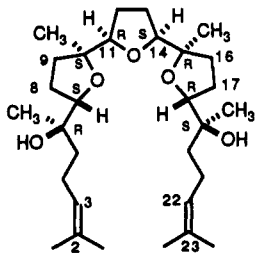
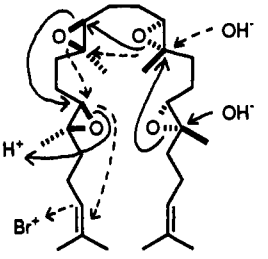
The first total synthesis of the triterpene ether teurilene (1) has been accomplished utilizing two vanadium(V)-catalyzed oxidation–cyclization reactions with different stereoselectivities. The synthesis involved stereoselective and step-by-step construction of 2,5-*cis*- and 2,5-*trans*-tetrahydrofuran rings, vanadium(V)-catalyzed oxidation of 4-substituted 4-en-1-ol **40** and subsequent cyclization of the resulting *anti*-epoxy alcohol **41**, and a similar oxidation–cyclization of 5-substituted 4-en-1-ol **49** by way of *syn*-epoxy alcohol **50**. This was followed by construction of a third tetrahydrofuran ring by more conventional means. An improved synthesis of **1**, which featured direct formation of bis(tetrahydrofuran) **51** from squalene derivative **66** by simultaneous double oxidation–cyclization, was also accomplished.

Introduction

Teurilene (1) is a tricyclic triterpene polyether that was isolated as a metabolite of *Laurencia obtusa* along with thyrsiferol (2) and its congeners by Kurosawa and coworkers in 1985.[1] The crystal structure of **1**[2] revealed that



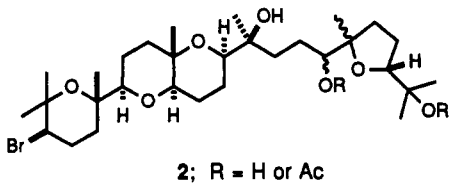
1



3

← for teurilene

←- - for thyrsiferols



2; R = H or Ac

the molecule is characterized by a link of three tetrahydrofurans in the center of the molecule and a beautiful arrangement of eight asymmetric carbons for C_s symmetry. Speculation about the biogenesis of this polyether has biosynthesis beginning by attack of a hydroxide ion on the terminal epoxide of the optically active squalene tetraepoxide (3), causing a series of cyclizations to form the framework of 1.[3] Thyrsiferol (2) and its congeners seem to be derived from the same molecule in an analogous manner.[4] The unique structure and the biogenetic features so appealed to us that we began a project directed toward the total synthesis of teurilene by assembly of chiral fragments.[5]

The excellent total syntheses and other synthetic studies of such natural polycyclic ethers as monensin,[6] lasalocid A,[7] pederin,[8] and brevetoxins[9] frequently used intramolecular attack of hydroxyl groups on epoxides to construct ether rings stereoselectively. Recently, we accomplished the total synthesis of **2** and its congeners by employing this strategy.[10] For the synthesis of the target molecule, we planned that each ether ring of 1 would also be constructed by following this same synthetic strategy. Furthermore, such an approach was interesting to us because it imitated the biogenesis of 1. We have already reported, in com-

(1) Suzuki, T.; Suzuki, M.; Furusaki, A.; Matsumoto, T.; Kato, A.; Imanaka, Y.; Kurosawa, E. *Tetrahedron Lett.* **1985**, *26*, 1329.

(2) Interestingly, X-ray analysis revealed that the two side chains of 1 stood side by side and the whole molecule was folded.[1] Molecular mechanics calculations (MM2) showed that the folded conformation A was more stable than the extended conformations B by 8.0 kcal/mol (see below). The stability of A seems to be attributable to van der Waals attractive forces between the two side chains. Analysis of the steric energies (kcal/mol) of two conformations A and B follows. Conformer A: total energy, 46.9; compression, 3.3; bending, 11.9; stretch bend, 0.8; van der Waals 1,4-energy, 24.7; van der Waals others, −19.5; torsion, 24.4; dipole, 1.3. Conformer B: total energy, 54.9; compression, 3.4; bending, 12.2; stretch bend, 0.8; van der Waals 1,4-energy, 24.4; van der Waals others, −11.7; torsion, 24.2; dipole, 1.5.

(3) Hoye, T. R.; Suhadolnick, J. C. *Tetrahedron* **1986**, *26*, 2855.

(4) Such a concept was advocated by Cane et al. in connection with the biogeneses of antibiotic polyethers originated by polyketides: Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.

(5) For another synthetic study of teurilene, see: Hoye, T. R.; Jenkins, S. A. *J. Am. Chem. Soc.* **1987**, *109*, 6196.

(6) (a) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105. (b) Shreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106. (c) Russel, S. T.; Robinson, J. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 351.

(7) (a) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933. (b) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2741.

(8) Tsuzuki, K.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 4745.

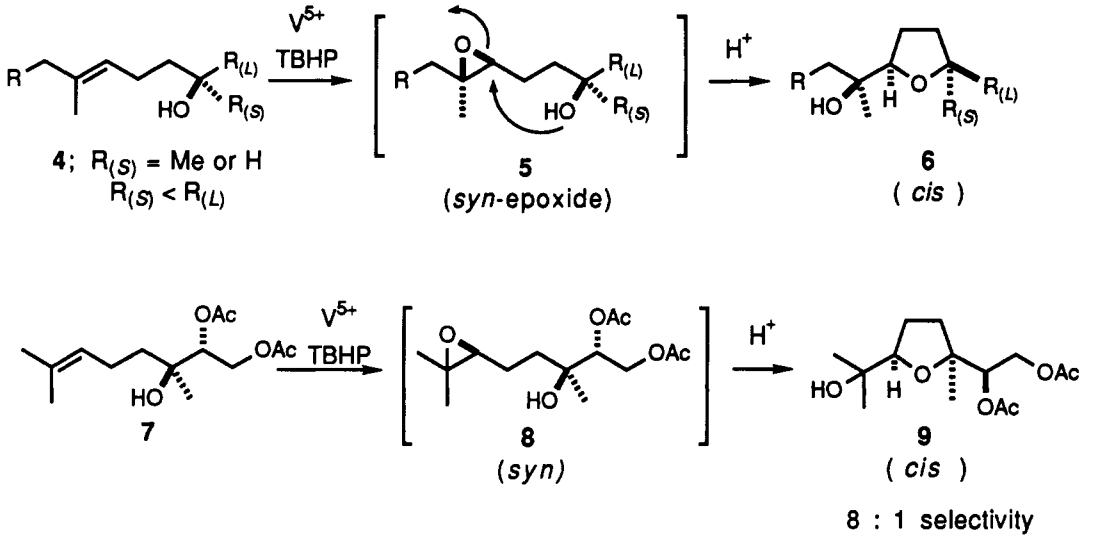
(9) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330, 5335.

(10) (a) Hashimoto, M.; Kan, T.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5665. (b) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1988**, *29*, 1143. (c) Kan, T.; Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5417. (d) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088.

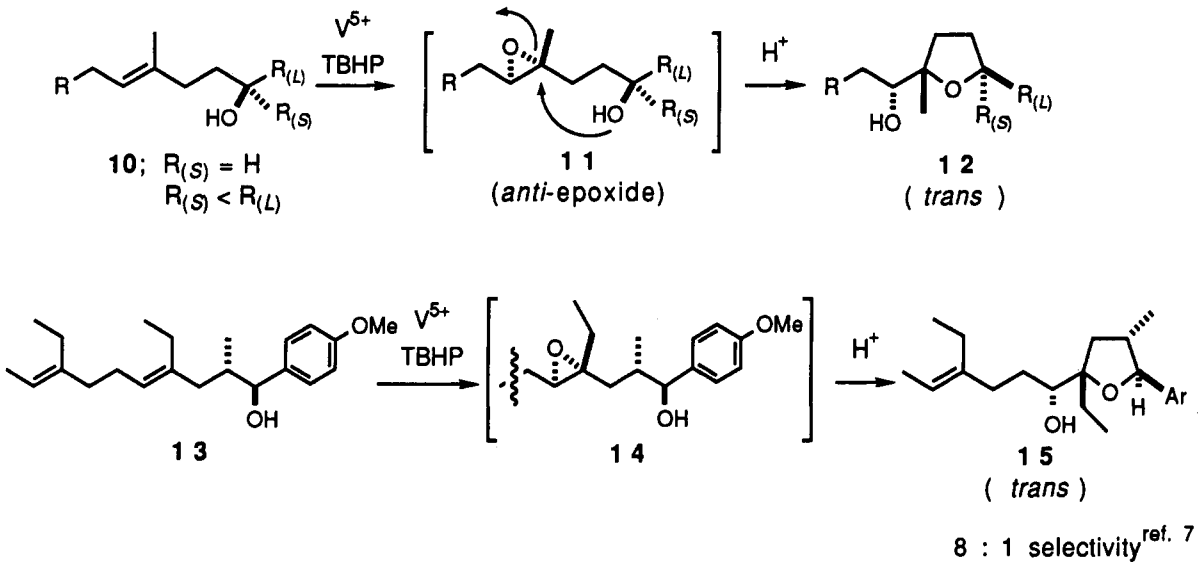
0022-3263/91/1956-2299$02.50/0

Scheme I. Selectivities in Vanadium(V)-Catalyzed Oxidation of Bishomoallyl Alcohols

Type A



Type B



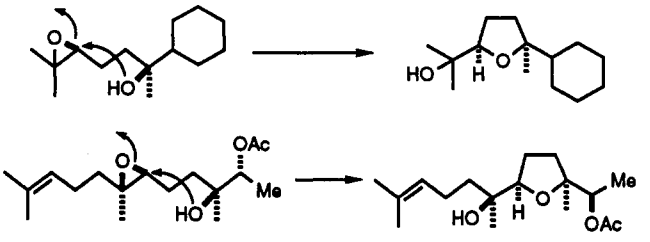
munication form, the total synthesis of 1.[11] Now, we describe in full detail the total syntheses of teurilene (1).

Discussion and Results

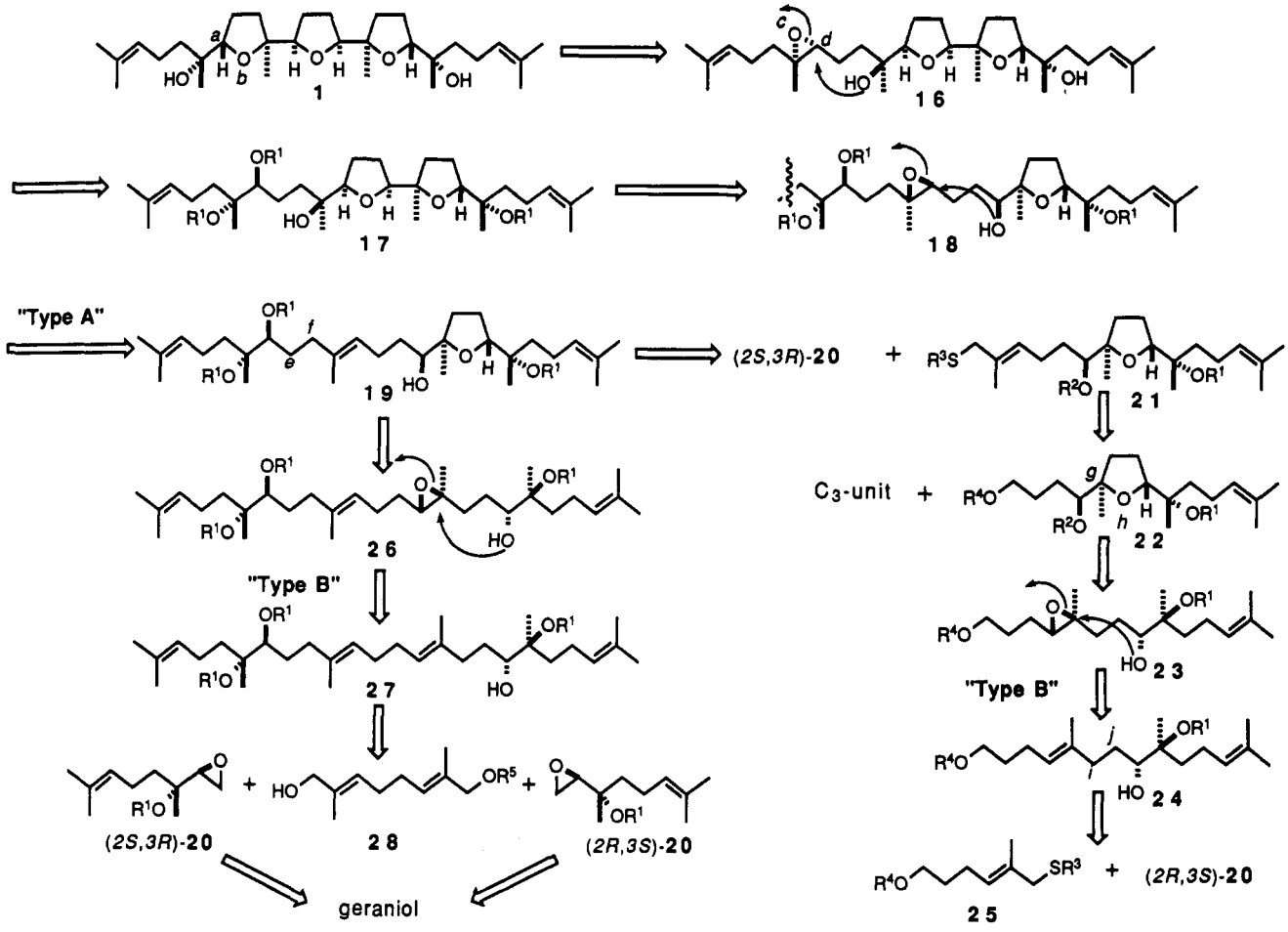
In the course of the synthetic study of 2 and its congeners, a new type of vanadium(V)-catalyzed oxidation–cyclization reaction of 4-en-1-ol systems was found. For example, geraniol derivative 7 was converted into *anti*-epoxy alcohol 8 stereoselectively (8:1 ratio) by oxidation with *tert*-butyl hydroperoxide (TBHP) and a catalytic amount of vanadyl acetylacetonate ($VO(acac)_2$), with sodium acetate as a buffer (Scheme I). Successive treatment of the unstable epoxide 8 with acid resulted in the formation of an ether ring through a 5-exo pathway to provide 2,5-*cis*-tetrahydrofuran 9 without loss of selectivity. Therefore, it was anticipated that oxidation of 5-substituted 4-en-1-ol 4 with vanadium(V) would stereoselectively produce *syn*-4-epoxy alcohol 5, which would cyclize to give cis-2,5-disubstituted tetrahydrofuran 6 by acid treatment.[12] Hereafter, this sequence of stereoselective oxidation and

(11) (a) Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Chem. Lett.* 1988, 645. (b) Hashimoto, M.; Harigaya, H.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* 1988, *29*, 5947.

