carbon disulfide (1 mL), and the mixture was refluxed for 30 min and then was treated with 1 mL of iodomethane. The entire mixture was refluxed for 6 h, at which time the reaction was judged to be complete by TLC examination. The reaction mixture was then cooled to room temperature and diluted with saturated aqueous ammonium chloride solution (10 mL), and the organic layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL) and dried (Na_2SO_4). The ether was removed under reduced pressure to give a 0.11-g (83%) yield of the xanthate after flash column chromatography (5% ether/hexane) (R_f = 0.18): IR (CCl_4) ν 2965, 2880, 1445, 1215, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 3 H), 1.21–2.51 (m, 8 H), 2.60 (s, 3 H), 3.19 (d, J = 8.72 Hz, 1 H), 5.67 (m, 1 H), 6.97–7.21 (m, 4 H); MS m/e (%) 290 (13), 261 (56), 205 (26), 167 (34), 153 (21), 95 (100), 77 (25); HRMS calcd for $C_{16}H_{20}OS_4$ 368.0397, found 368.0399.

To a solution of the xanthate (0.085 g, 0.23 mmol) in toluene (3 mL) at room temperature was added tri-*n*-butyltin hydride (0.876 g, 0.3 mmol). The mixture was refluxed for 24 h, at which time the reaction was shown to be almost complete by TLC examination. The toluene was removed under reduced pressure to give 0.034 g (56%) of the deoxygenated product **30** after flash column chromatography (hexane): IR (CCl_4) ν 2950, 2925, 2863, 1458, 1442 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 3 H), 1.21–2.51 (m, 10 H), 2.31 (d, J = 4.21 Hz, 1 H), 6.99–7.20 (m, 4 H); MS m/e (%) 262 (73), 247 (44), 219 (40), 193 (34), 179 (28), 166 (67), 153 (100), 121 (40), 91 (26), 79 (25), 77 (49); HRMS calcd for $C_{15}H_{18}S_2$ 262.0849, found 262.0854.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for **7a,f**, **13**, **15**, **17**, **19**, and **25** (14 pages). Ordering information is given on any current masthead page.

Total Syntheses of (+)-Thyrsiferol, (+)-Thyrsiferyl 23-Acetate, and (+)-Venustatriol

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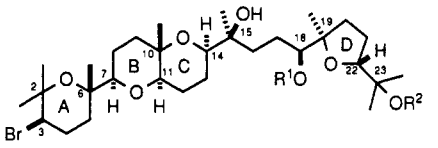
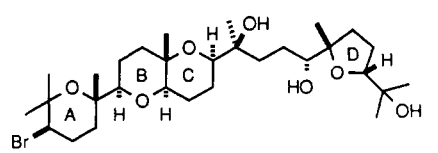
The first total syntheses of (+)-thyrsiferol (**1**), (+)-thyrsiferyl 23-acetate (**3**), and (+)-venustatriol (**5**) have been accomplished in a stereoselective manner. An effective synthetic scheme to construct the BC ring system, which adopts a chair/twist-boat conformation, was first developed by means of a model study. This method involves stereoselective formation of the strained C ring by intramolecular attack of the C_7-hydroxyl group at the C_3-position of the 2,3-epoxy alcohol, employing titanium tetraisopropoxide as an acidic activator. Based on the information accumulated in the model study and retrosynthetic considerations, the total syntheses of **1**, **3**, and **5** were performed in the sequence of (1) construction of the BC ring system equipped with a C_1–C_6 carbon unit, (2) elongation of the C_{17}–C_{24} carbon chain, (3) formation of a D ring through the stereoselective epoxidation of the 4-en-1-ol system and successive cyclization, and (4) construction of the A ring by bromonium ion induced cyclization of the 4-en-1-ol system.

Introduction

Thyrsiferol (**1**) and its 18-acetate (**2**), squalene-derived metabolites from *Laurencia thyrsiferia*, were isolated as a new type of triterpene–polyether by Munro's group in 1978.[1] Their relative stereochemistries were determined by X-ray diffraction. In 1985, Kurosawa and his coworkers isolated related polyethers such as thyrsiferyl 23-acetate (**3**),[2] 18,23-diacetate (**4**), $\Delta^{15,16}$- and $\Delta^{15,28}$-anhydrothyrsiferyl diacetates, and magireols from *Laurencia obtusa*, and found that these bromine-containing polyethers show strong citotoxicity against P388 murine leukemia in vitro.[3] Particularly, **3** exhibited ED_{50} values of 0.3 ng/mL in a P388 in vitro assay. Venustatriol (**5**), a diastereomeric isomer of **1**, was found as a metabolite of a congenial *Laurencia venusta* by Higa's group in 1986.[4] This tetracyclic polyether **5** exhibits significant antiviral activity against the vesicular stomatitis virus (VSV) and herpes simplex virus type 1 (HSV-1). X-ray structural analysis of **5** disclosed the absolute configuration depicted in formula **5**. These results permit the correct assignments of the absolute configurations of thyrsiferol (**1**) and its congeners.



1 $R^1 = R^2 = H$ (thyrsiferol)
2 R^1 = Ac, R^2 = H
3 R^1 = H, R^2 = Ac
4 R^1 = Ac, R^2 = Ac



5 (venustatriol)

All members of this family are characterized by a (bromotetrahydropyranyl)-2,7-dioxabicyclo[4.4.0]decane

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(1) Blunt, J. W.; Hartshorn, M. P.; McLennan, T. J.; Munro, M. H. G.; Robinson, W. T.; Yorke, S. C. *Tetrahedron Lett.* **1978**, 69.
(2) Suzuki, T.; Suzuki, M.; Furusaki, A.; Matsumoto, T.; Kato, A.; Imanaka, Y.; Kurosawa, E. *Tetrahedron Lett.* **1985**, *26*, 1329.
(3) Suzuki, T.; Takeda, S.; Suzuki, M.; Kurosawa, E.; Kato, A.; Imanaka, Y. *Chem. Lett.* **1987**, 361.

0022-3263/90/1955-5088$02.50/0

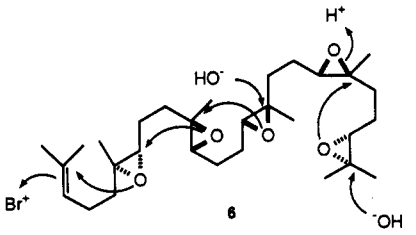


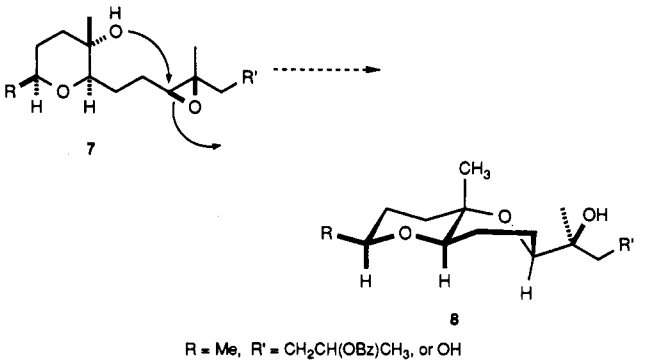
Figure 1. Biogenesis of thyrsiferol.

skeleton (ABC ring system). The X-ray studies conducted on **2**[1] and **5**[4] clearly indicate that the C ring in these molecules is forced to adopt a twist-boat conformation in order to avoid an unfavorable 1,3-diaxial interaction between the angular methyl group (C_{27}) and the side chain (C_{15}). These metabolites are the first examples of squalene-derived polyethers. Their biogenesis presumably involves an attack of bromonium ion on the terminal C_2–C_3 double bonds of squalene tetraepoxide **6**, which initiates sequential cyclizations to occur, thus forming the framework of these polyethers. This concept for the biogenesis of polyether antibiotics derived from polyketides was advocated by Cane, Celmer, and Westley in 1982.[5]

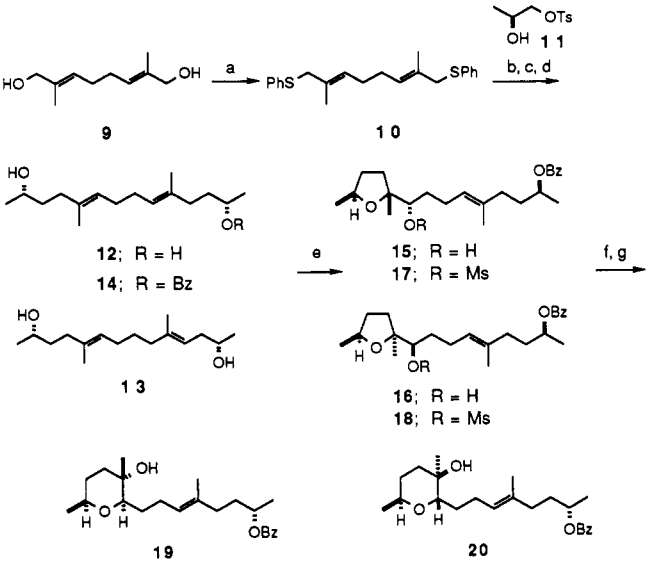
The remarkable biogenetic features, bioactivities, and unique structures present in these compounds prompted us to study the total syntheses of thyrsiferols and venustatriol in their optically active forms. We have previously reported the total syntheses of thyrsiferol (**1**), venustatriol (**5**), and thyrsiferyl 23-acetate (**3**) in communication form.[6] Corey et al. have also reported the total synthesis of venustatriol (**5**).[7,8]

In the total syntheses and synthetic studies of the natural polycyclic ethers, such as monensin,[9] lasalocid A,[10] pederin,[11] brevetoxins,[12] uvaricin,[13] and teurilene,[14] synthetic schemes involving the stereoselective construction of ether rings through intramolecular attack of hydroxyl groups on epoxides were frequently employed.[15] Thus, for the synthesis of the target molecules, it was planned that each ether ring would be elaborated according to this strategy. Furthermore, this synthetic method was of interest to us from the viewpoint of the biogenesis of these polyethers.

Scheme I

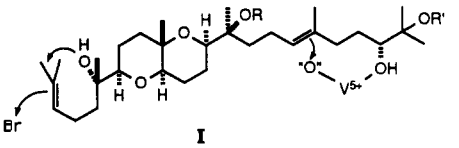


Scheme II[a]



[a] Conditions (a) BuLi, THF, 0 °C, 5 min, then TsCl then NaSPh, 0 °C → room temperature 3 h, 80%; (b) **10**, BuLi, TMEDA, THF, −20 °C, 5 h, 71%; (c) Na, BuOH, THF, reflux, 3 h, 91% as a mixture of **12** and **13**; (d) BzCl, Et_3N, CH_2Cl_2, room temperature, 20 h, 38%; (e) $VO(acac)_2$, TBHP, NaOAc, benzene, reflux, 16 h, then AcOH, room temperature, 1 h, 86% as a mixture of diastereomeric isomers; (f) MsCl, Et_3N, CH_2Cl_2, −10 °C, 1 h; (g) Ag_2CO_3, H_2O, acetone, 50 °C, 16 h, 73% (**19**), 12% (**20**), from **12**.

From a retrosynthetic perspective, it appeared that the bromotetrahydropyran (A ring) should be constructed at the last stage of the total synthesis, since the A ring seemd to be unstable under radical, strong basic, and/or soft acidic conditions. For this reason, a bromonium ion induced cyclization of the left hand 4-en-1-ol system in I



according to Kato's method[16] was considered most promising. Furthermore, we felt that the tetrahydrofuran (D ring) could probably be constructed by employing stereoselective epoxidation of the right hand 4-en-1-ol system in I followed by successive cyclization of the resulting epoxide, following Kishi's report.[10] Therefore, for the total synthesis of these molecules, it was imperative to find an effective synthetic scheme to construct the characteristic

(4) Sakemi, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4287.
(5) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.
(6) (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.
(7) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171.
(8) Synthesis of the ABC ring system of these polyethers was also reported; (a) Broka, C. A.; Hu, L.; Lee, W. J.; Shen, T. *Tetrahedron Lett.* **1987**, *28*, 4993. (b) Broka, C. A.; Lin, Y.-T. *J. Org. Chem.* **1988**, *53*, 5876.
(9) (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.
(10) (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**, *31*, 2741.
(11) Tsuzuki, K.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 4745.
(12) (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330, 5335. (b) Nicolau, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6666, 6676, 6682.
(13) Hoye, T. R.; Suhadonic, J. C. *Tetrahedron Lett.* **1986**, *26*, 2885.
(14) Preliminary synthetic studies: Hoye, T. R.; Jenkins, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 2106. We have accomplished the first total synthesis of teurilene: (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.
(15) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
(16) Kato, T.; Ichinose, I.; Hosogai, T.; Kitahara, Y. *Chem. Lett.* **1976**, 1187.

chair/twist-boat BC rings. Thus, a model synthesis of the BC rings was first conducted. After some experimentation, we were able to develop an efficient synthetic route to form the BC rings. This method involves stereoselective formation of the strained C ring by an intramolecular attack of the C_7-hydroxyl group at the C_3-position of the 2,3-epoxy 1,7-diol system, employing titanium tetraisopropoxide[17] as an acidic activator. Based on the information accumulated from the model study as well as the foregoing retrosynthetic considerations, it appeared reasonable to carry out the total syntheses in the sequence of (1) construction of the BC ring system equipped with a C_1–C_6 carbon unit, (2) elongation of the C_{17}–C_{24} carbon chain, (3) formation of the D ring, and (4) construction of the A ring. As mentioned below, our total syntheses of (+)-thyrsiferol (1), (+)-thyrsiferyl 23-acetate (3), and (+)-venustatriol (5) have been accomplished according to this synthetic plan. We would now like to describe, in full detail, our model study and our total syntheses.

Model Synthesis of B,C Rings. As a model study, a synthesis of the BC ring system (8) through the intramolecular cyclization of epoxy alcohol 7 was examined (Scheme I). First, a tetrahydropyran ring, corresponding to the B ring of thyrsiferols, was formed stereoselectively according to the synthetic route reported by Kishi and Nakata in the total synthesis of lasalocid A.[10] Diisoprene alcohol 9[18] was converted into bisphenylthio olefin **10** in 80% yield by sequential treatment with butyllithium, *p*-toluenesulfonyl chloride, and sodium thiophenoxide[19] (Scheme II). Treatment of **10** with 4 equiv of tosylate **11**[20] and 6 equiv of butyllithium in the presence of *N,N,N′,N′*-tetramethylethylenediamine at −10 °C resulted in the coupling of 2 molar equiv of (*S*)-propylene oxide, formed from **11** in situ, with the dianion generated from **10**. Reductive desulfurization of the adduct obtained under Bouveault–Blanc's conditions, employing sodium metal and 1-propanol in tetrahydrofuran at reflux temperature,[21] gave a mixture of diol **12** and rearranged isomer **13** in 64% yield (**12**:**13** = 7:4) from **10**. These products were separated by silver(I) nitrate coated silica gel column chromatography. One of the two hydroxyl groups of the C_2 symmetric diol was protected in the form of a benzoate ester group to afford an optically pure monoester **14** (38%) along with a dibenzoate (12%) and recovered starting diol (45%). Then, vanadyl acetylacetonate catalyzed epoxidation of the bishomoallylic alcohol system of **14** with *tert*-butyl hydroperoxide in the presence of sodium acetate and successive cyclization by acetic acid[10] yielded a mixture of tetrahydrofuran **15** and its diastereomer **16** (86%), which could not be separated by column chromatography. The ratio of the mixture **15**:**16** was ca. 6:1 by ^{1}H NMR spectral analysis. Following mesylation of the hydroxyl groups of the mixture **15** and **16**, exposure to silver(I) carbonate in aqueous acetone[10] effected the stereospecific ring expansion to give a mixture of tetrahydropyran **19** and **20**. Separation of the mixture by silica gel column chromatography gave diastereomerically pure **19** and **20** in 73 and 12% yields, respectively, from **14**.

In the ^{1}H NMR spectra of **19**, the spin–spin couplig constants, $J_{7,8\alpha}$ (thyrsiferol numbering) and $J_{7,8\beta}$ are 1.8 and 10.8 Hz, respectively (Figure 2). On the other hand, in the case of **20**, the corresponding *J* values are 5.1 and 7.5 Hz. These observations indicate that the C_7 protons of **19** and **20** reside in axial and equatorial orientations, respectively. Considering these results and the reaction pathway of this ring expansion on the assumption that (1) the C_{11} side chains are oriented equatorially and (2) both tetrahydropyrans adopt chair conformations, the stereochemistries of the major and minor tetrahydropyrans were tentatively assigned as **19** and **20**, respectively.

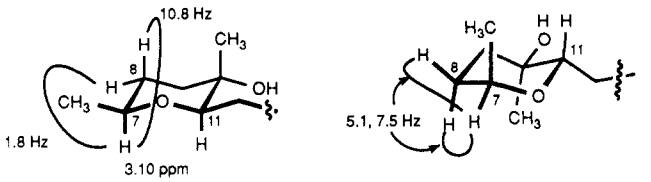
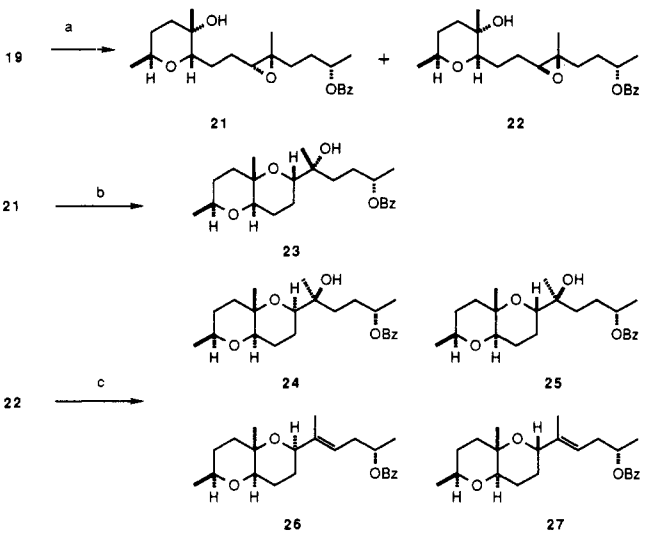


Figure 2. Stereostructure of tetrahydropyran derivatives **19** (left) and **20** (right).

Scheme III[a]



[a] Conditions: (a) MCPBA, CH_2Cl_2, 0 °C, 1 h, 80% as a mixture of **21** and **22**, then separation with MPLC; (b) PPTS, CH_2Cl_2, room temperature, 1 h, 90%; (c) PPTS, benzene, reflux, 20 min.

It was difficult to determine the stereostructure of the synthetic BC ring model systems by ^{1}H NMR spectroscopy because the overlapping signals the thyrsiferols could not be assigned fully. Therefore, diastereomers at the C_{14}- and C_{15}-positions were prepared in order to determine their ^{1}H NMR spectral properties. Epoxidation of the remaining double bond of **19** was carried out nonstereoselectively by employing *m*-chloroperbenzoic acid to give **21** and **22** in 80% yield as a 1:1 diastereomeric mixture (Scheme III), which was separated carefully by medium-pressure column chromatography (silica gel). The stereochemistries at the C_{14}–C_{15} positions of **21** and **22** are assigned on the basis of the stereostructures of the epoxide opened products **23**, **24**, **25**, **26**, and **27** (vide infra). Intramolecular tetrahydropyran formation from α-epoxide **21** was accomplished by employing camphorsulfonic acid or pyridinium *p*-toluenesulfonate[22] to afford bicyclic ether **23** in 90% yield. In contrast, β-epoxide **22** gave the desired bicyclic ether **24** in only 20% yield (isolated yield) along with C_{14} epimer **25** (20%), dehydrated products **26** (10%), and **27** (5.8%) using pyridinium *p*-toluenesulfonate in benzene. Under

(17) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.
(18) Bhalerao, U. T.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 5311.
(19) van Tamelen, E. E.; Lougheat, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 869.
(20) Tosylate 11 ($[\alpha]^{28}_D$ +9.78° (*c* 1.40, $CHCl_3$)) was prepared from (*S*)-(−)-ethyl lactate in four steps. Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tennen Yuki Kagoubutsu Toronkai Yoshishu* **1986**, *28*, 325.
(21) Kodama, M.; Takahashi, T.; Kojima, T.; Ito, S. *Tetrahedron Lett.* **1982**, *23*, 3397.
(22) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

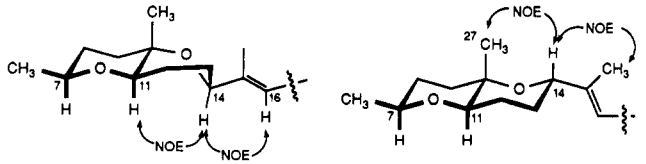


Figure 3. Stereochemistry of **26** (left) and **27** (right).

Table I. ^{1}H NMR Spectral Data of 23–27, 34, and 36 (in $CDCl_3$)

compd	chemical shifts (δ, ppm) C_{11}-H	chemical shifts (δ, ppm) C_{14}-H	coupling constants (Hz) C_{11}-H	coupling constants (Hz) C_{14}-H	conformations
23	3.06	3.50	4.3, 11.0	1.8, 11.6	chair–chair
24	3.62	3.72	6.0, 11.0	3.1, 12.2	chair–boat
25	3.07	3.50	3.8, 11.0	2.2, 11.0	chair–chair
26	3.55	4.23	6.0, 11.0	4.1, 9.5	chair–boat
27	3.11	4.06	4.0, 11.0	2.5, 10.6	chair–chair
34	3.65	3.94	7.3, 11.5	3.9, 12.2	chair–boat
36	3.11	3.74	4.3, 11.6	1.8, 11.6	chair–chair

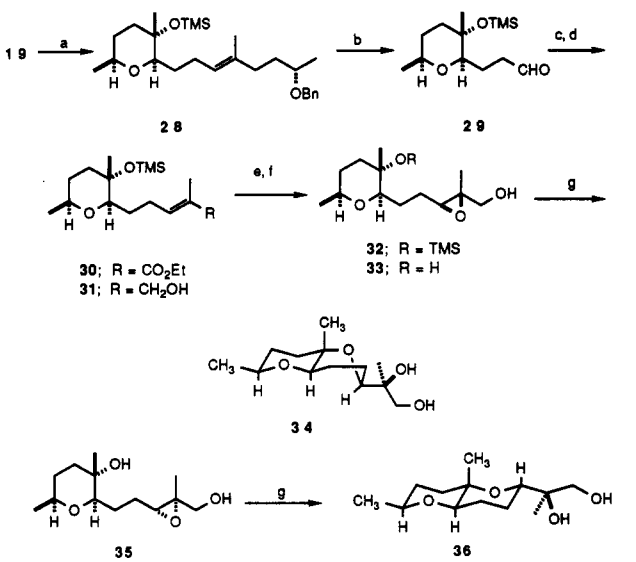
other conditions, no bicyclic ether was obtained from **22**. Therefore, construction of the strained BC ring system by acidic treatment of **22** was found to be inefficient.

Stereochemistries of the dehydrated compounds **26** and **27** were determined by ^{1}H NMR spectroscopy employing NOE techniques (Figure 3). An NOE (C_{11}-H ↔ C_{14}-H) was observed in the ^{1}H NMR spectrum of **26**, revealing that the newly formed C ring adopts a boat conformation and the stereochemistry of C_{14}-H must have the α-orientation. On the other hand, an NOE was observed between the signals for the angular methyl group (C_{27}) upon irradiation of the peak for the C_{14}-H in the ^{1}H NMR spectra of **27**. Thus, the C ring of isomer **27** assumes an ordinary chair conformation and the C_{14}-H is oriented β. Unfortunately, NOE's could not be observed in the ^{1}H NMR spectra of **23**, **24**, and **25**, owing to spectral crowding. However, a detailed comparison of the splitting patterns of **23–25** with those of **26** and **27** made it clear that the BC rings of **23** and **25** and of **24** adopt the same chair–chair and chair–boat conformations as **27** and **26**, respectively, as shown in Table I.

According to Caron and Sharpless, intermolecular attack of nucleophiles at the C_3 position of 2,3-epoxy alcohols is accelerated remarkably by titanium tetraisopropoxide as an acidic activator.[17] Therefore, it was anticipated that this reaction would be suitable for the intramolecular cyclization[23] of this strained C ring.

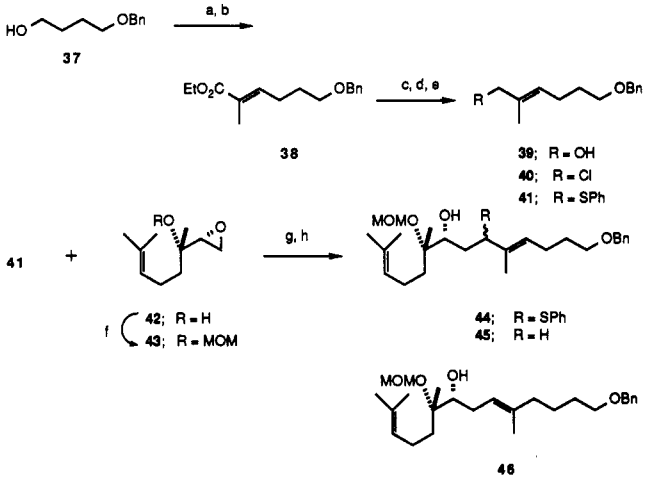
For this purpose, **19** was converted into the epoxy diol **33** (Scheme IV). Following protection of the hydroxyl group of **19** in the form of a trimethylsilyl ether, ozonolysis followed by reductive workup gave aldehyde **29**. Treatment of **29** with (α-carbethoxyethylidene)triphenylphosphorane[24] produced α,β-unsaturated ester **30** stereoselectively, which, on reduction with diisobutylaluminum hydride, afforded allylic alcohol **31** in 82% yield (three steps). Introduction of a β-epoxide was carried out by Sharpless' enantioselective epoxidation using L-(+)-diisopropyl tartrate (L-(+)-DIPT).[25] Removal of the trimethylsilyl group of β-epoxide **32** with tetrabutylammonium fluoride gave **33** in 85% yield from **31**. As expected, exposure of **33** to 1 equiv of titanium tetraisopropoxide in benzene at reflux temperature smoothly effected the formation of the tetrahydropyran ring to produce the desired BC ring system **34** in 58% yield, along with recovered epoxide **33** (16%). In contrast, treatment of α-epoxide **35**, which was prepared by employing D-(−)-DIPT instead of L-(+)-DIPT in the enantioselective epoxidation,[25] under the same conditions gave rise to the diastereomeric BC ring system **36** in 96% yield. The stereochemistries of **34** and **36** were determined by comparing their ^{1}H NMR spectra with those of **24** and **25** (Table I).

Scheme IV[a]



[a] Conditions: (a) TMSCl, Et_3N, DMAP, CH_2Cl_2, room temperature, 4 h, 85%; (b) O_3, CH_2Cl_2, −78 °C, 15 min, then DMS, 100%; (c) $CH_3C(PPh_3)CO_2Et$, CH_2Cl_2, reflux, 8 h, 96%; (d) DIBAH, hexane, −78 °C, 10 min, 77%; (e) L-(+)-DIPT, Ti(Oi-Pr)$_4$, TBHP, MS4A, CH_2Cl_2, −20 °C, 3 h; (f) TBAF, THF, room temperature, 4 h, 85% from **31**; (g) Ti(Oi-Pr)$_4$, benzene, reflux, 2 h.

