Synthesis of the FG Ring System of Brevetoxin B

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Abstract: A synthesis of an appropriately functionalized system (**1**) representing the FG ring skeleton of brevetoxin B is described. Beginning with the geraniol-derived lactone **6**, the reported sequence proceeds via key intermediates **15** and **27** and involves two 6-endo selective hydroxy epoxide openings leading to the optically active target **1**. The stereochemistry of the final product was confirmed by an X-ray crystallographic analysis of the crystalline derivative **30**.

In the preceding article,[2] a retrosynthetic analysis of brevetoxin B was outlined in which the functionalized FG ring system (**1**, Scheme I) was defined as a potential intermediate in a projected total synthesis of this complex marine natural product. The previous paper[2] also described the construction of the ABC ring system of brevetoxin B. In this article, we report a stereocontrolled synthesis of the FG ring system of brevetoxin B as phosphonium salt **1**.

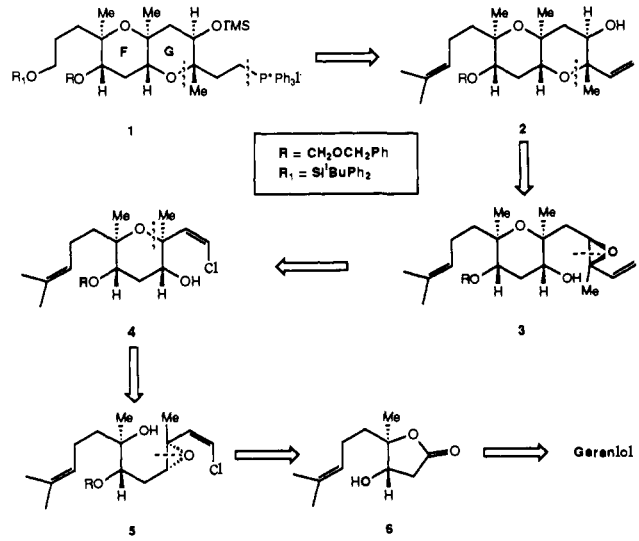
Results and Discussion

Retrosynthetic Analysis. A retrosynthetic analysis of the appropriately functionalized FG ring system **1** of brevetoxin B is shown in Scheme I. This strategy relies heavily on the regioselective 6-*endo*-epoxide activation technology discussed in a previous paper.[3] Thus, initial functional group manipulation of the appendages of **1** leads to the diolefin **2**. Disconnection of ring G in **2** as indicated reveals the hydroxy epoxide **3** as a potential precursor. Dissection of the side chain of intermediate **3** as indicated then leads to the chloroolefin **4**. Rupture of the indicated carbon–oxygen bond then allows hydroxy epoxide **5** to serve as a precursor. This intermediate (**5**) can then be tracked back to the Ganem lactone **6**,[4] which originates from geraniol. The Sharpless asymmetric epoxidation reaction[5,6] was expected to provide stereoselective epoxide formation, whereas the 6-endo activation technology[3] was to allow ring-selective tetrahydropyran formation at the key steps (**5** → **4** and **3** → **2**). The easily differentiated olefins in **2** were to serve as equivalents to the requisite ends of the two long chains of **1**.