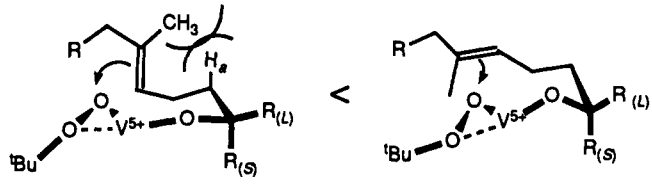
(12) The formation of tetrahedropyrans through a 6-endo pathway is also possible because tertiary carbocations are ordinarily more stable than secondary ones. However, the regioselective formation of tetrahydrofurans through a 5-exo pathway was observed in all cases we examined. Other cases, not described in the text, are shown below. It seems that the sterically hindered hydroxyl group tends to approach the secondary carbon (C_4-position) rather than the tertiary one (C_5-position).



Scheme II. Retrosynthesis of Teurilene (1)



cyclization reactions yielding a 2,5-*cis*-tetrahydrofuran ring will be referred to as type A oxidation–cyclization.[13] On the other hand, Kishi et al.[7] reported that oxidation of 4-substituted 4-en-1-ol **10** with TBHP in the presence of $VO(acac)_2$ afforded *anti*-4-epoxy alcohol **11** stereoselectively and that subsequent treatment of **11** with acetic acid gave trans-2,2,5-trisubstituted tetrahydrofuran **12** stereoselectively (type B oxidation–cyclization).[14] The selectivity observed may be due to steric factors. For example, in a type A reaction, the transition state leading to the formation of the minor epoxide (I) experiences more steric compression due to the interaction between H_a and the vinyl methyl group than does the transition state leading to the major epoxide (II).



It was believed that these two types of oxidation–cyclization reaction of 4-en-1-ol systems could be used to construct the *cis*- and *trans*-tetrahydrofuran rings of teurilene (1). A retrosynthetic study of 1 was undertaken to test this belief (Scheme II). Thus, cleavage of one ether ring of 1 between the skeletal atoms a and b affords epoxy alcohol **16**, which by intramolecular S_N2 attack of hydroxyl on the epoxide could form 1. Epoxy alcohol **16** can be converted to bicyclic tetrol **17** by cleavage between atoms c and d. Compound **17** could be stereoselectively transformed to **16** from a glycol by way of a 1,2-hydroxy sulfonate. Cleavage of **17** forms 5-substituted 4-en-1-ol **19**, which through *syn*-epoxide **18** by application of type A oxidation–cyclization could form **17**. Bishomoallylic alcohol **19** can be cleaved between atoms e and f to give two possible precursor units, linalool derivative (2*S*,3*R*)-**20** and sulfide **21**. Retrosynthetically, a few steps from **20** and **21** afford geraniol and *trans*-tetrahydrofuran **22**, as possible precursors. The ether ring of **22** can be cleaved between atoms g and h to provide 4-substituted 4-en-1-ol **24**, which by type B oxidation could be converted, by way of *anti*-epoxide **23**, to **22**. Cleavage of **24** between atoms i and j produces as possible precursors sulfide **25** and a second enantiomer, (2*R*,3*S*)-**20**, that can be derived from geraniol. The two enantiomers (2*S*,3*R*)- and (2*R*,3*S*)-**20** were, in fact, employed as sources of chirality in the synthesis. They could be prepared from geraniol enantioselectively by asymmetric epoxidation[15] by way of both enantiomers of diisopropyl tartrate (DIPT) and subsequent stereospecific transformations.

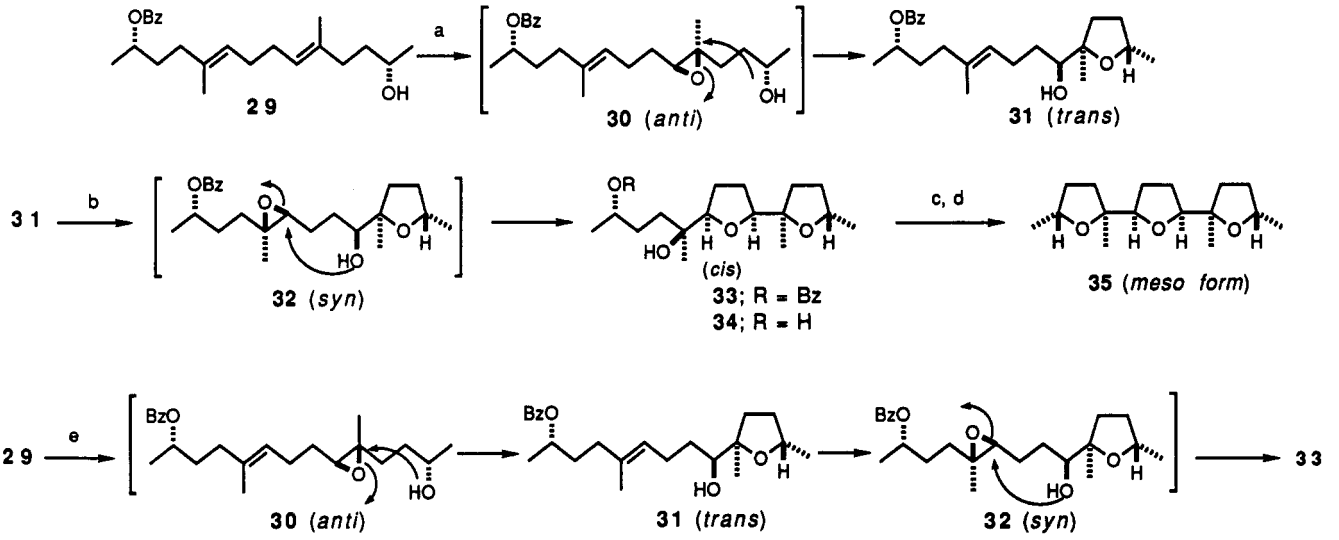
It was remarkable that oxidation of the bishomoallylic alcohols **4** and **10** and cyclization of the resulting epoxides

(13) (a) Nozaki, K.; Shirahama, H. *Chem. Lett.* **1988**, 1847. (b) After submission of this report, the similar stereospecificity to type A was reported: Hannesian, S.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276.

(14) Another example of type B: Wuts, P. G. M.; D'Costa, R.; Butler, W. *J. Org. Chem.* **1984**, *49*, 2582.

(15) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464.

Scheme III[a]



[a] Key: (a) $VO(acac)_2$, TBHP, NaOAc, benzene, reflux, 16 h, then AcOH, 84% (6:1 selectivity); (b) $VO(acac)_2$, TBHP, CH_2Cl_2, rt, 2 h, 72%; (c) K_2CO_3, MeOH, rt, 18 h, 91%; (d) TsCl, pyridine, CH_2Cl_2, rt, 12 h, 78%; (e) $VO(acac)_2$, TBHP, AcOH, CH_2Cl_2, rt, 4 h, 66%.

occurred under nearly identical conditions to stereoselectively produce 2,5-*cis*- and 2,5-*trans*-tetrahydrofurans **6** and **12**, respectively. Therefore, it was planned that 4,9-disubstituted 4,8-dien-1-ol **27** would be transformed into **17** directly, by simultaneous type B and type A oxidation–cyclization reactions, by way of *anti*-epoxide **26**, 5-substituted 4-en-1-ol **19**, and *syn*-epoxide **18**. For this reason, squalene derivative **27** was selected as a precursor that had suitable stereochemistry and functional groups. It would be synthesized by coupling the two enantiomers (2*S*,3*R*)- and (2*R*,3*S*)-**20** stepwise to diisoprene alcohol **28**. This synthetic strategy employing simultaneous double cyclization ultimately proved to be more effective than the one utilizing step-by-step cyclization.

To test the two synthetic strategies, syntheses of *meso*-tris(tetrahydrofuran) derivative **35**, which has two terminal methyl groups instead of the more elaborate side chains of **1**, were carried out as preliminary experiments, prior to the synthesis of **1**. The acyclic alcohol **29** was the starting material.

First, a synthesis of **35** by step-by-step cyclization was performed (Scheme III). As described earlier,[10] type B oxidation–cyclization of **29** took place smoothly to afford *trans*-tetrahydrofuran **31** stereoselectively (6:1 ratio), via *anti*-epoxide **30**,[16] by vanadium(V)-catalyzed oxidation, with sodium acetate as a buffer, and subsequent treatment with acetic acid. Formation of the *cis*-tetrahydrofuran ring by type A oxidation–cyclization reaction was next examined. Treatment of **31** with TBHP and a catalytic amount of $VO(acac)_2$, without buffer, effected type A oxidation–cyclization to afford bis(tetrahydrofuran) derivative **33** stereoselectively, by way of *syn*-epoxide **32**, in 72% yield. No diastereomers could be detected by either TLC or ^1H NMR. The stereochemistry of **33** was later confirmed by the stereostructure of **35**. Finally, the third tetrahydrofuran ring was constructed. After removal of the benzoyl group in **33** by basic methanolysis, selective tosylation of the secondary hydroxyl group of the resulting diol **34**, followed by spontaneous intramolecular alcoholysis of the tosylate, resulted in the formation of the third tetrahydrofuran ring of **35** in 71% yield in two steps. The 400-MHz ^1H NMR spectra of **35**, showed only a singlet and a doublet due to the methyl groups in both chloroform-*d* and benzene-d_6 and only two multiplet signals due to the methine protons. Measurement of optical rotation revealed that **35** was optically inactive. Therefore, the tris(tetrahydrofuran) derivative was a meso compound, and the stereochemistry of the central tetrahydrofuran unit was revealed to be cis.

Next, simultaneous double cyclization of **29** was attempted. As expected, bis(tetrahydrofuran) **33** was obtained directly and stereoselectively in 63% yield[17] by the treatment of **29** with TBHP, acetic acid, and a catalytic amount of $VO(acac)_2$ in dichloromethane at room temperature. The 250-MHz ^1H NMR and the IR spectra, the optical rotation, and the HPLC retention time of the compound were identical with those of **33** prepared by step-by-step cyclization. Therefore, both preliminary synthetic objectives were achieved. Based on the information accumulated during the preliminary syntheses and the insight gained from the retrosynthetic study, the total synthesis of teurilene (**1**) was begun.

First, a synthesis of **1** by step-by-step formation of the ether rings was performed. According to the published procedure,[10] *trans*-tetrahydrofuran derivative **42** was synthesized in an enantio- and stereoselective manner[18] from allylic sulfide **39** and (2*R*,3*S*)-linalool derivative (−)-**38**.[19] The latter was prepared from geraniol by asymmetric epoxidation using D-(−)-DIPT and subsequent stereospecific transformations, as shown in Scheme IV. Type B oxidation–cyclization reaction of 4-substituted 4-en-1-ol **40** resulted in the formation of a *trans*-tetrahydrofuran ring stereoselectively (ca. 4:1) to provide **42**, via *anti*-epoxide **41**, in good yield.

After protection of the hydroxyl group in **42** as a *tert*-butyldimethylsilyl ether, by means of *tert*-butyldimethylsilyl triflate,[20] the benzyl ether was cleaved under

(16) The diastereomer of **31**, derived from *syn*-epoxide, was removed by preparative TLC.

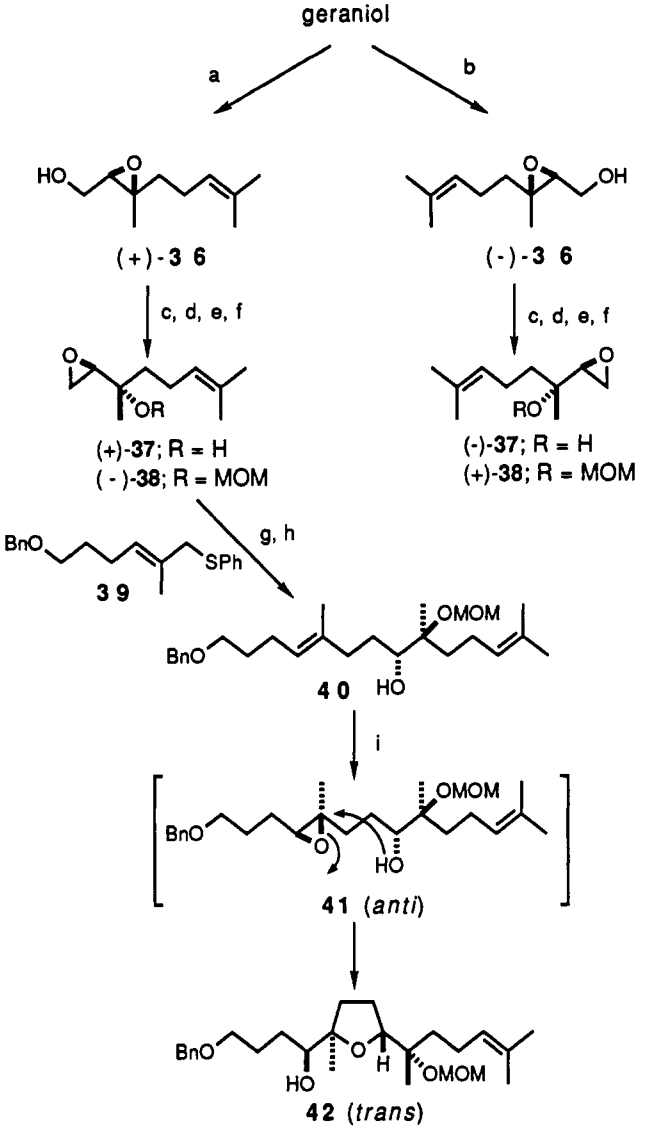
(17) In this reaction, small amounts of other diastereomers (<10%) were also produced. However, their stereochemistry was not determined.

(18) Compound **42** contained the cis isomer (ca. 20%, derived from the *syn*-epoxide), which could not be removed by column chromatography. Thus, the mixture was used in the next step. However, the minor isomer could be removed during the purification of crude **44**.

(19) (a) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(20) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

Scheme IV[a]



[a] Key: (a) (D)-(-)-DIPT, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, CH_2Cl_2, MS4A, -20 °C, 1 h, 90%; (b) (L)-(+)-DIPT, $Ti(O\text{-}i\text{-}Pr)_4$, TBHP, CH_2Cl_2, MS4A, -20 °C, 2 h, 100%; (c) TsCl, pyridine, CH_2Cl_2, 0 °C, 24 h; (d) TsOH, H_2O, CH_3CN, 50 °C, 24 h; (e) K_2CO_3, MeOH, -10 °C, 40 min, 44% (from (+)-**36**), 44% (from (-)-**36**; (f) (MOM)Cl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C → rt, 36 h, 99% (from (+)-**37**), 89% (from (-)-**37**); (g) BuLi, DABCO, THF, -60 °C, 3 h; (h) Na, 2-PrOH, THF, reflux, 2 h, 77% (in two steps); (i) $VO(acac)_2$, TBHP, CH_2Cl_2, rt, 3.5 h, 72%.