Scheme V[a]



[a] Conditions: (a) PCC, CH_2Cl_2, room temperature 30 min; (b) $Na^+CH_3C^-(P(OEt)_2)CO_2Et$, THF, 0 °C, 2 h, 73% from **37**; (c) DIBAH, benzene, 0 °C, 30 min, 72%; (d) CCl_4, PPh_3, benzene, reflux, 12 h, 80%; (e) NaSPh, DMF, 0 °C, 30 min, 90%; (f) MOMCl, i-Pr_2NEt, CH_2Cl_2, 0 °C → room temperature, 36 h, 99%; (g) BuLi, DABCO, THF, −60 °C, 3 h; (h) Na, 2-PrOH, THF, reflux, 2 h, 77% in two steps.

Synthesis of BC Ring System Equipped with a C_1–C_6 Carbon Unit. A synthesis of the BC ring system,

(23) Stereoselective formation of tetrahdrofuran rings based on intramolecular attack of a hydroxyl group on a 2,3-epoxy alcohol induced by Ti^{4+} has also been reported; Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochi, N.; Takano, S. *J. Am. Chem. Soc.* **1988**, *110*, 5201.

(24) Isler, O.; Gutmann, H.; Montavon, M.; Rüegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta* **1957**, *139*, 1242.

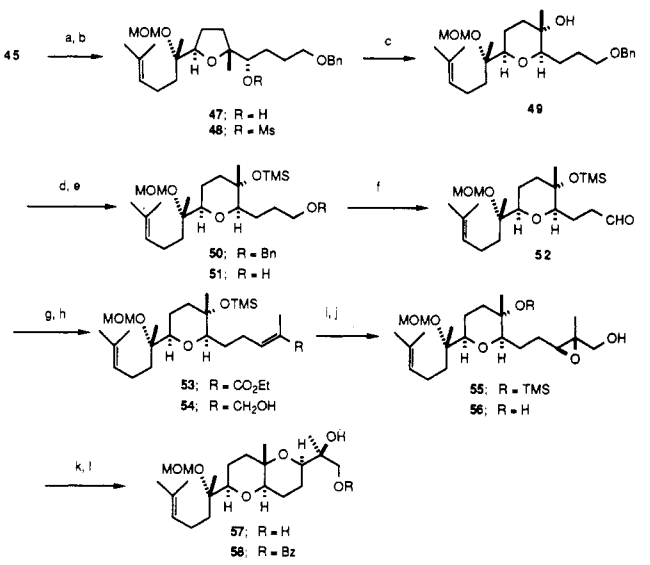
(25) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464.

equipped with a precursor of the A-ring moiety (5-methyl-1-(methoxymethoxy)hexa-4-enyl group), was attempted, based on the information accumulated from the model study and retrosynthetic considerations. Oxidation of 4-(benzyloxy)butanol **37**, prepared by partial etherification of 1,4-butanediol, with pyridinium chlorochromate and Horner–Emmons reaction with triethyl α-phosphinopropionate[26] gave (*E*)-α,β-unsaturated ester **38** in 52% yield (two steps). Following reduction of **38** with diisobutylaluminum hydride, the resulting allylic alcohol **39** was chlorinated to give chloride **40**[27] which, on substitution with sodium thiophenoxide, produced allylic sulfide **41** in 52% yield (three steps). On the other hand, (2*R*,3*S*)-(+)-linalool oxide **42** was prepared from geraniol in an optically active form according to the synthetic route reported by Sharpless et al. through several steps.[25,28] The hydroxyl group of **42** was protected as a methoxymethyl (MOM) ether to afford **43** in 99% yield. The coupling reaction of **43** with the lithium anion generated from **41** in the presence of diazabicyclo[2.2.0]octane at −60 °C gave adduct **44** as a 1,4-diastereomeric mixture, according to Itô and Kodama's method.[21] The phenylthio group was removed reductively under Bouveault-Blanc's conditions employing sodium metal and 2-propanol in tetrahydrofuran at reflux temperature to afford a mixture of the desired olefin **45** and isomeric olefin **46** in 77% yield from **41**. These products could not be separated by column chromatography. The ratio **45**:**46** was estimated at ca. 7:1 by ^{13}C NMR spectroscopy.

Vanadyl acetylacetonate catalyzed epoxidation[10] of bishomoallylic alcohol **45** using *tert*-butyl hydroperoxide without buffer, accompanied by simultaneous cyclization, yielded tetrahydrofuran derivative **47** along with its diastereomer in a 4:1 ratio (by ^1H NMR spectral analysis) in 72% yield. Mesylation of the mixture, followed by ring expansion with silver(I) carbonate in aqueous acetone, afforded the desired tetrahydropyran derivative **49** as the sole product in 42% yield. Another diastereomer, derived from the isomeric tetrahydrofuran, could not be detected by either ^1H NMR spectroscopy or TLC. The minor diastereomeric tetrahydrofuranyl mesylate was presumed decomposed during the ring expansion reaction. Comparing the ^1H NMR spectra data of **49** with those of **19** and **20**, it was clear from the coupling constants ($J_{7,8\alpha}$ = 2 Hz and $J_{7,8\beta}$ = 10 Hz) that the tetrahydropyran ring in **49** possessed the desired stereochemistry. Tetrahydropyran **49** was converted into allylic alcohol **54** by the sequence of (1) protection of the hydroxyl group of **49** in the form of trimethylsilyl ether (83%), (2) cleavage of the benzyl ether of **50** under Birch's conditions (85%), (3) oxidation of alcohol **51** with pyridinium dichromate in the presence of sodium acetate, (4) elongation of the carbon chain by Wittig reaction of the resulting aldehyde **52** with (α-carbethoxyethylidene)triphenylphosphorane[24] (98% yield through two steps), and (5) reduction of the ester part of **53** with diisobutylaluminum hydride (96%) (Scheme VI). Asymmetric epoxidation[25] of **54** employing L-(+)-DIPT introduced β-epoxide **55** stereoselectively. The trimethylsilyl group of **55** was removed by tetrabutylammonium fluoride to afford epoxy diol **56** in 98% yield from **54**.

As expected from the model study, the C ring forming reaction by treatment of **56** with 0.3 equiv of titanium tetraisopropoxide in toluene at 50 °C occurred smoothly to give the desired bicyclic ether **57** in 65% yield.[29] Stereochemistry of the bicyclic ether was established on the basis of the difference NOE experiment of benzoate **58**, which was derived from **57** in 99% yield. On irradiation of the signal due to the C_{11}-H of **58**, NOE's were observed at the peaks due to the C_7-H and the C_{14}-H, and it was revealed that the C_{14} side chain has a β-equatorial orientation and that the newly formed C ring assumes a boat conformation. Therefore, the stereochemistry of the bicyclic ether and its benzoate were determined to be as depicted in **57** and **58**, respectively.

Scheme VI[a]



[a] Conditions: (a) $VO(acac)_2$, TBHP, CH_2Cl_2, room temperature, 3.5 h, 72%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 12 h; (c) Ag_2CO_3, H_2O, acetone, 50 °C, 12 h, 42% in two steps; (d) TMSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 30 min, 83%; (e) Li, NH_3, THF, −78 °C, 2 h, 85%; (f) PDC, NaOAc, CH_2Cl_2, room temperature, 30 min; (g) $CH_3C(PPh_3)CO_2Et$, CH_2Cl_2, reflux, 3 h, 98%; (h) DIBAH, hexane, −78 °C, 5 min, 96%; (i) L-(+)-DIPT, $Ti(Oi\text{-}Pr)_4$, TBHP, MS4A, CH_2Cl_2, −20 °C, 1 h; (j) TBAF, THF, room temperature, 1 h, 98% in two steps; (k) $Ti(Oi\text{-}Pr)_4$ (0.25 equiv), toluene, 50 °C, 3 h, 65%; (l) BzCl, Et_3N, CH_2Cl_2, room temperature, 12 h, 99%.

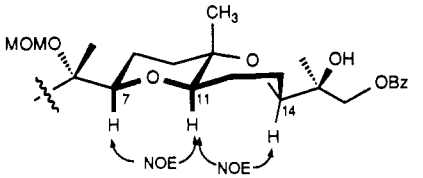
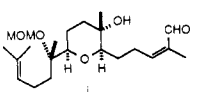


Figure 4. Stereochemistry of **58**.

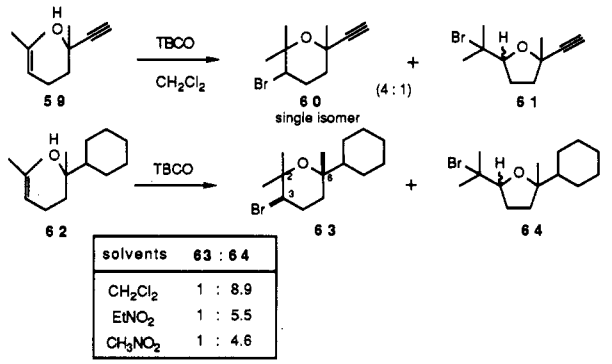
Construction of the ABC Ring System. Confirmation of the Stereochemistry. The task before us was the development of a synthetic method to assemble the A ring with the above-synthesized BC ring moiety **57**. The ABC fragment thus synthesized could then be compared with the compound derived from natural $\Delta^{15,16}$-anhydro-

(26) Gallagher, G., Jr.; Webb, R. L. *Synthesis* **1974**, 122.
(27) Calzada, J. G.; Hooz, J. *Org. Synth.* **1974**, *54*, 63.
(28) (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.

(29) In contrast to the model study, treatment of **56** with 1 equiv of titanium isopropoxide or at higher temperature in benzene reduced the yield of **48** considerably, and α,β-unsaturated aldehyde **i** was obtained along with **48** in a ratio of 1:1, approximately.



Scheme VII



solvents	63 : 64
CH_2Cl_2	1 : 8.9
$EtNO_2$	1 : 5.5
CH_3NO_2	1 : 4.6

thyrsiferyl diacetate through degradation of the side chain and would prove the correct stereochemistry of the synthetic compound.

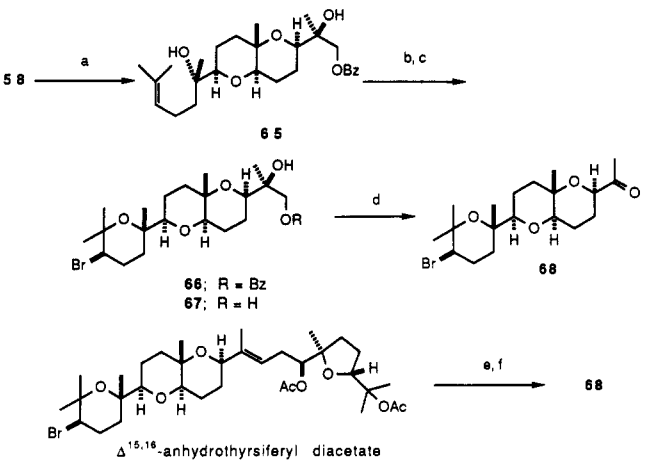
As Kato reported, bromonium ion induced cyclization of dehydrolinalool **59** with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) in dichloromethane afforded bromotetrahydropyran derivative **60** both regio- and stereoselectively.[16] It seemed that this synthetic method would be suitable for the construction of the A ring from the 4-en-1-ol system of **58**. Initially, a preliminary experiment employing model compound **62**, bearing a cyclohexyl group in place of the BC ring system, was performed. Treatment of **62** with TBCO in dichloromethane gave the desired tetrahydropyran **63** as a minor product along with tetrahydrofuran **64** (**63**:**64** = 1:8.9 by ^1H NMR spectral analysis). In an investigation concerning solvent effects on this reaction, nitromethane gave the best result among the solvents examined, yielding **63** and **64** in a ratio of 1:4.6. In all cases, tetrahydropyran derivative **63** was obtained as a single diastereomeric isomer, while tetrahydrofuran derivative **64** was a mixture of epimers (Scheme VII).

The stereochemistry of tetrahydropyran **63** was assigned as follows. In the ^1H NMR spectra of **63**, a splitting pattern of the signal due to C_3-H (dd, J = 4.3 and 12.3 Hz) indicated that the bromine substituent adopts an equatorial orientation. Since the cyclohexyl group, a larger substituent than the methyl group, probably occupies an equatorial position, the stereochemistry of the bromine and the cyclohexyl groups of **63** could be assumed to be trans. In the case of **60**, a smaller acetylene group was presumed to be in an axial orientation.

It may be rationalized that the cause of the unfavorable regioselectivity observed in the case of **62** is thermodynamic lability, giving rise to the 1,3-diaxial interactions between the C_2-Me_{ax} and the C_6-Me_{ax} groups of the tetrahydropyran ring. The selectivity difference between **59** and **62** may be due to the bulkiness of the C_{6eq}-substituents. The solvent effects on this reaction are probably attributable to the difference in stabilities between the secondary and the tertiary carbocations.[30]

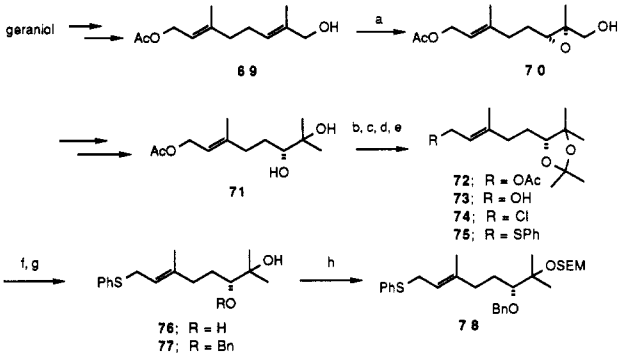
The MOM ether of BC ring system **58** was cleaved by acidic methanolysis, and the bishomoallylic alcohol **65** thus obtained was treated with TBCO in nitromethane to give tricyclic ether **66** in 36% yield along with a diastereomeric mixture of tetrahydrofuran derivatives (yield not determined). The ratio of the tetrahydrofuran to the tetrahydropyran derivative was not determined. For confirmation of the stereochemistry of the resulting tricyclic compound, **66** was converted into methyl ketone **68**[31] in 77% yield (two steps) by successive removal of the benzoyl ester by basic methanolysis and oxidative cleavage of the diol moiety with sodium periodate (Scheme VIII). On the other hand, methyl ketone **68** was also obtained in 66% yield from naturally occurring $\Delta^{15,16}$-anhydrothyrsiferyl diacetate[32] by treatment with osmium tetroxide followed by cleavage with sodium periodate. Both samples of **68**, derived from natural and synthetic sources, were completely identical by direct comparison of their IR, NMR, CD, and MS spectra and also in their chromatographic behavior. Thus, the stereochemistries of C_3, C_6, C_7, C_{11}, and C_{14} had been correctly introduced by our strategy.

Scheme VIII[a]



[a] Conditions: (a) HCl, MeOH, room temperature, 2 h, 88%; (b) TBCO, CH_3NO_2, room temperature, 1 h, 36%; (c) K_2CO_3, MeOH, room temperature, 3 h, 100%; (d) $NaIO_4$, MeOH, room temperature, 30 min, 77%; (e) OsO_4, pyridine, Et_2O, room temperature, 3 h; (f) $NaIO_4$, MeOH, room temperature, 2 h, 66% in two steps.

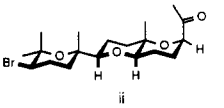
Scheme IX[a]



[a] Conditions: (a) D-(−)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, −20 °C, 4 h, 79%; (b) *p*-TsOH, acetone, room temperature, 2 h, 96%; (c) K_2CO_3, MeOH, room temperature, 1 h, 93%; (d) CCl_4, PPh_3, benzene, reflux, 24 h; (e) NaSPh, DMF, 0 °C, 30 min, 79% in two steps; (f) HCl, H_2O, MeOH, room temperature, 12 h, 91%; (g) NaH, BnCl, DMF, room temperature, 12 h, 85%; (h) SEMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C → room temperature, 12 h, 98%.

(30) The unfavorable selectivity of this reaction was also mentioned by Corey et al. and Broka et al. Broka et al. proposed a similar reason for this poor selectivity.

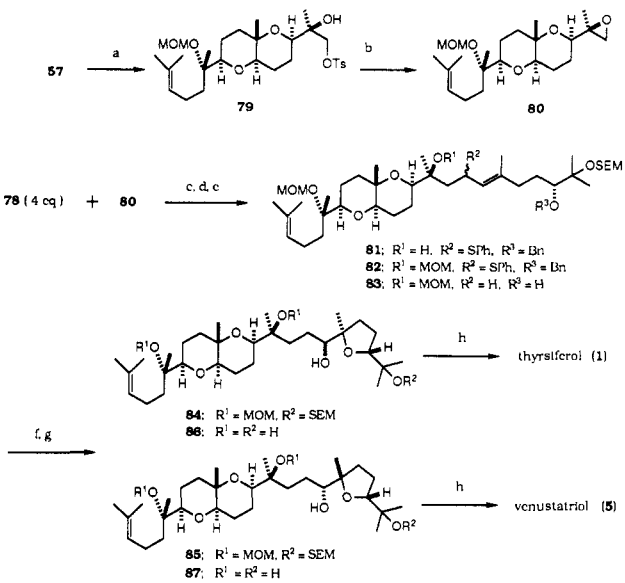
(31) Interestingly, it was found that the BC ring system of **68** adopts a chair–chair conformation (ii). Detailed conformational analysis will be described shortly.



ii

(32) The sample was kindly donated by Prof. Etsuro Kurosawa (Hokkaido Univ.).

Scheme X[a]



[a] Conditions: (a) TsCl, pyridine, CH_2Cl_2, room temperature, 12 h, 100%; (b) K_2CO_3, MeOH, room temperature, 3.5 h, 92%; (c) BuLi, TMEDA, THF, −20 °C, 10 min, 99%; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C → room temperature, 12 h, 95%; (e) Na, 2-PrOH, THF, −78 °C, 2 h, 76%; (f) VO(acac)$_2$, TBHP, CH_2Cl_2, room temperature, 2 h, 58% as mixture of **84** and **85**; (g) HCl, MeOH, room temperature, 3 h, 90%; (h) TBCO, CH_3NO_2, room temperature, 1 h, 22% (**1**), 22% (**5**).

Total Synthesis of Thyrsiferol (1), Thyrsiferyl 23-Acetate (3), and Venustatriol (5). For the total synthesis of the target molecules, construction of the D ring was next attempted. Following much experimentation, an efficient scheme to construct the D ring was developed after considering the fact that the coupling reaction of epoxides with α-sulfenyl carbanions followed by desulfurizations gives (*E*)-olefins regio- and stereoselectively.

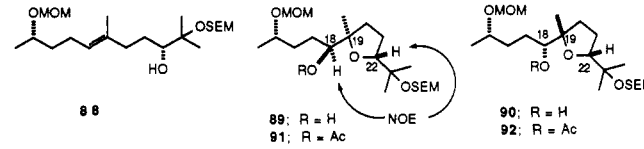
First, allylic sulfide **78**, a C_{10}-unit required to establish the carbon framework of the D ring, was synthesized in optically active form. Optically active (+)-glycol **71** was prepared from geraniol according to the known synthetic scheme,[33] which involves Sharpless' enantioselective epoxidation[25] of allylic alcohol **69** as a key step (Scheme IX). Following protection of the diol part of **71** as an acetonide, alcohol **73** was obtained in 89% yield from **71** by saponification of acetate **72**. Chlorination of the hydroxyl group of **73** followed by substitution with sodium thiophenoxide produced sulfide **75** in 79% yield (two steps). After removal of the acetonide protective group of **75** under acidic conditions, the secondary and tertiary hydroxyl groups of the resulting diol **76** were protected successively in the forms of benzyl and (2-(trimethylsilyl)ethoxy)methyl (SEM) ether,[34] respectively, to give **78** in 75% from **75**.

To construct the A ring in the final step of the total synthesis, the diol moiety of the bicyclic ether **57** was converted into epoxide **80**, a key intermediate for the coupling reaction, in 92% yield by selective tosylation of the primary hydroxyl group followed by basic methanolysis (Scheme X). The coupling reaction of epoxide **80** with the anion derived from the allyl sulfide **78** was carried out at −20 °C, employing 4 equiv of the anion to cleanly afford adduct **81** in 99% yield. After protection of the hydroxyl group of adduct **81** as a MOM ether, the benzyl and phenylthio groups were removed simultaneously under Birch's conditions in the presence of 2-propanol to give bishomoallylic alcohol **83** in 72% yield (two steps). Vanadium(V)-catalyzed oxidation followed by spontaneous cyclization of the 4-en-1-ol system[10] of **83** afforded a diastereomeric mixture of tricyclic ethers **84** and **85**, which were separated by HPLC, in 61 and 14% yield, respectively.

Table II. ^{1}H NMR Spectral Data of 84, 85, 89, and 90 (in $CDCl_3$)

	chemical shifts (δ, ppm)		coupling constants (Hz)		
compd	C_{18}-H	C_{22}-H	C_{18}-H	C_{22}-H	stereochem
84	3.46	3.90	1.5, 9.0	5.4, 10.3	trans
85	3.50	3.80	1.5, 9.0	7.2, 7.2	cis
89	3.50	3.90	1.5, 9.0	5.4, 10.2	trans
90	3.54	3.80	1.5, 9.0	7.3, 7.3	cis

The stereochemistries of **84** and **85** were deduced by comparison of their ^{1}H NMR spectral data with those of model compounds **89** and **90** which were prepared from **88**.[35] In the ^{1}H NMR spectrum of acetate **91** derived from



89, an NOE at the signal for the C_{22}-H was observed upon irradiation of the C_{18}-H peak. On the other hand, no NOE between the C_{18}-H and the C_{22}-H was observed in the ^{1}H NMR spectrum of acetate **92**, derived from **90**. Therefore, side chains at the C_{19} and C_{22} positions of **89** and **90** are assigned to be trans and cis geometries, respectively. Comparison of the splitting patterns and chemical shifts of the signals due to the C_{18}-H and C_{22}-H of **84** and **85** with those of model compounds **89** and **90** revealed that the stereochemistries at the C_{19} and C_{22} positions of major and minor tetrahydrofurans are determined as **84** and **85**, respectively (Table II).

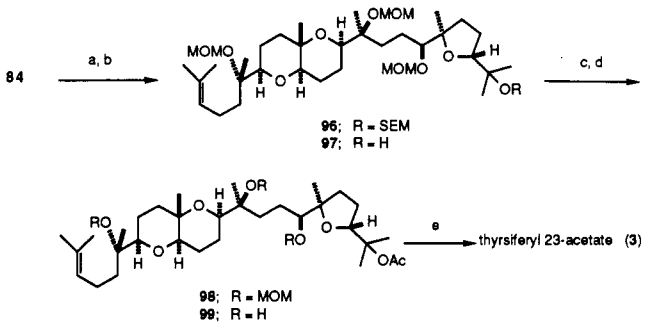
All protective groups of **84** were removed under acidic conditions to produce tetrol **86** in 90% yield. Exposure of the resulting tetrol to TBCO in nitromethane, as previously described, resulted in the bromonium ion induced cyclization to form a tetrahydropyran ring. The crude product was purified by HPLC to afford (+)-thyrsiferol (**1**), $[\alpha]^{23}_{400}$ +25°, $[\alpha]^{23}_{300}$ +50°, $[\alpha]^{23}_{220}$ +200° (*c* 0.2, MeOH), in 22% isolated yield. Other products obtained consisted of a diastereomeric mixture of tetrahydrofuran derivatives. The synthetic polyether was completely identical with the natural thyrsiferol[32] in all respects (400-MHz ^{1}H NMR, IR, MS, ORD, and HPLC retention time).

Another tricyclic ether **85** was also converted to (+)-venustatriol ($[\alpha]^{24}_D$ +11° (*c* 0.20, $CHCl_3$)) through the same sequence of reactions in 20% yield from **85**. The ^{1}H NMR signals of the synthetic polyether were perfectly coincident with those of (+)-venustatriol (**5**).[36] In both cyclization reactions, the ratios of the obtained tetrahydrofurans to tetrahydropyrans could not be assigned.

For the total synthesis of thyrsiferyl 23-acetate (**3**), the C_{18}-hydroxyl group of **84** was protected in the form of the MOM ether in 78% yield. Deprotection of the SEM ether

(33) Eschenmoser, W.; Uebelhart, P.; Eugster, C. H. *Helv. Chim. Acta* **1983**, *66*, 82.
(34) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.
(35) The compounds **88–92** were prepared from **78** and **11** by the sequential reactions of (1) BuLi, TMEDA, THF, −10 °C; (2) MOMCl, *i*-Pr_2NEt, room temperature; (3) Li, $EtNH_2$, THF, −78 °C (**88**, 60% in three steps); (4) **88**, VO(acac)$_2$, TBHP, CH_2Cl_2, room temperature, 62% (**89**), 9.7% (**90**).
(36) The ^{1}H NMR spectrum of (+)-venustatriol was kindly sent by Prof. Tatsuo Higa (Ryukyu Univ.).

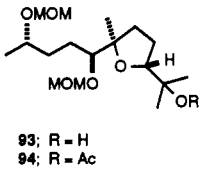
Scheme XI[a]

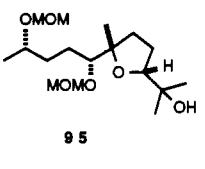


[a] Conditions: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, room temperature, 15 h, 87%; (b) TBAF, HMPA, MS4A, 120 °C, 3 h, 98%; (c) Ac_2O (excess), DMAP, 120 °C, 4 h, 45%; (d) HCl, MeOH, room temperature, 7 h, 78%; (e) TBCO, CH_3NO_2, room temperature, 5 min, 20%.

of **96** presented difficulties.[37] Ultimately, cleavage of the SEM ether group was accomplished by addition of finely powdered and activated molecular sieves (4 Å) into the reaction mixture to give the corresponding alcohol **97** in 98% yield.[6c,38]

Since the usual acetylating conditions were not effective, a model study was performed employing model **93** derived from **89** in order to determine the proper conditions needed to give the acetate of **97**. Under the usual conditions (Ac_2O, DMAP, Py, room temperature),[39] acetylation did not take place at all and starting alcohol **93** was recovered. Eventually it was found that treatment of **93** in the presence of 0.1 equiv of DMAP in excess acetic anhydride at 120 °C gave acetate **94** in 59% yield. On the other





hand, acetylation of diastereomer **95** was accomplished smoothly under the usual conditions (Ac_2O, DMAP, Py, room temperature). As expected from the model study, acetate **98** was obtained in 45% yield from alcohol **97** by carrying out the reaction with 0.1 equiv of DMAP in excess acetic anhydride at 120 °C (Scheme XI). Acidic methanolysis of **98** resulted in cleavages of all MOM ethers to afford triol **99** in 78% yield. The construction of the A ring was performed by treatment of the resulting triol **99** with TBCO in nitromethane, as previously mentioned. Purification using HPLC gave thyrsiferyl 23-acetate (**3**), $[\alpha]^{23}_{220}$ +190°, $[\alpha]^{23}_{300}$ +20° (*c* 0.02, MeOH), in 20% isolated yield which was identical with the natural product[32] in all respects (400-MHz ^1H NMR, IR, and ORD spectra, and HPLC retention time).