Synthesis of the FG Ring System (1) of Brevetoxin B. According to the above strategy, we began the construction of the brevetoxin B FG fragment **1** from the geraniol-derived and readily available lactone **6** (three steps, ca. 37% overall yield).[4] The olefin side chain of this optically active lactone provides a masked form of an oxygen function with the proper carbon chain length, whereas its two stereogenic centers correspond to those of the left edge of the requisite FG fragment. Scheme II shows the construction of ring F (compound **18**) from **6** by a highly stereoselective sequence. The hydroxy group in **6** was protected as a benzyloxymethyl ether by using benzyl chloromethyl ether and *N*,*N*-diisopropylamine at 75 °C, leading to **7** in 84% yield. Treatment of **7** with DIBAL at −78 °C produced a mixture (ca. 1:1) of lactols **8** (100%), which upon heating at 70 °C with (carbethoxyethylidene)triphenylphosphorane in benzene furnished the desired olefin **9** in 82% yield. Elaboration of the *E*-olefin **9** to the requisite hydroxy epoxide **15** was accomplished in six steps. Thus, the newly liberated hydroxy group in **9** was protected as its trimethylsilyl ether **10** by heating with 1-(trimethylsilyl)imidazole at 60 °C in 1,2-dichloromethane (100%). Reduction of the ester with DIBAL followed by Sharpless asymmetric epoxidation using (−)-diethyl tartrate as the chiral auxiliary furnished the hydroxy epoxide **12** via allylic alcohol **11** in 87% overall yield. Oxidation of **12** with SO_3·pyridine in DMSO–CH_2Cl_2 at 0 °C led to the labile aldehyde **13**, which was immediately reacted with the ylide derived from (chloromethyl)triphenylphosphonium chloride and $NaN(SiMe_3)_2$ at 0 °C to afford the allylic epoxide **14** in 79% yield. The *Z* geometry of the chloroolefin was deduced from the coupling constant (*J*) of 7.4 Hz for the two new olefinic protons. Fluoride-induced desilylation of **14** then led to hydroxy epoxide **15** in 96% yield. The conversion of **15** to **16** was to provide an interesting test for the 6-endo cyclization route to tetrahydropyrans due to the serious 1,3-diaxial nonbonding interaction of the two methyl groups, developing along the reaction coordinate as pictured in transition state **15A** (Figure 1). On the other hand, however, the methyl group at the desired point of attack should contribute to the stabilization of the incipient positive charge at the 6-endo center. In the event, treatment of **15** with camphorsulfonic acid (CSA) at 0 → 25 °C led exclusively to the desired tetrahydropyran **16** in 83% yield. The structure of the product **16** was tentatively assigned by decoupling experiments on the corresponding acetate **17** obtained by standard methods. An X-ray crystallographic analysis on a subsequent intermediate confirmed this assignment (vide infra). The silyl ether **18** was obtained quantitatively upon exposure of **16** to 1-(trimethylsilyl)imidazole at 25 °C.

Having efficiently formed the F-pyran system, we than turned our attention to the construction of the second pyran system as outlined in Scheme III. Conversion of the vinyl chloride **18** to the acetylene **19** was carried out by treatment with *n*-BuLi at −78 °C (86%). Hydroboration of **19** with disiamylborane followed by oxidative workup afforded the aldehyde **20** in 89% yield. Treatment of **20** with (carbethoxyethylidene)triphenylphosphorane in benzene at 25 °C gave predominantly the *E*-olefin **21** (75% yield), which was reduced with DIBAL to afford the allylic alcohol **22** in quantitative yield.

Scheme I. Retrosynthetic Analysis of the FG Ring System of Brevetoxin B



(1) Taken in part from the Ph.D. Thesis of M.E.D., Department of Chemistry, University of Pennsylvania, 1987.
(2) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.*, first of three papers in this issue.
(3) Nicolaou, K. C.; Prasad, C. V. C.; Somers, K. P.; Hwang, C.-K. *J. Am. Chem. Soc.*, in press.
(4) Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761.
(5) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976.
(6) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

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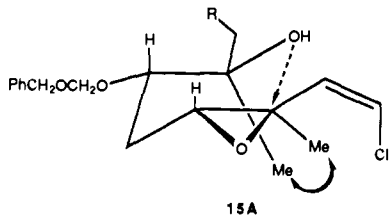
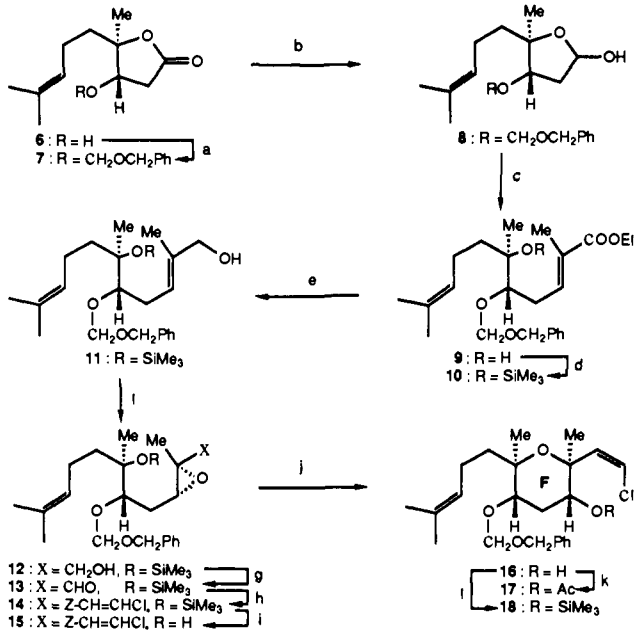


15A

Figure 1. Presumed transition state of the cyclization of **15** to **16**.