Birch conditions[21] to give alcohol **43** in 83% yield in two steps (Scheme V). Swern oxidation[22] of **43** produced the corresponding aldehyde, which underwent a Wittig reaction with (α-carbethoxyethylidene)triphenylphosphorane[23] to afford *E*-α,β-unsaturated ester **44** stereoselectively in 61% yield in two steps. Reduction of the ester group of **44** with diisobutylaluminum hydride gave alcohol **45** in 94% yield. Alcohol **45** was transformed into allylic sulfide **46** in 77% yield overall by chlorination[24] and subsequent treatment with sodium thiophenoxide. The coupling of (+)-**38** (synthesized from geraniol by nearly the same procedure as (-)-**38**, employing L-(+)-DIPT instead of D-(-)-DIPT) with the allylic thiocarbanion generated from **46** was found to take place smoothly to afford an adduct.[25] The phenylthio group of the adduct was removed reductively under Bouveault–Blanc conditions[25] to afford alcohol **47** in 80% yield in two steps. The hydroxyl group of **47** was protected as a methoxymethyl ether (MOM ether). Subsequent treatment of the MOM ether **48** with tetrabutylammonium fluoride[26] gave **49**, which possessed a 5-substituted 4-en-1-ol system in 74% yield in two steps.

As expected, treatment of **49** with TBHP and a catalytic amount of $VO(acac)_2$ in benzene at 50 °C, followed by exposure to acetic acid during the workup, effected type A oxidation–cyclization to form the desired *cis*-tetrahydrofuran ring in a highly stereoselective manner by way of the *syn*-epoxide **50** and gave bis(tetrahydrofuran) **51** in 54% yield. The diastereomer that could have arisen from the *anti*-epoxide could not be detected by TLC or ^1H NMR. The stereochemistry of the newly constructed tetrahydrofuran ring was confirmed by successful conversion of **51** into the target molecule.

To complete the total synthesis, construction of the third tetrahydrofuran ring was required. All MOM groups of **51** were removed by acid to afford tetrol **52** in 98% yield (Scheme VI). Selective mesylation of the secondary hydroxyl group of **52**, performed at -40 °C, gave monomesylate **53**, which was converted into epoxide **54** by treatment with potassium carbonate in methanol. Crude **54** was exposed to hydrochloric acid to effect the stereoselective formation of the third tetrahydrofuran ring. Teurilene (**1**) was obtained in 32% yield in three steps. The optical rotation of this compound, $[\alpha]^{18}_D$ +0.2°, and its ^1H NMR spectra indicated that the synthetic polyether was a meso form. Furthermore, the ^1H NMR and IR spectra, melting point, and HPLC retention time of the synthetic polyether were identical with those of natural teurilene (**1**), donated by Prof. Etsuro Kurosawa of Hokkaido University. Thus, the first total synthesis of **1** was achieved through step-by-step formation of three tetrahydrofuran rings.

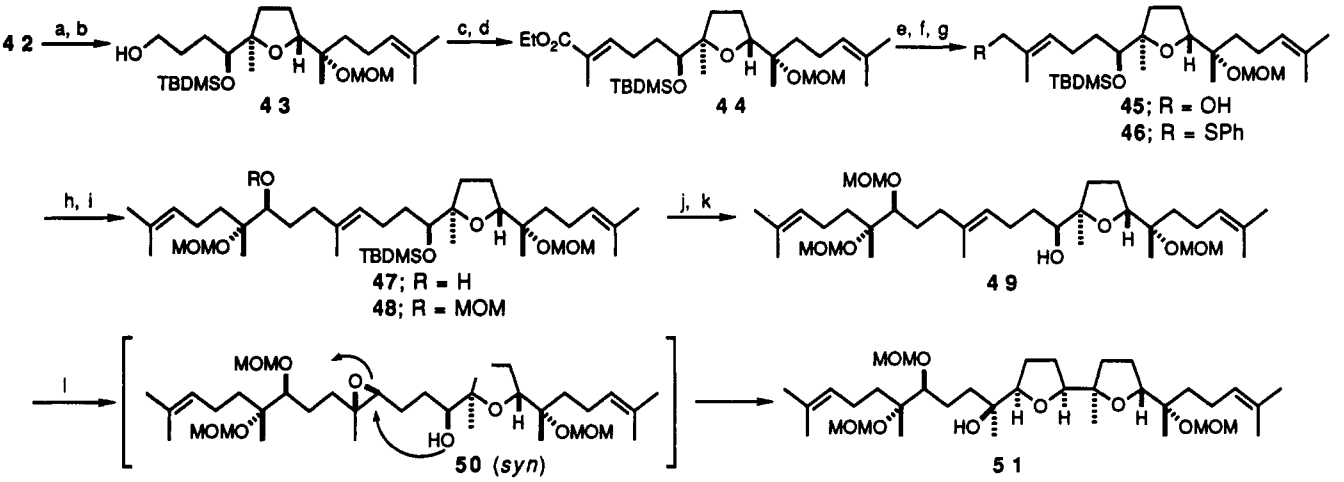
Next, a synthesis of **1** by simultaneous double cyclization of a 4,9-disubstituted 4,8-dien-1-ol system was attempted. A preliminary goal was the synthesis of a suitable starting material, squalene derivative **66**.

The diisoprene alcohol **60** was prepared from (*E*)-allyl alcohol **55**, a precursor employed in the synthesis of the thyrsiferols.[10] First, the hydroxyl group of **55** was protected as a tetrahydropyranyl ether, and then the benzyl group was removed under Birch conditions[21] to give alcohol **56** in 91% yield in two steps (Scheme VII). Oxidation of the alcohol moiety of **56** with pyridinium chlorochromate,[27] followed by Horner–Emmons reaction of the resulting aldehyde with triethyl α-phosphinopropionate[28] gave *E*-α,β-unsaturated ester **57** stereoselectively in 72% yield in two steps. Ester **57** was converted into allylic alcohol **58** in 81% yield by reduction with diisobutylaluminum hydride. After protection of the newly formed hydroxyl group of **58** as a benzyl ether, the tetrahydropyranyl group of the resulting benzyl ether **59** was removed by acidic methanolysis to afford allylic alcohol **60** in 64% yield overall.

Both enantiomers of (+)- and (-)-**38** were coupled stepwise to **60**. For the coupling reaction, the hydroxyl

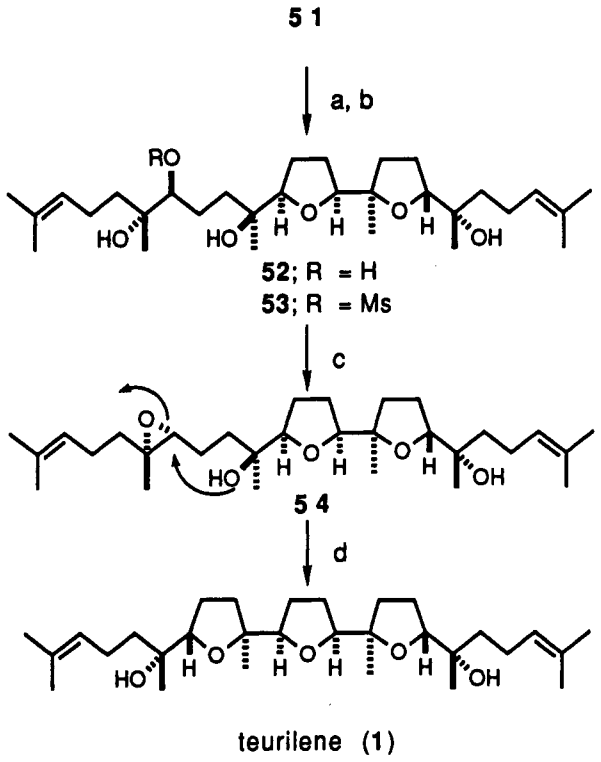
(21) McCloskey, C. M. *Advances in Carbohydrate Chemistry*; Wolfrom, M. L., Ed.; Academic Press: New York, 1957; Vol. 12, pp 137–156.
(22) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1987**, *43*, 2480.
(23) Isler, O.; Gutmann, H.; Montavon, M.; Rüegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta* **1957**, *139*, 1242.
(24) Calzada, J. G.; Hooz, J. *Organic Syntheses*; Ireland, R. E., Ed.; Wiley: New York, 1974; Vol. 54, pp 63–67.
(25) Kodama, M.; Takahashi, T.; Kojima, T.; Itô, S. *Tetrahedron Lett.* **1982**, *23*, 3397.
(26) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(27) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2467.
(28) Gallagher, G., Jr.; Webb, R. L. *Synthesis* **1974**, 122.

Scheme V[a]



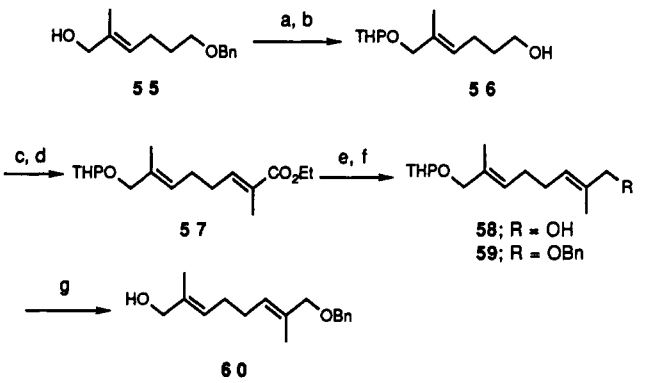
[a] Key: (a) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 94%; (b) Li, NH_3, THF, −78 °C, 1 h, 89%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −10 °C, 30 min, 66%; (d) $CH_3C(PPh_3)CO_2Et$, CH_2Cl_2, reflux, 2 h, 92%; (e) DIBAH, hexane, −78 °C, 5 min, 94%; (f) CCl_4, PPh_3, benzene, reflux, 10 h, 94%; (g) NaSPh, DMF, 0 °C, 1 h, 87%; (h) (+)-38, BuLi, TMEDA, THF, 0 °C, 30 min; (i) Na, 2-PrOH, THF, reflux, 2 h, 80% (in two steps); (j) (MOM)Cl, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, 100%; (k) (TBA)F, THF, reflux, 4 h, 74%; (l) $VO(acac)_2$, TBHP, benzene, 50 °C, 5 h, then AcOH, 54%.

Scheme VI[a]



[a] Key: (a) HCl, MeOH, rt, 12 h, 98%; (b) MsCl, Et_3N, CH_2Cl_2, −40 °C, 2 h; (c) K_2CO_3, MeOH, rt, 30 min; (d) HCl, H_2O, ether, rt, 1 h, 32% (in three steps).

Scheme VII[a]



[a] Key: (a) TsOH, DHP, CH_2Cl_2, 0 °C, 1 h, 94%; (b) Li, NH_3, ether, −78 °C, 40 min, 97%; (c) PCC, NaOAc, CH_2Cl_2, rt, 1 h; (d) $Na^+CH_3C^-(PO(OEt)_2)CO_2Et$, THF, 0 °C, 40 min, 72% (in two steps); (e) DIBAH, hexane, −78 °C, 5 min, 81%; (f) NaH, BnCl, DMF, 0 °C → rt, 36 h, 70%; (g) TsOH, MeOH, rt, 2 h, 91%.

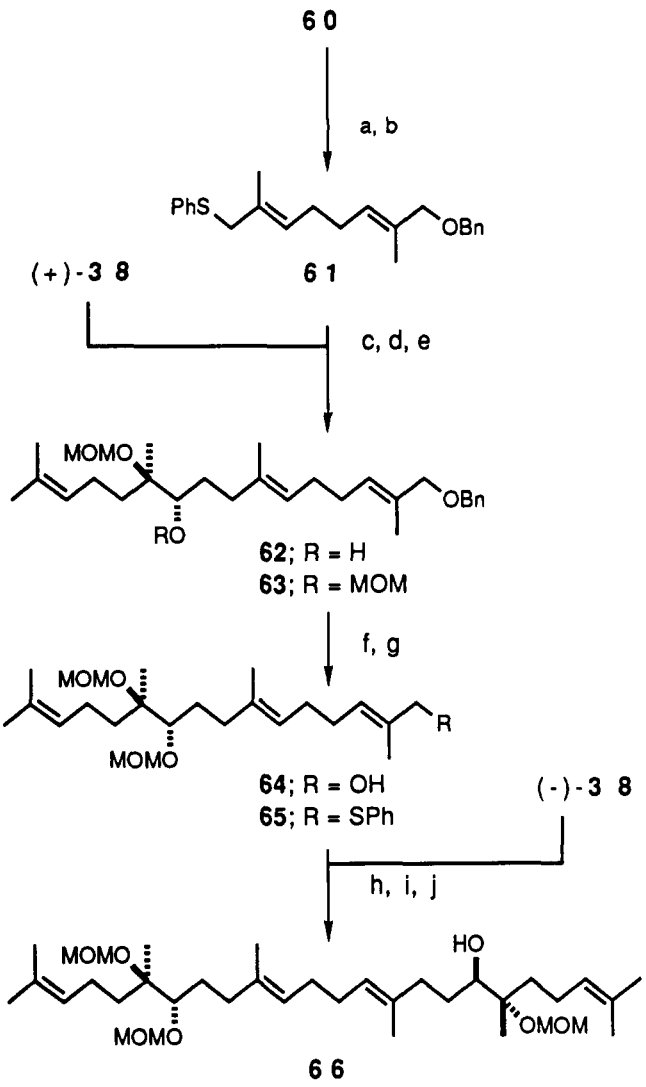
group of **60** was converted into a phenylthio group by chlorination and subsequent treatment with sodium thiophenoxide to produce allylic sulfide **61** in 77% yield in two steps (Scheme VIII). Then, **61** was coupled to (+)-**38** in the usual manner. Removal of the phenylthio group of the adduct gave alcohol **62** in 69% yield in two steps. Alcohol **62** was converted into allylic sulfide **65** in 82% yield overall by way of MOM ether **63** and alcohol **64**, formed sequentially by protection of the hydroxyl group as a MOM ether, cleavage of the benzyl ether under Birch conditions, and transformation of the newly formed hydroxyl group into a phenyl sulfide. Then, reaction of enantiomer (−)-**38** with the allylic thiocarbanion derived from **65** and subsequent desulfurization yielded **66** in 58% yield in two steps.

Thus, an opportunity to test the feasibility of a simultaneous double-cyclization reaction of the 4,9-disubstituted 4,8-dien-1-ol system of **66** was created. Type A and type B oxidation–cyclization reactions of **66** did, in fact, take place simultaneously in a stereoselective fashion by treatment with 0.01 equiv of $VO(acac)_2$, 3.0 equiv of TBHP, and 0.1 equiv of acetic acid in benzene at 50 °C for 7 h to form a bis(tetrahydrofuran) system. Bis(tetrahydrofuran) **51** was obtained in 25% yield,[17] along with ether **49** (30%). Ether **49** could be easily converted into **51**, as was demonstrated (Scheme V). Longer reaction times, higher temperatures, larger amounts of catalyst, or the use of other acids reduced considerably the yield of **51**[29] (Scheme IX).