Experimental Section

Melting points are uncorrected. ^1H NMR splitting patterns are designated as quint or sext to indicate quintets or sexlets, respectively. CD and ORD spectra were obtained on a JASCO J-20-A automatic recording spectropolarimeter.

Analytical and preparative thin-layer chromatographic separations were carried out on precoated silica gel plates (Machechery Nagel DC-Fertigplatten SIL G-25 UV_{254}). Silica gels used for column chromatography were Wako Wakogel C-200, Merck Kieselgel 60 Art 7734, and Amicon Matrex silica Si chromatography medium. Medium-pressure column chromatography was performed employing Lobar Grösse B (310-25) LiChroprep Si 60 (40–63 μm) (Merck). Analytical and preparative HPLC were carried out using UV and/or refractive index detectors.

Throughout the Experimental Section, the following abbreviations are used for solvents and reagents: Benzyl chloride (BnCl), benzoyl chloride (BzCl), 1,4-diazabicyclo[2.2.2]octane (DABCO), diisopropyl tartrate (DIPT), *N,N*-dimethyl-4-aminopyridine (DMAP), chloromethyl methyl ether (MOMCl), molecular sieves 4Å (MS4Å), methanesulfonyl chloride (MsCl), pyridinium *p*-toluenesulfonate (PPTS), tetrabutylammonium fluoride (TBAF), 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO), *tert*-butylchlorodimethylsilane (TBDMSCl), *tert*-butyl hydroperoxide (TBHP), (2-(trimethylsilyl)ethoxy)methyl chloride (SEMCl).

Reagents and solvents for reactions were dried and distilled before use; THF (from sodium benzophenone ketyl); CH_2Cl_2, CH_3NO_2, $EtNO_2$ (from diphosphorous pentoxide); DMF, Et_3N, pyridine, *i*-Pr_2NEt, TMEDA, benzene, hexane, HMPA (from calcium hydride); MeOH (from magnesium alkoxide), acetone (from potassium permanganate). Molecular sieves were finely powdered and activated at 180 °C for 10 h in vacuo.

(2*E*,6*E*)-2,7-Dimethyl-1,8-bis(phenylthio)octa-2,6-diene (10). Butyllithium (1.5 M in hexane, 52 mL, 78 mmol) was added slowly at 0 °C to a solution of **9**[15] (6.0 g, 35 mmol) in THF (150 mL). The clear solution became a white suspension and was stirred at the same temperature for 5 min. After the mixture was allowed to warm to room temperature, a solution of TsCl (15 g, 79 mmol) in THF (40 mL) and sodium thiophenoxide [prepared from NaH (2.0 g, 83 mmol) and thiophenol (990 mg, 90 mmol) in THF (20 mL) at 0 °C] were added successively at room temperature. The mixture was stirred at the same temperature for 3 h, poured into water (1 L), and extracted with ether (3 × 500 mL). The combined ethereal layers were washed with brine (1 L), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue on silica gel (250 g) with 50% hexane/benzene gave **10** (9.9 g, 28 mmol, 80%): IR (neat) 3150, 2840, 1588, 1485, 1440, 1090, 1030, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.68 (6 H, s, C_2-Me, C_7-Me), 1.8–2.0 (4 H, m, C_4-H_2, C_5-H_2), 3.43 (4 H, s, C_1-H_2, C_8-H_2), 5.09 (2 H, br t, *J* = 7 Hz, C_3-H, C_5-H), 7.1–7.4 (10 H, m, aromatic protons); EI-MS *m/z* 354 (1.1, M^+), 245 (84, M^+ - SPh), 177 (100, $PhSCH_2C(Me)=CHCH_2^+$); EI-HR-MS found *m/z* 354.1472, calcd for $C_{22}H_{26}S_2$ (M^+) 354.1478.

(2*S*,5*E*,9*E*,13*S*)-5,10-Dimethyltetradeca-5,9-diene-2,13-diol (12) and Its Δ^4,Δ^9-Isomer (13). Butyllithium (1.5 M in hexane, 140 mL, 210 mmol) was added to a mixture of **10** (9.8 g, 28 mmol), **11**[17] (24 g, 104 mmol), and TMEDA (20 mL, 170 mmol) in THF (400 mL) at −10 °C under an argon atmosphere. The mixture was stirred at the same temperature for 5 h, and then water (15 mL) was added. The resulting solution was poured into water (500 mL) and extracted with ether (4 × 300 mL). The combined extracts were washed with brine (500 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was subjected to column chromatography on silica gel (300 g) with 30% EtOAc/benzene to give an adduct (9.4 g, 20 mmol, 71%) as a diastereomeric mixture.

The adduct (9.4 g, 20 mmol) was dissolved in a mixture of THF (250 mL) and 1-butanol (25 mL). Metallic Na (6 g, 260 mmol) was added to the solution at reflux temperature under an Ar atmosphere. The mixture was refluxed vigorously with stirring for 3 h, then cooled to 0 °C, and excess Na was removed. After neutralization with 2 M HCl (10 mL), the mixture was poured into water (300 mL) and extracted with ether (4 × 200 mL). The combined ethereal solutions were washed with brine (500 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (300 g) with 7% acetone/$CHCl_3$ gave a mixture of **12** and its olefin isomer **13** (4.9 g, 19 mmol, 91%). The mixture was separated by column chromatography on $AgNO_3$-coated (5%) silica gel with 15% acetone/$CHCl_3$ to give pure **12** (2.9 g, 11.4 mmol) and **13** (1.7 g, 6.7 mmol).

12: R_f = 0.40 (silica gel (10% $AgNO_3$), EtOAc); $[\alpha]^{24}_D$ +16.5° (*c* 2.60, $CHCl_3$); IR (neat) 3400, 2950, 2900, 2850, 1450, 1375, 1130,

(37) Removal of SEM ethers is often sluggish. Indeed, demasking of hindered SEM ethers was not shown in the original paper. For example, Sugimura, T.; Paquette, L. A. *J. Am. Chem. Soc.* **1987**, *109*, 3017.
(38) Lipshutz, B. H.; Miller, T. A. *Tetrahedron Lett.* **1989**, *51*, 7149.
(39) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

1085, 950, 930, 903, 860, 840 cm^{-1}; ^1H NMR (90 MHz, C_6D_6) δ 1.05 (6 H, d, J = 6 Hz, C_2-Me, C_{13}-Me), 1.57 (6 H, s, C_5-Me, C_{10}-Me), 3.55 (2 H, sext, J = 6 Hz, C_2-H, C_{13}-H), 5.21 (2 H, br t, J = 7 Hz, C_6-H, C_9-H); EI-MS m/z 254, (0.23, M^+), 236 (0.91, $M^+ - H_2O$), 109 (100, MeCH=CHC(Me)CH_2^+); EI-HR-MS found m/z 254.2256, calcd for $C_{10}H_{30}O_2$ (M^+) 254.2247.

13: R_f = 0.50 (same as **12**); $[\alpha]^{24}_D$ +16.2° (c 2.50, $CHCl_3$); IR (neat) 3400, 2900, 1450, 1375, 1125, 1075, 940, 905, 865 cm^{-1}; ^1H NMR (90 MHz, C_6D_6) δ 1.03 (3 H, d, J = 6 Hz, C_{13}-Me), 1.10 (3 H, d, J = 6 Hz, C_2-Me), 1.57 (6 H, s, C_5-Me, C_{10}-Me), 3.55 (2 H, m, C_2-H, C_{13}-H), 5.21 (2 H, m, C_4-H, C_9-H); EI-MS m/z 254 (0.05, M^+), 236 (0.36, $M^+ - H_2O$), 109 (100, MeCH=CHC(Me)CH_2^+); EI-HR-MS found m/z 254.2246, calcd for $C_{10}H_{30}O_2$ (M^+) 254.2247.

(2*S*,5*E*,9*E*,13*S*)-13-(Benzoyloxy)-5,10-dimethyltetradeca-5,9-dien-2-ol (14). A mixture of **12** (2.2 g, 8.5 mmol), BzCl (1.2 g, 8.5 mmol), and Et_3N (1.7 g, 17 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 20 h, poured into water (100 mL), and extracted with ether (4 × 100 mL). The ethereal solutions were combined, washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residual oil was chromatographed over silica gel (100 g). Successive elution with benzene, 15–50% EtOAc/benzene gave dibenzoate (500 mg, 1.0 mmol, 12%), monobenzoate **14** (1160 mg, 3.2 mmol, 38%), and recovered diol **12** (980 mg, 3.8 mmol, 45%), respectively.

Dibenzoate: $[\alpha]^{22}_D$ +32.5° (c 2.60, $CHCl_3$); IR (neat) 2970, 2920, 2850, 1717, 1452, 1275, 1112, 1070, 1030, 713 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.34 (6 H, d, J = 6 Hz, C_2-Me, C_{13}-Me), 1.61 (6 H, s, C_5-Me, C_{10}-Me), 1.9–2.2 (8 H, m, C_4-H_2, C_7-H_2, C_8-H_2, C_{11}-H_2), 4.9–5.3 (4 H, m, C_2-H, C_6-H, C_9-H, C_{13}-H), 7.3–7.6 (6 H, m, aromatic protons), 7.9–8.1 (4 H, m, aromatic protons); EI-MS m/z 462 (0.01, M^+), 340 (1.3, M^+ - PhCOOH), 218 (2.4, M^+ - 2(PhCOOH)), 109 (100, MeCH=CHC(Me)CH_2^+).

14: $[\alpha]^{23}_D$ +31.6° (c 3.10, $CHCl_3$); IR (neat) 3400, 2970, 2920, 2850, 1720, 1457, 1277, 1117, 1070, 715 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.17 (3 H, d, J = 6 Hz, C_2-Me), 1.34 (3 H, d, J = 6 Hz, C_{13}-Me), 1.61 (6 H, s, C_5-Me, C_{10}-Me), 1.9–2.2 (8 H, m, C_4-H_2, C_7-H_2, C_8-H_2, C_{11}-H_2), 3.75 (1 H, sext, J = 6 Hz, C_2-H), 5.0–5.3 (3 H, m, C_6-H, C_9-H, C_{13}-H), 7.3–7.6 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons); EI-MS m/z 358 (0.06, M^+), 340 (0.12, $M^+ - H_2O$), 109 (100, MeCH=CHC(Me)CH_2^+); EI-HR-MS found m/z 358.2498, calcd for $C_{23}H_{34}O_3$ (M^+) 358.2509.

(2*R*,5*S*)-2-[(1*S*,4*E*,8*S*)-8-(Benzoyloxy)-1-hydroxy-5-methylnon-4-enyl]tetrahydro-2,5-dimethylfuran (15). A suspension of **14** (190 mg, 530 μmol), NaOAc (70 mg, 850 μmol), $VO(acac)_2$ (10 mg, 37 μmol), and TBHP (4.0 M in CH_2Cl_2, 300 μL, 1.2 mmol) in benzene (5.0 mL) was refluxed for 16 h. The mixture was poured into water (20 mL), and extracted with ether (4 × 30 mL). The combined ethereal solutions were washed with brine (40 mL) and dried (Na_2SO_4). AcOH (5 mL) was added to the solution, and the solution was left for 1 h at room temperature. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (5 g) with 15% EtOAc/hexane to give a mixture of **15** and its isomer **16** (134 mg, 460 μmol, 86%). An analytical sample of **15** was obtained by purification of the mixture (30 mg), employing preparative TLC with 20% EtOAc/benzene to afford diastereomerically pure **15** (20 mg): $[\alpha]^{22}_D$ +20.1° (c 1.00, $CHCl_3$); IR (neat) 3480, 2970, 2950, 2870, 1720, 1455, 1278, 1115, 1070, 1027, 717 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.13 (3 H, s, C_2-Me), 1.26 (3 H, d, J = 6.1 Hz, C_5-Me), 1.34 (3 H, d, J = 6.1 Hz, C_8-Me), 1.64 (3 H, s, C_5-Me), 3.48 (1 H, dd, J = 2.4 and 9.8 Hz, $C_{1'}$-H), 4.06 (1 H, m, C_5-H), 5.0–5.2 (2 H, m, C_4-H, C_8-H), 7.4–7.6 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons); EI-MS m/z 374 (0.01, M^+), 356 (0.17, $M^+ - H_2O$), 99 (100, $C_6H_{11}O^+$ (tetrahydrofuran moiety)); EI-HR-MS found m/z 374.02439, calcd for $C_{23}H_{34}O_4$ (M^+) 374.2458.

(2*R*,3*S*,6*S*)-2-[(*E*,*S*)-7-(Benzyloxy)-4-methyloct-3-enyl]-tetrahydro-3,6-dimethyl-2*H*-pyran-3-ol (19) and Its 2*S*,3*R* Isomer 20. Methanesulfonyl chloride (55 mg, 480 μmol) and Et_3N (500 μL, 3.5 mmol) were added successively to a solution of a mixture of **15** and **16** (134 mg, 460 μmol) in CH_2Cl_2 (5.0 mL) at −10 °C. After stirring for 1 h at the same temperature, the resulting mixture was poured into water (30 mL) and extracted with $CHCl_3$ (4 × 20 mL). The extracts were combined, washed with brine (40 mL), dried (Na_2SO_4), concentrated in vacuo, and diluted with a mixture of acetone (5.0 mL) and water (5.0 mL); then Ag_2CO_3 (370 mg, 1.34 mmol) was added to the solution at 50 °C. After stirring for 16 h at the same temperature in the dark, the resulting mixture was filtered through Celite pad with suction and concentrated under reduced pressure. The residue was chromatographed over silica gel (3 g). Successive elution with 10 and 20% EtOAc/benzene afforded **19** (93 mg, 250 μmol, 73%) and its isomer **20** (15 mg, 40 μmol, 12%), respectively.

19: $[\alpha]^{23}_D$ +34.6° (c 1.00 $CHCl_3$); IR (neat) 3450, 2970, 2950, 2850, 1720, 1455, 1280, 1090, 1070, 717 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.16 (3 H, s, C_3-Me), 1.20 (3 H, d, J = 6.1 Hz, C_6-Me), 1.36 (3 H, d, J = 6.1 Hz, $C_{7'}$-Me), 1.62 (3 H, s, $C_{4'}$-Me), 3.10 (1 H, dd, J = 1.8 and 10.8 Hz, C_2-H), 3.39 (1 H, ddq, J = 1.8, 10.8, and 6.1 Hz, C_6-H), 5.02 (1 H, br t, J = 7.1 Hz, $C_{3'}$-H), 5.13 (1 H, m, $C_{7'}$-H), 7.4–7.6 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons); EI-MS m/z 356 (3.6, $M^+ - H_2O$), 252 (1.2, M^+ - PhCOOH), 251 (1.3, M^+ - PhCOOH - H), 234 (4.6, $M^+ - H_2O$ - PhCOOH), 99 (100); EI-HR-MS found m/z 356.2357, calcd for $C_{23}H_{32}O_3$ ($M^+ - H_2O$) 356.2353.

20: $[\alpha]^{23}_D$ −6.00° (c 1.00, $CHCl_3$); IR (neat) 3500, 2950, 2850, 1715, 1450, 1380, 1110, 1025, 712 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.06 (3 H, s, C_3-Me), 1.15 (3 H, d, J = 6.1 Hz, C_6-Me), 1.35 (3 H, d, J = 6.1 Hz, $C_{7'}$-Me), 1.64 (3 H, s, $C_{4'}$-Me), 3.45 (1 H, dd, J = 3.0 and 11.6 Hz, C_2-H), 3.66 (1 H, ddq, J = 5.1, 7.5, and 6.1 Hz, C_6-H), 5.10 (2 H, m, $C_{3'}$-H, $C_{7'}$-H), 7.4–7.6 (3 H, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons); EI-MS m/z 374 (0.09, M^+), 356 (5.0, $M^+ - H_2O$), 252 (0.80, M^+ - PhCOOH), 251 (1.1, M^+ - PhCOOH - H), 234 (5.1, $M^+ - H_2O$ - PhCOOH), 43 (100); EI-HR-MS found m/z 374.2472, calcd for $C_{23}H_{34}O_4$ (M^+) 374.2458.

(2*R*,3*S*,6*S*)-2-[2-[(2*R*,3*R*)-3-[(*S*)-3-(Benzoyloxy)butyl]-3-methyloxiran-2-yl]ethyl]tetrahydro-3,6-dimethyl-2*H*-pyran-3-ol (21) and Its 2″*S*,3″*S* Isomer 22. *m*-Chloroperbenzoic acid (80% activity, 420 mg, 2.0 mmol) was added to a solution of **19** (600 mg, 1.6 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred at the same temperature for 1 h, poured into saturated aqueous $NaHCO_3$ solution (50 mL), and extracted with ether (4 × 50 mL). The ethereal layers were combined, washed successively with water (50 mL) brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (20 g) with 30% EtOAc/benzene to yield a mixture of **21** and **22** (500 mg, 1.3 mmol, 80%) as a 1:1 diastereomeric mixture. The diastereomers were separated by medium-pressure column chromatography with 2-propanol/acetone/$CHCl_3$ (1/5/95) to afford pure **21** (240 mg, 620 μmol, 38%) and **22** (230 mg, 590 μmol, 37%).

21: R_f = 0.35 (above conditions); $[\alpha]^{21}_D$ +62.6° (c 1.00, $CHCl_3$); IR (neat) 3420, 2920, 2850, 1715, 1452, 1385, 1317, 1275, 1110, 1025, 920, 897, 715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.17 (3 H, d, J = 6.1 Hz, C_6-Me), 1.19 (3 H, s, C_3-Me), 1.28 (3 H, s, $C_{3'}$-Me), 1.35 (3 H, d, J = 6.1 Hz, $C_{3''}$-Me), 2.73 (1 H, t, J = 6.1 Hz, $C_{2''}$-H), 3.11 (1 H, dd, J = 2.4 and 9.8 Hz, C_2-H), 3.43 (1 H, ddq, J = 2.4, 9.2, and 6.1 Hz, C_6-H), 5.15 (1 H, m, $C_{3'''}$-H), 7.4–7.6 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons).

22: R_f = 0.31 (above conditions); $[\alpha]^{22}_D$ +40° (c 0.80, $CHCl_3$); IR (neat) 3400, 2970, 2920, 2850, 1717, 1450, 1387, 1275, 1110, 1025, 920, 712 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.17 (3 H, d, J = 6.1 Hz, C_6-Me), 1.18 (3 H, s, C_3-Me), 1.28 (3 H, s, $C_{3'}$-Me), 1.35 (3 H, d, J = 6.1 Hz, $C_{3''}$-Me), 2.79 (1 H, dd, J = 5.5 and 7.3 Hz, $C_{2''}$-H), 3.12 (1 H, dd, J = 1.0 and 9.8 Hz, C_2-H), 3.45 (1 H, ddq, J = 2.4, 6.7, and 6.1 Hz, C_6-H), 5.13 (1 H, sext, J = 6.1 Hz, $C_{3'''}$-H), 7.4–7.6 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons).

(2*S*,4a*R*,6*S*,8a*S*)-2-[(1*R*,4*S*)-5-(Benzoyloxy)-1-hydroxy-1-methylpentyl]octahydro-6,8a-dimethylpyrano[3,2-*b*]pyran (23). A mixture of **21** (20 mg, 50 μmol) and PPTS (3.0 mg, 12 μmol) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 1 h under an Ar atmosphere. After the mixture was cooled to room temperature, the solvent was removed in vacuo. The crude product was chromatographed on silica gel (1 g) with 15% EtOAc/benzene to give **23** (18 mg, 45 μmol, 90%). HPLC analysis (μPOLASIL, 7.8 × 300 φmm, 1.3% 2-propanol/hexane, 1.0 mL/min flow, detected by RI) showed a single product: t_R = 46 min (above conditions); $[\alpha]^{22}_D$ +60° (c 0.30, $CHCl_3$); IR (neat) 3500, 2950, 2870, 1720, 1455, 1280, 1115, 1100, 717 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.15 (3 H, s, C_{8a}-Me or $C_{1'}$-Me), 1.19 (3 H, d, J = 6.5 Hz, C_6-Me), 1.21 (3 H, s, C_{8a}-Me or $C_{1'}$-Me), 1.36 (3 H, d, J = 6.2 Hz, $C_{4'}$-Me), 3.06 (1 H, dd, J = 4.3 and 11.0 Hz, C_{4a}-H),

3.50 (1 H, dd, J = 1.8 and 11.6 Hz, C_2-H), 3.55 (1 H, m, C_6-H), 5.14 (1 H, sext, J = 6.2 Hz, $C_{4'}$-H), 7.4–7.6 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons); EI-MS m/z 372 (0.71, $M^+ - H_2O$), 169 (10, $C_{10}H_{17}O_2^+$ (BC ring moiety)), 105 (16, $PhCO^+$), 99 (100); FI-MS m/z 391 (92, $M^+ + H$), 390 (100, M^+); FI-HR-MS found m/z 390.2442, calcd for $C_{23}H_{34}O_5$ (M^+) 390.2407.

(2*R*,4a*R*,6*S*,8a*S*)-2-[(1*S*,5*S*)-4-(Benzoyloxy)-1-hydroxy-1-methylpentyl]octahydro-6,8a-dimethylpyrano[3,2-*b*]pyran (24), Its 2*S* Epimer 25, (2*R*,4a*R*,6*S*,8a*S*)-2-[(*E*)-(*S*)-4-(Benzoyloxy)-1-methylpent-1-enyl]octahydro-6,8a-dimethylpyrano[3,2-*b*]pyran (26), and Its 2*S* Epimer 27. A suspension of **22** (15 mg, 38 μmol) and PPTS (5.0 mg, 20 μmol) in benzene (1.0 mL) was stirred at 80 °C for 20 min under an Ar atmosphere. The mixture was cooled to room temperature, concentrated under reduced pressure, and chromatographed over silica gel (1 g). Successive elution with 7 and 15% EtOAc/benzene afforded a mixture of bicyclic **26** and **27** (3.0 mg) and a mixture of **24** and **25** (7.0 mg), respectively. The less polar mixture was subjected to HPLC (μPOLASIL, 3.9 × 300 ϕmm, 0.5% 2-propanol/hexane, 1.0 mL/min flow, detected by RI) to afford **26** (1.4 mg, 3.8 μmol, 10%) and **27** (800 μg, 2.2 μmol, 5.8%). Similarly, further purification of the polar mixture employing HPLC (μPOLASIL, 7.8 × 300 ϕmm, 1.3% 2-propanol/hexane, 1.0 mL/min flow, detected by RI) gave **24** (3.0 mg, 7.7 μmol, 20%) and **25** (3.0 mg, 7.7 μmol, 20%).

24: t_R = 58 min (above conditions); $[\alpha]^{20}_D$ +23° (c 0.30, $CHCl_3$); IR (neat) 3550, 2970, 2850, 1720, 1460, 1382, 1280, 1120, 1100, 1070, 717 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.11 (3 H, s, $C_{1'}$-Me or C_{8a}-Me), 1.18 (3 H, d, J = 6.5 Hz, C_6-Me), 1.20 (3 H, s, C_{8a}-Me or $C_{1'}$-Me), 1.36 (3 H, d, J = 6.5 Hz, $C_{4'}$-Me), 3.51 (1 H, ddq, J = 2.4, 11.0 and 6.5 Hz, C_6-H), 3.62 (1 H, dd, J = 6.0 and 11.0 Hz, C_2-H), 3.72 (1 H, dd, J = 3.1 and 12.2 Hz, C_{4a}-H), 5.14 (1 H, sext, J = 6.5 Hz, $C_{4'}$-H), 7.4–7.6 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons); EI-MS m/z 391 (0.04, $M^+ + H$), 390 (0.02, M^+), 373 (0.16, $M^+ - OH$), 372 (0.16, $M^+ - H_2O$), 169 (15, $C_{10}H_{17}O_2^+$ (BC ring moiety)), 105 (16, $PhCO^+$), 99 (100); EI-HR-MS found m/z 372.2309, calcd for $C_{23}H_{32}O_4$ ($M^+ - H_2O$) 372.2302.

25: t_R = 50 min (above conditions); $[\alpha]^{22}_D$ +68° (c 0.30, $CHCl_3$); IR (neat) 3550, 2950, 2870, 1720, 1455, 1382, 1280, 1120, 1100, 717 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.09 (3 H, s, C_{8a}-Me or $C_{1'}$-H), 1.19 (3 H, d, J = 6.7 Hz, C_6-Me), 1.21 (3 H, s, C_{8a}-Me or $C_{1'}$-Me), 1.35 (3 H, d, J = 6.1 Hz, $C_{4'}$-Me), 3.07 (1 H, dd, J = 3.8 and 11.0 Hz, C_{4a}-H), 3.50 (1 H, dd, J = 2.2 and 11.0 Hz, C_2-H), 3.58 (1 H, m, C_6-H), 5.13 (1 H, sext, J = 6.1 Hz, $C_{4'}$-H), 7.4–7.6 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons); EI-MS m/z 372 (0.28, $M^+ - H_2O$), 250 (0.32, $M^+ - H_2O$ - PhCOOH), 169 (11, $C_{10}H_{17}O_2^+$ (BC ring moiety)), 105 (16, $PhCO^+$), 99 (100); FI-MS m/z 391 (100, $M^+ + H$), 390 (76, M^+); FI-HR-MS found m/z 390.2426, calcd for $C_{23}H_{34}O_5$ (M^+) 390.2407.

26: t_R = 13.5 min (above conditions); IR (neat) 2950, 2850, 1725, 1460, 1385, 1275, 1003, 720 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.19 (3 H, d, J = 6.2 Hz, C_6-Me), 1.24 (3 H, s, C_{8a}-Me), 1.34 (3 H, d, J = 6.2 Hz, $C_{4'}$-Me) 1.67 (3 H, s, $C_{1'}$-Me), 2.40, 2.45 (each 1 H, dt, J = 14.0 and 7.1 Hz, $C_{3'}$-H_2), 3.55 (1 H, dd, J = 6.0 and 11.0 Hz, C_{4a}-H), 3.55 (1 H, ddq, J = 2.8, 13.0, and 6.2 Hz, C_6-H), 4.23 (1 H, dd, J = 4.1 and 9.5 Hz, C_2-H), 5.16 (1 H, sext, J = 6.2 Hz, $C_{4'}$-H), 5.49 (1 H, br t, J = 7.1 Hz, $C_{2'}$-H), 7.4–7.6 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons); EI-MS m/z 372 (2.0, M^+), 250 (18, M^+ - PhCOOH), 105 (32, $PhCO^+$), 99 (100); EI-HR-MS found m/z 372.2290, calcd for $C_{23}H_{32}O_4$ (M^+) 372.2302.