Scheme II[a]

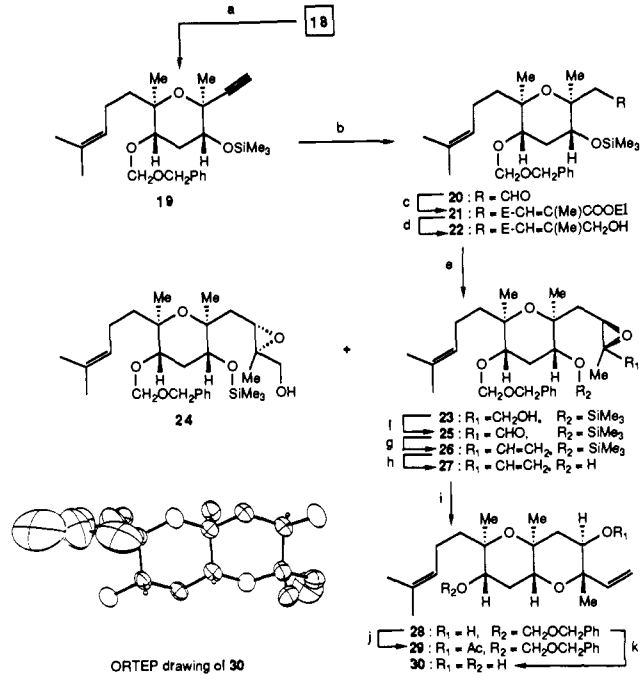


[a] Reagents and conditions: (a) 1.1 equiv of $PhCH_2OCH_2Cl$, 2.0 equiv of $NEtPr_2$, $ClCH_2CH_2Cl$, 75 °C, 18 h, 84%; (b) 1.2 equiv of DIBAL, CH_2Cl_2, −78 °C, 45 min, 100%; (c) 1.1 equiv of $Ph_3P{=}C$(Me) COOEt, benzene, 70 °C, 18 h, 82%; (d) 1.1 equiv of Me_3Si-imidazole, $ClCH_2CH_2Cl$, 60 °C, 6 h, 100%; (e) 2.2 equiv of DIBAL, CH_2Cl_2, −78 °C, 45 min, 100%; (f) 0.05 equiv of $Ti(O\text{-}Pr)_4$, 0.08 equiv (−)-DET, 1.5 equiv of BuOOH, 4 A MS, CH_2Cl_2, −20 °C, 16 h, 87%; (g) 5.0 equiv of Et_3N, 4.0 equiv of SO_3–pyr., CH_2Cl_2–DMSO (5:1), 0 °C, 2 h, 95%; (h) 2.0 equiv of $Ph_3P^+CH_2ClCl^-$, 2.0 equiv of NaN($SiMe_3$)$_2$, THF, 0 °C, 30 min, 79%; (i) 1.3 equiv of $^nBu_4NF$, THF, 0 °C, 1.5 h, 96%; (j) 0.1 equiv of CSA, CH_2Cl_2, 0–25 °C, 2.5 h, 83%; (k) 3.0 equiv of DMAP, 2.0 equiv of Ac_2O, CH_2Cl_2, 25 °C, 30 min, 92%; (l) 1.2 equiv of Me_3Si-imidazole, CH_2Cl_2, 25 °C, 2 h, 100%.

Sharpless asymmetric epoxidation[5,6] of the allylic alcohol **22** using (−)-diethyl tartrate afforded two epoxides, **23** and **24**, in 94% yield and ca. 3:1 ratio. The major epoxide **23** was assumed to possess the indicated stereochemistry on the basis of the tartrate auxiliary used, an assumption later confirmed by decoupling experiments and X-ray crystallographic analysis on subsequent intermediates (vide infra). Treatment of allylic alcohol **22** with mCPBA led to a 1:1 mixture of the two epoxides **23** and **24**, whereas changing the nature of the substituent on the allylic oxygen (Si^tBuPh_2 or Si^tBuMe_2) did not improve the selectivity. The apparent failure of the Sharpless epoxidation reaction to deliver high asymmetric induction in this and related systems[3] probably originates in interference by the large, stereogenic appendage with binding sites. The major hydroxy epoxide **23** was then oxidized with SO_3·pyridine in DMSO–CH_2Cl_2 at 0 °C followed by reaction of the resulting aldehyde **25** with the appropriate ylide, furnishing the allylic epoxide **26** in 72% overall yield. Fluoride-induced deprotection of **26** led to hydroxy epoxide **27** in 97% yield.