The ^1H NMR and IR spectra and the optical rotation of the resulting bis(tetrahydrofuran) derivative were identical with those of the compound synthesized by

(29) The low yields were probably due to cleavage of the MOM ethers or oxidation of the olefinic bonds at the end of the molecule, or both.

Scheme VIII[a]



[a] Key: (a) CCl_4, PPh_3, benzene, reflux, 24 h; (b) NaSPh, DMF, 0 °C, 1 h, 77% (in two steps); (c) (+)-38, BuLi, TMEDA, THF, -78 °C, 10 min, 69%; (d) Na, 2-PrOH, THF, reflux, 5 h, 100%; (e) (MOM)Cl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C → rt, 12 h, 97%; (f) Li, NH_3, THF, -78 °C, 30 min, 89%; (g) CCl_4, PPh_3, benzene, reflux, 12 h; (h) NaSPh, DMF, 0 °C, 1 h, 95% (in two steps); (g) (-)-38, BuLi, TMEDA, THF, -78 °C, 30 min; (h) Na, 2-PrOH, THF, reflux, 1 h, 58% (in two steps).

step-by-step cyclization. It was also converted to teurilene (Scheme VI). Thus, an improved synthesis of 1 employing simultaneous double oxidation–cyclization was successfully accomplished.

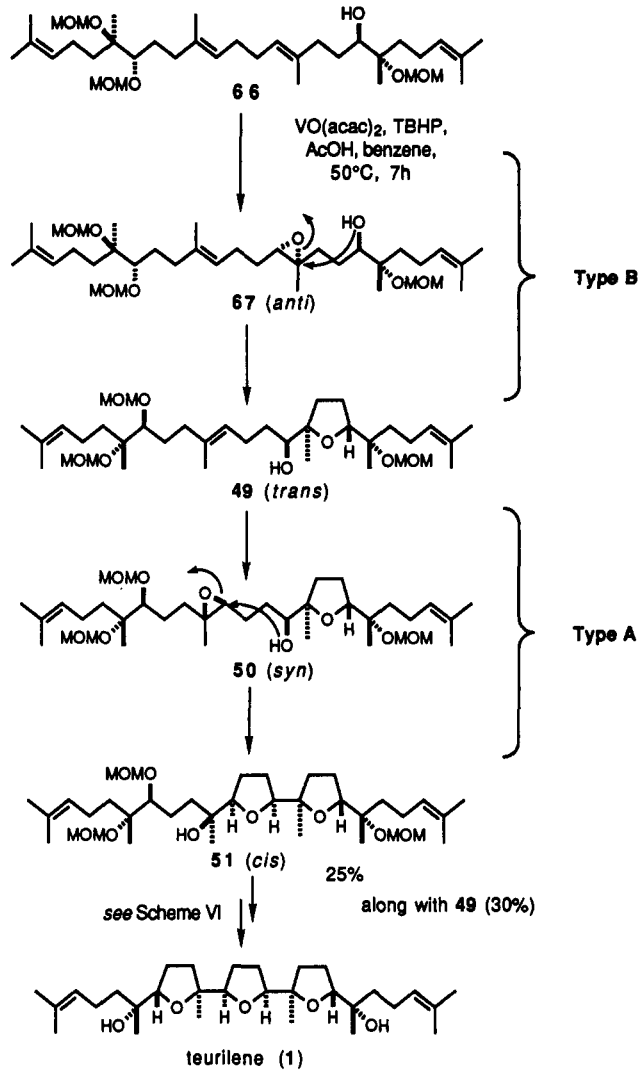
Experimental Section

General Procedures. Melting points are uncorrected. ^1H NMR splitting patterns are designated quint or hex to indicate quintets and hextets, respectively.

Analytical and preparative thin-layer chromatographies were performed with precoated silica gel plates (Machery-Nagel DC-Fertigplatten SIL G-25 UV_{254}). Silica gel used for column chromatography was Merck Kieselgel 60, Art 7734, or Amicon Matrex silica chromatography medium. Analytical and preparative HPLC procedures were performed with use of either UV or refractive index detectors.

Reagents and solvents were dried and distilled before use: THF, distilled from sodium benzophenone ketyl; CH_2Cl_2, distilled from phosphorus pentoxide; Et_3N, pyridine, *i*-Pr_2NEt, TMEDA, DMSO, benzene, hexane, HMPA, all distilled from calcium hydride; MeOH, distilled from magnesium alcoxide. Molecular

Scheme IX



sieves, Type 4A, were finely powdered and activated at 180 °C for 10 h in vacuo.

(2*R*,5*S*)-2-[(2*S*,5*R*)-5-[(1*S*,4*S*)-4-(Benzoyloxy)-1-hydroxy-1-methylpentyl]tetrahydrofuran-2-yl]tetrahydro-2,5-dimethylfuran (33). A solution of 4-substituted 4-en-1-ol **31**[10] (32 mg, 86 μmol), $VO(acac)_2$ (1.5 mg, 5.7 μmol), and TBHP (5.6 M in CH_2Cl_2, 20 μL, 110 μmol) in CH_2Cl_2 was stirred at room temperature for 2 h. The mixture was then poured into water (20 mL) and was extracted with ether (15 mL × 3). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (1.5 g). Elution with 15 and 30% EtOAc/benzene gave unreacted **31** (4.0 mg, 11 μmol, 12%) and diastereomerically pure **33** (24 mg, 61 μmol, 72%). The diastereomer of **33** could not be detected by ^1H NMR or TLC. **33**: $[\alpha]^{21}_D$ +40.5° (*c* 1.00, $CHCl_3$); IR (neat) 3400, 2970, 2850, 1720, 1457, 1280, 1115, 1093, 720 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (3 H, d, *J* = 6.1 Hz, C_5-Me), 1.26, 1.29 (each 3 H, s, C_2-Me, $C_{1'}$-Me), 1.36 (3 H, d, *J* = 6.7 Hz, $C_{4'}$-Me), 3.81 (1 H, dd, *J* = 4.3 and 6.7 Hz, C_2-H or C_5-H), 3.91 (1 H, t, *J* = 6.1 Hz, C_2-H or C_5-H), 4.06 (1 H, ddq, *J* = 4.8, 8.5 and 6.1 Hz, C_5-H), 5.13 (1 H, hex, *J* = 6.7 Hz, $C_{4'}$-H), 7.2–8.1 (5 H, m, aromatic protons); EIMS *m*/*z* (rel intens) 391 (0.02, $M^+ + H$), 390 (0.01, M^+), 169 (2.5, $C_{10}H_{17}O_2^+$, bis(tetrahydrofuran) moiety), 99 (100, $C_6H_{11}O^+$, left tetrahydrofuran moiety); HREIMS for $C_{23}H_{35}O_5$ ($M^+ + H$), calcd 391.2486, found 391.2498.

(2*R*,5*S*)-2-[(2*S*,5*R*)-5-((1*S*,4*S*)-1,4-Dihydroxy-1-methylpentyl)tetrahydrofuran-2-yl]tetrahydro-2,5-dimethylfuran (34). A suspension of **33** (10 mg, 27 μmol) and K_2CO_3 (5.0 mg, 36 μmol) in MeOH (2.5 mL) was stirred at room temperature for 18 h. The mixture was then poured into water (20 mL) and was extracted with ether (15 mL × 3). The combined extracts were

washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the resulting oil by column chromatography on silica gel (1 g) with 20% acetone/$CHCl_3$ gave alcohol **34** (7.0 mg, 24 μmol, 91%): $[\alpha]^{20}_D$ +10.3° (*c* 1.00, $CHCl_3$); IR (neat) 3400, 2970, 2920, 2850, 1460, 1375, 1075, 1028, 907 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20, 1.23 (each 3 H, d, *J* = 6.1 Hz, C_5-Me, $C_{4''}$-Me), 1.25, 1.30 (each 3 H, s, C_2-Me, $C_{1''}$-Me), 3.81 (1 H, dd, *J* = 4.8 and 6.7 Hz, $C_{2'}$-H or $C_{5'}$-H), 3.87 (1 H, m, $C_{4''}$-Me), 3.92 (1 H, t, *J* = 6.7 Hz, $C_{2'}$-H or $C_{5'}$-H), 4.06 (1 H, ddq, *J* = 4.5, 8.3, and 6.1 Hz, $C_{5''}$-H); EIMS *m/z* (rel intens) 269 (0.06, M^+ – HO), 169 (3.1, $C_{10}H_{17}O_2^+$, bis(tetrahydrofuran) moiety), 99 (100, $C_6H_{11}^+$, left tetrahydrofuran moiety); HREIMS for $C_{16}H_{29}O_3$ (M^+ – HO), calcd 269.2118, found 269.2111.

(2*R,5*S**)-Tetrahydro-2-[(2*S**,5*R**)-tetrahydro-5-((2*S**,5*R**)-tetrahydro-2,5-dimethylfuran-2-yl)furan-2-yl]-2,5-dimethylfuran (35).** A solution of **34** (7.0 mg, 24 μmol) and TsCl (5.0 mg, 26 μmol) in a mixture of pyridine (200 μL) and CH_2Cl_2 (600 μL) was stirred at room temperature for 12 h. The mixture was then poured into water (20 mL) and was extracted with EtOAc (15 mL × 3). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (1 g) with 3% acetone/$CHCl_3$ to afford tris(tetrahydrofuran) **35** (5.0 mg, 19 μmol, 78%): $[\alpha]^{23}_D$ 0.0° (*c* 0.50, $CHCl_3$); IR (neat) 2970, 2920, 2850, 1460, 1385, 1107, 843, 715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (6 H, s, C_2-Me, $C_{2''}$-Me), 1.22 (6 H, d, *J* = 5.9 Hz, C_5-Me, $C_{5''}$-Me), 1.4–1.7 (6 H, m, C_3-H, C_4-H, $C_{3'}$-H, $C_{4'}$-H, $C_{3''}$-H, $C_{4''}$-H), 1.84 (2 H, m, $C_{3'}$-H, $C_{4'}$-H), 1.98 (2 H, m, C_4-H, $C_{4''}$-H), 2.11 (2 H, ddd, *J* = 7.8, 9.7, and 12.2 Hz, C_3-H, $C_{3''}$-H), 3.82 (2 H, m, $C_{2''}$-H, $C_{5''}$-H), 4.10 (2 H, m, C_5-H, $C_{5''}$-H); ^1H NMR (500 MHz, C_6D_6) δ 1.19 (6 H, d, *J* = 5.9 Hz, C_5-Me, $C_{5''}$-Me), 1.24 (6 H, s, C_2-Me, $C_{2''}$-Me), 1.36 (2 H, m, C_3-H, $C_{3''}$-H), 1.5–1.6 (4 H, m, C_4-H, $C_{3'}$-H, $C_{4'}$-H, $C_{4''}$-H), 1.60 (2 H, m, $C_{3'}$-H, $C_{4'}$-H), 1.78 (2 H, m, C_4-H, $C_{4''}$-H), 2.04 (2 H, ddd, *J* = 8.3, 9.8, and 12.2 Hz, C_3-H, $C_{3''}$-H), 3.91 (2 H, m, $C_{2''}$-H, $C_{5''}$-H), 4.23 (2 H, m, C_5-H, $C_{5''}$-H); FIMS *m/z* (rel intens) 269 (26, M^+ + H), 268 (3.5, M^+), 169 (69, $C_{10}H_{17}O_2^+$, bis(tetrahydrofuran) moiety), 99 (100, $C_6H_{11}O^+$, terminal tetrahydrofuran moiety); HRFIMS for $C_{16}H_{29}O_3$ (M^+ + H), calcd 269.2118, found 269.2116.

Simultaneous Double Cyclization of 29. A solution of $VO(acac)_2$ (1 mM in CH_2Cl_2, 500 μL, 0.5 μmol), AcOH (10 μL), and TBHP (5.6 M in CH_2Cl_2, 30 μL) were added, successively, to 4,9-disubstituted 4,8-dien-1-ol **29**[10] (12 mg, 32 μmol) at room temperature. After being stirred at room temperature for 4 h, the resulting solution was poured into water (15 mL) and was extracted with $CHCl_3$ (10 mL × 3). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. After short-column chromatography of the residual oil on silica gel (200 mg) with 25% acetone/$CHCl_3$, further purification by HPLC (column LiChrosorb RP-18, 4 × 250 mm (o.d.), eluent 70% CH_3CN/H_2O, flow rate 1.0 mL/min, detection UV at 220 nm) provided pure **33** (8.0 mg, 21 μmol, 66%): t_R = 8.25 min; $[\alpha]^{21}_D$ +38.9° (*c* 0.80, $CHCl_3$). Stereostructures of other diastereomers (<1.5 mg each) were not determined. Compound **33** so obtained was identical with that synthesized by step-by-step cyclization, by comparison of ^1H NMR and IR spectra, HPLC retention times, and optical rotations.

(2*R*,5*R*)-2-[(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-hydroxybutyl]tetrahydro-5-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-2-methylfuran (43). *tert*-Butyldimethylsilyl trifluoromethanesulfonate (1.5 g, 5.7 mmol) was added to a solution of *trans*-tetrahydrofuran derivative **42**[10] (1.6 g, 3.7 mmol) and 2,6-lutidine (830 mg, 7.6 mmol) in CH_2Cl_2 (15 mL) at 0 °C under Ar atmosphere. After being stirred at 0 °C for 10 min, the mixture was poured into water (100 mL) and was extracted with ether (70 mL × 3). The combined extracts were washed with brine (100 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. Column chromatography of the residue on silica gel (50 g) with benzene gave a silyl ether (1.9 g, 3.5 mmol, 94%): $[\alpha]^{19}_D$ –5.30° (*c* 2.50, $CHCl_3$); IR (neat) 2970, 2850, 1465, 1380, 1255, 1150, 1100, 1040, 925, 845, 780, 735, 635 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 1.12 (3 H, s, C_2-Me), 1.15 (3 H, s, $C_{1''}$-Me), 1.61, 1.69 (each 3 H, s, $C_{5''}$-Me_2), 3.36 (3 H, s, OCH_2OMe), 3.40 (3 H, m, $C_{4'}$-H_2, $C_{1'}$-H), 3.76 (1 H, t, *J* = 8 Hz, C_5-H), 4.48 (2 H, s, $PhCH_2O$), 4.60, 4.90 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 5.05 (1 H, bt, *J* = 7 Hz, $C_{4''}$-H), 7.29 (5 H, s, aromatic protons); FIMS *m/z* (rel intens) 548 (100, M^+), 517 (31, M^+ – MeO), 516 (28, M^+ – MeOH), 491 (42, M^+ – *t*-Bu), 171 (47, $Me_2C{=}C(CH_2)_2C^+$(Me)OMOM); HRFIMS for $C_{32}H_{56}O_5Si$ (M^+), calcd 548.3899, found 548.3890.