27: t_R = 9.5 min (above conditions); IR (neat) 2950, 2850, 1725, 1455, 1380, 1273, 1100, 720 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.18 (3 H, d, J = 6.5 Hz, C_6-Me), 1.24 (3 H, s, C_{8a}-Me), 1.34 (3 H, d, J = 6.2 Hz, $C_{4'}$-Me), 1.67 (3 H, s, $C_{1'}$-Me), 2.37, 2.49 (each 1 H, dt, J = 14.0 and 7.1 Hz, $C_{3'}$-H_2), 3.11 (1 H, dd, J = 4.0 and 11.0 Hz, C_{4a}-H), 3.57 (1 H, m, C_6-H), 4.06 (1 H, dd, J = 2.5 and 10.6 Hz, C_2-H), 5.16 (1 H, sext, J = 6.2 Hz, $C_{4'}$-H), 5.49 (1 H, br t, J = 7.1 Hz, $C_{2'}$-H), 7.4–7.6 (3 H, m, aromatic protons), 8.05 (2 H, m, aromatic protons); EI-MS m/z 372 (1.4, M^+), 250 (1.6, M^+ - PhCOOH), 105 (34, $PhCO^+$), 99 (100); EI-HR-MS found m/z 372.2294, calcd for $C_{23}H_{32}O_4$ (M^+) 372.2302.

(2*R*,3*S*,6*S*)-2-[(*E*,*S*)-7-(Benzoyloxy)-4-methyloct-3-enyl]tetrahydro-3,6-dimethyl-3-[(trimethylsilyl)oxy]-2*H*-pyran (28). A solution of **19** (76 mg, 180 μmol), TMSCl (40 mg, 370 μmol), Et_3N (0.5 μL, 3.5 mmol), and DMAP (1.0 mg, 8.2 μmol) was stirred in CH_2Cl_2 (3.0 mL) at room temperature for 4 h. The mixture was poured into water (30 mL), and extracted with ether (4 × 20 mL). The extracts were combined, washed with brine (30 mL), and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was subjected to column chromatography (silica gel, 2 g) with benzene to give **28** (70 mg, 150 μmol, 85%): $[\alpha]^{24}_D$ +42.2° (c 1.00, $CHCl_3$); IR (neat) 2950, 2850, 1720, 1453, 1274, 1138, 1070, 843, 715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.09 (9 H, s, $SiMe_3$), 1.16 (3 H, d, J = 6.1 Hz, C_6-Me), 1.17 (3 H, s, C_3-Me), 1.35 (3 H, d, J = 6.1 Hz, $C_{7'}$-Me), 1.63 (3 H, s, $C_{4'}$-Me), 3.00 (1 H, dd, J = 1.8 and 10.4 Hz, C_2-H), 3.40 (1 H, ddq, J = 2.2, 10.6, and 6.1 Hz, C_6-H) 5.15 (2 H, m, C_3-H, $C_{7'}$-H), 7.40–7.60 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons); EI-MS m/z 446 (0.03, M^+), 431 (0.14, M^+ - Me), 356 (4.7, M^+ - Me_3SiOH), 130 (100); EI-HR-MS found m/z 446.2839, calcd for $C_{26}H_{42}O_4Si$ (M^+) 446.2853.

(2*R*,3*S*,6*S*)-2-[(*E*)-4-(Ethoxycarbonyl)pent-3-enyl]tetrahydro-3,6-dimethyl-3-[(trimethylsilyl)oxy]-2*H*-pyran (30). Ozone gas was bubbled through a solution of **28** (230 mg, 520 μmol) in CH_2Cl_2 (20 mL) with stirring at −78 °C for 15 min. The colorless solution turned a pale blue. After excess ozone was removed by bubbling oxygen through the solution, dimethyl sulfide (1.0 mL) was added, and the mixture was left at room temperature for 1 h in order to decompose the ozonide product. The mixture was allowed to warm to room temperature, and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel with 12% EtOAc/benzene to give **29** (130 mg, 520 mol, 100%): ^1H NMR (250 MHz, $CDCl_3$) δ 0.09 (9 H, s, $SiMe_3$), 1.13 (3 H, d, J = 6.1 Hz, C_6-Me), 1.21 (3 H, s, C_3-Me), 3.02 (1 H, dd, J = 1.8 and 10.4 Hz, C_2-H), 3.41 (1 H, m, C_6-H), 9.75 (1 H, t, J = 2.4 Hz, $C_{3'}$-H).

A solution of **29** (130 mg, 520 mmol) and $MeC(PPh_3)CO_2Et$[23] (500 mg, 1.4 mmol) in CH_2Cl_2 (20 mL) was stirred at reflux temperature for 8 h under an Ar atmosphere and then concentrated in vacuo. Column chromatography of the crude product on silica gel (5 g) with 3% EtOAc/benzene gave **30** (170 mg, 490 μmol, 96%): $[\alpha]^{20}_D$ +32.2° (c 1.00, $CHCl_3$); IR (neat) 2970, 2950, 1712, 1450, 1380, 1275, 1263, 1250, 1140, 873, 843, 757 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.10 (9 H, s, $SiMe_3$), 1.17 (3 H, d, J = 6.1 Hz, C_6-Me), 1.18 (3 H, s, C_3-Me), 1.30 (3 H, t, J = 7.3 Hz, CO_2CH_2Me), 1.84 (3 H, s, $C_{4'}$-Me), 3.02 (1 H, dd, J = 1.8 and 10.4 Hz, C_2-H), 3.42 (1 H, m, C_6-H), 4.18 (2 H, q, J = 7.3 Hz, CO_2CH_2Me), 6.79 (1 H, br t, J = 7.3 Hz, $C_{3'}$-H); EI-MS m/z 342 (3.3, M^+), 327 (1.4, M^+ - Me), 199 (19, $M^+ - CH_2CH{=}C(Me)$-CO_2Et), 143 (96), 130 (100); EI-HR-MS found m/z 342.2240, calcd for $C_{18}H_{34}O_4Si$ (M^+) 342.2227.

(2*R*,3*S*,6*S*)-Tetrahydro-2-[(*E*)-5-hydroxy-4-methylpent-3-enyl]-3,6-dimethyl-3-[(trimethylsilyl)oxy]-2*H*-pyran (31). Diisobutylaluminum hydride (1.0 M in hexane, 1.2 mL, 1.2 mmol) was added to a solution of **30** (150 mg, 430 μmol) in hexane (10 mL) at −78 °C under an argon atmosphere. After stirring at the same temperature for 10 min, MeOH (500 μL) and water (1.0 mL) were added successively to the mixture. After stirring at room temperature for an additional 30 min, the resulting suspension was filtered through a Celite pad with suction, and the filtrates were concentrated in vacuo. Purification of the residue by column chromatography on silica gel (6 g) with 15% EtOAc/benzene gave **31** (100 mg, 330 μmol, 77%): $[\alpha]^{20}_D$ +20.3° (c 1.00, $CHCl_3$); IR (neat) 3380, 2950, 2850, 1450, 1380, 1318, 1250, 1140, 1067, 1010, 870, 845, 760 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.10 (9 H, s, $SiMe_3$), 1.17 (3 H, d, J = 6.1 Hz, C_6-Me), 1.18 (3 H, s, C_3-Me), 1.68 (3 H, s, $C_{4'}$-Me), 2.16 (2 H, m, $C_{2'}$-H_2), 3.03 (1 H, dd, J = 1.8 and 10.4 Hz, C_2-H), 3.42 (1 H, m, C_6-H), 4.01 (2 H, s, $C_{5'}$-H_2), 5.43 (1 H, br t, J = 7.3 Hz, $C_{3'}$-H); EI-MS m/z 300 (0.07, M^+), 282 (0.47, $M^+ - H_2O$), 143 (78), 130 (100); HR-MS found m/z 300.2133, calcd for $C_{16}H_{32}O_3Si$ (M^+) 300.2121.

(2*R*,3*S*,6*S*)-Tetrahydro-2-[2-[(2*S*,3*S*)-3-(hydroxymethyl)-3-methyloxiran-2-yl]ethyl]-3,6-dimethyl-2*H*-pyran-3-ol (33). Titanium tetraisopropoxide (40 mg, 140 μmol), and L-(+)-DIPT (69 mg, 260 μmol) were added to a suspension of **31** (40 mg, 130 μmol) and MS4Å (100 mg) in CH_2Cl_2 (1.5 mL) at −10 °C under an argon atmosphere. Then, TBHP (4.0 M in CH_2Cl_2, 100 μL, 400 μmol) was added to the mixture at −20 °C, and the mixture was stirred for 3 h. Saturated aqueous Na_2SO_4 solution (100 μL) was added at −20 °C, and the resulting mixture was allowed to warm to room temperature. After stirring for an

additional 1 h, the mixture was filtered through a Celite pad with suction, concentrated in vacuo, and diluted with THF (1.0 mL). Tetrabutylammonium fluoride (1.0 M in THF, 150 μL, 150 μmol) was added to the solution, and the mixture was stirred for 4 h at room temperature. After the solvent was removed under reduced pressure, the resulting oil was purified by column chromatography on silica gel (1 g) with 35% acetone/$CHCl_3$ to afford **33** (27 mg, 110 μmol, 85%): $[\alpha]^{24}_D$ +26° (*c* 0.30, $CHCl_3$); IR (neat) 3400, 2970, 2950, 2840, 1460, 1380, 1130, 1085, 1037 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (3 H, d, *J* = 6.1 Hz, C_6-Me), 1.19 (3 H, s, C_3-Me), 1.30 (3 H, s, $C_{3'}$-Me), 3.09 (1 H, dd, *J* = 4.9 and 7.3 Hz, $C_{2''}$-H), 3.13 (1 H, br d, *J* = 10.5 Hz, C_2-H), 3.45 (1 H, m, C_6-H), 3.57, 3.68 (each 1 H, d, *J* = 12.2 Hz, $C_{3'}$-CH_2OH).

(2*R*,4a*R*,6*S*,8a*S*)-Octahydro-2-[(*S*)-1,2-dihydroxy-1-methylethyl]-6,8a-dimethylpyrano[3,2-*b*]pyran (34). A solution of **33** (12 mg, 49 μmol) and Ti(O*i*-Pr)$_4$ (15 mg, 52 μmol) in benzene (2.0 mL) was refluxed for 2 h under an Ar atmosphere. After cooling to room temperature, 5% aqueous citric acid solution (100 μL) and Celite (ca. 200 mg) were added to the mixture, and the resulting mixture was stirred at the same temperature for an additional 1 h. The mixture was filtered through a Celite pad with suction. The filtrates were concentrated in vacuo and chromatographed on silica gel (1 g). Successive elution with 10 and 35% acetone/$CHCl_3$ gave **34** (7.0 mg, 28 μmol, 58%) and starting **33** (2.0 mg, 8.1 μmol, 16%), respectively.

34: $[\alpha]^{23}_D$ +0.70° (*c* 0.50, $CHCl_3$); IR (neat) 3400, 2970, 2950, 2850, 1463, 1382, 1100, 1077, 1020 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.07 (3 H, s, C_{8a}-Me or $C_{1'}$-Me), 1.19 (3 H, d, *J* = 6.1 Hz, C_6-Me), 1.25 (3 H, s, C_{8a}-Me or $C_{1'}$-Me), 3.37 (1 H, br d, *J* = 11.0 Hz, C_2-H), 3.53 (1 H, ddq, *J* = 2.4, 10.7, and 6.1 Hz, C_6-H), 3.65 (1 H, dd, *J* = 7.3 and 11.5 Hz, C_{4a}-H), 3.75 (1 H, d, *J* = 11.0 Hz, C_2-H), 3.94 (1 H, dd, *J* = 3.9 and 12.2 Hz, C_2-H); EI-MS *m*/*z* 213 (2.3, $M^+ - CH_2OH$), 195 (1.8, $M^+ - CH_2OH - H_2O$), 169 (31, $C_{10}H_{17}O_2^+$ (BC ring moiety)), 43 (100); FI-MS *m*/*z* 245 (100, $M^+ + H$), 244 (52, M^+), 169 (35, $C_{10}H_{17}O_2^+$ (BC ring moiety)); FI-HR-MS found *m*/*z* 244.1683, calcd for $C_{13}H_{24}O_4$ (M^+) 244.1675.

(2*R*,3*S*,6*S*)-Tetrahydro-2-[2-[(2*R*,3*R*)-3-(hydroxymethyl)-3-methyloxiran-2-yl]ethyl]-3,6-dimethyl-2*H*-pyran-3-ol (35). Allyl alcohol **31** (9.0 mg, 33 μmol) was treated in a similar manner as that described for **33** employing MS4Å (50 mg), Ti(O*i*-Pr)$_4$ (10 mg, 35 μmol), D-(−)-DIPT (12 mg, 51 μmol), and TBHP (4.0 M in CH_2Cl_2, 50 μL) in CH_2Cl_2 (1.0 mL), and the obtained crude material was stirred with TBAF (50 μL) in THF (1.0 mL). Similar workup as before gave a crude product, which was purified by column chromatography on silica gel (1 g) with 35% acetone/$CHCl_3$ to yield **35** (5.0 mg, 20 μmol, 61%): $[\alpha]^{23}_D$ +32° (*c* 0.50, $CHCl_3$); IR (neat) 3380, 2970, 2950, 2860, 1460, 1383, 1135, 1107, 1085, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (3 H, d, *J* = 6.1 Hz, C_6-Me), 1.19 (3 H, s, C_3-Me), 1.31 (3 H, s, $C_{3''}$-Me), 3.08 (1 H, t, *J* = 6.1 Hz, $C_{2''}$-H), 3.13 (1 H, dd, *J* = 2.4 and 10.4 Hz, C_2-H), 3.45 (1 H, m, C_6-H), 3.60, 3.66 (each 1 H, d, *J* = 12.2 Hz, $C_{3''}$-CH_2OH).

(2*S*,4a*R*,6*S*,8a*S*)-Octahydro-2-[(*R*)-1,2-dihydroxy-1-methylethyl]-6,8a-dimethylpyrano[3,2-*b*]pyran (36). Treatment of **35** (25 mg, 100 μmol) with Ti(O*i*-Pr)$_4$ (30 mg, 110 μmol) in benzene (2.0 mL) according to the same procedure as **34** gave a crude material which was purified by column chromatography on silica gel (1 g) with 10% acetone/$CHCl_3$ to give bicyclic **36** (23 mg, 96 μmol, 96%): $[\alpha]^{23}_D$ +35° (*c* 0.20, $CHCl_3$); IR (neat) 3400, 2920, 2850, 1460, 1380, 1127, 1097, 1038, 913 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.09 (3 H, s, C_{8a}-Me or $C_{1'}$-Me), 1.21 (3 H, d, *J* = 6.1 Hz, C_6-Me), 1.23 (3 H, s, C_{8a}-Me or $C_{1'}$-Me), 3.11 (1 H, dd, *J* = 4.3 and 11.6 Hz, C_{4a}-H), 3.37 (1 H, d, *J* = 11.6 Hz, $C_{2'}$-H), 3.59 (1 H, ddq, *J* = 3.6, 11.0, and 6.1 Hz, C_6-H), 3.74 (1 H, dd, *J* = 1.8 and 11.6 Hz, C_2-H), 3.80 (1 H, d, *J* = 11.6 Hz, C_2-H); EI-MS *m*/*z* 213 (1.1, $M^+ - CH_2OH$), 195 (1.0, $M^+ - CH_2OH - H_2O$), 169 (31, $C_{10}H_{17}O_2^+$ (BC ring moiety)), 43 (100); FI-MS *m*/*z* 245 (65, $M^+ + H$), 244 (100, M^+); FI-HR-MS found *m*/*z* 244.1690, calcd for $C_{13}H_{24}O_4$ (M^+) 244.1675.

4-(Benzyloxy)butanol (37). Under an Ar atmosphere, 1,4-butanediol (90 mL, 1.0 mol) was added to a suspension of NaH (60% in oil, 41 g, ca. 1.0 mol) in DMF (600 mL) over 3 h at 0 °C, and then BnCl (120 mL, 1.0 mol) was added to the mixture at room temperature. The mixture was stirred at the same temperature for 36 h, poured into cold water (1 L), and extracted with ether (4 × 700 mL). The combined ethereal layers were washed successively with water (1 L) and brine (1 L), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue on silica gel (1.5 kg) with 15% EtOAc/benzene gave **37** (130 g, 740 mmol, 74%): IR (neat) 3420, 2940, 2880, 1450, 1360, 1090, 725, 685 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.5–1.8 (4 H, C_2-H_2, C_3-H_2), 1.96 (1 H, br s, OH), 3.50, 3.62 (each 2 H, t, *J* = 7 Hz, C_1-H_2, C_4-H_2), 4.49 (2 H, s, OCH_2Ph), 7.28 (5 H, s, aromatic protons); EI-MS *m*/*z* 180 (2.0, M^+), 91 (100, $PhCH_2^+$); EI-HR-MS found *m*/*z* 180.1151, calcd for $C_{11}H_{16}O_2$ (M^+) 180.1151.

Ethyl (*E*)-6-(Benzyloxy)-2-methyl-2-hexenoate (38). A solution of **37** (89 g, 500 mmol) in CH_2Cl_2 (200 mL) was added to a suspension of PCC (540 g, 2.5 mol) in CH_2Cl_2 (700 mL) over 5 min, and the mixture was stirred for 1 h at room temperature. Celite (150 g) and ether (1 L) were added to the mixture. After stirring at room temperature for an additional 30 min, the resulting mixture was filtered through a Celite pad with suction, concentrated in vacuo, and then dissolved in THF (50 mL). The solution was added to a solution of $Na^+MeC^-(PO(OEt)_2)CO_2Et$[26] (600 mmol) in THF (700 mL) at 0 °C under an Ar atmosphere. The mixture was stirred at the same temperature for 2 h, poured into water (1 L), and extracted with ether (4 × 700 mL). The ethereal solutions were combined, washed with brine (1 L), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel (1.5 kg) with 10% EtOAc/benzene to give **38** (94 g, 360 mmol, 73%): IR (neat) 2980, 2950, 2870, 1715, 1455, 1370, 1260, 1095, 745, 700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.27 (3 H, t, *J* = 7 Hz, CO_2CH_2*Me*), 1.80 (3 H, s, C_2-Me), 2.30 (2 H, m, C_4-H_2), 3.45 (2 H, t, *J* = 6 Hz, C_6-H_2), 4.14 (2 H, q, *J* = 7 Hz, CO_2CH_2Me), 4.46 (2 H, s, OCH_2Ph), 6.69 (1 H, br t, *J* = 7 Hz, C_3-H), 7.27 (5 H, s, aromatic protons); EI-MS *m*/*z* 263 (2.5, $M^+ + H$), 262 (0.55, M^+), 91 (100, $PhCH_2^+$); EI-HR-MS found *m*/*z* 262.1481, calcd for $C_{16}H_{22}O_3$ (M^+) 262.1569.

(*E*)-6-(Benzyloxy)-2-methyl-2-hexen-1-ol (39). Diisobutylaluminum hydride (1 M in hexane, 800 mL) was added to a solution of **38** (99 g, 390 mmol) in benzene (700 mL) with stirring at 0 °C over 30 min under an Ar atmosphere. After stirring at the same temperature for an additional 1 h, EtOAc (20 mL), EtOH (20 mL), and water (20 mL) were added successively at 0 °C to the mixture. The resulting suspension was stirred at room temperature for an additional 30 min, filtered through a Celite pad with suction, and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel (1 kg) with 20% EtOAc/benzene to afford **39** (62 g, 280 mmol, 72%): IR (neat) 3300, 3000, 2930, 2840, 1500, 1455, 1365, 1205, 1100, 1070, 1025, 735, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.65 (3 H, s, C_2-Me), 2.12 (2 H, br q, *J* = 7 Hz, C_4-H_2), 3.44 (2 H, t, *J* = 7 Hz, C_6-H_2), 3.95 (2 H, s, C_1-H_2), 4.46 (2 H, s, OCH_2Ph), 5.36 (1 H, br t, *J* = 7 Hz, C_3-H), 7.28 (5 H, s, aromatic protons); EI-MS *m*/*z* 220 (0.88, M^+), 202 (0.32, $M^+ - H_2O$), 91 (100, $PhCH_2^+$); EI-HR-MS found *m*/*z* 220.1458, calcd for $C_{14}H_{20}O_2$ (M^+) 220.1464.

(*E*)-6-(Benzyloxy)-1-chloro-2-methyl-2-hexene (40). A mixture of **39** (26 g, 118 mmol), CCl_4 (43 mL, 450 mmol), and PPh_3 (48 g, 180 mmol) in benzene (250 mL) was refluxed for 12 h under an Ar atmosphere. After cooling, the white suspension obtained was diluted with hexane (500 mL) at 0 °C, filtered with suction, and concentrated in vacuo. Column chromatography of the resulting paste on silica gel (500 g) with 50% hexane/benzene gave **40** (23 g, 95 mmol, 80%): IR (neat) 2950, 2850, 1460, 1275, 1265, 1120, 1100, 1075, 1030, 750, 700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.72 (3 H, s, C_2-Me), 2.07 (2 H, br q, *J* = 7 Hz, C_4-H_2), 3.44 (2 H, t, *J* = 7 Hz, C_6-H_2), 3.97 (2 H, s, C_1-H_2), 4.46 (2 H, s, OCH_2Ph), 5.46 (1 H, br t, *J* = 7 Hz, C_3-H), 7.28 (5 H, s, aromatic protons); EI-MS *m*/*z* 238 (0.31, M^+), 203 (5.4, $M^+ - Cl$), 91 (100, $PhCH_2^+$); EI-HR-MS found *m*/*z* 238.1121, calcd for $C_{14}H_{19}OCl$ (M^+) 238.1126.

(*E*)-6-(Benzyloxy)-2-methyl-1-(phenylthio)-2-hexene (41). A solution of **40** (23 g, 95 mmol) in DMF (50 mL) was added to a solution of sodium thiophenoxide [prepared from NaH (60% in oil, 4.8 g, 120 mmol) and thiophenol (12.0 g, 132 mmol) in DMF (250 mL) at 0 °C] at 0 °C. The mixture was stirred at 0 °C for 30 min, poured into water (1 L), and extracted with ether (3 × 700 mL). The combined extracts were washed with brine (700 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (700 g) with 50% benzene/hexane to afford **41** (29 g, 94 mmol, 99%): IR (neat) 3080, 3060, 2950, 2870, 1590, 1490, 1460, 1445,

1370, 1100, 745, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.72 (3 H, s, C_2-Me), 1.99 (2 H, br q, J = 7 Hz, C_4-H_2), 3.31 (2 H, t, J = 6 Hz, C_6-H_2), 3.46 (2 H, s, C_1-H_2), 4.41 (2 H, s, OCH_2Ph), 5.17 (1 H, br t, J = 7 Hz, C_3-H) 7.1–7.4 (10 H, m, aromatic protons); EI-MS m/z 312 (4.0, M^+), 203 (15, M^+ - SPh), 91 (100, $PhCH_2^+$); EI-HR-MS found m/z 312.1545, calcd for $C_{20}H_{24}OS$ (M^+) 312.1566.

(2*R*,3*S*)-Linalool Oxide (42). Titanium tetraisopropoxide (4.6 g, 16 mmol) and TBHP (5.6 M in CH_2Cl_2, 80 mL, 450 mmol) were added successively to a suspension of D-(-)-DIPT (5.6 g, 24 mmol) and MS4Å (30 g) in CH_2Cl_2 (500 mL) at -10 °C under an Ar atmosphere. After stirring at -10 °C for 20 min, the mixture was cooled to -23 °C, and then freshly distilled geraniol (60 g, 390 mmol) was added over 1 h, keeping the mixture under -20 °C. After the mixture was stirred at -23 °C for an additional 2 h, water (50 mL) was added to the mixture with vigorous stirring and the mixture was allowed to warm to room temperature. After 30 min, 3 M NaOH (30 mL) was added to the mixture, which was stirred at room temperature for an additional 30 min, filtered thorugh a Celite pad with suction, and concentrated in vacuo. Distillation of the crude product under reduced pressure afforded (2*R*,3*R*)-2,3-epoxygeraniol (60 g, 350 mmol, 90%): bp 110–113 °C (2.5 mmHg); $[\alpha]^{18}_D$ +4.50° (*c* 2.50, $CHCl_3$); 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, br q , J = 7 Hz, C_5-H_2), 2.95 (1 H, dd, J = 5 and 7 Hz, C_2-H), 3.72 (2 H, br, C_1-H_2), 5.05 (1 H, br t, J = 7 Hz, C_6-H).

A solution of (2*R*,3*R*)-2,3-epoxygeraniol (60 g, 350 mmol), TsCl (86 g, 450 mmol), and pyridine (44 mL, 560 mmol), in CH_2Cl_2 was stirred at 0 °C for 24 h. The resulting mixture was poured into water (1 L) and extracted with ether (4 × 700 mL). The extracts were combined, washed with brine (1 L), dried (Na_2SO_4), and concentrated in vacuo to give a crude product which was dissolved in a mixture of CH_3CN (800 mL) and water (550 mL). *p*-Toluenesulfonic acid (1.0 g, 5.8 mmol) was added to the solution at 50 °C, and the mixture was stirred at the same temperature for 24 h. After cooling to room temperature, the solution was extracted with ether (3 × 700 mL). The extracts were combined, 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 the corresponding tosylate (73 g, 210 mmol, 60%): $[\alpha]^{23}_D$ +22.2° (*c* 1.00, $CHCl_3$); IR (neat) 3530, 2950, 2900, 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 (3 H, s, C_7-Me_{cis}), 1.68 (3 H, s, C_7-Me_{trans}), 2.43 (3 H, s, $SO_2C_6H_4Me$), 3.65 (1 H, br dd, J = 9 and 2 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, br t, J = 7 Hz, C_6-H), 7.30, 7.33 (each 2 H, d, J = 11 Hz, aromatic protons); FI-MS m/z 342 (100, M^+); FI-HR-MS found m/z 342.1480, calcd for $C_{17}H_{26}O_5S$ (M^+) 342.1502.

A suspension of the tosylate (73 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 poured into 10% aqueous citric acid solution (1 L) and extracted with ether (4 × 700 mL). The combined ethereal solutions were washed successively with water (700 mL) and brine (700 mL), dried (Na_2SO_4), and concentrated in vacuo. Distillation of the residue under reduced pressure gave **42** (27 g, 160 mmol, 73%): $[\alpha]^{22}_D$ +23.5° (*c* 2.75, $CHCl_3$); 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 (3 H, s, C_7-Me_{cis}), 1.69 (3 H, s, C_7-Me_{trans}), 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, br t, J = 7 Hz, C_6-H); FI-MS m/z 170 (100, M^+); FI-HR-MS found m/z 170.1321, calcd for $C_{10}H_{18}O_2$ (M^+) 170.1307.