Cyclization of **27** was effected by pyridinium *p*-toluenesulfonate at 0 → 25 °C, furnishing the FG bicycle **28** in 85% yield. The coupling constants (J = 11.8, 5.2 Hz) for the corresponding acetate **29** revealed an axial disposition of the acetoxy methine proton, indicating the correctness of the assigned structures (**27**, **28**, and **29**). Removal of the (benzyloxy)methyl protecting group from **28** with BF_3·Et_2O/EtSH[7] in CH_2Cl_2 at −20 °C led to the highly crystalline diol **30**, mp 134–135 °C (from ether–hexane). An X-ray crystallographic analysis on **30** proved its structure and the assigned structures of its progenitors. The ORTEP drawing of **30** shown in Scheme III depicts a significant puckering of the FG bicyclic system imposed by the repulsive interaction of the 1,3-diaxial methyl groups.

Scheme III[a]



[a] Reagents and conditions: (a) 2.2 equiv of ^{n}BuLi, THF, −78 °C, 20 min, 86%; (b) 1.2 equiv of BH_3–THF, 3.0 equiv of 2-methyl-2-butene, THF, 0 °C, 45 min, then 3 N NaOH, 30% H_2O_2, 89%; (c) 1.3 equiv of $Ph_3P{=}C$(Me)–COOEt, benzene, 25 °C, 3 h, 75%; (d) 2.2 equiv of DIBAL, CH_2Cl_2, −78 °C, 1 h, 100%; (e) 0.05 equiv of $Ti(O\text{-}^iPr)_4$, 0.08 equiv of (−)-DET, 1.5 equiv of ^{t}BuOOH, 4 A molecular sieves, CH_2Cl_2, −20 °C, 16 h, **23** (70%), **24** (24%); (f) 7.0 equiv of Et_3N, 4.0 equiv of SO_3·pyr, CH_2Cl_2–DMSO (4:1), 0 °C, 4 h, 90%; (g) 2.4 equiv of $Ph_3P{=}CH_2$, THF, 0 °C, 30 min, 79%; (h) 1.2 equiv of $^nBu_4NF$, THF, 25 °C, 3 h, 97%; (i) 0.9 equiv of PPTS, CH_2Cl_2, 0 °C, 85%; (j) 3.0 equiv of DMAP, 3.0 equiv of Ac_2O, CH_2Cl_2, 25 °C, 30 min, 93%; (k) 3.0 equiv of BF_3–Et_2O, 10.0 equiv of EtSH, CH_2Cl_2, −20 °C, 1 h, 92%.

Elaboration of the FG bicycle **28** to the desired phosphonium salt **1** was accomplished in six steps as indicated in Scheme IV. Protection of the alcohol **28** with 1-(trimethylsilyl)imidazole gave **31** in quantitative yield. Hydroboration of **31** followed by oxidative workup afforded the primary alcohol **32** in 87% yield. Iodide formation using PPh_3–I_2/imidazole in benzene at 10 °C gave **33** in 89% yield. Careful ozonolysis of the olefin **33** in CH_2Cl_2 at −78 °C and subsequent in situ reduction of the resulting ozonide with BH_3·Me_2S yielded the alcohol **34** in 86% yield. Finally, protection of this alcohol as the silyl ether **35** (98%) followed by heating in acetonitrile at 90 °C with Ph_3P gave the targeted FG fragment **1** in quantitative yield.

Conclusion

Construction of the FG bicycle of brevetoxin B demonstrates clearly the efficiency and flexibility of the 6-endo activation method for tetrahydropyran synthesis. Both rings were constructed by this type of cyclization, which occurred in high yield and essentially with complete regioselectivity. These examples extend the scope of the method to encompass epoxy alcohols carrying a methyl