Metallic Li (ca. 300 mg) was added to liquid NH_3 (ca. 50 mL) at –78 °C under Ar atmosphere. The mixture was stirred at –78 °C for 15 min, and then a solution of the silyl ether (1.9 g, 3.5 mmol) in THF (10 mL) was added at –78 °C to the purple suspension. After the mixture was stirred for 1 h at –78 °C, NH_4Cl (ca. 1 g) was added to quench the reaction. The mixture was allowed to warm to room temperature, and NH_3 was allowed to evaporate. The resulting suspension was diluted with water (100 mL) and was extracted with ether (70 mL × 3). The combined extracts were washed with brine (100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Purification of the crude product by column chromatography on silica gel (30 g) with 25% EtOAc/benzene afforded alcohol **43** (1.4 g, 3.1 mmol, 89%): $[\alpha]^{22}_D$ –6.30° (*c* 1.70, $CHCl_3$); IR (neat) 3400, 2970, 2850, 1465, 1380, 1255, 1150, 1100, 1040, 925, 845, 780 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 1.12 (3 H, s, C_2-Me), 1.15 (3 H, s, $C_{1''}$-Me), 1.61, 1.68 (each 3 H, s, $C_{5''}$-Me_2), 3.36 (3 H, s, OCH_2OMe), 3.60 (3 H, m, C_4-H_2, $C_{1'}$-H), 3.81 (1 H, t, *J* = 8 Hz, C_5-H), 4.65, 4.92 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 5.07 (1 H, bt, *J* = 7 Hz, $C_{4''}$-H); FDMS *m/z* (rel intens) 459 (100, M^+ + H), 458 (69, M^+), 427 (30, M^+ – MeO), 426 (19, M^+ – MeOH), 401 (15, M^+ – *t*-Bu); HRFIMS for $C_{25}H_{50}O_5Si$ (M^+), calcd 458.3429, found 458.3881.

(2*R*,5*R*)-2-[(*E*)-(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-(ethoxycarbonyl)hex-4-enyl]tetrahydro-5-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-2-methylfuran (44). Oxalyl chloride (15 mg, 120 μmol) was added to a mixture of DMSO (11 mg, 140 μmol) and CH_2Cl_2 (2.0 mL) at –10 °C under Ar atmosphere. The mixture was stirred for 15 min at –10 °C, and then a solution of **43** (50 mg, 110 μmol) in CH_2Cl_2 (1.0 mL) was added. The mixture was stirred at the same temperature for 30 min, and then Et_3N (200 μL) was added. The mixture was stirred at –10 °C for an additional 1 h, then was poured into water (20 mL), and was extracted with ether (20 mL × 3). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography of the residue on silica gel (2.0 g) with 5% EtOAc/benzene gave an aldehyde (33 mg, 720 μmol, 66%): ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 1.11 (3 H, s, C_2-Me), 1.26 (3 H, s, $C_{1''}$-Me), 1.62, 1.69 (each 3 H, s, $C_{5'}$-H), 2.57 (2 H, dt, *J* = 2 and 7 Hz, $C_{3'}$-H), 3.35 (3 H, s, OCH_2OMe), 3.54 (1 H, t, *J* = 7 Hz, $C_{1'}$-H), 3.80 (1 H, m, C_5-H), 4.63, 4.91 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 5.08 (1 H, bt, *J* = 7 Hz, $C_{4''}$-H), 9.72 (1 H, t, *J* = 2 Hz, $C_{3'}$-H).

A solution of the aldehyde (33 mg, 720 μmol) and (α-carbethoxyethylidene)triphenylphosphorane[23] (50 mg, 140 μmol) in CH_2Cl_2 (2.0 mL) was boiled under reflux, with stirring, for 2 h under Ar atmosphere. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure to provide a crude product, which was purifed by column chromatography on silica gel (3 g). Elution with 2% EtOAc/benzene gave *Z*-α,β-unsaturated ester **44** (36 mg, 670 μmol, 92%): $[\alpha]^{19}_D$ –5.46° (*c* 1.30, $CHCl_3$); IR (neat) 2980, 1720, 1650, 1470, 1375, 1260, 1035, 920, 840, 780 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.09 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 1.10 (3 H, s, C_2-Me), 1.23 (3 H, s, $C_{1''}$-Me), 1.29 (3 H, t, *J* = 7 Hz, CO_2CH_2Me), 1.61, 1.69 (each 3 H, s, $C_{5''}$-Me_2), 1.83 (3 H, s, $C_{5'}$-Me), 3.36 (3 H, s, OCH_2OMe), 3.50 (1 H, dd, *J* = 5 and 7 Hz, $C_{1'}$-H), 3.82 (1 H, m, C_5-H), 4.18 (2 H, q, *J* = 7 Hz, CO_2CH_2Me), 4.65, 4.90 (each 1 H, *J* = 7 Hz, OCH_2OMe), 5.05 (1 H, bt, *J* = 7 Hz, $C_{4''}$-H), 6.71 (1 H, bt, *J* = 7 Hz, $C_{4'}$-H); FDMS *m/z* (rel intens) 541 (65, M^+ + H), 540 (78, M^+), 509 (52, M^+ – MeO), 508 (21, M^+ – MeOH), 483 (31, M^+ – *t*-Bu), 255 (100, $C_{15}H_{27}O_3^+$, right half); HRFIMS for $C_{30}H_{56}O_6Si$ (M^+), calcd 540.3848, found 540.3794.

(2*R*,5*R*)-2-[(*E*)-(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-6-hydroxy-5-methylhex-4-enyl]tetrahydro-5-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-2-methylfuran (45). Diisobutylaluminum hydride (1 M in hexane, 4.1 mL, 4.1 mmol) was added to a solution of **44** (900 mg, 1.7 mmol) in hexane (20 mL) at –78 °C under Ar atmosphere. The mixture was stirred for 5 min at –78 °C, and then EtOH (1.0 mL) and water (2.0 mL) were added, successively, to the solution. The resulting suspension

was stirred for 30 min at room temperature and then was filtered through a Celite pad under suction. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (30 g) with 20% EtOAc/benzene to give allylic alcohol **45** (800 mg, 1.6 mmol, 94%): $[\alpha]^{19}_D$ −6.14° (*c* 2.80, $CHCl_3$); IR (neat) 3400, 2960, 2850, 1465, 1375, 1255, 1150, 1100, 1035, 920, 840, 780 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.10 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 1.10 (3 H, s, C_2-Me), 1.25 (3 H, s, $C_{1''}$-Me), 1.62, 1.68, 1.68 (each 3 H, s, $C_{5''}$-Me_2, $C_{5''}$-Me), 3.37 (3 H, s, OCH_2OMe), 3.50 (1 H, dd, *J* = 5 and 7 Hz, $C_{1''}$-H), 3.82 (1 H, t, *J* = 7 Hz, C_5-H), 4.00 (2 H, s, C_6-H_2), 4.65, 4.93 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 5.10 (1 H, bt, *J* = 7 Hz, $C_{4''}$-H), 5.40 (1 H, bt, *J* = 6 Hz, $C_{4'}$-H); FDMS *m/z* (rel intens) 499 (64, $M^+ + H$), 4.98 (60, M^+), 467 (28, $M^+ - MeO$), 466 (16, $M^+ - MeOH$); HRFIMS for $C_{28}H_{54}O_5Si$ (M^+), calcd 498.3742, found 498.3775.

(2*R*,5*R*)-2-[(*E*)-(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-5-methyl-6-(phenylthio)hex-4-enyl]tetrahydro-5-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-2-methylfuran (46). A solution of **45** (800 mg, 1.6 mmol), PPh_3 (500 mg, 1.9 mmol), and CCl_4 (2.0 mL) in benzene (20 mL) was boiled under reflux for 10 h under Ar atmosphere. Hexane (20 mL) was then added, and the mixture was cooled to 0 °C. After being stirred for an additional 30 min, the mixture was filtered under suction. The solvent was removed in vacuo, and purification of the resulting oil by column chromatography on silica gel (20 g) with 5% EtOAc/benzene afforded a chloride (770 mg, 1.5 mmol, 94%): $[\alpha]^{20}_D$ −6.33° (*c* 2.10, $CHCl_3$); IR (neat) 2960, 2850, 1465, 1380, 1265, 1150, 1100, 1040, 920, 845, 780 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 1.10 (3 H, s, C_2-Me), 1.23 (3 H, s, $C_{1''}$-Me), 1.60, 1.69, 1.69 (each 3 H, s, $C_{5''}$-Me_2, $C_{5''}$-Me), 3.35 (3 H, s, OCH_2OMe), 3.47 (1 H, dd, *J* = 5 and 7 Hz, $C_{1''}$-H), 3.80 (1 H, bt, *J* = 8 Hz, C_5-H), 3.97 (2 H, s, C_6-H_2), 4.64, 4.89 (each 1 H, d, *J* = 6 Hz, OCH_2OMe), 5.05 (1 H, b′, *J* = 7 Hz, $C_{4''}$-H), 5.50 (1 H, bt, *J* = 6 Hz, $C_{4'}$-H); FIMS *m/z* (rel intens) 518 (46, M^+), 516 (73, M^+), 487 (13, $M^+ - MeO$), 485 (17, $M^+ - MeO$), 255 (100, $C_{15}H_{27}O_3^+$, right half), 171 (27, $Me_2C{=}C(CH_2)_2C^+(Me)O(MOM)$); HRFIMS for $C_{28}H_{53}O_4{}^{35}ClSi$ (M^+), calcd 516.3404, found 516.3396.

A solution of sodium thiophenoxide [prepared from NaH (48 mg, 2.0 mmol) and thiophenol (300 mg, 2.7 mmol) in DMF (5.0 mL) at 0 °C] was added to a solution of the chloride (770 mg, 1.5 mmol) in DMF (10 mL) at 0 °C. After being stirred for 1 h at 0 °C, the resulting suspension was poured into water (100 mL) and was extracted with ether (70 mL × 3). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give a crude product, which was purified by column chromatography on silica gel (40 g). Elution with 1% EtOAc/benzene provided allylic sulfide **46** (740 mg, 1.3 mmol, 87%): $[\alpha]^{22}_D$ −2.90 ° (*c* 2.00, $CHCl_3$); IR (neat) 2960, 2850, 1590, 1465, 1445, 1380, 1255, 1150, 1100, 1040, 925, 845, 785, 760, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.05 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiCMe_3$), 1.05 (3 H, s, C_2-Me), 1.22 (3 H, s, $C_{1''}$-Me), 1.60, 1.68, 1.68 (each 3 H, s, $C_{5''}$-Me_2, $C_{5''}$-Me), 3.35 (3 H, s, OCH_2OMe), 3.46 (3 H, m, C_6-H_2, $C_{1'}$-H), 3.80 (1 H, m, C_5-H), 4.63, 4.90 (each 1 H, d, *J* = 6 Hz, OCH_2OMe), 5.1–5.3 (2 H, m, C_4-H, $C_{4''}$-H), 7.1–7.4 (5 H, m, aromatic protons); FDMS *m/z* (rel intens) 591 (57, $M^+ + H$), 590 (100, M^+), 559 (43, $M^+ - MeO$), 558 (54, $M^+ - MeOH$), 255 (53, $C_{15}H_{27}O_3^+$, right half), 171 (47, $Me_2C{=}C(CH_2)_2C^+(Me)OMOM$); HREIMS for $C_{33}H_{55}O_3SSi$ ($M^+ - MeOH$), calcd 559.3646, found 559.3604; HREIMS for $C_{32}H_{53}O_2SSi$ ($M^+ - MeOCH_2O$), calcd 529.3538, found 529.3521.

(2*S*,3*S*)-2,3-Epoxygeraniol ((−)-36). Titanium tetraisopropoxide (4.6 g, 16 mmol) and TBHP (4.2 M in CH_2Cl_2, 120 mL, 500 mmol) were added, successively, to a suspension of L-(+)-DIPT (5.6 g, 24 mmol) and molecular sieves 4A (30 g) in CH_2Cl_2 (500 mL) at −10 °C under Ar atmosphere. After being stirred at −10 °C for 20 min, the mixture was cooled to −23 °C and freshly distilled geraniol (50 g, 320 mmol) was added at such a rate that the temperature remained under −20 °C. The mixture was stirred at −23 °C for an additional 2 h, and then water (50 mL) was added, with vigorous stirring, to stop the reaction. The mixture was allowed to warm to room temperature. After 30 min, 3 M aqueous NaOH (30 mL) was added and the mixture was stirred at room temperature for an additional 30 min and then filtered through a Celite pad under suction. The filtrate was stirred vigorously with 10% aqueous citric acid (150 mL) at room temperature for 1 h. After the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (100 mL × 3). The combined organic layers were washed with brine (300 mL), dried (Na_2SO_4), and concentrated in vacuo. Distillation of the crude product under reduced pressure afforded (−)-**36** (54 g, 320 mmol, 100%): bp 110–113 °C (2.5 mmHg); $[\alpha]^{18}_D$ −4.60° (*c* 3.00, $CHCl_3$); IR (neat) 3450, 2950, 2850, 1457, 1390, 1035, 757 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.31 (3 H, s, C_3-Me), 1.61, 1.68 (each 3 H, s, C_7-Me_2), 2.10 (2 H, bq, *J* = 7 Hz, C_5-H_2), 2.95 (1 H, dd, *J* = 5 and 7 Hz, C_2-H), 3.72 (2 H, m, C_1-H_2), 5.05 (1 H, bt, *J* = 7 Hz, C_6-H). The ^1H NMR and IR spectra of this sample were identical with those of (+)-**36**.[10]

(2*S*,3*R*)-Linalool Oxide ((−)-37). A solution of (−)-**36** (54 g, 350 mmol), TsCl (90 g, 470 mmol), and pyridine (45 mL, 560 mmol) in CH_2Cl_2 (400 mL) was stirred at 0 °C for 24 h. The resulting suspension was poured into water (1 L) and was extracted with ether (700 mL × 4). The combined extracts were washed with brine (1 L), dried (Na_2SO_4), and concentrated in vacuo to give a crude tosylate. The crude tosylate was dissolved in a mixture of CH_3CN (800 mL) and water (550 mL). *p*-Toluenesulfonic acid monohydrate (4.0 g, 23 mmol) was added at 50 °C, and the mixture was stirred at 50 °C for 24 h. After cooling to room temperature, the solution was extracted with ether (700 mL × 3). The combined extracts were washed with brine (1 L), dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography of the residue on silica gel (1 kg) with 30% EtOAc/benzene afforded a corresponding diol (71 g, 210 mmol, 60%): $[\alpha]^{23}_D$ −20.7° (*c* 0.90, $CHCl_3$); IR (neat) 3530, 2950, 2900, 1715, 1600, 1500, 1455, 1360, 1190, 1175, 1095, 1020, 965, 840, 820, 765 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.19 (3 H, s, C_3-Me), 1.60, 1.68 (each 3 H, s, C_7-Me_2), 2.43 (3 H, s, $SO_2C_6H_4Me$), 3.65 (1 H, bdd, *J* = 2 and 9 Hz, C_2-H), 4.02 (1 H, t, *J* = 9 Hz, C_1-H), 4.24 (1 H, dd, *J* = 2 and 9 Hz, C_1-H), 5.05 (1 H, bt, *J* = 7 Hz, C_6-H), 7.30, 7.33 (each 2 H, d, *J* = 11 Hz, aromatic protons).