(2*R*,3*S*)-1,2-Epoxy-3-[(methoxymethyl)oxy]-3,7-dimethyl-6-octene (43). A solution of **42** (30 g, 170 mmol), *i*-Pr_2NEt (89 mL, 510 mmol), MOMCl (26 mL, 340 mmol), and DMAP (2.1 g, 17 mmol) in CH_2Cl_2 (200 mL) was stirred at room temperature for 36 h. The mixture was poured into 10% aqueous citric acid solution (500 mL) and extracted with ether (300 mL × 4). The extracts were combined, washed successively with water (500 mL) and brine (500 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue on silica gel (1 kg) with 5% EtOAc/benzene yielded **43** (37 g, 170 mmol, 99%): $[\alpha]^{20}_D$ -3.65° (*c* 4.00, $CHCl_3$); 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 (3 H, s, C_7-Me_{cis}), 1.68 (3 H, s, C_7-Me_{trans}), 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, OMe), 4.60, 4.74 (each 1 H, d, J = 8 Hz, OCH_2OMe) 5.05 (1 H, br t, J = 7 Hz, C_6-H); EI-MS m/z 152 (2.5, M^+ - $HOCH_2OMe$), 45 (100, $MeOCH_2^+$); FI-MS m/z 214 (100, M^+); FI-HR-MS found m/z 214.1592, calcd for $C_{12}H_{22}O_3$ (M^+) 214.1570.

(2*R*,3*S*,6*R*)-2-[3-(Benzyloxy)propyl]tetrahydro-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-3-methyl-2*H*-pyran-3-ol (49). A solution of **41** (3.2 g, 10 mmol) and DABCO (1.5 g, 13 mmol) in THF (50 mL) was stirred at -60 °C under an Ar atmosphere, and BuLi (1.5 M in hexane, 7.1 mL, 11 mmol) was added to the solution. The colorless solution turned red upon addition of BuLi. After stirring at -60 °C for 10 min, a solution of **43** (2.1 g, 9.8 mmol) in THF (5 mL) was added to the mixture. After stirring at the same temperature for 30 min, 10% aqueous citric acid solution (50 mL) was added to the mixture, which was allowed to warm to room temperature. The resulting mixture was poured into water (150 mL) and extracted with ether (4 × 100 mL). The combined ethereal solutions were washed successively with water (150 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography of the residue on silica gel (70 g) with 7% EtOAc/benzene gave **44** as a diastereomeric mixture, which was dissolved in a mixture of 2-propanol (20 mL) and THF (40 mL). The solution was heated to reflux, and metallic Na (1.0 g, 43 mmol) was added to the solution under an Ar atmosphere. The mixture was refluxed vigorously for 2 h, cooled to room temperature, and the remaining excess Na was removed. The mixture was poured into 10% aqueous citric acid solution (100 mL) and extracted with ether (4 × 150 mL). The combined extracts were washed successively with water (100 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (100 g) with 8% EtOAc/benzene to afford a mixture of **45** and **46** in the ratio of 7:1 (2.5 g, 5.9 mmol, 77%): $[\alpha]^{24}_D$ +6.74° (*c* 2.40, $CHCl_3$); IR (neat) 3460, 2920, 2850, 1450, 1375, 1145, 1095, 1030, 915, 735, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.20 (3 H, s, C_6-H), 1.59 (6 H, s, C_2-Me_{cis}, C_{10}-Me), 1.66 (3 H, s, C_2-Me_{trans}), 2.10 (6 H, m, C_4-H_2, C_9-H_2, C_{12}-H_2), 3.35 (3 H, s, OMe), 3.44 (3 H, C_7-H, C_{14}-H_2), 4.45 (2 H, s, OCH_2Ph), 5.05 (2 H, m, C_3-H, C_{11}-H), 7.25 (5 H, s, aromatic protons); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 15.82, 17.38, 19.76, 21.80, 23.17 (minor), 24.30, 25.43, 28.78 (minor), 29.51, 29.64, 34.79, 36.68, 55.13, 69.55, 69.97 (minor), 72.50, 75.58, 80.52 (minor), 80.86, 90.71, 123.82, 124.34, 127.02, 127.14, 127.90, 130.80, 135.16, 138.36; FI-MS m/z 418 (100, M^+), 91 (61, $PhCH_2^+$).

Vanadyl acetylacetonate (30 mg, 0.11 mmol) and TBHP (neat, 80% activity, 810 mg, 7.2 mmol) were added to a solution of the mixture, **45** and **46** (2.03 g, 4.85 mmol), in CH_2Cl_2 (30 mL) at room temperature. The mixture was stirred at the same temperature for 3.5 h, poured into 10% aqueous $Na_2S_2O_3$ solution (150 mL), and extracted with ether (4 × 100 mL). The combined ethereal solutions were washed successively with water (150 mL) and brine (150 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was subjected to column chromatography on silica gel (100 g) with 15% EtOAc/benzene to give a mixutre of **47** and its diastereomeric isomer (1.5 g, 3.3 mmol, 72%) in the ratio of 4:1 by 90-MHz ^1H NMR: IR (neat) 3440, 2960, 2920, 2850, 1455, 1380, 1145, 1100, 1035, 920, 740, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.11 (3 H × 0.8, s, C_2-Me_{major}), 1.14 (3 H × 0.2, s, C_2-Me_{minor}), 1.19 (3 H × 0.8, s, $C_{1''}$-Me_{major}), 1.22 (3 H × 0.2, s, $C_{1''}$-Me_{minor}), 1.61 (3 H, s, $C_{5''}$-Me_{cis}), 1.69 (3 H, s, $C_{5''}$-Me_{trans}), 3.35 (3 H, s, OMe), 3.50 (3 H, m, $C_{1''}$-H, $C_{4''}$-H_2), 3.90 (1 H, dd, J = 8 and 10 Hz, C_5-H), 4.48 (2 H, s, OCH_2Ph), 4.57, 4.90 (each 1 H, d, J = 8 Hz, OCH_2OMe), 5.05 (1 H, br t, J = 7 Hz, $C_{4''}$-H), 7.25 (5 H, s, aromatic protons); FI-MS m/z 435 (100, M^+), 434 (63, M^+ - $PhCH_2O(CH_2)_3CH(OH)$).

A solution of the mixture, **47** and its isomer (3.4 g, 7.8 mmol), Et_3N (4.3 mL, 30 mmol), and MsCl (1300 mg, 11 mmol) in CH_2Cl_2 (80 mL) was stirred at 0 °C for 12 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (150 mL) and extracted with ether (4 × 100 mL). The combined extracts were washed successively with 0.5 M HCl (100 mL), water (100 mL), and brine (100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residual oil was diluted with a mixture of acetone (80 mL) and water (50 mL). Silver carbonate (8.6 g, 31 mmol) was added to the solution at room temperature under

an Ar atmosphere, and the suspension was stirred for 12 h at 50 °C. The resulting mixture was cooled to room temperature, filtered through a Celite pad with suction, and concentrated in vacuo. Column chromatography of the residue on silica gel (100 g) with 25% EtOAc/benzene gave diastereomerically pure **49** (1.4 g, 3.3 mmol, 42%): $[\alpha]^{24}_D$ +7.96° (*c* 3.10, $CHCl_3$); IR (neat) 3430, 2930, 2850, 1455, 1380, 1370, 1150, 1100, 1035, 920, 740, 700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.15, 1.20 (each 3 H, s, C_3-Me, $C_{1''}$-Me), 1.60 (3 H, s, $C_{5''}$-Me_{cis}), 1.67 (3 H, s, $C_{5''}$-Me_{trans}), 3.02 (1 H, br d, *J* = 10 Hz, C_2-H), 3.2–3.6 (3 H, m, C_6-H, $C_{3'}$-H_2), 3.33 (3 H, s, OMe), 4.47 (2 H, s, OCH_2Ph), 4.63, 4.77 (each 1 H, d, *J* = 6 Hz, OCH_2OMe), 5.07 (1 H, br t, *J* = 7 Hz, $C_{4''}$-H), 7.28 (5 H, s, aromatic protons); FI-MS *m/z* 435 (65, M^+ + H), 434 (100, M^+), 403 (35, M^+ – MeO), 402 (25, M^+ – MeOH); FI-HR-MS found *m/z* 434.3029, calcd for $C_{26}H_{42}O_5$ (M^+) 434.3034.

(2*R*,3*S*,6*R*)-2-[3-(Benzyloxy)propyl]tetrahydro-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-3-methyl-3-[(trimethylsilyl)oxy]-2*H*-pyran (50). A solution of **49** (590 mg, 1.4 mmol), DMAP (20 mg, 160 μmol), Et_3N (700 μL, 5.0 mmol), and TMSCl (0.3 mL, 2.4 mmol) in CH_2Cl_2 (6.0 mL) was stirred at 0 °C for 30 min. The resulting mixture was poured into saturated aqueous $NaHCO_3$ solution (40 mL) and extracted with ether (4 × 30 mL). The combined ethereal solutions were washed successively with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue on silica gel (15 g) with 5% EtOAc/benzene gave **50** (570 mg, 1.1 mmol, 83%): $[\alpha]^{24}_D$ +11.2° (*c* 2.70, $CHCl_3$); IR (neat) 2920, 2840, 1450, 1375, 1245, 1145, 1095, 915, 870, 840, 735 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.10 (9 H, s, $SiMe_3$), 1.16, 1.20 (each 3 H, s, C_3-Me, $C_{1''}$-Me), 1.60 (3 H, s, $C_{5''}$-Me_{cis}), 1.67 (3 H, s, $C_{5''}$-Me_{trans}), 2.98 (1 H, br d, *J* = 9 Hz, C_2-H), 3.23 (1 H, br d, *J* = 9 Hz, C_6-H), 3.34 (3 H, s, OMe), 3.47 (2 H, t, *J* = 7 Hz, $C_{3'}$-H_2), 4.48 (2 H, s, OCH_2Ph), 4.63, 4.75 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 5.04 (1 H, br t, *J* = 7 Hz, $C_{4''}$-H), 7.29 (5 H, s, aromatic protons); EI-MS *m/z* 506 (0.01, M^+), 474 (0.02, M^+ – MeOH), 91 (100, $PhCH_2^+$); EI-HR-MS found *m/z* 506.3469, calcd for $C_{29}H_{50}O_5Si$ (M^+) 506.3429.

(2*R*,3*S*,6*R*)-2-(3-Hydroxypropyl)tetrahydro-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-3-methyl-3-[(trimethylsilyl)oxy]-2*H*-pyran (51). Liquid NH_3 (ca. 20 mL) and metallic Li (300 mg, excess) were added successively to a solution of **50** (50 mg, 98 μmol) in THF (10 mL) with stirring at −78 °C under an Ar atmosphere. After the mixture was stirred for 2 h at the same temperature, NH_4Cl (ca. 1 g) was added to the mixture to quench the reaction. The mixture was allowed to warm to room temperature, and NH_3 was then allowed to evaporate. The resulting mixture was dissolved in water (40 mL) and extracted with ether (4 × 40 mL). The extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), concentrated in vacuo, and chromatographed over silica gel (10 g). Elution with 15% EtOAc/benzene yielded **51** (35 mg, 84 μmol, 85%): $[\alpha]^{24}_D$ +19.2° (*c* 2.00, $CHCl_3$); IR (neat) 3400, 2940, 2850, 1450, 1380, 1250, 1140, 1095, 1035, 920, 870, 840, 755 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.10 (9 H, s, $SiMe_3$), 1.16, 1.20 (each 3 H, s, C_3-Me, $C_{1''}$-Me), 1.60 (3 H, s, $C_{4''}$-Me_{cis}), 1.67 (3 H, s, $C_{4''}$-Me_{trans}), 3.03 (1 H, br d, *J* = 10 Hz, C_2-H), 3.27 (1 H, br d, *J* = 9 Hz, C_6-H), 3.34 (3 H, s, OMe), 3.62 (2 H, br t, *J* = 7 Hz, $C_{3'}$-H_2), 4.66, 4.77 (each 1 H, d, *J* = 8 Hz, OCH_2OMe), 5.04 (1 H, br t, *J* = 7 Hz, $C_{4''}$-H); EI-MS *m/z* 416 (0.10, M^+), 384 (0.75, M^+ – MeOH), 111 (87), 73 (100, Me_3Si^+); EI-HR-MS found *m/z* 416.2912, calcd for $C_{22}H_{44}O_5Si$ (M^+) 416.2959.

(2*R*,3*S*,6*R*)-2-[(*E*)-4-(Ethoxycarbonyl)pent-3-enyl]tetrahydro-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-3-methyl-3-[(trimethylsilyl)oxy]-2*H*-pyran (53). A suspension of **51** (35 mg, 84 μmol), NaOAc (78 mg, 950 μmol), and PDC (400 mg, 1.1 mmol) in CH_2Cl_2 (3.0 mL) was stirred at room temperature for 30 min, and then Celite (500 mg) and ether (20 mL) were added to the mixture. After stirring at the same temperature for an additional 10 min, the mixture was filtered through a Celite pad with suction, and the filtrates were washed successively with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to give almost pure **52** (35 mg, 84 μmol, 100%): ^1H NMR (90 MHz, $CDCl_3$) δ 0.10 (9 H, s, $SiMe_3$), 1.19 (6 H, s, C_3-Me, $C_{1''}$-Me), 1.60 (3 H, s, $C_{5''}$-Me_{cis}), 1.67 (3 H, s, $C_{5''}$-Me_{trans}), 2.45 (2 H, m, $C_{2'}$-H_2), 2.97 (1 H, dd, *J* = 2 and 9 Hz, C_2-H), 3.25 (1 H, br d, *J* = 9 Hz, C_6-H), 3.30 (3 H, s, OMe), 4.60, 4.74 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 5.05 (1 H, br t, *J* = 7 Hz, $C_{4''}$-H), 9.68 (1 H, t, *J* = 2 Hz, $C_{3'}$-H). A solution of **52** (350 mg, 84 μmol) and $MeC(PPh_3)CO_2Et$[21] (40 mg, 110 μmol) in CH_2Cl_2 (2.0 mL) was stirred at reflux temperature for 3 h under an Ar atmosphere. After cooling to room temperature, the solvent was removed under reduced pressure, and column chromatography of the residue on silica gel (7 g) with 5% EtOAc/benzene gave **53** (41 mg, 82 μmol, 98%): $[\alpha]^{24}_D$ +14.4° (*c* 3.40, $CHCl_3$); IR (neat) 2960, 2850, 1715, 1450, 1380, 1265, 1250, 1130, 1100, 875, 845 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.10 (9 H, s, $SiMe_3$), 1.17, 1.21 (each 3 H, s, C_3-Me, $C_{1''}$-Me), 1.30 (3 H, t, *J* = 7 Hz, CO_2CH_2Me), 1.60 (3 H, s, $C_{5''}$-Me_{cis}), 1.67 (3 H, s, $C_{5''}$-Me_{trans}), 1.82 (3 H, d, *J* = 1 Hz $C_{4''}$-Me), 2.98 (1 H, dd, *J* = 2 and 10 Hz, C_2-H), 3.25 (1 H, br d, *J* = 9 Hz, C_6-H), 3.33 (3 H, s, OMe), 4.16 (2 H, q, *J* = 7 Hz, CO_2CH_2Me), 4.64, 4.77 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 5.03 (1 H, br t, *J* = 7 Hz, $C_{4''}$-H), 6.74 (1 H, dt, *J* = 1 and 7 Hz, $C_{3'}$-H); EI-MS *m/z* 498 (0.11, M^+), 446 (1.9, M^+ – MeOH), 139 (100), 73 (93, Me_3Si^+); EI-HR-MS found *m/z* 498.3395, calcd for $C_{27}H_{50}O_6Si$ (M^+) 498.3378.

(2*R*,3*S*,6*R*)-Tetrahydro-2-[(*E*)-5-hydroxy-4-methylpent-3-enyl]-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-3-methyl-3-[(trimethylsilyl)oxy]-2*H*-pyran (54). Diisobutylaluminum hydride (1 M in hexane, 5.5 mL, 5.5 mmol) was added to a solution of **53** (1.1 g, 2.2 mmol) in hexane (40 mL) at −78 °C under an Ar atmosphere. After stirring at the same temperature for 5 min, MeOH (1.0 mL) and water (500 μL) were added successively to the mixture, and the mixture was allowed to warm to room temperature. The resulting white suspension was filtered through a Celite pad with suction, and the filtrates were concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (30 g) with 15% EtOAc/benzene to afford **54** (950 mg, 2.1 mmol, 96%): $[\alpha]^{24}_D$ +16.0° (*c* 5.50, $CHCl_3$); IR (neat) 3400, 2970, 2870, 1455, 1250, 1140, 1100, 1040, 925, 875, 845, 760 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.10 (9 H, s, $SiMe_3$), 1.13, 1.20 (each 3 H, s, C_3-Me, $C_{1''}$-Me), 1.58 (3 H, s, $C_{5''}$-Me_{cis}), 1.65 (6 H, s, $C_{4'}$-Me, $C_{5''}$-Me_{trans}), 2.96 (1 H, dd, *J* = 2 and 10 Hz, C_2-H), 3.22 (1 H, d, *J* = 10 Hz, C_6-H), 3.32 (3 H, s, OMe), 3.95 (2 H, br s, $C_{5'}$-H_2), 4.64, 4.77 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 5.04 (1 H, br t, *J* = 7 Hz, $C_{4''}$-H), 5.39 (1 H, br t, *J* = 7 Hz, $C_{3'}$-H); EI-MS *m/z* 456 (0.13, M^+), 438 (0.52, M^+ – H_2O), 424 (0.24, M^+ – MeOH), 73, (100, Me_3Si^+); EI-HR-MS found *m/z* 456.3281, calcd for $C_{25}H_{48}O_5Si$ (M^+) 456.3272.

(2*R*,3*S*,6*R*)-Tetrahydro-2-[2-[(2*S*,3*S*)-3-(hydroxymethyl)-3-methyloxiran-2-yl]ethyl]-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-3-methyl-2*H*-pyran-3-ol (56). A suspension of **54** (960 mg, 2.10 mmol) and MS4Å (1.50 g) in CH_2Cl_2 (30 mL) was stirred at −20 °C under an Ar atmosphere, and then $Ti(Oi\text{-}Pr)_4$ (650 mg, 2.3 mmol) and L-(+)-DIPT (730 mg, 3.1 mmol) were added successively to the suspension. After the mixture was stirred at the same temperature for 10 min, TBHP (5.6 M in CH_2Cl_2, 630 μL, 3.5 mmol) was added. The mixture was stirred for additional 1 h at −20 °C, and then 2 M NaOH in saturated aqueous Na_2SO_4 solution (3.0 mL) was added to the mixture, which was allowed to warm to room temperature with stirring. After stirring at the same temperature for an additional 1 h, the resulting suspension was filtered through a Celite pad with suction, poured into water (50 mL), and extracted with EtOAc (4 × 30 mL). The extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrted in vacuo. The remaining DIPT was removed by column chromatography on silica gel (20 g) with 30% EtOAc/benzene. The oil thus obtained was dissolved in THF (30 mL), and then TBAF (1 M in THF, 4.0 mL, 4.0 mmol) was added to the solution at room temperature. After stirring at the same temperature for 1 h, the mixture was adsorbed on silica gel (50 g). Elution with 5% MeOH/$CHCl_3$ gave **56** (830 mg, 2.1 mmol, 98%): $[\alpha]^{24}_D$ +3.00° (*c* 5.00, $CHCl_3$); IR (neat) 3400, 2920, 2870, 1450, 1380, 1140, 1095, 1035, 920 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.15, 1.22 (each 3 H, s, C_3-Me, $C_{1''}$-Me), 1.26 (3 H, s, $C_{3''}$-Me), 1.59 (3 H, s, $C_{5''}$-Me_{cis}), 1.68 (3 H, s, $C_{5''}$-Me_{trans}), 2.8–3.2 (3 H, m, C_2-H, C_6-H, $C_{2''}$-H), 3.32 (3 H, s, OMe), 3.53, 3.65 (each 1 H, d, *J* = 14 Hz, $C_{3''}$-CH_2OH), 4.65, 4.75 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 5.05 (1 H, br t, *J* = 7 Hz, $C_{4''}$-H); FI-MS *m/z* 401 (100, M^+ + H), 400 (62, M^+); FI-HR-MS found *m/z* 400.2777, calcd for $C_{22}H_{40}O_6$ (M^+) 400.2826.

(2*R*,4a*R*,6*R*,8a*S*)-Octahydro-2-[(*S*)-1,2-dihydroxy-1-methylethyl]-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (57). A solution of **56** (180 mg, 440 μmol) and Ti(O*i*-Pr)$_4$ (20 mg, 70 μmol) in toluene (10 mL) was stirred at 50 °C for 20 h under an Ar atmosphere. After cooling to room temperature, 10% aqueous citric acid solution (1.0 mL) and EtOAc (10 mL) were added to the mixture, which was stirred at the same temperature for an additional 3 h. The mixture was filtered through a Celite pad with suction, poured into water (30 mL), and extracted with EtOAc (15 mL × 4). The combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was subjected to column chromatography on silica gel (5 g) with 10% acetone/$CHCl_3$ to give **57** (110 mg, 285 μmol, 65%): $[\alpha]^{24}_D$ −7.80° (*c* 2.00, $CHCl_3$); IR (neat) 3430, 2950, 2930, 2880, 1460, 1380, 1150, 1100, 1035, 920, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07, 1.20, 1.22 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me), 1.61 (3 H, s, $C_{5''}$-Me_{cis}), 1.68 (3 H, s, $C_{5''}$-Me_{trans}), 3.36 (2 H, m, C_6-H, $C_{2'}$-H), 3.37 (3 H, s, OMe), 3.59 (1 H, dd, *J* = 7.8 and 11.4 Hz, C_{4a}-H), 3.74 (1 H, br d, *J* = 11.2 Hz, $C_{2'}$-H), 3.93 (1 H, dd, *J* = 3.9 and 11.7 Hz, $C_{2'}$-H), 4.69, 4.77 (each 1 H, d, *J* = 7.3 Hz, OCH_2OMe), 5.10 (1 H, tt, *J* = 1.5 and 7.3 Hz, $C_{4''}$-H); FI-MS *m*/*z* 401 (86, M$^+$ + H), 400 (100, M$^+$), 369 (62, M$^+$ − MeO), 368 (75, M$^+$ − MeOH); FI-HR-MS found *m*/*z* 400.2835, calcd for $C_{22}H_{40}O_6$ (M$^+$) 400.2826.

(2*R*,4a*R*,6*R*,8a*S*)-2-[(*S*)-2-(Benzoyloxy)-1-hydroxy-1-methylethyl]octahydro-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (58). A solution of **57** (40 mg, 100 μmol), Et_3N (200 μL, 1.4 mmol), and BzCl (100 μL, 710 μmol) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 12 h. The mixture was poured into water (20 mL) and extracted with ether (4 × 15 mL). 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 (2 g) with 7% EtOAc/benzene to yield **58** (50 mg, 99 μmol, 99%): $[\alpha]^{24}_D$ +12.0° (*c* 2.50, $CHCl_3$); IR (neat) 3450, 2970, 2870, 1725, 1455, 1385, 1320, 1275, 1095, 1035, 920, 760, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20, 1.20, 1.25 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me), 1.61 ($C_{5''}$-Me_{cis}), 1.68 ($C_{5''}$-Me_{trans}), 3.38 (3 H, s, OMe), 3.38 (1 H, dd, *J* = 2.3 and 11.0 Hz, C_6-H), 3.59 (1 H, dd, *J* = 7.3 and 11.2 Hz, C_{4a}-H), 3.92 (1 H, dd, *J* = 2.9 and 12.7 Hz, $C_{2'}$-H), 4.26, 4.34 (each 1 H, d, *J* = 11.2 Hz, $C_{2'}$-H_2), 4.69, 4.77 (each 1 H, d, *J* = 7.3 Hz, OCH_2OMe), 5.12 (1 H, tt, *J* = 1.0 and 6.8 Hz, $C_{4''}$-H), 7.46 (2 H, m, aromatic protons), 7.57 (1 H, m, aromatic protons), 8.05 (2 H, m, aromatic protons); FI-MS *m*/*z* 505 (49, M$^+$ + H), 504 (100, M$^+$), 473 (42, M$^+$ − MeO), 472 (50.3, M$^+$ − MeOH); FI-HR-MS found *m*/*z* 504.3103, calcd for $C_{29}H_{44}O_7$ (M$^+$) 504.3088.

2-Cyclohexyl-6-methyl-5-hepten-2-ol (62). Under an Ar atmosphere, 6-methyl-5-hepten-2-one (2.0 g, 16 mmol) was added to a solution of cyclohexylmagnesium bromide [prepared from Mg (800 mg, 33 mmol) and bromocyclohexane (3.3 g, 20 mmol) in THF (50 mL) at 0 °C under an Ar atmosphere according to the usual procedure] at 0 °C over 10 min. After the mixture was stirred at the same temperature for 3 h, water (3.0 mL) was added to the mixture, and the resulting suspension was poured into 2 M HCl (100 mL) and extracted with ether (3 × 70 mL). The combined extracts were concentrated and diluted with EtOH (30 mL), and then $NaBH_4$ (300 mg, 8.1 mmol) was added to the solution at 0 °C to reduce the aldol compound which was produced in a Grignard reaction. Excess $NaBH_4$ was decomposed by addition of 2 M HCl (ca. 3.0 mL) at 0 °C. The mixture was poured into water (150 mL) and extracted with ether (3 × 100 mL). The organic layers were combined, washed with brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was subjected to column chromatography on silica gel (100 g) with 5% EtOAc/benzene to give **62** (2.0 g, 9.5 mmol, 59%): IR (neat) 3400, 2920, 2850, 1455, 1380, 1115, 925, 900 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.12 (3 H, s, C_2-Me), 1.63, 1.69 (each 3 H, s, C_6-Me_2), 5.10 (1 H, br t, *J* = 7 Hz, C_5-H); EI-MS *m*/*z* 192 (4.5, M$^+$ − H_2O), 127 (15, M$^+$ − C_6H_{11}), 109 (100, CMe_2=CH-$(CH_2)_2$CH=CH_2^+); EI-HR-MS found *m*/*z* 192.1895, calcd for $C_{14}H_{24}$ (M$^+$ − H_2O) 192.1879.

(2*R,3*S**)-3-Bromo-6-cyclohexyltetrahydro-2,2,6-trimethyl-2*H*-pyran (63) and (2*S**,5*RS*)-5-(2-Bromo-1-methylethyl)-2-cyclohexyltetrahydro-2-methylfuran (64).**
(1) Cyclization in CH_3NO_2. A solution of **62** (100 mg, 480 μmol) and TBCO (230 mg, 580 μmol) in CH_3NO_2 (15 mL) was stirred at room temperature for 30 min. The mixture was poured into 10% aqueous $Na_2S_2O_3$ solution (100 mL) and extracted with ether (3 × 70 mL). The combined ethereal solutions were washed successively with 2 M NaOH (150 mL), water (150 mL), and brine (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a mixture of **63** and **64** (120 mg, 420 μmol, 86%) in a ratio of 1:4.6 by 90-MHz ^{1}H NMR spectroscopy. An analytical sample was obtained by column chromatography on silica gel (Merck, Art. 7754) with 10% benzene/hexane to give pure **63** (20 mg, 69 μmol, 14%), **64** (50 mg, 280 μmol, 34%), and its epimer (33 mg, 110 μmol, 23%).