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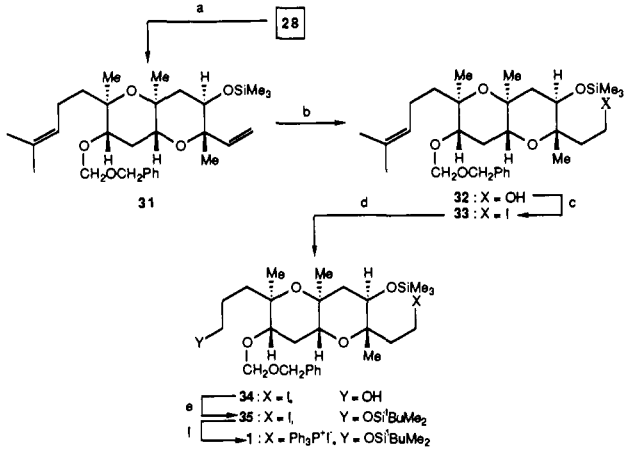
(8) This X-ray crystallographic analysis was carried out by Dr. Patrick Carroll of this Department. We thank Dr. Carroll for his assistance in this work.

Scheme IV[a]



[a] Reagents and conditions: (a) 1.3 equiv of Me_3Si-imidazole, CH_2Cl_2, 25 °C, 100%; (b) 1.3 equiv of BH_3–THF, 0 °C, 3.0 equiv of 2-methyl-2-butene, THF, 0 °C, 45 min, then 3 N NaOH, 30% H_2O_2, 87%; (c) 3.0 equiv of Ph_3P, 3.0 equiv of imidazole, 2.0 equiv of I_2, benzene, 10 °C, 20 min, 89%; (d) O_3, CH_2Cl_2, −78 °C, 0.5 h, then 3.8 equiv of BH_3–Me_2S, 86%; (e) 1.5 equiv of ^{t}BuMe$_2$SiCl, 3.0 equiv of imidazole, DMF, 0 °C, 1 h, 98%; (f) 8.0 equiv of Ph_3P, CH_3CN, 90 °C, 24 h, 100%.

group at the 6-endo position leading to systems with steric congestion. Furthermore, the synthesis demonstrated the ease by which the olefin functionality may be manipulated to more advanced intermediates once its purpose for regiospecificity is served. This sequence provided optically active **1** from the Ganem lactone **6** in 26 steps and ca. 7% overall yield.

Experimental Section

General Methods. See the Experimental Section in ref 2.

(4*S*,5*R*)-4-[(Benzyloxy)methoxy]dihydro-5-methyl-5-(4-methyl-3-pentenyl)-2(3*H*)-furanone (7). A stirred mixture of the alcohol **6**[4] (43.6 g, 0.22 mol), *N*,*N*-diisopropylethylamine (76.6 mL, 0.44 mol), and dry 1,2-dichloroethane (440 mL) at 25 °C was treated dropwise with benzyl chloromethyl ether (45.9 mL, 0.33 mol) over a 15-min period. After stirring at 75 °C for 18 h, the cooled reaction mixture was diluted with ether (500 mL) and washed sequentially with H_2O (100 mL) and brine (50 mL), followed by drying ($MgSO_4$) and solvent removal. Flash column chromatography (silica, 20% ether in petroleum ether) of the crude oil gave the ether **7** (58.8 g, 84%). **7**: oil; R_f = 0.27 (silica, 30% ether in petroleum ether); $[\alpha]^{21}_D$ +20.4° (*c* 1.40, $CHCl_3$); IR (neat) ν_{max} 3030, 2970, 2930, 2860, 1785 (s, $-CO_2-$), 1455, 1385, 1265, 1050, 740, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5 H, Ar), 5.12 (br t, *J* = 8.0 Hz, 1 H, *HC*=C), 4.82, 4.77 (2 × d, 9.7 Hz, 2 × 1 H, $-CH_2Ar$), 4.61 (s, 2 H, OCH_2O), 4.20 (dd, *J* = 7.0, 5.4 Hz, 1 H, $OCHCH_2$), 2.87 (dd, *J* = 17.8, 7.0 Hz, 1 H, CH_2CO_2), 2.60 (dd, *J* = 17.8, 5.5 Hz, 1 H, CH_2CO_2), 2.10 (m, 2 H, CH_2C=C), 1.68, 1.59 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.56 (m, 2 H, CH_2), 1.40 (s, 3 H, CH_3); MS *m*/*e* (rel intensity) 336 (M + NH_4, 92), 319 (M + 1, 94), 289 (13), 271 (26), 244 (14), 216 (100), 198 (100), 185 (100), 173 (42), 155 (58), 129 (100), 111 (100); HRMS calcd for $C_{19}H_{30}NO_4$ (M + NH_4) 336.2175, found 336.2187.