A suspension of the diol (71 g, 210 mmol) and K_2CO_3 (74 g, 530 mmol) in MeOH (700 mL) was stirred at −10 °C for 40 min. The mixture was then poured into 10% aqueous citric acid (1 L) and was extracted with ether (700 mL × 4). The combined extracts were washed with water (700 mL) and brine (700 mL), dried (Na_2SO_4), and concentrated in vacuo. Distillation of the residue under reduced pressure gave linalool oxide derivative (−)-**37** (27 g, 160 mmol, 73%): bp 80 °C (2.0 mmHg); $[\alpha]^{22}_D$ −23.8° (*c* 3.70, $CHCl_3$); IR (neat) 3420, 2960, 2920, 2870, 1460, 1380, 1270, 1165, 1110, 1085, 1060, 990, 895, 885 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (3 H, s, C_3-Me), 1.60, 1.69 (each 3 H, s, C_7-Me_2), 2.10 (2 H, m, C_5-H_2), 2.6–2.9 (3 H, m, C_1-H_2, C_2-H), 5.07 (1 H, bt, *J* = 7 Hz, C_6-H). The absolute value of optical rotation and the ^1H NMR and IR spectra of this sample were identical with those of (+)-**37**.[10]

(2*S*,3*R*)-1,2-Epoxy-3-(methoxymethoxy)-3,7-dimethyl-6-octene ((+)-38). A solution of (−)-**37** (10 g, 58 mmol), *i*-Pr_2NEt (29 mL, 166 mmol), MOMCl (9.0 mL, 120 mmol), and DMAP (500 mg, 4.1 mmol) in CH_2Cl_2 (200 mL) was stirred at room temperature for 36 h. The mixture was then poured into 10% aqueous citric acid (200 mL) and was extracted with ether (150 mL × 4). The combined extracts were washed with water (150 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue on silica gel (300 g) with 5% EtOAc/benzene yielded MOM ether (+)-**38** (11 g, 51 mmol, 89%): $[\alpha]^{20}_D$ +4.16° (*c* 2.30, $CHCl_3$); IR (neat) 2980, 2950, 1460, 1380, 1150, 1040, 920 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.21 (3 H, s, C_3-Me), 1.60, 1.68 (each 3 H, s, C_7-Me_2), 2.15 (2 H, m, C_5-H_2), 2.6–2.8 (2 H, m, C_1-H_2), 2.92 (1 H, t, *J* = 4 Hz, C_2-H), 3.32 (3 H, s, OCH_2OMe), 4.60, 4.74 (each 1 H, d, *J* = 8 Hz, OCH_2OMe), 5.05 (1 H, bt, *J* = 7 Hz, C_6-H). The absolute value of optical rotation and the ^1H NMR and IR spectra of this sample were identical with those of (−)-**38**.[10]

(2*R*,5*R*)-2-[(*E*)-(1*S*,8*S*,9*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-8-hydroxy-9-(methoxymethoxy)-5,9,13-trimethyltetradeca-4,12-dienyl]tetrahydro-5-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-2-methylfuran (47). Butyllithium (1.5 M in hexane, 300 μL) was added to a mixture of **46** (210 mg, 350 μmol), epoxide (+)-**38** (90 mg, 420 μmol), and TMEDA (300 μL) in THF (3.0 mL) at 0 °C under Ar atmosphere. The mixture was stirred at 0 °C for 30 min, and then water (500 μL) was added to quench the reaction. The mixture was poured

into water (70 mL) and extracted with ether (50 mL × 3). The combined extracts were washed with brine (100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and column chromatography of the resulting oil on silica gel (20 g) with 5% EtOAc/benzene yielded a mixture of diastereomers (170 mg, 210 μmol, 100%).

The product was dissolved in a mixture of THF (3.0 mL) and 2-propanol (3.0 mL). Metallic Na (ca. 150 mg) was added to the boiling solution under reflux. Boiling under reflux was continued for 2 h, and then the mixture was cooled to room temperature and concentrated in vacuo. The residual paste was dilted with water (100 mL) and extracted with ether (70 mL × 3). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude product by column chromatography on silica gel (5 g) with 7% EtOAc/benzene gave alcohol **47** (100 mg, 140 μmol, 80%): $[\alpha]^{22}_D$ −13.4° (*c* 1.60, $CHCl_3$); IR (neat) 3450, 2960, 1460, 1375, 1250, 1145, 1100, 1030, 920, 840, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06, 0.7 (each 3 H, s, $SiMe_2$), 0.89 (9 H, s, $SiCMe_3$), 1.09, 1.21, 1.24 (each 3 H, s, C_2-Me, C_9-Me, $C_{1'''}$-Me), 1.61, 1.61, 1.61, 1.68, 1.68 (each 3 H, s, C_5-Me, C_{13}-Me_2, $C_{5'''}$-Me_2), 3.37, 3.41 (each 3 H, s, OCH_2OMe × 2), 3.49 (1 H, dd, *J* = 4.4 and 6.8 Hz, $C_{1'}$-H), 3.82 (1 H, dd, *J* = 5.9 and 9.3 Hz, C_5-H), 4.65, 4.74 (each 1 H, d, *J* = 7.3 Hz, OCH_2OMe), 4.68, 4.93 (each 1 H, d, *J* = 7.3 Hz, OCH_2OMe), 5.15 (2 H, m, $C_{12'}$-H, $C_{4'''}$-H), 5.17 (1 H, bt, *J* = 6.8 Hz, $C_{4'}$-H); FDMS *m/z* (rel intens) 697 (22, M^+ + H), 665 (13, M^+ − MeO), 255 (100, $C_{15}H_{27}O_3^+$, right half), 171 (26, Me_2C=C-$(CH_2)_2C^+$(Me)O(MOM)); HRFIMS for $C_{40}H_{77}O_7Si$ (M^+ + H), calcd 697.5441, found 697.5449.

(2*R*,5*R*)-2-[(*E*)-(1*S*,8*S*,9*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-8,9-bis(methoxymethoxy)-5,9,13-trimethyltetradeca-4,12-dienyl]tetrahydro-5-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-2-methylfuran (48). A solution of **47** (94 mg, 130 μmol) and MOMCl (200 mg, 2.5 mmol) in a mixture of *i*-Pr_2NEt (1.0 mL) and CH_2Cl_2 (2.0 mL) was stirred at room temperature for 12 h. The mixture was then poured into water (20 mL) and extracted with ether (15 mL × 3). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (5 g) with 5% EtOAc/benzene gave MOM ether **48** (100 mg, 130 μmol, 100%): $[\alpha]^{20}_D$ −3.47° (*c* 2.10, $CHCl_3$); IR (neat) 2960, 1460, 1375, 1255, 1150, 1100, 1035, 920, 840, 780 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.07 (6 H, s, $SiMe_2$), 0.88 (9 H, s, $SiCMe_3$), 1.08, 1.22, 1.23 (each 3 H, s, C_2-Me, C_9-Me, $C_{1'}$-Me), 1.61, 1.61, 1.61, 1.68, 1.68 (each 3 H, s, C_5-Me, C_{13}-Me_2, $C_{5'}$-Me_2), 3.36, 3.36, 3.39 (each 3 H, s, OCH_2OMe × 3), 3.80 (1 H, m, C_5-H), 4.6–4.9 (6 H, m, OCH_2OMe × 3), 5.0–5.3 (3 H, m, C_4-H, C_{12}'-H, $C_{4'}$-H); FDMS *m/z* (rel intens) 741 (15, M^+ + H), 740 (10, M^+), 709 (20, M^+ − MeO), 255 (100, $C_{15}H_{27}O_3^+$, right half), 171 (27, Me_2C=$C(CH_2)_2C^+$(Me)O(MOM)).

(2*R*,5*R*)-Tetrahydro-2-[(*E*)-(1*S*,8*S*,9*R*)-1-hydroxy-8,9-bis(methoxymethoxy)-5,9,13-trimethyltetradeca-4,12-dienyl]-5-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-2-methylfuran (49). A solution of **48** (100 mg, 130 μmol) and TBAF (1 M in THF, 300 μL, 300 μmol) in THF (2.0 mL) was boiled under reflux, with stirring, for 4 h. After cooling, the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (3 g) with 15% EtOAc/benzene to afford 5-substituted 4-en-1-ol **49** (65 mg, 100 μmol, 74%): $[\alpha]^{20}_D$ −9.57° (c 1.90, $CHCl_3$); IR (neat), 3450, 2960, 1465, 1380, 1210, 1155, 1100, 1040, 925 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.10, 1.19, 1.22 (each 3 H, s, C_2-Me, C_9-Me, $C_{1'}$-Me), 1.61, 1.61, 1.61, 1.68, 1.68 (each 3 H, s, C_5-Me, C_{13}'-Me_2, $C_{5'}$-Me_2), 2.91 (1 H, bs, alcoholic proton), 3.38, 3.39, 3.40 (each 3 H, s, OCH_2OMe × 3), 3.52 (1 H, dd, *J* = 2.7 and 9.3 Hz, C_1-H), 3.93 (1 H, dd, *J* = 5.3 and 10.4 Hz, C_5-H), 4.62, 4.95 (each 1 H, d, *J* = 7.3 Hz, OCH_2OMe), 4.65, 4.80 (each 1 H, d, *J* = 7.3 Hz, OCH_2OMe), 4.68 (2 H, s, OCH_2OMe), 5.11, 5.14, 5.18 (each 1 H, bt, *J* = 6.8 Hz, C_4-H, C_{12}-H, $C_{4'}$-H); FDMS *m/z* (rel intens) 627 (65, M^+ + H), 626 (100, M^+), 595 (20, M^+ − MeO), 565 (22, M^+ − $MeOCH_2O$), 255 (74, $C_{15}H_{27}O_3^+$, right half), 171 (73, Me_2C=$C(CH_2)_2C^+$(Me)O(MOM)); HRFIMS for $C_{36}H_{66}O_8$ (M^+), calcd 626.4760, found 626.4744.

(2*R*,5*R*)-Tetrahydro-2-[(2*S*,5*R*)-tetrahydro-5-[(1*S*,4*S*,5*R*)-1-hydroxy-4,5-bis(methoxymethoxy)-1,5,9-trimethyldec-8-enyl]furan-2-yl]-5-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-2-methylfuran (51). A solution of **49** (47 mg, 75 μmol), $VO(acac)_2$ (1.0 mg, 3.8 μmol), and TBHP (4.0 M in dichloromethane, 50 μL, 200 μmol) in benzene (2.0 mL) was stirred at 50 °C for 5 h. The mixture was poured into water (20 mL) and was extracted with ether (15 mL × 3). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residual oil was diluted with a mixture of AcOH (1.0 mL) and ether (10 mL), and the solution was allowed to stand at room temperature for 30 min. After addition of toluene (30 mL) to the mixture, the solvents were evaporated under reduced pressure, keeping the temperature under 30 °C. The residual oil was purified by column chromatography on silica gel (2 g) with 40% EtOAc/benzene to afford ether **51** (26 mg, 40 μmol, 54%): $[\alpha]^{20}_D$ −7.31° (*c* 1.90, $CHCl_3$); IR (neat) 3430, 2960, 1470, 1455, 1380, 1210, 1145, 1030, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22, 1.23, 1.25, 1.26 (each 3 H, s, C_2-Me, $C_{1'}$-Me, $C_{1'''}$-Me, $C_{5'''}$-Me), 1.61, 1.61, 1.68, 1.68 (each 3 H, s, $C_{5'''}$-Me_2, $C_{9'''}$-Me_2), 3.37, 3.37, 3.39 (each 3 H, s, OCH_2OMe × 3), 3.80 (1 H, t, *J* = 6.8 Hz, C_5-H), 3.90 (2 H, m, C_2-H, C_5-H), 4.6–4.9 (6 H, m, OCH_2OMe × 3), 5.09 (2 H, m, $C_{4'''}$-H, $C_{8'''}$-H); FDMS *m/z* (rel intens) 643 (100, M^+ + H), 642 (48, M^+), 611 (35 M^+ − MeO), 581 (30, M^+ − $MeOCH_2O$), 255 (58, $C_{15}H_{27}O_3^+$, right half), 171 (47, Me_2C=$C(CH_2)_2C^+$(Me)O(MOM)); HRFIMS for $C_{36}H_{66}O_9$ (M^+), calcd 642.4709, found 642.4762.

(2*R*,5*R*)-Tetrahydro-2-[(2*S*,5*R*)-tetrahydro-5-[(1*S*,4*S*,5*R*)-1,4,5-trihydroxy-1,5,9-trimethyldec-8-enyl]-furan-2-yl]-5-[(*S*)-1-hydroxy-1,5-dimethylhex-4-enyl]-2-methylfuran (52). A solution of **51** (26 mg, 40 μmol) in a mixture of 12 M aqueous HCl (10 μL) and MeOH (1.0 mL) was stirred at room temperature for 12 h. Triethylamine (100 μL) was added to the mixture, and then the solvent was evaporated in vacuo. Column chromatography of the residue on silica gel (3 g) with 20% acetone/$CHCl_3$ yielded tetraol **52** (20 mg, 39 μmol, 98%): $[\alpha]^{20}_D$ −14.1° (*c* 0.50, $CHCl_3$); IR (neat) 3450, 2970, 2930, 2870, 1455, 1377, 1185, 900 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.16, 1.20, 1.27, 1.33 (each 3 H, s, C_2-Me, $C_{1'}$-Me, $C_{1'''}$-Me, $C_{5'''}$-Me), 1.60, 1.61, 1.68, 1.68 (each 3 H, s, $C_{5'''}$-Me_2, $C_{9'''}$-Me_2), 3.33 (1 H, dd, *J* = 1.0 and 9.8 Hz, $C_{4'''}$-H), 3.78 (1 H, dd, *J* = 4.9 and 10.3 Hz, C_5-H, C_2-H, or C_5-H), 3.81 (1 H, dd, *J* = 4.9 and 6.3 Hz, C_5-H, C_2-H, or C_5-H), 3.99 (1 H, t, *J* = 7.3 Hz, C_5-H, C_2-H, or C_5-H), 5.10, 5.14 (each 1 H, bt, *J* = 6.8 Hz, $C_{4'}$-H, $C_{8'''}$-H); FDMS *m/z* (rel intens) 511 (100, M^+ + H), 510 (30, M^+), 211 (20, $C_{13}H_{23}O_2^+$, right half), 127 (21, Me_2C=$C(CH_2)_2C^+$(Me)OH); HRFIMS for $C_{30}H_{54}O_6$ (M^+), calcd 510.3922, found 510.3962.