63: IR (neat) 2920, 2850, 1455, 1383, 1130, 1050, 983, 845, 773, 738 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.16 (3 H, s, C_6-Me), 1.28, 1.41 (each 3 H, s, C_2-Me_2), 2.08 (1 H, dq, *J* = 13.5 and 3.5 Hz, C_4-H_{eq}), 2.23 (1 H, dq, *J* = 4.3 and 13.5 Hz, C_4-H_{ax}), 3.87 (1 H, dd, *J* = 4.3 and 12.3 Hz, C_3-H); EI-MS *m*/*z* 275 (2.0, M$^+$ − Me), 273 (2.0, M$^+$ − Me), 207 (63, M$^+$ − C_6H_{11}), 205 (65, M$^+$ − C_6H_{11}), 43 (100); EI-HR-MS found *m*/*z* 273.0860, calcd for $C_{13}H_{22}O^{79}Br$ (M$^+$ − Me) 273.0855.

64: IR (neat) 2950, 2920, 2850, 1453, 1390, 1375, 1145, 1113, 1087, 1025, 870 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.09 (3 H, s, C_2-Me), 1.72 (6 H, s, C_5-CMe_2), 3.91 (1 H, dd, *J* = 6.1 and 7.0 Hz, C_5-H); EI-MS *m*/*z* 275 (3.6, M$^+$ − Me), 273 (3.7, M$^+$ − Me), 207 (43, M$^+$ − C_6H_{11}), 205 (83, M$^+$ − C_6H_{11}), 167 (24, M$^+$ − Me_2CBr), 149 (72, M$^+$ − Me_2CBr − H_2O), 125 (100), 107 (99).

Epimer of **64**: IR (neat) 2950, 2920, 2850, 1543, 1390, 1375, 1145, 1113, 1087, 1025, 870 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (3 H, s, C_2-Me), 1.71, 1.72 (each 3 H, s, C_5-CMe_2), 3.78 (1 H, dd, *J* = 6.1 and 8.5 Hz, C_5-H).

(2) Cyclization in CH_2Cl_2. A solution of **62** (15 mg, 71 μmol) and TBCO (30 mg, 76 μmol) in CH_2Cl_2 (1.0 mL) was stirred at room temperature. After being stirred at the same temperature for 30 min, the mixture was poured into 10% aqueous $Na_2S_2O_3$ solution (20 mL) and extracted with ether (3 × 20 mL). The extracts were combined, washed successively with 1 M NaOH (20 mL), water (20 mL), and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo to give a mixture of **63** and **64** (19 mg, 66 μmol, 92%) in the ratio of 1:8.9 by 90-MHz ^{1}H NMR spectroscopy.

(3) Cyclization in Nitroethane. A solution of **62** (15 mg, 71 μmol) and TBCO (30 mg, 76 μmol) in nitroethane (1.0 mL) was treated at room temperature for 30 min. Similar workup gave a mixture of **63** and **64** (18 mg, 62 μmol, 87%) in the ratio of 1:5.5 by 90-MHz ^{1}H NMR spectroscopy.

(2*R*,4a*R*,6*R*,8a*S*)-2-[(*S*)-2-(Benzoyloxy)-1-hydroxy-1-methylethyl]octahydro-6-[(*S*)-1-hydroxy-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (65). A solution of **58** (50 mg, 99 μmol) in a mixture of 12 M HCl (50 μL) in MeOH (2.0 mL) was stirred at room temperature for 2 h. The mixture was neutralized by addition of Et_3N (100 μL) and concentrated in vacuo. Column chromatography of the residue on silica gel (2 g) with 20% EtOAc/benzene afforded **65** (40 mg, 86 μmol, 88%): $[\alpha]^{24}_D$ −15.5° (*c* 2.50, $CHCl_3$); IR (neat) 3440, 2970, 2850, 1730, 1455, 1385, 1280, 1110, 1070, 760, 715 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.15, 1.21, 1.24 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me), 1.60 (3 H, s, $C_{5''}$-Me_{cis}), 1.67 (3 H, s, $C_{5''}$-Me_{trans}), 3.2–3.9 (3 H, m, C_2-H, C_{4a}-H, C_6-H), 4.20, 4.33 (each 1 H, d, *J* = 11 Hz, $C_{2'}$-H_2), 5.10 (1 H, br t, *J* = 7 Hz, $C_{4''}$-H) and 7.2–7.6 (3 H, m, aromatic protons), 7.9–8.1 (2 H, m, aromatic protons); FI-MS *m*/*z* 461 (100, M$^+$ + H), 460 (85, M$^+$), 442 (43, M$^+$ − H_2O), 179 (59, $PhCOOCH_2C^+$(OH)Me); FI-HR-MS found *m*/*z* 460.2809, calcd for $C_{27}H_{40}O_6$ (M$^+$) 460.2836.

(2*R*,4a*R*,6*R*,8a*S*)-2-[(*S*)-2-(Benzoyloxy)-1-hydroxy-1-methylethyl]-6-[(2*S*,5*R*)-5-bromotetrahydro-2,6,6-trimethyl-2*H*-pyran-2-yl]octahydro-8a-methylpyrano[3,2-*b*]pyran (66). A solution of **65** (17 mg, 36 μmol) and TBCO (17.0 mg, 43.1 μmol) in CH_3NO_2 (1.0 mL) was stirred at room temperature for 1 h. The mixture was poured into 0.5 M NaOH (20 mL) and extracted with ether (4 × 15 mL). The combined ethereal solutions were washed successively with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Preparative TLC (silica gel) of the crude product with 15% EtOAc/benzene gave **66** (7.0 mg, 14 μmol, 36%): R_f = 0.60 (silica gel, 15% EtOAc/benzene): $[\alpha]^{24}_D$ −6.0° (*c* 0.50, $CHCl_3$); IR (neat) 3480, 2970, 2850, 1730, 1460, 1385, 1280, 1105, 1025, 760, 715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18, 1.19, 1.24, 1.27 (each 3 H, s, C_{8a}-Me,

$C_{1'}$-Me, $C_{2''}$-Me, $C_{6''}$-Me), 1.40 (3 H, s, $C_{6''}$-Me), 2.23 (1 H, dq, J = 3.9, 13.0 Hz, $C_{4''}$-H_β), 2.70, (1 H, br s, OH), 3.05 (1 H, dd, J = 2.5 and 11.7 Hz, C_6-H), 3.59 (1 H, dd, J = 6.8 and 11.2 Hz, C_{4a}-H), 3.88, 3.89 (each 1 H, dd, J = 3.9 and 12.2 Hz, C_2-H, $C_{5''}$-H), 4.27, 4.34 (each 1 H, d, J = 11.2 Hz, $C_{2'}$-H_2), 7.4–7.6 (3 H, m, aromatic protons), 8.05 (2 H, m, aromatic protons); FI-MS m/z 541 (44, M^+ + H), 540 (32, M^+), 539 (43, M^+ + H), 538 (19, M^+), 458 (59, M^+ - Br), 207 (88, $C_8H_{14}O^{81}Br^+$ (A ring moiety)), 205 (61, $C_8H_{14}O^{79}Br^+$ (A ring moiety)), 179 (100, $BzOCH_2C^+(OH)Me$); FI-HR-MS found m/z 539. 1986, calcd for $C_{27}H_{40}O_6{}^{79}Br$ (M^+ + H) 539.2009.

(2*R*,4a*R*,6*R*,8a*S*)-6-[(2*S*,5*R*)-5-Bromotetrahydro-2,6,6-trimethyl-2*H*-pyran-2-yl]octahydro-2-[(*S*)-1,2-dihydroxy-1-methylethyl]-8a-methylpyrano[3,2-*b*]pyran (67). A suspension of **66** (9 mg, 16 μmol) and K_2CO_3 (50 mg, 35 μmol) in MeOH (3.0 mL) was stirred at room temperature for 3 h. The mixture was poured into water (20 mL) and extracted with $CHCl_3$ (4 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over silica gel (500 mg) with 5% acetone/$CHCl_3$ to yield **67** (7.0 g, 16 μmol, 100%): $[\alpha]^{23}_D$ +1.3° (*c* 0.70, $CHCl_3$); IR (neat) 3400, 2970, 2880, 1470, 1380, 1260, 890 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06, 1.19, 1.20, 1.27 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{2''}$-Me, $C_{6''}$-Me), 1.40 (3 H, s, $C_{6''}$-Me), 2.22 (1 H, dq, J = 3.9 and 13.0 Hz, $C_{4''}$-H_β), 2.65 (1 H, br dd, J = 2.9 and 8.3 Hz, $C_{2'}$-O*H*), 2.82 (1 H, br s, $C_{1'}$-O*H*), 3.04 (1 H, dd, J = 2.4 and 11.2 Hz, C_6-H), 3.36, (1 H, br dd, J = 8.3 and 10.7 Hz, $C_{2'}$-H), 3.59 (1 H, dd, J = 7.3 and 11.3 Hz, C_{4a}-H), 3.73 (1 H, br dd, J = 2.9 and 10.7 Hz, $C_{2'}$-H), 3.88, 3.90 (each 1 H, dd, J = 3.9 and 12.2, C_2-H, $C_{5''}$-H); FI-MS m/z 437 (98, M^+ + H), 436 (47, M^+), 435 (96, M^+ + H), 434 (15, M^+), 354 (100, M^+ - Br), 207 (59, $C_8H_{14}O^{81}Br^+$ (A ring moiety)), 205 (70, $C_8H_{14}O^{79}Br^+$ (A ring moiety)), 75 (90, $MeC^+(OH)CH_2OH$); FI-HR-MS found m/z 435.1759, calcd for $C_{20}H_{36}O_5{}^{79}Br$ (M^+ + H) 435.1747.

(2*R*,4a*R*,6*R*,8a*S*)-2-Acetyl-8-[(2*S*,5*R*)-5-bromotetrahydro-2,6,6-trimethyl-2*H*-pyran-2-yl]octahydro-8a-methylpyrano[3,2-*b*]pyran (68). A suspension of **67** (7.0 mg, 16 μmol) and $NaIO_4$ (5.0 mg, 23 μmol) in a solution of MeOH (2.0 mL) and water (100 μL) was stirred at room temperature for 30 min. The resulting suspension was poured into water (20 mL) and extracted with ether (4 × 15 mL). The extracts were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude product was performed by column chromatography of the residue on silica gel (500 mg) with 5% EtOAc/benzene to give **68** (5.0 mg, 12 μmol, 77%): $\Delta_{\epsilon 305}$ +0.11 (*c* 1.9 × 10^{-3} M, MeOH at 23 °C); IR (neat) 2970, 2870, 1725, 1465, 1385, 1100, 900, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06, 1.19, 1.27 (each 3 H, s, C_{8a}-Me, $C_{2''}$-Me, $C_{6''}$-Me), 1.39 (3 H, s, $C_{6''}$-Me), 2.10 (1 H, dq, J = 13.2 and 3.9 Hz, $C_{4''}$-H_α), 2.23 (1 H, dq, J = 3.4 and 13.2 Hz, $C_{4''}$-H_β), 2.28 (3 H, s, $C_{1'}$-Me), 2.44 (1 H, dq, J = 13.5 and 2.5 Hz, C_3-H_β), 3.10 (1 H, dd, J = 2.4 and 11.2 Hz, C_6-H), 3.16 (1 H, dd, J = 4.4 and 11.3 Hz, C_{4a}-H), 3.88 (1 H, dd, J = 3.9 and 12.2 Hz, $C_{5''}$-H), 3.98 (1 H, dd, J = 2.0 and 6.8 Hz, C_2-H); FI-MS m/z 405 (34, M^+ + H), 404 (45, M^+), 403 (52, M^+ + H), 402 (M^+), 361 (100, M^+ - Ac), 359 (87, M^+ - Ac), 207 (86, $C_8H_{14}O^{81}Br^+$ (A ring moiety)), 205 (81, $C_8H_{14}O^{79}Br^+$ (A ring moiety)); FI-HR-MS found m/z 403.1464, calcd for $C_{19}H_{32}O_4{}^{79}Br$ (M^+ + H) 403.1484. The 500-MHz ^1H NMR, IR, and CD spectra of this sample were identical with those of authentic **68**, derived from natural $\Delta^{15,16}$-anhydrothyrsiferyl diacetate.[3,32]

Preparation of Authentic 68 from $\Delta^{15,16}$-Anhydrothyrsiferyl Diacetate. A suspenison of $\Delta^{15,16}$-anhydrothyrsiferyl diacetate[3,32] (10 mg, 15 μmol), OsO_4 (10 mg, 39 μmol), and pyridine (10 μL) in ether (1.0 mL) was stirred at room temperature for 3 h. Hydrogen sulfide gas was bubbled into the mixture at room temperature for 1 min, and the resulting suspension was filtered through a Celite pad with suction and concentrated in vacuo. The resulting oil was dissolved in a mixture of MeOH (1.0 mL) and water (100 μL), and then $NaIO_4$ (7.0 mg, 32 μmol) was added to the mixture at room temperature. After being stirred at the same temperature for 2 h, the mixture was poured into brine (10 mL) and extracted with $CHCl_3$ (3 × 10 mL). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure. Purification of the residue by column chromatography on silica gel (500 mg) with 5% EtOAc/benzene gave **68** (4.0 mg, 9.9 μmol, 66%): $\Delta_{\epsilon 305}$ +0.12 (*c* 2.2 × 10^{-3} M, MeOH at 23 °C); HR-MS found m/z 403.1440, calcd for $C_{19}H_{32}O_4{}^{79}Br$ (M^+ + H) 403.1484.

(2*E*,6*E*)-8-Acetoxy-2,6-dimethylocta-2,6-dien-1-ol (69). A solution of geranyl acetate (27 g, 140 mmol) and SeO_2 (20 g, 79 mmol) in EtOH (700 mL) was refluxed for 3 h. After cooling to 0 °C, the mixture was filtered through a Celite pad with suction, and the filtrates were concentrated in vacuo. The residue was diluted with a mixture of ether (500 mL) and ethanol (150 mL), and then $NaBH_4$ (1.1 g, 30 mmol) was added slowly to the solution at 0 °C. After stirring for 30 min at the same temperature, the resulting mixture was filtered through a Celite pad with suction. After addition of ether (500 mL), the mixture was washed with water (700 mL), and the aqueous layers were extracted with ether (2 × 500 mL). The combined extracts were washed successively with water (1 L) and brine (1 L), dried (Na_2SO_4), and concentrated in vacuo. Distillation of the crude product under reduced pressure gave **69** (15 g, 70 mmol, 51%): bp 132–137 °C (1 mmHg); IR (neat) 3400, 2920, 1740, 1440, 1382, 1365, 1230, 1020, 950 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.65, 1.69 (each, 3 H, s, C_2-Me, C_6-Me), 2.02 (3 H, s, O_2CMe), 3.94 (2 H, br s, C_1-H_2), 4.55 (2 H, br d, J = 7 Hz, C_8-H_2), 5.32 (1 H, br t, J = 7 Hz, C_7-H).

(2*R*,3*R*,6*E*)-8-Acetoxy-2,3-epoxy-2,6-dimethyloct-6-en-1-ol (70). D-(-)-DIPT (24 g, 100 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (28 g, 100 mmol) were added to a solution of **69** (19 g, 89 mmol) in CH_2Cl_2 at -10 °C under an Ar atmosphere, and the mixture was stirred for 20 min. The mixture was cooled to -20 °C, and then TBHP (5.6 M in CH_2Cl_2, 21 mL, 120 mmol) was added to the mixture. After stirring at the same temperature for 4 h, 10% aqueous tartaric acid solution (100 mL) was added to the mixture, which was stirred at room temperature for an additional 1 h. The resulting suspension was filtered through a Celite pad with suction and washed with water (1 L) and brine (1 L), successively. The organic solutions were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1 kg) with 10% acetone/$CHCl_3$ to afford **70** (16 g, 70 mmol, 79%): $[\alpha]^{24}_D$ +13.2° (*c* 2.30, $CHCl_3$); IR (neat) 3480, 2920, 1745, 1390, 1375, 1240, 1030 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.27 (3 H, s, C_2-Me), 1.71 (3 H, s, C_6-Me), 2.03 (3 H, s, O_2CMe), 2.10 (2 H, m, C_5-H_2), 2.97 (1 H, t, J = 6 Hz, C_3-H), 3.58 (2 H, br s, C_1-H_2), 4.55 (2 H, d, J = 7 Hz, C_8-H_2), 5.34 (1 H, br t, J = 7 Hz, C_7-H).

(3*R*,6*E*)-8-Acetoxy-2,6-dimethyloct-6-ene-2,3-diol (71). A solution of **70** (6.0 g, 26 mmol) and TsCl (6.5 g, 34 mmol) in pyridine (100 mL) was stirred at 0 °C for 15 h. The resulting mixture was poured into saturated $NaHCO_3$ solution (500 mL) and extracted with ether (3 × 300 mL). The combined ethereal solutions were washed successively with 10% aqueous citric acid solution (500 mL) and brine (500 mL), dried (Na_2SO_4), and concentrated in vacuo. After the residue was dissolved in acetone (300 mL), NaI (10 g, 67 mmol) was added to the solution at room temperature, and the mixture was stirred at the same temperature for 24 h in the dark. The resulting mixture was poured into 10% aqueous $Na_2S_2O_3$ solution (1 L) and extracted with ether (5 × 300 mL). The combined ethereal layers were washed with brine (700 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was diluted with a mixture of HMPA (75 mL) and THF (200 mL). The solution was stirred with $NaBH_3CN$ (9 g, 150 mmol) at 80 °C for 3 h under an Ar atmosphere. After cooling, the mixture was poured into water (500 mL) and extracted with ether (3 × 300 mL). The organic layers were combined, washed successively with water (300 mL) and brine (300 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was subjected to column chromatography on silica gel (200 g) with 10% EtOAc/benzene to give (+)-6,7-epoxygeranyl acetate (2.7 g, 13 mmol, 48% overall): $[\alpha]^{24}_D$ +1.40° (*c* 1.00, EtOH); IR (neat) 2950, 1735, 1445, 1375, 1225, 1015 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.27, 1.31 (each 3 H, s, C_7-Me_2), 1.73 (3 H, s, C_3-Me), 2.03 (3 H, s, O_2CMe), 2.15 (2 H, m, C_4-H_2), 2.67 (1 H, t, J = 5 Hz, C_6-H), 4.56 (2 H, d, J = 7 Hz, C_1-H_2), 5.35 (1 H, br t, J = 7 H, C_2-H).

A solution of the epoxide (1.0 g, 4.7 mmol) and 18 M H_2SO_4 (2.0 mL) in a mixture of water (2.0 mL) and THF (85 mL) was stirred at 0 °C for 30 min. The mixture was poured into brine (100 mL) and extracted with ether (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo, and purification of the crude product was effected by column chromatography on silica gel (20 g) with 15% acetone/$CHCl_3$ to give

71 (920 mg, 4.0 mmol, 85%): $[\alpha]^{23}_D$ +19.5° (*c* 1.75, EtOH); IR (neat) 3450, 2970, 1730, 1390, 1373, 1240, 1085, 1030 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.16, 1.21 (each 3 H, s, C_2-Me_2), 1.72 (3 H, s, C_6-Me), 2.03 (3 H, s, O_2CMe), 2.23 (2 H, m, C_5-H_2), 3.32 (1 H, m, C_3-H), 4.55 (2 H, d, *J* = 7 Hz, C_8-H_2), 5.36 (1 H, br t, *J* = 7 Hz, C_7-H).

(3*R*,6*E*)-8-Acetoxy-2,3-(isopropylidenedioxy)-2,6-dimethyl-6-octene (72). A solution of **71** (3.7 g, 16.1 mmol) and *p*-toluenesulfonic acid (150 mg, 0.79 mmol) in acetone (200 mL) was stirred at room temperature for 2 h, and then Et_3N (3.0 mL) was added. After the solvent was removed in vacuo, the residue was chromatographed on silica gel (150 g) with 1% EtOAc/benzene to afford **72** (4.2 g, 16 mmol, 96%): $[\alpha]^{23}_D$ +1.46° (*c* 2.25, EtOH); IR (neat) 2960, 2880, 1750, 1460, 1370, 1230, 1020, 950, 910, 860 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.09, 1.22 (each 3 H, s, C_2-Me_2), 1.31, 1.41 (each 3 H, isopropylidenyl Me × 2), 1.70 (3 H, s, C_6-Me), 2.03 (3 H, s, O_2CMe), 2.20 (2 H, m, C_5-H_2), 3.62 (1 H, dd, *J* = 5 and 9 Hz, C_3-H), 4.55 (2 H, d, *J* = 7 Hz, C_8-H_2), 5.35 (1 H, br t, *J* = 7 Hz, C_7-H); EI-MS *m*/*z* 270 (0.02, M^+), 255 (7.9, M^+ - Me), 43 (100, Ac^+); EI-HR-MS found *m*/*z* 270.1800, calcd for $C_{15}H_{26}O_4$ (M^+) 270.1832.

(2*E*,6*R*)-6,7-(Isopropylidenedioxy)-3,7-dimethyl-2-octen-1-ol (73). A suspension of **72** (4.2 g, 16 mmol) and K_2CO_3 (8.3 g, 59.7 mmol) in MeOH (80 mL) was stirred at room temperature for 1 h. The resulting mixture was poured into water (300 mL) and extracted with ether (4 × 150 mL). The combined ethereal solutions were washed successively with water (200 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue on silica gel (100 g) with 5% acetone/$CHCl_3$ afforded **73** (3.5 g, 15 mmol, 93%): $[\alpha]^{23}_D$ +1.54° (*c* 1.10, EtOH); IR (neat) 3400, 2960, 2880, 1450, 1370, 1235, 1215, 1200, 1115, 1000, 910, 860, 760 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.10, 1.22 (each 3 H, s, C_7-Me_2), 1.31, 1.40 (each 3 H, isopropylidenyl Me × 2), 1.70 (3 H, s, C_3-Me), 2.10 (2 H, m, C_4-H_2), 3.62 (1 H, dd, *J* = 5 and 8 Hz, C_6-H), 4.12 (2 H, br d, *J* = 7 Hz, C_1-H_2), 5.40 (1 H, br t, *J* = 7 Hz, C_2-H); EI-MS *m*/*z* 229 (0.36, M^+ + H), 228 (0.13, M^+), 213 (6.7, M^+ - Me), 43 (100, Ac^+); EI-HR-MS found *m*/*z* 228.1748, calcd for $C_{13}H_{24}O_3$ (M^+) 228.1726.

(3*R*,6*E*)-2,6-Dimethyl-2,3-(isopropylidenedioxy)-8-(phenylthio)-6-octene (75). A solution of **73** (3.2 g, 14.0 mmol), CCl_4 (25 mL, 250 mmol), and PPh_3 (4.7 g, 18 mmol) in benzene (100 mL) was refluxed for 24 h under an Ar atmosphere. The mixture was cooled to 0 °C, and then hexane (15 mL) was added. After being stirred at 0 °C for an additional 15 min, the resulting suspension was filtered with suction and concentrated in vacuo. Without purification, the resulting oil was dissolved in DMF (70 mL). Then, a solution of sodium thiophenoxide [prepared from sodium hydride (500 mg, 21 mmol) and thiophenol (2.4 g, 22 mmol) in DMF (10 mL) at 0 °C] was added to the solution at 0 °C, and the mixture was stirred at the same temperature for 30 min. The resulting mixture was poured into water (250 mL) and extracted with ether (4 × 150 mL). The extracts were combined, washed successively with water (250 mL) and brine (250 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting oil was subjected to column chromatography on silica gel (150 g) with 5% EtOAc/benzene to give **75** (3.5 g, 11 mmol, 79%): $[\alpha]^{20}_D$ +4.90° (*c* 1.00, EtOH); IR (neat) 2960, 2940, 1475, 1445, 1375, 1217, 2005, 1118, 1005, 860, 745, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.05, 1.20 (each 3 H, s, C_2-Me_2), 1.28, 1.38 (each 3 H, isopropylidenyl Me × 2), 1.58 (3 H, s, C_6-Me), 2.07 (2 H, m, C_5-H_2), 3.4–3.7 (3 H, m, C_3-H, C_8-H_2), 5.31 (1 H, br t, *J* = 7 Hz, C_7-H), 7.1–7.4 (5 H, m, aromatic protons); EI-MS *m*/*z* 320 (4.1, M^+), 305 (5.7, M^+ - Me), 71 (100); EI-HR-MS found *m*/*z* 320.1804, calcd for $C_{19}H_{28}O_2S$ (M^+) 320.1811.

(3*R*,6*E*)-2,6-Dimethyl-8-(phenylthio)-6-octene-2,3-diol (76). A solution of **75** (3.5 g, 11 mmol) in a mixture of 1 M HCl (15 mL) and MeOH (50 mL) was stirred at room temperature for 12 h, and then Et_3N (3.0 mL) was added to the mixture and the solvent was evaporated in vacuo. Column chromatography of the crude material on silica gel (120 g) with 7% acetone/$CHCl_3$ afforded **76** (2.9 g, 10 mmol, 91%): mp 35–36 °C; $[\alpha]^{21}_D$ +21.4° (*c* 4.50, EtOH); IR ($CHCl_3$) 3400, 2950, 2920, 1590, 1485, 1440, 1385, 1155, 1070, 740, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.16, 1.20 (each 3 H, s, C_2-Me_2), 1.61 (3 H, s, C_6-Me), 2.23 (2 H, m, C_5-H_2), 3.25 (1 H, dd, *J* = 3 and 9 Hz, C_3-H), 3.53 (2 H, d, *J* = 7 Hz, C_8-H_2), 5.33 (1 H, br t, *J* = 7 Hz, C_7-H), 7.1–7.4 (5 H, m, aromatic protons); EI-MS *m*/*z* 281 (0.66, M^+ + H), 280 (0.52, M^+), 263 (5.0, M^+ - OH), 153 (100); EI-HR-MS found *m*/*z* 280.1500, calcd for $C_{16}H_{24}O_2S$ (M^+) 280.1498.

(3*R*,6*E*)-3-(Benzyloxy)-2,6-dimethyl-8-(phenylthio)-6-octen-2-ol (77). A solution of **76** (2.1 g, 7.5 mmol) in DMF (10 mL) was added to a suspension of NaH (220 mg, 9.2 mmol) in DMF (20 mL) at 0 °C under an Ar atmosphere. The mixture was stirred at the same temperature for 15 min, and then BnCl (1.1 g, 9.0 mmol) was added to the mixture. After stirring at room temperature for an additional 12 h, the mixture was poured into water (70 mL) and extracted with ether (4 × 40 mL). The combined ethereal solutions were washed successively with water (60 mL) and brine (60 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Column chromatography of the residue on silica gel (80 g) with 15% EtOAc/benzene afforded **77** (2.4 g, 6.4 mmol, 85%): $[\alpha]^{23}_D$ +16.9° (*c* 1.00, EtOH); IR (neat) 3450, 2950, 2920, 1590, 1485, 1460, 1445, 1390, 1095, 1025, 740, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.16, 1.18 (each 3 H, s, C_2-Me_2), 1.56 (3 H, s, C_6-Me), 2.10 (2 H, m, C_5-H_2), 3.12 (1 H, dd, *J* = 5 and 7 Hz, C_3-H), 3.53 (2 H, d, *J* = 7 Hz, C_8-H_2), 4.52, 4.63 (each 1 H, d, *J* = 11 Hz, OCH_2Ph), 5.30 (1 H, br t, *J* = 7 Hz, C_7-H), 7.1–7.4 (10 H, m, aromatic protons); EI-MS *m*/*z* 370 (0.28, M^+), 353 (0.29, M^+ - OH), 261 (1.0, M^+ - PhS), 91 (100, Ph^+); EI-HR-MS found *m*/*z* 370.1981, calcd for $C_{23}H_{30}O_2S$ (M^+) 370.1968.