(4*S*,5*R*)-4-[(Benzyloxy)methoxy]-2-hydroxy-5-methyl-5-(4-methyl-3-pentenyl)tetrahydrofuran (8). The lactone **7** (58.8 g, 0.18 mol) in dry dichloromethane (800 mL) stirring at −78 °C was treated dropwise with DIBAL (220 mL, 1 M in hexanes, 0.22 mmol) over 15 min. After stirring for an additional 45 min, the excess DIBAL was quenched with CH_3OH (10 mL) and then was transferred to a stirring mixture of EtOAc (2 L) and saturated aqueous solution of potassium sodium tartrate (200 mL). Once the emulsion dissipated, the organic portion was dried ($MgSO_4$) and the solvent evaporated to give a mixture of lactols **8** (58.8 g, 100%). **8**: oil; R_f = 0.41 (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3430 (s, OH), 3030, 2970, 2930, 1455, 1380, 1165, 1115, 1050, 740, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5 H, Ar), 5.42 (m, 0.5 H, *CH*OH), 5.37 (dd, *J* = 9.8, 5.0 Hz, 0.5 H, *CH*OH), 5.09 (m, 1 H, *HC*=C), 4.87–4.60 (m, 4 H, $-CH_2Ar$ and OCH_2O), 4.25 (t, *J* = 7.2 Hz, 0.5 H, $OCHCH_2$), 4.06 (dd, *J* = 7.0, 2.3 Hz, 0.5 H, $OCHCH_2$), 3.46 (d, *J* = 9.8 Hz, 0.5 H, O*H*), 3.01 (d, *J* = 2.0 Hz, 0.5 H, O*H*), 2.43–1.78 (m, 4 H, CH_2C=C and CH_2), 1.67, 1.59 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.62 (m, 2 H, CH_2), 1.40 (s, 0.5 H, CH_3), 0.19 (s, 1.5 H, CH_3); MS *m*/*e* (rel intensity) 310 (M, 27), 303 (100), 285 (24), 273 (48), 231 (14), 211 (46), 195 (100), 181 (100), 165 (100), 147 (96), 121 (97), 109 (100); HRMS calcd for $C_{19}H_{28}O_4$ (M) 320.1987, found 320.2038. Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.80. Found: C, 71.08; H, 8.50.

Ethyl (2*E*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-6-hydroxy-2,6,10-trimethyl-2,9-undecadienoate (9). A stirred mixture of lactols **8** (58.8 g, 0.18 mol) and (carbethoxyethylidene)triphenylphosphorane (72.5 g, 0.20 mol) in dry benzene (260 mL) was heated at 70 °C for 18 h. The cooled reaction mixture was diluted with ether (360 mL) followed by washing with 1 N HCl (50 mL) and brine (50 mL). Drying over $MgSO_4$ and removal of solvents gave a residue that upon flash chromatography (silica, 15–20% ether in petroleum ether) furnished the olefin **9** (59.7 g, 82%). **9**: oil; R_f = 0.56 (silica, 50% ether in petroleum ether); $[\alpha]^{21}_D$ +1.6° (*c* 0.51, $CHCl_3$); IR (neat) ν_{max} 3470 (s, OH), 3030, 2970, 2930, 1710 (s, CO_2Et), 1650, (m, CH=$CHCO_2Et$), 1500, 1455, 1380, 1285, 1250, 1230, 1165, 1105, 1030, 1020, 740, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H, Ar), 6.87 (t, *J* = 7.4 Hz, 1 H, *HC*=CCO_2), 5.12 (br t, *J* = 8.0 Hz, 1 H, *HC*=C), 4.87, 4.76 (2 × d, *J* = 7.0 Hz, 2 × 1 H, CH_2Ar), 4.70, 4.59 (2 × d, *J* = 8.5 Hz, 2 × 1 H, OCH_2O), 4.16 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 3.53 (t, *J* = 6.0 Hz, 1 H, $OCHCH_2$), 2.86 (s, 1 H, O*H*), 2.43 (t, *J* = 6.6 Hz, 2 H, CH_2C=CCO_2), 2.38–1.95 (m, 2 H, CH_2C=C), 1.86 (s, 3 H, C=CCH_3CO_2), 1.65 (m, 1 H, CH_2), 1.69, 1.62 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.46 (m, 1 H, CH_2), 1.26 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2-), 1.19 (s, 3 H, CH_3); MS *m*/*e* (rel intensity) 4.22 (M + NH_4, 100), 405 (M + 1, 75), 387 (46), 357 (100), 251 (100), 221 (100), 203 (83), 175 (100), 157 (100), 123 (100); HRMS calcd for $C_{24}H_{40}NO_5$ (M + NH_4) 422.2906, found 422.2871.