Teurilene (1). Methanesulfonyl chloride (10 mg, 88 μmol) was added to a solution of **52** (16 mg, 31 μmol) and Et_3N (30 mg, 300 μmol) in CH_2Cl_2 (1.0 mL) at −40 °C. The mixture was stirred at −40 °C for 2 h, and then MeOH (100 μL) was added to decompose excess MsCl. The mixture was allowed to warm to room temperature, then was poured into water (20 mL), and was extracted with chloroform (15 mL × 3). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to provide crude mesylate **53**. The crude product was dissolved in methanol (1.0 mL), and potassium carbonate (14 mg, 100 μmol) was added at room temperature. The mixture was stirred at room temperature for 30 min, and then the resulting suspension was poured into water (20 mL) and was extracted with chloroform (15 mL × 3). The combined extracts were added to 2 M aqueous HCl (20 mL), and the resulting heterogeneous solution was stirred vigorously at room temperature for 1 h. The organic layer was separated, then was washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. After short-column chromatography of the residue on silica gel (500 mg) with 20% acetone/$CHCl_3$, further purification by HPLC (column LiChrosorb RP-18, 4 × 250 mm (i.d.) (Merck), eluent 90% MeOH/H_2O, flow rate 1.0 mL/min, detection UV at 210 nm) gave teurilene (**1**) (5.0 mg, 10 μmol, 32%): t_R = 7.2 min; $[\alpha]^{18}_D$ +0.2° (*c* 0.43, $CHCl_3$) [lit.[1] $[\alpha]^{22}_D$ 0° (*c* 0.37, $CHCl_3$)]; mp 85.0–85.5 °C (recrystallized from diisopropyl ether) [lit.[1] mp 84–85 °C]; IR ($CHCl_3$) 3570, 2970, 2920, 2850, 1460, 1380, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18, 1.20 (each 6 H, s, C_6-Me, C_{10}-Me, C_{15}-Me, C_{19}-Me), 1.61, 1.68 (each 6 H, s, C_2-Me_2, C_{23}-Me_2), 3.82 (2 H, dd, *J* = 5.9 and 9.7 Hz, C_7-H, C_{18}-H or C_{11}-H, C_{14}-H), 3.87 (2 H, bt, *J* = 5.1 Hz, C_7-H, C_{18}-H or C_{11}-H, C_{14}-H), 5.11 (2 H, bt, *J* = 6.8 Hz, C_3-H, C_{22}-H). The ^1H NMR and IR spectra, optical rotation, melting point, and HPLC retention time of the sample were identical with those of natural teurilene (**1**) provided by Prof.

Etsuro Kurosawa of Hokkaido University.

(*E*)-6-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-5-methyl-4-hexen-1-ol (56). *p*-Toluenesulfonic acid (770 mg, 4.5 mmol) was added to a solution of (*E*)-6-(benzoyloxy)-2-methyl-2-hexen-1-ol (**55**)[10] (20 g, 91 mmol) and 3,4-dihydro-2*H*-pyran (14 g, 170 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then Et_3N (2.0 mL) was added to quench the reaction. The solvent was removed under reduced pressure, and column chromatography of the residue on silica gel (600 g) with 5% EtOAc/benzene provided a THP ether (26 g, 86 mmol, 94%): IR (neat) 2980, 2900, 1458, 1365, 1200, 1117, 1075, 1020, 980, 910, 870, 820, 738, 700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.52 (3 H, s, C_2-Me), 2.15 (2 H, bq, J = 6 Hz, C_4-H_2), 3.46 (2 H, t, J = 6 Hz, C_6-H_2), 3.80, 4.05 (each 1 H, m, C_6-H_2), 4.02 (2 H, s, C_6-H_2), 4.48 (2 H, s, PhCH_2O), 4.58 (1 H, bs, C_1-H), 5.40 (1 H, bt, J = 7 Hz, C_3-H), 7.30 (5 H, s, aromatic protons); FIMS m/z (rel intens) 305 (52, M^+ + H), 304 (100, M^+), 203 (51, M^+ - (THP)O), 91 (26, Bn^+), 85 (53, THP^+); HRFIMS for $C_{19}H_{28}O_3$ (M^+), calcd 304.2039, found 304.2069.

Metallic Li was added to a liquid NH_3 (ca. 500 mL) at -78 °C under Ar atmosphere. After the mixture was stirred at -78 °C for 15 min, a solution of the THP ether (7.3 g, 24 mmol) in ether (30 mL) was added, with stirring, at -78 °C to the purple suspension. The stirring was continued for 40 min at -78 °C, and NH_4Cl (ca. 7 g) was added to quench the reaction. The mixture was allowed to warm to room temperature, and NH_3 was allowed to evaporate. The residue was diluted with water (300 mL) and extracted with ether (300 mL × 3). The combined extracts were washed with brine (700 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (150 g) with 50% EtOAc/benzene to give alcohol **56** (4.9 g, 23 mmol, 97%): IR (neat) 3400, 2940, 2860, 1455, 1440, 1390, 1350, 1200, 1120, 1020, 1078, 1020, 907, 870, 820 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.60 (3 H, s, C_5-Me), 2.14 (2 H, bq, J = 7 Hz, C_3-H_2), 3.5–4.2 (6 H, m, C_1-H_2, C_8-H_2, C_6-H_2), 4.59 (1 H, bs, C_2-H_2), 5.44 (1 H, bt, J = 7 Hz, C_4-H); FIMS m/z (rel intens) 265 (57, M^+ + H), 214 (70, M^+), 113 (25, M^+ - THPO), 85 (100, THP^+); HRFIMS for $C_{12}H_{22}O_3$ (M^+), calcd 214.1569, found 214.1511.

Ethyl (2*E*,6*E*)-8-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-2,7-dimethylocta-2,6-dienoate (57). A solution of **56** (12 g, 56 mmol) in CH_2Cl_2 (50 mL) was added, with stirring, to a suspension of NaOAc (47 g, 570 mmol) and PCC (61 g, 280 mmol) in CH_2Cl_2 (1.0 L) at room temperature. The mixture was stirred at room temperature for 1 h, and then Celite (ca. 100 g) and ether (ca. 100 mL) were added successively. After being stirred at room temperature for an additional 15 min, the mixture was filtered through a Celite pad under suction and the filtrate was concentrated under reduced pressure. The residue was diluted with ether (500 mL) and washed with brine (500 mL). After separation, the ethereal layer was concentrated in vacuo to give an aldehyde, which was dissolved in THF (50 mL). The solution was added to a solution of Horner–Emmons reagent [prepared by the method of Gallagher and Webb[27] from triethyl α-phosphinopropionate (33 g, 140 mmol) and NaH (60% in oil, 4.5 g, ca. 110 mmol) in THF (200 mL) at 0 °C] at 0 °C over 5 min under Ar atmosphere. After being stirred at 0 °C for 40 min, the mixture was poured into cold water (500 mL) containing cracked ice (ca. 200 g) and extracted with ether (300 mL × 3). The combined extracts were washed with water (500 mL) and brine (500 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (500 g) with 5% EtOAc/benzene to afford α,β-unsaturated ester **57** (12 g, 41 mmol, 72%): IR (neat) 2900, 2850, 1715, 1460, 1440, 1360, 1260, 1115, 1070, 1015, 975, 905, 825, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (3 H, t, J = 7 Hz, CO_2CH_2Me), 1.60 (3 H, s, C_7-Me), 1.83 (3 H, s, C_2-Me), 2.0–2.2 (4 H, m, C_4-H_2, C_5-H_2), 3.5–4.3 (6 H, m, C_8-H_2, C_6-H_2, CO_2CH_2Me), 4.60 (1 H, bs, C_2-H), 5.44 (1 H, bt, J = 7 Hz, C_6-H), 6.77 (1 H, bt, J = 7 Hz, C_3-H); FIMS m/z (rel intens) 296 (86, M^+), 195 (36, M^+ - (THP)O), 85 (100, THP^+); HRFIMS for $C_{17}H_{28}O_4$ (M^+), calcd 296.1988, found 296.2009.

(2*E*,6*E*)-8-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-2,7-dimethylocta-2,6-dien-1-ol (58). Diisobutylaluminum hydride (1 M in hexane, 100 mL) was added to a solution of **57** (12 g, 41 mmol) in hexane (200 mL) at -78 °C under Ar atmosphere. The mixture was stirred at -78 °C for 5 min, and then EtOAc (20 mL) and water (15 mL) were added, successively, to decompose the excess hydride. The mixture was allowed to warm to room temperature, and after being stirred for an additional 30 min, the resulting suspension was filtered through a Celite pad under suction. The filtrate was concentrated in vacuo, and column chromatography of the residue on silica gel (300 g) with 20% EtOAc/benzene afforded allylic alcohol **58** (8.4 g, 33 mmol, 81%): IR (neat) 3400, 2950, 2880, 1460, 1440, 1390, 1360, 1205, 1185, 1120, 1080, 1020, 910, 875, 820 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.65, 1.65 (each 3 H, s, C_2-Me, C_7-Me), 2.1–2.3 (4 H, m, C_4-H_2, C_5-H_2), 3.3–4.3 (6 H, m, C_1-H_2, C_8-H_2, C_6-H_2), 4.60 (1 H, bs, C_2-H), 5.36 (2 H, m, C_3-H, C_7-H); FIMS m/z (rel intens) 255 (84, M^+ + H), 153 (13, M^+ - (THP)O), 85 (100, THP^+); HRFIMS for $C_{15}H_{27}O_3$ (M^+ + H), calcd 255.1961, found 255.1935.

(2*E*,6*E*)-8-(Benzyloxy)-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,7-dimethylocta-2,6-diene (59). A solution of **58** (7.3 g, 29 mmol) in DMF (5.0 mL) was added slowly to a suspension of NaH (1.1 g, 47 mmol) in DMF (18 mL) at 0 °C under Ar atmosphere. The mixture was stirred at 0 °C for 30 min, then the cooling bath was removed, and BnCl (6.0 g, 48 mmol) was added. The mixture was stirred at room temperature for 36 h, then was poured into water (500 mL), and was extracted with ether (300 mL × 3). The combined extracts were washed with water (500 mL) and brine (500 mL), dried (Na_2SO_4), and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (200 g) with 5% EtOAc/benzene to yield benzyl ether **59** (7.0 g, 20 mmol, 70%): IR (neat) 2920, 2840, 1450, 1350, 1270, 1255, 1197, 1110, 1070, 1020, 903, 870, 815, 735, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.69, 1.69 (each 3 H, s, C_2-Me, C_7-Me), 2.0–2.2 (4 H, m, C_4-H_2, C_5-H_2), 3.3–4.2 (4 H, m, C_8-H_2, C_6-H_2), 3.85 (2 H, s, C_1-H_2), 4.43 (2 H, s, PhCH_2O), 4.55 (1 H, bs, C_2-H), 5.40 (2 H, m, C_3-H, C_7-H), 7.28 (5 H, s, aromatic protons); FIMS m/z (rel intens) 345 (52, M^+ + H), 344 (56, M^+), 243 (30, M^+ - (THP)O), 91 (28, Bn^+), 85 (100, THP^+).

(2*E*,6*E*)-8-(Benzyloxy)-2,7-dimethylocta-2,6-dien-1-ol (60). A solution of **59** (6.4 g, 19 mmol) and $TsOH \cdot H_2O$ (500 mg, 2.6 mmol) in MeOH (200 mL) was stirred at room temperature for 2 h, and then Et_3N (1.0 mL) was added to stop the reaction. After the solvent was removed in vacuo, purification of the residue by column chromatography on silica gel (200 g) with 20% EtOAc/benzene gave allylic alcohol **60** (4.5 g, 17 mmol, 91%): IR (neat) 3360, 2900, 2840, 1500, 1450, 1380, 1360, 1070, 1005, 860, 740, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.64, 1.64 (each 3 H, s, C_2-Me, C_7-Me), 2.0–2.2 (4 H, m, C_4-H_2, C_5-H_2), 3.89, 3.98 (each 2 H, s, C_8-H_2, C_1-H_2), 4.44 (2 H, s, PhCH_2O), 5.40 (2 H, m, C_3-H, C_7-H), 7.30 (5 H, s, aromatic protons); FIMS m/z (rel intens) 261 (100, M^+ + H), 260 (37, M^+), 91 (62, Bn^+); HRFIMS for $C_{17}H_{24}O_2$ (M^+), calcd 260.1777, found 260.1822.

(2*E*,6*E*)-1-(Benzyloxy)-2,7-dimethyl-8-(phenylthio)octa-2,6-diene (61). A solution of **60** (4.3 g, 17 mmol) and PPh_3 (6.5 g, 25 mmol) in a mixture of CCl_4 (30 mL) and benzene (100 mL) was boiled under reflux, with stirring, for 24 h under Ar atmosphere. The mixture was cooled to 0 °C, and hexane (100 mL) was added. The resulting suspension was stirred for an additional 30 min and then was filtered under suction. The filtrate was concentrated under reduced pressure. The residue was dissolved in DMF (5.0 mL), and the solution was added to a solution of sodium thiophenoxide [prepared from NaH (600 mg, 25 mmol) and thiophenol (2.7 g, 28 mmol) in DMF (70 mL) at 0 °C] at 0 °C. The mixture was stirred at 0 °C for 1 h, then was poured into water (300 mL), and was extracted with ether (150 mL × 3). The combined extracts were washed with water (300 mL) and brine (300 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (120 g) with benzene to give allylic sulfide **61** (4.6 g, 13 mmol, 77%): IR (neat) 3040, 2920, 2850, 1590, 1485, 1457, 1440, 1090, 1070, 1030, 743, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.67 (3 H, s, C_2-Me), 1.74 (3 H, s, C_7-Me), 1.9–2.1 (4 H, m, C_4-H_2, C_5-H_2), 3.49 (2 H, s, C_8-H_2), 3.89 (2 H, s, C_1-H_2), 4.44 (2 H, s, PhCH_2O), 5.30 (2 H, m, C_3-H, C_6-H), 7.2–7.4 (10 H, m, aromatic protons); FIMS m/z (rel intens) 352 (100, M^+); HREIMS for $C_{23}H_{28}OS$ (M^+), calcd 358.1862, found 352.1851.

(10*E*,14*E*)-(6*R*,7*S*)-16-(Benzyloxy)-6-(methoxymethoxy)-2,6,10,15-tetramethylhexadeca-2,10,14-trien-7-ol (62). Butyllithium (1.5 M in hexane, 11 mL, 17 mmol) was added to

a solution of the sulfide **61** (3.9 g, 11 mmol) and (+)-**38** (2.8 g, 13 mmol) in a mixture of TMEDA (6.0 mL) and THF (60 mL) at −78 °C under Ar atmosphere. The mixture was stirred at −78 °C for 10 min, and then water (3.0 mL) was added to quench the reaction. The mixture was poured into water (200 mL) and was extracted with ether (15 mL × 3). The combined extracts were washed with brine (200 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and purification of the crude product by column chromatography on silica gel (120 g) with 30% EtOAc/benzene gave a mixture of diastereomers (4.3 g, 7.6 mmol, 69%).