(3*R*,6*E*)-3-(Benzyloxy)-2,6-dimethyl-8-(phenylthio)-2-[[2-(trimethylsilyl)ethoxy]methoxy]-6-octene (78). A solution of **77** (1.5 g, 4.1 mmol), *i*-Pr_2NEt (2.2 g, 17 mmol), and SEMCl (1.4 mL, 7.9 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 12 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (60 mL) and extracted with ether (4 × 40 mL). The combined ethereal solutions were washed successively with water (40 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (100 g) with 1% EtOAc/benzene to give **78** (2.0 g, 4.0 mmol, 98%): $[\alpha]^{23}_D$ +1.92° (*c* 1.00, EtOH); IR (neat) 2920, 2850, 1485, 1455, 1440, 1380, 1245, 1100, 1053, 1025, 860, 835, 740, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.05 (9 H, s, $SiMe_3$), 0.95 (2 H, dd, *J* = 8 and 9 Hz, OCH_2CH_2TMS), 1.23, 1.30 (each 3 H, s, C_2-Me_2), 1.59 (3 H, s, C_6-Me), 2.17, (2 H, m, C_5-H_2), 3.17 (1 H, dd, *J* = 3 and 8 Hz, C_3-H), 3.4–3.8 (4 H, m, C_8-H_2, OCH_2CH_2TMS), 4.50, 4.70 (each 1 H, d, *J* = 12 Hz, OCH_2Ph), 4.78 (2 H, s, $OCH_2OCH_2CH_2TMS$), 5.30 (1 H, br t, *J* = 7 Hz, C_7-H), 7.1–7.4 (10 H, m, aromatic protons); EI-MS *m*/*z* 500 (0.01, M^+), 91 (100, Ph^+), 73 (80, Me_3Si^+); EI-HR-MS found *m*/*z* 500.2791, calcd for $C_{29}H_{44}O_3SSi$ (M^+) 500.2782.

(2*R*,4a*R*,6*R*,8a*S*)-Octahydro-2-[(*S*)-1-hydroxy-1-methyl-2-[(*p*-tolylsulfonyl)oxy]ethyl]-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (79). A solution of **57** (100 mg, 250 μmol), TsCl (240 mg, 1.26 mmol), and in a mixture of pyridine (1.0 mL) and CH_2Cl_2 (5.0 mL) was stirred at room temperature for 12 h. The mixture was poured into 10% aqueous citric acid solution (20 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (3 g) with 3% acetone/$CHCl_3$ to afford **79** (138 mg, 250 μmol, 100%): $[\alpha]^{24}_D$ -17° (*c* 0.30, $CHCl_3$); IR (neat) 3500, 2930, 2850, 1600, 1450, 1370, 1175, 1100, 1035, 980, 815 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.07, 1.09, 1.17 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me), 1.60 (3 H, s, $C_{5''}$-Me_{cis}), 1.67 (3 H, s, $C_{5''}$-Me_{trans}), 2.42 (3 H, s, $OSO_2C_6H_4Me$), 3.33 (3 H, s, OMe), 3.4–3.9 (3 H, m, C_2-H, C_{4a}-H, C_6-H), 3.92 (2 H, s, $C_{2'}$-H_2), 4.68, 4.73 (each 1 H, d, *J* = 7 Hz, OCH_2OMe), 5.10 (1 H, br t, *J* = 7 Hz, $C_{4''}$-H), 7.33, 7.73 (each 2 H, d, *J* = 8 Hz, aromatic protons); FD-MS *m*/*z* 555 (57, M^+ + H), 554 (100, M^+), 523 (70, M^+ - MeO), 522 (85, M^+ - MeOH), 383 (M^+ - $MeC_6H_4SO_3$); FI-HR-MS found *m*/*z* 554.2890, calcd for $C_{29}H_{46}O_8S$ (M^+) 554.2914.

(2*R*,4a*R*,6*R*,8a*S*)-Octahydro-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-8a-methyl-2-[(*S*)-2-methyloxiran-2-yl]pyrano[3,2-*b*]pyran (80). A suspension of **79** (140 mg, 250 μmol) and K_2CO_3 (300 mg, 2.1 mmol) in MeOH (5.0 mL) was stirred at room temperature for 3.5 h. The mixture was poured into water (30 mL) and extracted with ether (4 × 20 mL). The combined ethereal solutions were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue on silica gel (3 g) with 10% EtOAc/

benzene yielded **80** (88 mg, 230 μmol, 92%): $[\alpha]^{24}_D$ −12.3° (*c* 1.00, $CHCl_3$); IR (neat) 2950, 2850, 1450, 1385, 1150, 1100, 1035, 920, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20, 1.27, 1.32 (each 3 H, s, C_{8a}-Me, $C_{2'}$-Me, $C_{1''}$-Me), 1.61 (3 H, s, $C_{5''}$-Me_{cis}), 1.68 (3 H, s, $C_{5''}$-Me_{trans}), 2.61, 2.71 (each 1 H, d, *J* = 4.9 Hz, $C_{3'}$-H_2), 3.37 (3 H, s, OMe), 3.45 (1 H, dd, *J* = 6.8 and 11.1 Hz, C_{4a}-H), 3.61 (1 H, dd, *J* = 3.9 and 9.8 Hz, C_2-H), 4.70, 4.77 (each 1 H, d, *J* = 7.3 Hz, OCH_2OMe), 5.10 (1 H, br t, *J* = 7.3 Hz, $C_{4''}$-H); FI-MS *m/z* 383 (53, M^+ + H), 382 (100, M^+); FI-HR-MS found *m/z* 382.2718, calcd for $C_{22}H_{38}O_5$ (M^+) 382.2720.

(2*R*,4a*R*,6*R*,8a*S*)-Octahydro-2-[(1*S*,4*E*,8*R*)-8-hydroxy-1-(methoxymethoxy)-1,5,9-trimethyl-9-[[2-(trimethylsilyl)ethoxy]methoxy]deca-4-enyl]-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (83). A solution of **80** (240 mg, 620 μmol), **78** (1.230 g, 2.46 mmol), and TMEDA (500 μL, 4.31 mmol) in THF (15 mL) was stirred at −20 °C under an Ar atmosphere, and BuLi (1.5 M in hexane, 1.64 mL, 2.46 mmol) was then added dropwise to the mixture. The colorless solution turned orange upon addition of BuLi. After stirring for 10 min at −20 °C, water (3.0 mL) was added to the mixture, and the resulting mixture was poured into water (30 mL) and extracted with ether (4 × 20 mL). The extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was subjected to column chromatography on silica gel (50 g) with 10% EtOAc/benzene to give **81** (540 mg, 610 μmol, 99%) as a diastereomeric mixture.

A solution of **81** (540 mg, 610 mmol), *i*-Pr_2NEt (1.0 mL, 5.7 mmol), and MOMCl (300 μL, 3.9 mmol) in CH_2Cl_2 (5.0 mL) was stirred at 0 °C, and the mixture was then allowed to warm to room temperature with stirring. After 12 h, the mixture was poured into 10% aqueous citric acid solution (50 mL) and extracted with ether (3 × 40 mL). The combined ethereal layers were washed successively with water (50 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (20 g) with 5% EtOAc/benzene to give **82** (540 mg, 580 μmol, 95%) as a diastereomeric mixture.

Liquid NH_3 (ca. 30 mL) and metallic Li (500 mg, 72 mmol) were added successively to a solution of **82** (540 mg, 580 μmol) in a mixture of THF (30 mL) and 2-propanol (30 mL) at −78 °C with stirring under an Ar atmosphere. After stirring at the same temperature for 2 h, NH_4Cl (ca. 1 g) was added to the mixture until the purple color disappeared. Excess NH_3 was evaporated by slowly warming the mixture to room temperature. Water (120 mL) was added to the mixture, and the resulting solution was extracted with ether (4 × 100 mL). The combined extracts were washed with brine (120 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. Column chromatography of the residual oil on silica gel (15 g) with 15% EtOAc/benzene gave **83** (320 mg, 440 mmol, 76%): $[\alpha]^{24}_D$ +4.15° (*c* 2.00, $CHCl_3$); IR (neat) 3400, 2950, 2850, 1450, 1380, 1250, 1150, 1100, 1035, 925, 865, 845 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.07 (9 H, s, $SiMe_3$), 1.03 (2 H, t, *J* = 8.2 Hz, OCH_2CH_2TMS), 1.26, 1.31, 1.34, 1.36, 1.38 (each 3 H, s, C_{8a}-Me, C_1-Me, C_9-Me_2, $C_{1''}$-Me), 1.65, 1.72, 1.79 (each 3 H, s, C_5-Me, $C_{5''}$-Me_2), 3.2–3.8 (5 H, m, C_{4a}-H, C_6-H, C_8-H, OCH_2CH_2TMS), 3.38, 3.38 (each 3 H, s, OMe × 2), 4.05 (1 H, dd, *J* = 3.7 and 13.0 Hz, C_2-H), 4.7–7.9 (6 H, m, OCH_2OMe × 2, $OCH_2OCH_2CH_2TMS$), 5.41, 5.62 (each 1 H, br t, *J* = 7.1 Hz, $C_{4'}$-H, $C_{4''}$-H); FI-MS *m/z* 729 (100, M^+ + H), 728 (50, M^+); FI-HR-MS found *m/z* 728.5241, calcd for $C_{40}H_{76}O_9Si$ (M^+) 728.5261.

(2*R*,4a*R*,6*R*,8a*S*)-Octahydro-3-[(1*S*,4*S*)-4-[(2*R*,5*R*)-tetrahydro-2-methyl-5-[1-methyl-1-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]furan-2-yl]-4-hydroxy-1-(methoxymethoxy)butyl]-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (84) and Its 4′*R*,2‴*S* Isomer 85. A solution of $VO(acac)_2$ (1 mM in CH_2Cl_2, 1.0 mL) and TBHP (5.6 M in CH_2Cl_2, 30 μL) were added to **83** (25 mg, 34 μmol), and the whole solution was stirred at room temperature for 2 h. The resulting mixture was poured into water (15 mL) and extracted with ether (4 × 10 mL). The ethereal solutions were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue on silica gel (1 g) with 20% EtOAc/benzene afforded a mixture of **84** and **85** (15 mg, 20 μmol, 58%), which was separated by HPLC (μ-PORASIL, 7.8 × 300 φmm, 1.3% 2-propanol/hexane, 2.0 mL/min flow, detected by RI) to give diastereomerically pure **84** (11 mg, 15 μmol, 44%) and **85** (2.5 mg, 3.3 μmol, 9.7%).

84: t_R = 19.2 min (above conditions); $[\alpha]^{24}_D$ −13.4° (*c* 1.10, $CHCl_3$); IR (neat) 3400, 2930, 1460, 1380, 1250, 1150, 1100, 1035, 920, 860, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (9 H, s, $SiMe_3$), 0.93 (2 H, t, *J* = 8.3 Hz, OCH_2CH_2TMS), 1.13, 1.14, 1.18, 1.20, 1.20 1.20 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me, $C_{2'''}$-Me, $C_{5'''}$-CMe_2), 1.61 (3 H, s, $C_{5''}$-Me_{cis}), 1.68 (3 H, s, $C_{5''}$-Me_{trans}), 2.8 (1 H, br s, OH), 3.36, 3.37 (each, 3 H, s, OMe × 2), 3.46 (1 H, dd, *J* = 1.5 and 9.0 Hz, $C_{4'}$-H), 3.57 (1 H, dd, *J* = 7.3 and 11.2 Hz, C_{4a}-H), 3.60, 3.65 (each 1 H, dd, *J* = 8.3 and 8.5 Hz, OCH_2CH_2TMS), 3.82 (1 H, dd, *J* = 5.0 and 11.0 Hz, C_2-H), 3.90 (1 H, dd, *J* = 5.4 and 10.3 Hz, $C_{5'''}$-H), 4.69 (1 H, d, *J* = 6.8 Hz, OCH*H*O), 4.71, 4.77 (each 1 H, d, *J* = 7.3 Hz, OCH_2O), 4.78 (1 H, d, *J* = 6.8 Hz, OCH*H*O), 4.79 (1 H, d, *J* = 6.8 Hz, OCH*H*O), 4.88 (1 H, d, *J* = 6.8 Hz, OCH*H*O), 5.11 (1 H, br t, *J* = 7.1 Hz, $C_{4''}$-H); FI-MS *m/z* 745 (58, M^+ + H), 744 (20, M^+), 101 (100, $Me_3SiMe_3CH_2CH_2^+$); EI-HR-MS found *m/z* 745.5220, calcd for $C_{40}H_{77}O_{10}Si$ (M^+ + H) 745.5288.

85: t_R = 13.3 min (above conditions); ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (9 H, s, $SiMe_3$), 0.88 (2 H, t, *J* = 8.0 Hz, OCH_2CH_2TMS), 1.15, 1.16, 1.18, 1.20, 1.25, 1.31, (each 3 H, s, C_{8a}-Me, C_1-Me, $C_{1'}$-Me, $C_{2'''}$-Me, $C_{5'''}$-CMe_2), 1.61 (3 H, s, $C_{5''}$-Me_{cis}), 1.69 (3 H, s, $C_{5''}$-Me_{trans}), 3.36 (6 H, s, OMe × 2), 3.50 (1 H, dd, *J* = 1.5 and 9.0 Hz, $C_{4'}$-H), 3.57 (1 H, dd, *J* = 7.3 and 11.2 Hz, C_{4a}-H), 3.61, 3.66 (each 1 H, dd, *J* = 8.0 and 9.4 Hz, $OCH_2OCH_2CH_2TMS$), 3.80 (1 H, t, *J* = 7.2 Hz, $C_{5'''}$-H), 3.83 (1 H, dd, *J* = 5.4 and 10.3 Hz, C_2-H), 4.6–4.8 (6 H, m, OCH_2O × 3), 5.10 (1 H, br t, *J* = 7.1 Hz, $C_{4''}$-H).

(3*R*,6*E*,10*S*)-10-(Methoxymethoxy)-2,6-dimethyl-2-[[2-(trimethylsilyl)ethoxy]methoxy]undec-6-en-3-ol (88). Butyllithium (1.5 M in hexane, 5.0 mL, 7.5 mmol) was added to a solution of **78** (1.2 g, 2.5 mmol), **11** (1.1 g, 4.8 mmol), and TMEDA (1.5 mL, 10 mmol) in THF (25 mL) at −10 °C under an Ar atmosphere. The mixture was stirred at −10 °C for 30 min, poured into saturated aqueous NH_4Cl solution (20 mL), and extracted with ether (3 × 20 mL). The combined ethereal layers were washed successively with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue on silica gel (25 g) with 10% EtOAc/benzene gave an adduct (1.0 g, 1.8 mmol, 72%).

A solution of the adduct (1.0 g, 1.9 mmol), MOMCl (500 μL, 5.9 mmol), and *i*-Pr_2NEt (1.0 mL, 10 mmol) in CH_2Cl_2 (5.0 mL) was stirred at room temperature for 15 h. The mixture was poured into water (10 mL) and extracted with ether (3 × 20 mL). The combined ethereal layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a crude oil which was dissolved in a mixture of THF (5.0 mL). The solution was added to a suspension of Li (10 mg, 1.4 mmol) in monoethylamine (20 mL) at −78 °C under an Ar atmosphere. After stirring at the same temperature for 1 h, NH_4Cl (ca. 100 mg) was added to the mixture to stop the reaction. The mixture was allowed to warm to room temperature with stirring to evaporate the excess monoethylamine, and the resulting paste was then dissolved in water (20 mL) and extracted with ether (3 × 20 mL). The combined extracts were washed with brine (20 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. Column chromatography of the residue on silica gel (20 g) with 10% EtOAc/benzene gave **88** (620 mg, 1.5 mmol, 83%): $[\alpha]^{33}_D$ +9.99° (*c* 1.70, $CHCl_3$); IR (neat) 3600, 2960, 1380, 1250, 1150, 1100, 1040, 910, 850, 835 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.02 (9 H, s, $SiMe_3$), 0.92 (2 H, t, *J* = 8.5 Hz, OCH_2CH_2TMS), 1.15 (3 H, d, *J* = 6.8 Hz, C_{10}-Me), 1.16, 1.19 (each 3 H, s, C_2-Me_2), 1.60 (3 H, s, C_6-Me), 3.13 (1 H, m, C_3-H), 3.35 (3 H, s, OMe), 3.5–3.7 (2 H, m, C_{10}-H, OCH_2CH_2TMS), 4.60, 4.67 (each 1 H, d, *J* = 7.0 Hz, OCH_2O), 4.72, 4.78 (each 1 H, d, *J* = 7.5 Hz, OCH_2O), 5.16 (1 H, t, *J* = 6.4 Hz, C_7-H); EI-MS *m/z* 273 (0.51, M^+ − $Me_3SiCH_2CH_2OCH_2$), 255 (0.44, M^+ − $Me_3SiCH_2CH_2OCH_2$ − H_2O), 73 (100); FD-MS *m/z* 404 (43, M^+), 101 (100); EI-HR-MS found *m/z* 255.1980, calcd for $C_{15}H_{27}O_3$ (M^+ − $Me_3SiCH_2CH_2OCH_2$ − H_2O) 255.1961.

(2*R*,5*R*)-Tetrahydro-2-[(1*S*,4*S*)-1-hydroxy-4-(methoxymethoxy)pentyl]-2-methyl-5-[1-methyl-1-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]furan (89) and Its 2*S*,1′*R* Isomer 90. A solution of **88** (620 mg, 1.5 mmol), $VO(acac)_2$ (20 mg, 75 μmol), and TBHP (5.6 M in CH_2Cl_2, 250 μL, 1.4 mmol) in CH_2Cl_2

(12 mL) was stirred at room temperature for 3 h. The mixture was poured into saturated aqueous $Na_2S_2O_3$ solution (10 mL) and extracted with ether (3 × 20 mL). The combined ethereal solutions were washed successively with water (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residual oil was chromatographed on silica gel (15 g) with 10, 15, and 20% EtOAc/benzene to give **88** (120 mg, 300 μmol, 20%), **90** (59 mg, 140 μmol, 9.7%), and **89** (380 mg, 940 μmol, 62%), respectively.

89: R_f = 0.41 (20% EtOAc/benzene); $[\alpha]^{30}_D$ −1.7° (*c* 0.30, $CHCl_3$); IR (neat) 3650, 2960, 2880, 1480, 1470, 1390, 1260, 920, 870, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (9 H, s, $SiMe_3$), 0.92 (2 H, t, *J* = 9.1 Hz, OCH_2CH_2TMS), 1.14, 1.19, 1.20 (each 3 H, s, C_2-Me, $C_{1''}$-Me_2), 1.18 (3 H, d, *J* = 6.8 Hz, C_4-Me), 3.37 (3 H, s, OMe), 3.50 (1 H, dd, *J* = 1.5 and 9.0 Hz, $C_{1'}$-H), 3.5–3.8 (3 H, m, OCH_2CH_2TMS, $C_{4'}$-H), 3.90 (1 H, dd, *J* = 5.4 and 10.2 Hz, C_5-H), 4.62, 4.70 (each 1 H, d, *J* = 7.2 Hz, OCH_2O), 4.75, 4.90 (each 1 H, d, *J* = 7.8 Hz, OCH_2O); EI-MS *m/z* 303 (0.31, $M^+ - Me_3SiCH_2CH_2O$), 285 (0.39, $M^+ - Me_3SiCH_2CH_2O - H_2O$), 125 (59, $C_8H_{11}O^+$), 73 (100); FD-MS *m/z* 421 (100, $M^+ + H$), 420 (11, M^+); EI-HR-MS found *m/z* 303.2172, calcd for $C_{16}H_{31}O_5$ ($M^+ - Me_3SiCH_2CH_2O$) 303.2166.

90: R_f = 0.35 (same as **89**); $[\alpha]^{30}_D$ +5.3° (*c* 0.30, $CHCl_3$); IR (neat) 3650, 2960, 2880, 1480, 1470, 1390, 1260, 920, 870, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (9 H, s, $SiMe_3$), 0.90 (2 H, t, *J* = 8.3 Hz, OCH_2CH_2TMS), 1.13, 1.15, 1.30 (each 3 H, s, C_2-Me, $C_{1''}$-Me_2), 1.17 (3 H, d, *J* = 6.8 Hz, C_4-Me), 3.37 (3 H, s, OMe), 3.54 (1 H, dd, *J* = 1.5 and 9.0 Hz, $C_{1'}$-H), 3.5–3.7 (3 H, m, $C_{4'}$-H, OCH_2CH_2TMS), 3.80 (1 H, t, *J* = 7.3 Hz, C_5-H), 4.62, 4.68 (each 1 H, d, *J* = 7.2 Hz, OCH_2O), 4.78, 4.80 (each 1 H, d, *J* = 7.8 Hz, OCH_2O); EI-MS *m/z* 303 (0.21, $M^+ - Me_3SiCH_2CH_2OCH_2$), 125 (52, $C_8H_{11}O^+$), 73 (100); FD-MS *m/z* 421 (100, $M^+ + H$), 420 (42, M^+); EI-HR-MS found *m/z* 303.2149, calcd for $C_{16}H_{31}O_5$ ($M^+ - Me_3SiCH_2CH_2OCH_2$) 303.2166.

(2*R*,5*R*)-2-[(1*S*,4*S*)-1-Acetoxy-4-(methoxymethoxy)pentyl]tetrahydro-2-methyl-5-[1-methyl-1-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]furan (91). A solution of **89** (10 mg, 23 μmol) and Ac_2O (100 μL, 1.0 mmol) in pyridine (0.5 mL, 6.2 mmol) was stirred at room temperature for 15 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with ether (3 × 10 mL). The combined extracts were washed successively with aqueous saturated $CuSO_4$ solution (20 mL), water (20 mL), and brine (20 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residual oil was subjected to column chromatography on silica gel (200 mg) with 10% EtOAc/benzene to give **91** (10 mg, 21 μmol, 94%): $[\alpha]^{28}_D$ −12.0° (*c* 1.00, $CHCl_3$); IR (neat) 2940, 1730, 1450, 1380, 1250, 1140, 1090, 1040, 910, 840, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (9 H, s, $SiMe_3$), 0.92 (2 H, t, *J* = 8.3 Hz, OCH_2CH_2TMS), 1.14 (3 H, d, *J* = 6.8 Hz, C_4-Me), 1.16, 1.18, 1.20 (each 3 H, s, C_2-Me, $C_{1''}$-Me_2), 2.05 (3 H, s, O_2CMe), 3.35 (3 H, s, OMe), 3.4–3.7 (3 H, m, $C_{4'}$-H, OCH_2CH_2TMS), 3.78 (1 H, dd, *J* = 5.9 and 10.2 Hz, C_5-H), 4.59, 4.66 (each 1 H, d, *J* = 6.8 Hz, OCH_2O), 4.75, 4.82 (each 1 H, d, *J* = 7.8 Hz, OCH_2O), 4.89 (1 H, dd, *J* = 1.5 and 9.1 Hz, $C_{1'}$-H); EI-MS *m/z* 401 (0.12, $M^+ - MeOCH_2O$), 315 (2.1, $M^+ - Me_3SiCH_2CH_2OCH_2O$), 125 (42, $C_8H_{13}O^+$), 73 (100); FD-MS *m/z* 462 (12, M^+), 273 (100); EI-HR-MS found *m/z* 401.2709, calcd for $C_{21}H_{41}O_5Si$ ($M^+ - MeOCH_2O$) 401.2745.

(2*S*,5*R*)-2-[(1*R*,4*S*)-1-Acetoxy-4-(methoxymethoxy)pentyl]tetrahydro-2-methyl-5-[1-[[2-(trimethylsilyl)ethoxy]methoxy]-1-methylethyl]furan (92). The treatment applied to **89** was applied to **90** (10 mg, 23 μmol), employing Ac_2O (100 μL, 1.0 mmol) and pyridine (500 μL, 6.2 mmol). Similar workup and purification of the crude acetate by column chromatography on silica gel (200 mg) with 10% EtOAc/benzene gave **92** (10 mg, 21 μmol, 91%): $[\alpha]^{30}_D$ +2.7° (*c* 0.30, $CHCl_3$); IR (neat) 2940, 1730, 1450, 1380, 1250, 1140, 1060, 1040, 910, 860, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (9 H, s, $SiMe_3$), 0.93 (2 H, t, *J* = 8.3 Hz, OCH_2CH_2TMS), 1.15 (3 H, d, *J* = 6.8 Hz, C_4-Me), 1.19, 1.19, 1.20 (each 3 H, s, C_2-Me, $C_{1''}$-Me_2), 2.05 (3 H, s, O_2CMe), 3.36 (3 H, s, OMe), 3.5–3.6 (3 H, m, $C_{4'}$-H, OCH_2CH_2TMS), 3.90 (1 H, t, *J* = 7.3 Hz, C_5-H), 4.60, 4.67 (each 1 H, d, *J* = 6.5 Hz, OCH_2O), 4.76, 4.81 (each 1 H, d, *J* = 7.3 Hz, OCH_2O), 4.90 (1 H, dd, *J* = 1.5 and 9.0 Hz, $C_{1'}$-H); EI-MS *m/z* 401 (0.25, $M^+ - MeOCH_2O$), 315 (3.3, $M^+ - Me_3SiCH_2CH_2OCH_2O$), 125 (48, $C_8H_{13}O^+$), 73 (100); FD-MS *m/z* 462 (11, M^+), 273 (100); EI-HR-MS found *m/z* 401.2739, calcd for $C_{21}H_{41}O_5Si$ ($M^+ - MeOCH_2O$) 401.2724.

(2*R*,4a*R*,6*R*,8a*S*)-Octahydro-2-[(1*S*,4*S*)-1,4-dihydroxy-4-[(2*R*,5*R*)-tetrahydro-5-(1-hydroxy-1-methylethyl)-2-methylfuran-2-yl]-1-methylbutyl]-6-[(*S*)-1-hydroxy-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (86). A solution of **84** (30 mg, 40 μmol) in a mixture of 12 M HCl (5.0 μL) and MeOH (1.0 mL) was stirred for 3 h at room temperature. The mixture was neutralized by addition of Et_3N (ca. 100 μL), and the solvent was evaporated in vacuo. Purification of the residue employing column chromatography on silica gel (1 g) with 30% acetone/$CHCl_3$ gave **86** (19 mg, 36 μmol, 90%): $[\alpha]^{27}_D$ −11° (*c* 0.90, $CHCl_3$); $[\alpha]^{23}_{300}$ −35°, $[\alpha]^{23}_{220}$ −200° (*c* 0.50, MeOH); IR (neat) 3530, 2970, 2860, 1450, 1370, 1080, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10, 1.13, 1.15, 1.16, 1.21, 1.22 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me, $C_{2''}$-Me, $C_{5''}$-CMe_2), 1.61 (3 H, s, $C_{5'}$-Me_{cis}), 1.69 (3 H, s, $C_{5'}$-Me_{trans}), 3.26 (1 H, dd, *J* = 2.4 and 10.3 Hz, C_6-H), 3.45 (1 H, dd, *J* = 1.9 and 9.8 Hz, $C_{4'}$-H), 3.64 (1 H, dd, *J* = 7.3, and 11.2 Hz, C_{4a}-H), 3.72 (1 H, dd, *J* = 2.9 and 12.6 Hz, C_2-H), 3.76 (1 H, dd, *J* = 6.0 and 9.0 Hz, $C_{5''}$-H), 5.11 (1 H, br t, *J* = 7.1 Hz, $C_{4''}$-H); FD-MS *m/z* 527 (100, $M^+ + H$), 526 (74, M^+), 509 (21, $M^+ - OH$), 508 (20, $M^+ - H_2O$), 143 (47, $C_8H_{15}O_2^+$ (D ring moiety)); FI-HR-MS found *m/z* 526.3931, calcd for $C_{30}H_{54}O_7$ (M^+) 526.3871.