Ethyl (2*E*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-6-(trimethylsiloxy)-2,6,10-trimethyl-2,9-undecadienoate (10). To a stirred solution of the alcohol **9** (59.7 g, 0.15 mol) and 1,2-dichloromethane (150 mL) at 25 °C was added 1-(trimethylsilyl)imidazole (24.9 mL, 0.17 mol) followed by heating at 60 °C for 6 h. After cooling to 25 °C, the excess 1-(trimethylsilyl)imidazole was quenched by dropwise addition of methanol (1.8 mL) followed by solvent evaporation. The residue was diluted with petroleum ether (300 mL), then washed with H_2O (2 × 50 mL) and brine (50 mL), and dried ($MgSO_4$), and the solvent was removed to obtain the silyl ether **10** (70 g, 100%). **10**: oil; R_f = 0.32 (silica, 10% ether in petroleum ether); $[\alpha]^{21}_D$ −6.0° (*c* 0.77, $CHCl_3$); IR (neat) ν_{max} 3030, 2970, 1720 (s, CO_2Et), 1655 (HC=CCH_3CO_2), 1465, 1380, 1290, 1260, 1185, 1120, 1050, 1035, 850, 755, 705 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5 H, Ar), 6.97 (br t, *J* = 7.0 Hz, 1 H, *HC*=CCO_2), 5.04 (br t, *J* = 7.1 Hz, 1 H, *HC*=C), 4.82, 4.77 (2 × d, *J* = 6.2 Hz, 2 × 1 H, CH_2Ar), 4.63, 4.58 (2 × d, *J* = 11.1 Hz, 2 × 1 H, OCH_2O), 4.13 (*J* = 7.0 Hz, 2 H, OCH_2CH_3), 3.61 (dd, *J* = 7.3, 4.1 H, 1 H, $OCHCH_2$), 2.59 (m, 1 H, CH_2C=CCO_2), 2.42 (ddd, *J* = 16.0, 8.0, 8.0 Hz, 1 H, CH_2C=CCO_2), 2.06 (m, 2 H, CH_2C=C), 1.86 (s, 3 H, C=CCH_3CO), 1.70 (m, 1 H, CH_2), 1.66, 1.59 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.42 (m, 1 H, CH_2), 1.24 (dd, *J* = 8.0, 7.1 Hz, 3 H, CH_3CH_2), 0.12 (s, 9 H, $(CH_3)_3Si$); MS *m*/*e* (rel intensity) 494 (M + NH_4, 18), 350 (83), 279 (100), 249 (100), 200 (100), 175 (38), 131 (100), 109 (100); HRMS calcd for $C_{27}H_{48}NO_5Si$ (M + NH_4) 494.3301, found 494.3260.