A solution of the mixed diastereomers (4.3 g, 7.6 mmol) in a mixture of THF (150 mL) and 2-propanol (70 mL) was heated to boiling, and then metallic Na (ca. 1 g, 43 mmol) was added. Boiling under reflux was continued for 5 h, then the mixture was cooled to 0 °C, and MeOH (10 mL) was added to decompose excess Na. After removal of the solvent in vacuo, the residue was diluted with water (300 mL) and was extracted with ether (150 mL × 3). The combined extracts were washed with brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude material by column chromatography on silica gel (120 g) with 10% EtOAc/benzene afforded alcohol **62** (3.5 g, 7.6 mmol, 100%): $[\alpha]^{18}_D$ −11.1° (*c* 3.50, $CHCl_3$); IR (neat) 3500, 2960, 1465, 1390, 1320, 1150, 1100, 1080, 1040, 930, 750, 705 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.20 (3 H, s, C_8-Me), 1.61, 1.62, 1.68, 1.68 (each 3 H, s, C_2-Me_2, C_{10}-Me, C_{15}-Me), 3.39 (3 H, s, OCH_2OMe), 3.89 (2 H, s, C_{16}-H_2), 4.42 (2 H, s, $PhCH_2O$), 4.68 (2 H, s, OCH_2OMe), 5.0–5.4 (3 H, m, C_3-H, C_{11}-H, C_{14}-H), 7.30 (5 H, s, aromatic protons); FIMS *m/z* (rel intens) 459 (54, $M^+ + H$), 458 (48, M^+), 171 (44, $Me_2C{=}C(CH_2)_2C^+(Me)O(MOM)$), 91 (100, Bn^+); HRFIMS for $C_{29}H_{46}O_4$ (M^+), calcd 458.3398, found 458.3386.

(2*E*,6*E*)-(10*S*,11*R*)-1-(Benzyloxy)-10,11-bis(methoxymethoxy)-2,7,11,15-tetramethylhexadeca-2,6,14-triene (63). A solution of **62** (300 mg, 660 μmol), MOMCl (90 μL, 1.2 mmol), and *i*-Pr_2NEt (340 μL, 1.9 mmol) in CH_2Cl_2 (1.0 mL) was stirred at 0 °C for 30 min, then the cooling bath was removed, and the mixture was allowed to warm to room temperature. After being stirred at room temperature for 12 h, the mixture was poured into water (70 mL) and was extracted with ether (30 mL × 3). The combined extracts were washed with brine (70 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the resulting oil on silica gel (10 g) with 5% EtOAc/benzene afforded MOM ether **63** (320 mg, 640 μmol, 97%): $[\alpha]^{21}_D$ +1.91° (*c* 3.20, $CHCl_3$); IR (neat) 2920, 2780, 1500, 1455, 1380, 1310, 1210, 1150, 1100, 1040, 920, 740, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.21 (3 H, s, C_{11}-Me), 1.60, 1.60, 1.68, 1.68 (each 3 H, s, C_2-Me, C_7-Me, C_{15}-Me_2), 3.35, 3.38 (each 3 H, s, OCH_2OMe × 2), 3.90 (2 H, s, C_2-H_2), 4.43 (2 H, s, $PhCH_2O$), 4.65, 4.83 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 4.66 (2 H, s, OCH_2OMe), 5.0–5.5 (3 H, m, C_3-H, C_6-H, C_{14}-H), 7.30 (5 H, s, aromatic protons); FIMS *m/z* (rel intens) 503 (27, $M^+ + H$), 502 (43, M^+), 471 (21, $M^+ - MeO$), 470 (21, $M^+ - MeOH$), 171 (100, $Me_2C{=}C(CH_2)_2C^+(Me)OMOM$), 91 (41, Bn^+); HRFIMS for $C_{31}H_{50}O_5$ (M^+), calcd 502.3660, found 502.3611.

(2*E*,6*E*)-(10*S*,11*R*)-10,11-Bis(methoxymethoxy)-2,7,11,15-tetramethylhexadeca-2,6,14-trien-1-ol (64). Metallic Li was added to liquid NH_3 (ca. 50 mL) at −78 °C under Ar atmosphere. After the mixture was stirred at −78 °C for 15 min, a solution of **63** (300 mg, 600 μmol) in THF (5.0 mL) at −78 °C was added to the purple suspension. The mixture was stirred for 30 min at −78 °C, and then NH_4Cl (ca. 2 g) was added to stop the reaction. The mixture was allowed to warm to room temperature, and NH_3 was allowed to evaporate. The residue was diluted with water (100 mL) and extracted with ether (70 mL × 3). The combined extracts were washed with brine (100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The resulting oil was purified by column chromatography on silica gel (10 g) with 15% EtOAc/benzene to give alcohol **64** (220 mg, 530 μmol, 89%): $[\alpha]^{23}_D$ +4.01° (*c* 2.90, $CHCl_3$); IR (neat) 3480, 2980, 1450, 1380, 1210, 1150, 1100, 1030, 920 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.21 (3 H, s, C_{11}-Me), 1.61, 1.61, 1.68, 1.68 (each 3 H, s, C_2-Me, C_7-Me, C_{15}-Me_2), 3.38, 3.39 (each 3 H, s, OCH_2OMe × 2), 3.98 (2 H, s, C_1-H_2), 4.6–4.8 (4 H, m, OCH_2OMe × 2), 5.0–5.5 (3 H, m, C_3-H, C_6-H, C_{14}-H); FIMS *m/z* (rel intens) 413 (100, $M^+ + H$), 381 (16, M^+), 171 (44, $Me_2C{=}C(CH_2)_2C^+(Me)O(MOM)$), 91 (41, Bn^+); HRFIMS for $C_{24}H_{45}O_5$ (M^+), calcd 413.3269, found 413.3253.

(2*E*,6*E*)-(10*S*,11*R*)-10,11-Bis(methoxymethoxy)-2,7,11,15-tetramethyl-1-(phenylthio)hexadeca-2,6,14-triene (65). A solution of **64** (950 mg, 2.3 mmol), PPh_3 (900 mg, 3.4 mmol), and CCl_4 (10 mL) in benzene (25 mL) was boiled under reflux for 12 h under Ar atmosphere. The mixture was cooled to 0 °C, and then hexane (25 mL) was added. The resulting suspension was stirred for 30 min and then was filtered under suction. The filtrate was concentrated under reduced pressure to give a crude chloride, which was dissolved in DMF (3.0 mL). The solution was added to a solution of sodium thiophenoxide [prepared with NaH (83 mg, 3.4 mmol) and thiophenol (430 mg, 3.9 mmol) in DMF (150 mL) at 0 °C] at 0 °C. The mixture was stirred at 0 °C for 1 h, then was poured into water (150 mL), and was extracted with ether (100 mL × 3). The combined extracts were washed with water (150 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel (30 g) with 5% EtOAc/benzene afforded allylic sulfide **65** (1.1 g, 2.2 mmol, 95%): $[\alpha]^{26}_D$ +1.51° (*c* 3.10, $CHCl_3$); IR (neat) 2930, 1485, 1440, 1383, 1150, 1100, 1030, 925, 750, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.21 (3 H, s, C_{11}-Me), 1.60, 1.60, 1.68, 1.74 (each 3 H, s, C_2-Me, C_7-Me, C_{15}-Me_2), 3.37, 3.39 (each 3 H, s, OCH_2OMe × 2), 3.51 (2 H, s, C_1-H_2), 4.5–4.9 (4 H, m, OCH_2OMe × 2), 5.0–5.5 (3 H, m, C_3-H, C_6-H, C_{14}-H), 7.30 (5 H, m, aromatic protons); FIMS *m/z* (rel intens) 504 (100, M^+), 472 (73, $M^+ - MeOH$), 171 (14, $Me_2C{=}C(CH_2)_2C^+(Me)O(MOM)$), 109 (7.0, PhS^+); HRFIMS for $C_{30}H_{48}O_4S$ (M^+), calcd 504.3275, found 504.3287.

(10*E*,14*E*)-(6*S*,7*R*,18*S*,19*R*)-6,18,19-Tris(methoxymethoxy)-2,6,10,15,19,23-hexamethyltetracosa-2,10,14,22-trien-7-ol (66). Butyllithium (1.5 M in hexane, 1.3 mL, 2.0 mmol) was added to a mixture of **65** (620 mg, 1.3 mmol), (−)-**38** (280 mg, 1.3 mmol),[10] and TMEDA (1.0 g, 8.6 mmol) in THF (10 mL) at −78 °C under Ar atmosphere. After the mixture was stirred at −78 °C for 30 min, water (1.0 mL) was added. The mixture was poured into water (100 mL) and was extracted with ether (70 mL × 3). The combined extracts were washed with brine (100 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Column chromatography of the residual oil on silica gel (15 g) with 50% ether/hexane gave an adduct, which was dissolved in a mixture of THF (20 mL) and 2-propanol (6.0 mL). The solution was vigorously boiled under reflux, and metallic Na (ca. 500 mg) was added. After boiling under reflux for 1 h, the mixture was cooled to 0 °C, was poured into cold water (150 mL), and was extracted with ether (70 mL × 3). The combined extracts were washed with water (70 mL) and brine (70 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (15 g) with 20% EtOAc/benzene to give squalene derivative **66** (430 mg, 690 μmol, 58% in two steps): $[\alpha]^{23}_D$ +9.76° (*c* 2.90 $CHCl_3$); IR (neat) 3460, 2920, 1450, 1380, 1150, 1100, 1033, 920, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21, 1.22 (each 3 H, s, C_6-Me, C_{19}-Me), 1.61, 1.61, 1.61, 1.61, 1.68, 1.68 (each 3 H, s, C_2-Me_2, C_{10}-Me, C_{15}-Me, C_{23}-Me_2), 3.38, 3.40, 3.41 (each 3 H, s, OCH_2OMe × 3), 4.65–4.80 (6 H, OCH_2OMe × 3), 5.10–5.20 (4 H, m, C_3-H, C_{11}-H, C_{14}-H, C_{22}-H); FIMS *m/z* (rel intens) 611 (21, $M^+ + H$), 610 (16, M^+), 171 (100, $Me_2C{=}C(CH_2)_2C^+(Me)O(MOM)$); HRFIMS for $C_{36}H_{67}O_7$ ($M^+ + H$), calcd 611.4889, found 611.4902.

Simultaneous Double-Cyclization Reaction of 66. $VO(acac)_2$ (340 μM in benzene, 1.0 mL, 340 μmol), TBHP (4.3 M in CH_2Cl_2, 98 μL, 420 μmol), and AcOH (1.0 mM in benzene, 13 μL, 13 μmol) were added, successively, to **66** (80 mg, 130 μmol) at 50 °C under Ar atmosphere. After being stirred at 50 °C for 7 h, the mixture was poured into water (20 mL) and extracted with chloroform (20 mL × 3). The combined extracts were washed with brine (30 mL) and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (1.0 g). Successive elution with 20 and 30% EtOAc/benzene gave almost pure monocyclic **49** (25 mg, 40 μmol, 30%) and almost pure bis(tetrahydrofuran) **51** (28 mg). Further purification of **51** by HPLC (column LiChrosorb RP-8 (7 μm) 4 × 250 mm (i.d.) (Merck), eluent 80% $MeOH/H_2O$, flow rate 1.0 mL/min, detection UV at 215 nm) gave pure **51** (21 mg, 33 μmol, 25%): $[\alpha]^{22}_D$ −7.02° (*c* 1.00, $CHCl_3$); t_R = 10.2 min. The recovered **49** was converted into bis(tetrahydrofuran) **51** [(10 mg, 16 μmol, 39%; $[\alpha]^{22}_D$ −7.14° (*c* 1.10, $CHCl_3$)] by the method described above, employing $VO(acac)_2$

(500 μg, 1.9 μmol), TBHP (4.0 M in CH_2Cl_2, 50 μL), benzene (1.0 mL), and subsequent purification by HPLC. The IR and 400-MHz ^1H NMR spectra and HPLC retention times of both sample were identical with those of the sample prepared by the step-by-step method.

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Registry No. 1, 96304-92-6; **29**, 116216-69-4; **31**, 123908-75-8; **33**, 123908-76-9; **34**, 132298-82-9; **35**, 123908-77-0; (-)-**36**, 82188-73-6; **36** tosylate, 121401-06-7; (-)-**37**, 76985-25-6; **37** diol tosylate, 132341-93-6; (+)-**38**, 121400-91-7; **39**, 116216-77-4; **40**, 116216-78-5; **41**, 121429-28-5; **42**, 116216-79-6; **42** TBDMS ether, 121400-96-2; **43**, 121400-97-3; **43** aldehyde, 121400-98-4; **44**, 121400-92-8; **45**, 121400-99-5; **45** chloride, 121401-00-1; **46**, 121400-93-9; **47**, 121429-29-6; **48**, 132298-83-0; **49**, 121400-94-0; **50**, 121400-95-1; **51**, 121429-30-9; **52**, 121401-03-4; **53**, 121401-04-5; **54**, 121401-05-6; **55**, 109307-91-7; **55** THP ether, 132298-84-1; **56**, 132298-85-2; **56** aldehyde, 132298-86-3; (±)-**57**, 132341-94-7; (±)-**58**, 132298-87-4; (±)-**59**, 132298-88-5; **60**, 123908-78-1; **61**, 122554-78-3; **62**, 132298-89-6; **63**, 122554-81-8; **64**, 122554-82-9; **65**, 122554-84-1; **66**, 124018-82-2; $CH_3C(PPh_3)CO_2Et$, 5717-37-3; geraniol, 106-24-1.

Supplementary Material Available: ^1H NMR spectra of **1**, **33-38**, **43-49**, **51**, **52**, and **56-66** (30 pages). Ordering information is given on any current masthead page.

Stereoselectivities of Intramolecular Diels-Alder Reactions. Formation of the Taxane Skeleton

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The stereodirecting effect of an alkyl (Me) group on the diene and/or dienophile on the intramolecular Diels-Alder reaction leading to the formation of an eight-membered ring has been studied under both thermal and Lewis acid catalyzed cyclization conditions. The synthesis and cycloaddition reactions of tetraenes **2a-d**, leading to the formation of the taxane skeleton, is described. Selectivity is shown to vary under thermal conditions depending upon substitution pattern, while the catalyzed cycloaddition invariantly gives the cis-fused product.

Introduction

The taxane diterpenes[3] such as taxol (**1a**) and cephalomannine (**1b**) have received much attention over the past decade. These materials have shown significant anti-leukemic and tumor-inhibitory properties.[4] Structurally, the taxanes have posed may challenges to the organic chemist. The unusual tricyclic carbon framework that contains a bridgehead olefin, a sterically congested eight-membered ring system, and a bicyclo[5.3.1]undecene system trans fused to a cyclohexane ring has not yet yielded to a total synthesis of these complex molecules, although a synthesis of the simplest member of this family of compounds, taxusin, has appeared.[6f] Numerous synthetic approaches to the taxane skeleton ring system have been reported with the earliest entry dating back to 1974.[5a] The question of the construction of the basic carbon framework has been addressed via a biogenetical consideration, extensive chemical modifications of camphor,[6] a skeletal reorganization of the bicyclo[2.2.2]octane system via an anionic oxy-Cope reaction,[7] several photolysis processes,[8] novel rearrangements and fragmentation routes,[9] annulation strategies,[10] intercalation of enediol silyl eth-

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