Thyrsiferol (1). A solution of **86** (10 mg, 19 μmol) and TBCO (11 mg, 27 μmol) in CH_3NO_2 (800 μL) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. After all polar material was removed by short column chromatography on silica gel (200 mg) with 10% acetone/$CHCl_3$, HPLC purification (LiChrosorb RP-18 (Merck) 250 × 4 *φ*mm, 90% CH_3CN/H_2O, 1 mL/min flow, detected by UV at 215 nm) gave thyrsiferol (**1**) (2.5 mg, 4.1 μmol, 22%): t_R = 9.0 min (above conditions); $[\alpha]^{23}_{400}$ 25° $[\alpha]^{23}_{300}$ 50°, $[\alpha]^{23}_{220}$ 200° (*c* 0.2, MeOH); IR ($CHCl_3$) 3560, 3390, 2920, 2860, 1460, 1375, 1260, 1120, 1100, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, thyrsiferol numbering) δ 1.10, 1.13, 1.16, 1.18, 1.20, 1.21, 1.27, 1.40 (each 3 H, s, C_2-Me_2, C_6-Me, C_{10}-Me, C_{15}-Me, C_{19}-Me, C_{23}-Me_2), 2.25 (1 H, dq, *J* = 3.4 and 12.7 Hz, C_4-H_β), 3.04 (1 H, dd, *J* = 2.4 and 11.9 Hz, C_7-H), 3.44 (1 H, dd, *J* = 2.0 and 10.3 Hz, C_{18}-H), 3.57 (1 H, dd, *J* = 7.3 and 11.2 Hz, C_{11}-H), 3.72 (1 H, dd, *J* = 2.9 and 13.2 Hz, C_{14}-H), 3.76 (1 H, dd, *J* = 6.3 and 9.8 Hz, C_{22}-H), 3.89 (1 H, dd, *J* = 3.9 and 12.2 Hz, C_3-H); FD-MS *m/z* 607 (36, $M^+ + H$), 606 (17, M^+), 605 (37, $M^+ + H$), 589 (8.3, $M^+ - OH$), 588 (8.2, $M^+ - H_2O$), 587 (9.6, $M^+ - OH$), 586 (7.0, $M^+ - H_2O$), 527 (24, $M^+ - Br$), 361 (16, $M^+ - C_{13}H_{25}O_4$ (ABC ring moiety)), 359 (17, $M^+ - C_{13}H_{25}O_4$ (ABC ring moiety)), 242, (100), 207 (24, $C_8H_{14}O^{81}Br^+$ (A ring moiety)), 205 (37, $C_8H_{14}O^{79}Br^+$ (A ring moiety)), 143 (70, $C_8H_{15}O_2^+$ (D ring moiety)); FI-HR-MS found *m/z* 605.3097, calcd for $C_{30}H_{54}O_7Br$ ($M^+ + H$) 605.3054. The 400-MHz ^1H NMR, IR, MS, and ORD spectra and HPLC retention of this sample were completely identical with those of natural thyrsiferol[32] ($[\alpha]^{23}_{400}$ 25°, $[\alpha]^{23}_{300}$ 60°, $[\alpha]^{23}_{220}$ 220° (*c* 0.2, MeOH)).

(2*R*,4a*R*,6*R*,8a*S*)-Octahydro-2-[(1*S*,4*R*)-1,4-dihydroxy-4-[(2*S*,5*R*)-tetrahydro-5-(1-hydroxy-1-methylethyl)-2-methylfuran-2-yl]-1-methylbutyl]-6-[(*S*)-1-hydroxy-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (87). Treatment of **85** (16 mg, 21 μmol) with 12 M HCl (5.0 μL) in MeOH (1.0 mL) under the same conditions as **84** gave the crude product, which was purified employing column chromatography on silica gel (1 g) with 30% acetone/$CHCl_3$ to give **87** (10 mg, 19 μmol, 90%): $[\alpha]^{23}_{300}$ −20.0°, $[\alpha]^{23}_{220}$ −140° (*c* 0.125, MeOH); IR (neat) 3420, 2970, 1457, 1386, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10, 1.14, 1.15, 1.18, 1.20, 1.27 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me, $C_{2''}$-Me, $C_{5''}$-CMe_2), 1.62 (3 H, s, $C_{5'}$-Me_{cis}), 1.69 (3 H, s, $C_{5'}$-Me_{trans}), 3.25 (1 H, dd, *J* = 2.4 and 10.3 Hz, C_6-H), 3.60 (1 H, dd, *J* = 2.4 and 10.3 Hz, $C_{4'}$-H), 3.63 (1 H, dd, *J* = 7.3 and 11.2 Hz, C_{4a}-H), 3.72 (1 H, dd, *J* = 2.9 and 12.7 Hz, C_2-H), 3.83 (1 H, t, *J* = 7.3 Hz, $C_{5''}$-H), 5.11 (1 H, br t, *J* = 7.1 Hz, $C_{4''}$-H); FD-MS *m/z* 527 (100, $M^+ + H$), 526 (67, M^+), 509 (16, $M^+ - OH$), 508 (14, $M^+ - H_2O$); FI-HR-MS found *m/z* 526.3881, calcd for $C_{30}H_{54}O_7$ (M^+) 526.3871.

Venustatriol (5). Treatment of **87** (10 mg, 19 μmol) with TBCO (11 mg, 27 μmol) in CH_3NO_2 (0.8 mL) under the same conditions as **86** gave the crude product. Similar workup and purification of the crude material employing HPLC (LiChrosorb RP-18 (Merck) 250 × 4 *φmm*, 90% CH_3CN/H_2O, 1 mL/min flow,

detected by UV at 215 nm) gave venustatriol (**5**) (2.5 mg, 4.1 μmol, 22%): t_R = 9.5 min (above conditions); $[\alpha]^{24}_D$ +11° (*c* 0.20 $CHCl_3$); IR ($CHCl_3$) 3420, 2960, 1460, 1375, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, venustatriol numbering) δ 1.09, 1.14, 1.17, 1.18, 1.20, 1.27, 1.27, 1.40 (each 3 H, s C_2-Me_2, C_6-Me, C_{10}-Me, C_{15}-Me, C_{19}Me, C_{23}-Me_2), 2.25 (1 H, dq, *J* = 2.9 and 12.2 Hz, C_4-H_β), 3.04 (1 H, dd, *J* = 2.0 and 11.2 Hz, C_7-H), 3.56 (1 H, dd, *J* = 6.8 and 13.0 Hz, C_{11}-H), 3.59 (1 H, dd, *J* = 1.5 and 10.0 Hz, C_{18}-H), 3.72 (1 H, dd, *J* = 3.0 and 13.0 Hz, C_{14}-H), 3.83 (1 H, t, *J* = 7.6 Hz, C_{22}-H), 3.89 (1 H, dd, *J* = 3.8 and 12.0 Hz, C_3-H); FD-MS *m/z* 607 (35, M^+ + H), 606 (15, M^+), 605 (31, M^+ + H), 589 (6.6, M^+ - OH), 587 (7.3, M^+ - OH), 586 (6.2, M^+ - H_2O), 527 (7.1, M^+ - Br), 361 (18, M^+ - $C_{13}H_{25}O_4$ (ABC ring moiety)), 359 (22, M^+ - $C_{13}H_{25}O_4$ (ABC ring moiety)), 207 (38, $C_8H_{14}O^{81}Br$), 205 (39, $C_8H_{14}O^{79}Br$), 143 (100, $C_8H_{15}O_2$ (D ring moiety)). The 400-MHz ^1H NMR spectrum and the optical rotation of this sample are perfectly coincident with those of natural venustatriol (**5**)[36] (lit.[4] $[\alpha]^{20}_D$ +9.4° (*c* 3.2, $CHCl_3$)).

(2*R*,4a*R*,6*R*,8a*S*)-Octahydro-2-[(1*S*,4*S*)-1,4-bis(methoxymethoxy)-4-[(2*R*,5*R*)-tetrahydro-2-methyl-5-[1-methyl-1-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]furan-2-yl]-1-methylbutyl]-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (96). A solution of **84** (10 mg, 13 μmol), MOMCl (10 mg, 130 μmol), and *i*-Pr_2NEt (15 mg, 110 μmol) in CH_2Cl_2 (150 μL) was stirred at room temperature for 15 h. The mixture was poured into water (15 mL) and extracted with ether (4 × 15 mL). The ethereal solutions were combined, washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography of the residue on silica gel (1 g) with 20% EtOAc/benzene afforded **96** (9.0 mg, 11 μmol, 87%): $[\alpha]^{20}_D$ -10.3° (*c* 1.00, $CHCl_3$); IR (neat) 2930, 1460, 1380, 1245, 1140, 1030, 915, 855, 840, cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.03 (9 H, s, $SiMe_3$), 0.95 (2 H, t, *J* = 8.0 Hz, OCH_2CH_2TMS), 1.23, 1.25, 1.27, 1.28, 1.30, 1.31 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me, $C_{2'''}$-Me, $C_{5'''}$-CMe_2), 1.65 (3 H, s, $C_{5'''}$-Me_{cis}), 1.70 (3 H, s, $C_{5'''}$-Me_{trans}), 3.26, 3.29, 3.36 (each 3 H, s, OMe × 3), 3.51 (1 H, dd, *J* = 7.5 and 11.0 Hz, C_{4a}-H), 3.61 (1 H, dd, *J* = 3.8 and 6.4 Hz, $C_{4'}$-H), 3.71, 3.76 (each 1 H, dt, *J* = 9.4 and 8.0 Hz, $OCH_2CH_2SiMe_3$), 3.86 (1 H, dd, *J* = 5.9 and 9.8 Hz, $C_{5'''}$-H), 3.94 (1 H, dd, *J* = 3.0 and 12.3 Hz, C_2-H), 4.67, 4.77 (each 1 H, d, *J* = 7.3 Hz, OCH_2O), 4.73, 4.81 (each 1 H, d, *J* = 7.3 Hz, OCH_2O), 4.80, 4.83 (each 1 H, d, *J* = 6.3 Hz, OCH_2O), 4.85, 4.94 (each 1 H, d, *J* = 7.3 Hz, OCH_2O), 5.29 (1 H, br t, *J* = 7.2 Hz, $C_{4''}$-H); FI-MS *m/z* 789 (49, M^+ + H), 788 (25, M^+), 757 (64, M^+ - MeO), 325 (25, $C_{19}H_{33}O_4^+$ (right half)), 273 (100, $C_{14}H_{29}O_3Si^+$ (D ring moiety)), 101 (48, $Me_3SiH_2CH_2^+$); FI-HR-MS found *m/z* 789.5561, calcd for $C_{42}H_{81}O_{11}Si$ (M^+ + H) 789.5503.

(2*R*,4*R*,6*R*,8a*S*)-2-[(1*S*,4*S*)-4-[(2*R*,5*R*)-Tetrahydro-5-(1-hydroxy-1-methylethyl)-2-methylfuran-2-yl]-1,4-bis(methoxymethoxy)-1-methylbutyl]octahydro-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (97). A suspension of **96** (23 mg, 29 μmol), TBAF (1M in THF, 30 μL), and MS4Å in HMPA (1.0 mL) was stirred at 120 °C for 3 h under an Ar atmosphere. After cooling, the mixture was filtered with suction. Then the filtrates were poured into water (15 mL) and extracted with ether (4 × 15 mL). The combined ethereal solutions were washed successively with water (20 mL) and brine (20 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (1 g) with 30% EtOAc/benzene to give **97** (19 mg, 28 μmol, 98%): $[\alpha]^{21}_D$ -12° (*c* 0.60, $CHCl_3$); IR (neat) 3520, 2960, 1450, 1375, 1140, 1090, 1030, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11, 1.14, 1.15, 1.17, 1.19, 1.20 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me, $C_{2'''}$-Me, $C_{5'''}$-CMe_2), 1.68 (3 H, s, $C_{5'''}$-Me_{cis}), 1.74 (3 H, s, $C_{5'''}$-Me_{trans}), 3.35, 3.37, 3.40 (each 3 H, s, OMe × 3), 3.40 (1 H, m, $C_{4'}$-H), 3.58 (1 H, dd, *J* = 7.5 and 11.0 Hz, C_{4a}-H), 3.69 (1 H, dd, *J* = 5.9 and 9.8 Hz, C_2-H), 3.80 (1 H, dd, *J* = 5.6 and 9.2 Hz, $C_{5'''}$-H), 4.67, 4.78 (each 1 H, d, *J* = 6.8 Hz, OCH_2OMe), 4.69, 4.77 (each 1 H, d, *J* = 7.3 Hz, OCH_2OMe), 4.70, 4.74 (each 1 H, d, *J* = 7.3 Hz, OCH_2OMe), 5.10 (1 H, br t, *J* = 7.2 Hz, $C_{4''}$-H); FI-MS *m/z* 659 (17, M^+ + H), 658 (7.5, M^+), 627 (23, M^+ - MeO), 626 (25 M^+ - MeOH), 143 (100, $C_8H_{15}O_2$ (D ring moiety)); FI-HR-MS found *m/z* 659.4678, calcd for $C_{36}H_{67}O_{10}$ (M^+ + H) 659.4736.

(2*R*,5*R*)-5-(1-Acetoxy-1-methylethyl)tetrahydro-2-[(1*S*,4*S*)-1,4-bis(methoxymethoxy)butyl]-2-methylfuran (94). A solution of **93** (27 mg, 80 μmol) and DMAP (50 μg, 0.4 μmol) in Ac_2O (1.0 mL) was heated at 120 °C with stirring for 3 h. After colling to room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with ether (3 × 20 mL). The extracts were washed with brine (20 mL), dried (Na_2SO_4), and evaporated in vacuo. The residual oil was chromatographed over silica gel (100 mg) with 50% ether/hexane to give **94** (18 mg, 48 μmol, 60%): $[\alpha]^{30}_D$ -13° (*c* 0.80, $CHCl_3$); IR (neat) 2990, 2960, 1730, 1460, 1370, 1250, 1150, 1100, 1050, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (3 H, s, C_2-Me), 1.19 (3 H, d, *J* = 6.8 Hz, $C_{4'}$-Me), 1.43, 1.46 (each 3 H, s, $C_{1''}$-Me_2), 1.97 (3 H, s, O_2CMe), 3.37, 3.40 (each 3 H, s, OMe × 2), 3.43 (1 H, dd, *J* = 2.0 and 9.1 Hz, $C_{1'}$-H), 3.68 (1 H, m, $C_{4'}$-H), 3.96 (1 H, dd, *J* = 5.9 and 9.8 Hz, C_5-H), 4.63, 4.69 (each 1 H, d, *J* = 7.1 Hz, OCH_2OMe), 4.67, 4.83 (each 1 H, d, *J* = 6.9 Hz, OCH_2OMe); FI-MS *m/z* 376 (30, M^+), 334 (2.0, M^+ - CH_3CO_2H), 191 (35, M^+ - 2 (CH_3OCH_2OH) - CH_3CO_2), 143 (100); FI-HR-MS found *m/z* 376.2438, calcd for $C_{19}H_{36}O_7$ (M^+) 376.2461.

(2*R*,4a*R*,6*R*,8a*S*)-2-[(1*S*,4*S*)-4-[(2*R*,5*R*)-5-(1-Acetoxy-1-methylethyl)tetrahydro-2-methylfuran-2-yl]-1,4-bis(methoxymethoxy)-1-methylbutyl]octahydro-6-[(*S*)-1-(methoxymethoxy)-1,5-dimethylhex-4-enyl]-8a-methylpyrano[3,2-*b*]pyran (98). A solution of **97** (13 mg, 19 μmol) in Ac_2O (200 μL) was stirred with DMAP (50 μg, 0.4 μmol) at 120 °C for 4 h. After cooling to room temperature, the resulting mixture was poured into saturated aqueous $NaHCO_3$ solution (15 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed successively with water (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. The residual oil was subjected to column chromatography on silica gel (100 mg) with 50% ether/hexane to give **98** (6.0 mg, 8.6 μmol, 45%): $[\alpha]^{19}_D$ -11° (*c* 0.6, $CHCl_3$); IR (neat) 2930, 2850, 1735, 1645, 1455, 1370, 1255, 1150, 1100, 1040, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14, 1.15, 1.17, 1.20 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me, $C_{2'''}$-Me), 1.43, 1.46 (each 3 H, s, $C_{5'''}$-CMe_2), 1.61 (3 H, s, $C_{5'''}$-Me_{cis}), 1.68 (3 H, s, $C_{5'''}$-Me_{trans}), 1.99 (3 H, s, O_2CMe), 3.35, 3.37, 3.40 (each 3 H, s, OMe × 3), 3.57 (1 H, dd, *J* = 7.3 and 11.5 Hz, C_{4a}-H), 3.80 (1 H, dd, *J* = 6.0 and 8.8 Hz, $C_{5'''}$-H), 3.97 (1 H, dd, *J* = 5.4 and 9.8 Hz, C_2-H), 4.60, 4.74 (each 1 H, d, *J* = 7.1 Hz, OCH_2OMe), 4.67, 4.78 (each 1 H, d, *J* = 6.8 Hz, OCH_2OMe), 4.69, 4.77 (each 1 H, d, *J* = 7.3 Hz, OCH_2OMe), 5.10 (1 H, br t, *J* = 7.2 Hz, $C_{5''}$-H); FI-MS *m/z* 701 (4.0, M^+ + H), 700 (8.5, M^+), 668 (10, M^+ - MeOH), 641 (15, M^+ - Ac), 640 (21, M^+ - AcOH), 185 (100); FI-HR-MS found *m/z* 700.4732, calcd for $C_{38}H_{68}O_{11}$ (M^+) 700.4763.

Thyrsiferyl 23-Acetate (3). A solution of **98** (5.0 mg, 7.1 μmol) in a mixture of 12 M HCl (5 μL) and MeOH (300 μL) was stirred at room temperature for 7 h. After neutralization by addition of Et_3N (ca. 15 μL), the solvent was removed in vacuo. Column chromatography of the residue on silica gel (500 mg) with 20% acetone/$CHCl_3$ gave **99** (3.0 mg, 5.5 μmol, 78%): $[\alpha]^{20}_D$ -9.3° (*c* 0.3, $CHCl_3$); IR (neat) 3400, 2970, 2930, 2850, 1735, 1450, 1370, 1250, 1090, 1020, 940, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10, 1.15, 1.16, 1.21 (each 3 H, s, C_{8a}-Me, $C_{1'}$-Me, $C_{1''}$-Me, $C_{2'''}$-Me), 1.45, 1.48 (each 3 H, s, $C_{5'''}$-CMe_2), 1.62 (3 H, s, $C_{5'''}$-Me_{cis}), 1.69 (3 H, s, $C_{5'''}$-Me_{trans}), 1.99 (3 H, s, O_2CMe), 3.25 (1 H, dd, *J* = 3.3 and 8.2 Hz, C_6-H), 3.44 (1 H, dd, *J* = 2.5 and 11.0 Hz, C_4-H), 3.63 (1 H, dd, *J* = 7.0 and 11.0 Hz, C_{4a}-H), 3.71 (1 H, dd, *J* = 3.7 and 12.6 Hz, C_2-H), 4.01 (1 H, dd, *J* = 5.4 and 9.5 Hz, $C_{5'''}$-H), 5.11 (1 H, br t, *J* = 7.2 Hz, $C_{5''}$-H).

A mixture of **99** (3.0 mg, 5.5 μmol) and TBCO (2.0 mg, 5.1 μmol) in CH_3NO_2 (1.0 mL) was stirred at room temperature for 5 min. The solvent was evaporated under reduced pressure, and the residual oil was chromatographed quickly on silica gel (500 mg) with 10% acetone/$CHCl_3$. Further purification of the oil was performed employing HPLC (LiChrosorb RP-18 (4 × 250 *φmm*, Merck), 90% MeOH/H_2O, 1.0 mL/min flow, detected at 215 nm) to give thyrsiferyl 23-acetate (**3**) (0.7 mg, 1.1 μmol, 20%): t_R = 11.0 min; $[\alpha]^{23}_{220}$ +190°, $[\alpha]^{23}_{300}$ +20° (*c* 0.02, MeOH); IR ($CHCl_3$) 3450, 1730, 1270, 1120, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.09, 1.16, 1.18, 1.20, 1.27, 1.40, 1.44, 1.48, 1.99 (each 3 H, s, C_2-Me_2, C_6-Me, C_{10}-Me, C_{15}-Me, C_{19}-Me, C_{23}-Me_2, O_2CMe), 3.04 (1 H, dd, *J* = 2.7 and 11.5 Hz, C_7-H), 3.45 (1 H, dd, *J* = 2.0 and 10.3 Hz, C_{18}-H), 3.57 (1 H, dd, *J* = 7.6 and 10.9 Hz, C_{11}-H), 3.70 (1 H, dd, *J* = 2.4 and 12.7 Hz, C_{14}-H), 3.89 (1 H, dd, *J* = 3.9 and 12.2 Hz, C_3-H), 4.00 (1 H, dd, *J* = 6.1 and 9.5 Hz, C_{22}-H). The 400-MHz ^1H NMR, ORD, and IR spectra are completely identical with those

of natural thyrsiferyl 23-acetate (3)[32] ($[\alpha]^{23}_{220}$ +250°, $[\alpha]^{23}_{300}$ +27° (c 0.02, MeOH)).

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Supplementary Material Available: ^{1}H NMR spectra of 1, 3, 5, 10, 12-15, 19-31, 34, 36-43, 45, 47, 49-54, 56-58, 62-73, 75-80, 83-92, 94, and 96-99 and ^{13}C NMR spectrum of 45 (78 pages). Ordering information is given on any current masthead page.

Lucidene, a Bis(benzopyranyl) Sesquiterpene from *Uvaria lucida* ssp. *lucida*

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Lucidene (1), a bis(benzopyranyl) sesquiterpene was isolated from the rootbark of *Uvaria lucida* ssp. *lucida*, and its structure was determined by spectroscopic methods and single-crystal X-ray crystallography. It is optically inactive and crystallizes in enantiomeric pairs. High-resolution ^{1}H NMR (400 and 600 MHz) spectroscopy allowed the assignment of all protons and indicated the existence of relatively slowly interconverting conformations. The three known dihydrochalcones, uvaretin, diuvaretin, and chamuvaretin, as well as benzyl benzoate were isolated from the same plant as well.

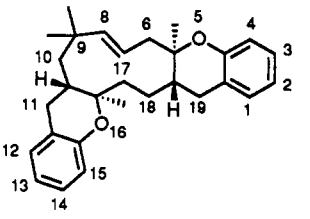
Introduction

Uvaria species have been a source of several new compounds,[1,2] some with cytotoxic,[3] antimicrobial,[4] and antimalarial[5] activity. A typical structural feature that occurs frequently in compounds isolated from *Uvaria* species is the presence of benzyl or *o*-hydroxybenzyl groups, as in the uvaretins[3,6] and some indoles.[7,8] Sesquiterpenes containing *o*-hydroxylbenzyl groups occur in *Uvaria* species as well, and three such compounds have thus far been reported.[9] In this paper we describe the determination of the structure of a new sesquiterpene, viz. a bis(benzopyranyl) sesquiterpene, which we have named lucidene (1). The present investigation was carried out as part of our project on antimalarial constituents of *Uvaria* species. Lucidene was isolated from the petroleum ether extract of the rootbark of *Uvaria lucida* spp. *lucida*, which showed relatively high in vitro activity against the multidrug resistant K_1 strain of *Plasmodium falciparum*; however, lucidene itself showed no such activity.[10]

Results and Discussion

The title compound (1) was isolated from the petroleum ether extract of the rootbark of *Uvaria lucida* using gradient silica gel chromatography (hexane/ethyl acetate), in addition to the known compounds benzyl benzoate,[8] chamuvaretin,[8,11] uvaretin,[3,8] and diuvaretin.[3,8]

Lucidene (1), which was recrystallized from hexane, showed a mass spectrum with characteristic ions at *m/e* 416 (M^+), 309 (monooxybenzyl sesquiterpene: M^+ - hydroxybenzyl) and 107 (*o*-hydroxybenzyl). The high-resolution MS showed the M^+ at *m/z* 416.2720, which corresponds with $C_{29}H_{36}O_2$ (calcd 416.2715). These mass spectral data suggest for 1 a sesquiterpene structure containing two oxybenzyl fragments.



1

The UV (λ_{max} (hexane) 284, 277, 228, 220 nm) and IR spectra (KBr, 1610, 1584 (C=C), 1262, 1246, 1235, 1221 (C—O), 760, and 753 cm^{-1} (ortho-substituted phenyl)) suggest the presence of two benzopyran moieties in 1.

Since it was not possible to fully characterize compound 1 with the available spectral data (400- and 600-MHz ^{1}H NMR, UV, IR, and MS), single-crystal X-ray diffraction

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(1) Leboeuf, M.; Cavé, A.; Bhaumik, P. K.; Mukherjee, B.; Mukherjee, R. *Phytochemistry* **1982**, *21*, 2783.
(2) Thebtaranonth, C.; Thebtaranonth, Y. *Acc. Chem. Res.* **1986**, *19*, 84.
(3) Lasswell, W. L., Jr.; Hufford, C. D. *J. Org. Chem.* **1977**, *42*, 1295.
(4) Hufford, C. D.; Lasswell, W. L., Jr. *Lloydia* **1978**, *41*, 156.
(5) Nkunya, M. H. H.; Weenen, H.; Koyi, N. J.; Thijs, L.; Zwanenburg, B. *Phytochemistry* **1987**, *26*, 2563.
(6) Nkunya, M. H. H.; Achenbach, H.; Renner, C.; Weenen, H., submitted to *Phytochemistry*.
(7) Waterman, P. G.; Muhammad, I. *J. Chem. Soc., Chem. Commun.* **1984**, 1280.
(8) Muhammad, I.; Waterman, P. G. *J. Nat. Prod.* **1985**, *48*, 571.
(9) Muhammad, I.; Waterman, P. G. *J. Nat. Prod.* **1988**, *51*, 719.
(10) Nkunya, M. H. H.; Weenen, H.; Bray, D. H., submitted to *Planta Medica*.
(11) Okorie, D. A. *Phytochemistry* **1977**, *16*, 1591.

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