(2*E*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-2,6,10-trimethyl-6-(trimethylsiloxy)-2,9-undecadien-1-ol (11). The ester **10** (70 g, 0.15 mol) in dichloromethane (800 mL) at −78 °C was treated dropwise with DIBAL (370 mL, 1 M in hexanes, 0.37 mol, 1 M in hexanes) over a 45-min period. After stirring for an additional 30 min, the excess DIBAL was quenched by careful dropwise addition of methanol (4 mL). The reaction mixture was then added to a 6-L Erlenmeyer flask containing a stirring mixture of EtOAc (2.5 L) and saturated aqueous solution of potassium sodium tartrate (400 mL). After 1 h, the emulsion dissipated and the organic portion was dried ($MgSO_4$). The solvent was removed to yield the alcohol **11** (63.9 g, 100%). **11**: oil; R_f = 0.25 (silica, 30% ether in petroleum ether); $[\alpha]^{21}_D$ −2.9° (*c* 1.6, $CHCl_3$); IR (neat) ν_{max} 3420 (s, OH), 3030, 2960, 2910, 1455, 1380, 1265, 1165, 1120, 1105, 1045, 1030, 840, 750, 735, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5 H), Ar), 5.68 (br t, *J* = 8.0 Hz, 1 H, *HC*=C), 5.06 (br t, *J* = 7.0 Hz, 1 H, *HC*=C), 4.82 4.77 (2 × d, *J* = 6.8 Hz, 2 × 1 H, CH_2Ar), 4.63, 4.58 (2 × d, *J* = 12.1 Hz, 2 × 1 H, OCH_2O), 3.91 (br d, *J* = 4.8 Hz, 2 H, CH_2OH), 3.49 (dd, *J* = 8.3, 3.0 Hz, $OCHCH_2$), 2.47 (m, 1 H, CH_2C=CCH_2OH) 2.22 (ddd, *J* = 16.0, 8.0, 8.0 Hz, CH_2=CCH_2OH), 2.07 (m, 2 H, CH_2C=C), 1.67 (s, 6 H, $(CH_3)_2C$=C), 1.66 (m, 1 H, CH_2), 1.59 (s, 3 H, CH_3C=C), 1.40 (m, 1 H, CH_2), 1.24 (s, 3 H, CH_3), 0.12 (s, 9 H, $(CH_3)_3Si$); MS *m*/*e* (rel intensity)] 452 (M + NH_4, 37), 417 (40), 387 (17), 327 (100), 279 (100), 219 (100), 151 (100), 131 (100), 109 (100); HRMS calcd for $C_{25}H_{46}O_4NSi$ (M + NH_4) 452.3196, found 452.3177.

(2*R*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-2,3-epoxy-2,6,10-trimethyl-6-(trimethylsiloxy)-9-undecen-1-ol (12). A stirring mixture of powdered activated 4A molecular sieves (20 g), allylic alcohol **11** (63.9

g, 0.15 mol), and dry dichloromethane (1 L) was cooled to −40 °C and treated sequentially with D-(−)-diethyl tartrate (1.9 mL, 11.0 mmol) and titanium(IV) isopropoxide (2.1 mL, 7.3 mmol). After 30 min, *tert*-butyl hydroperoxide (5 mL, 4.5 M in dichloromethane, 225 mmol) was added and the reaction mixture was stored at −20 °C in a freezer for 16 h. The sieves were removed by filtration, the filtrate was diluted with ether (1 L), and while stirring vigorously, saturated Na_2SO_4 (2.1 mL) was added. After 1 h, the fine suspension was removed by filtration through a Celite pad. The filtrate was concentrated followed by flash chromatography (silica, 50% ether in petroleum ether) to yield the epoxide **12** (57.6 g, 87%). **12**: oil; R_f = 0.33 (silica, 50% ether in petroleum ether); $[\alpha]^{21}_D$ −29.7° (*c* 0.95, $CHCl_3$); IR (neat) ν_{max} 3450 (s, OH), 3030, 2960, 2940, 1455, 1380, 1265, 1255, 1170, 1120, 1040, 870, 840, 750, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.36–7.30 (m, 5 H, Ar), 5.05 (br t, *J* = 7.0 Hz, 1 H, *H*C=C$(CH_3)_2$), 4.86, 4.80 (2 × d, *J* = 7.2 Hz, 2 × 1 H, CH_2Ar), 4.71, 4.60 (2 × d, *J* = 12.0 Hz, 2 × 1 H, OCH_2O), 3.53 (m, 2 H, OC*H*CH_2 and CH_2OH), 3.39 (dd, *J* = 12.0, 4.2 Hz, 1 H, CH_2OH), 3.20 (dd *J* = 7.0, 6.1 Hz, 1 H, *H*-epox), 2.06 (m, 3 H, CH_2C=C, O*H*), 1.87 (dd, *J* = 6.1, 5.8 Hz, 2 H, CH_2), 1.71 (m, 1 H, CH_2), 1.67, 1.62 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.41 (m, 1 H, CH_2), 1.33 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 0.16 (s, 9 H, $(CH_3)_3$Si); MS *m/e* (rel intensity) 468 (M + NH_4, 35), 433 (100), 403 (30), 361 (100), 313 (100), 224 (100), 205 (100), 139 (100), 109 (100); HRMS calcd for $C_{25}H_{46}NO_5Si$ (M + NH_4) 468.3145, found 468.3150.

(2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-2,3-epoxy-2,6,10-trimethyl-6-(trimethylsiloxy)-9-undecenal (13). To a mixture of the epoxy alcohol **12** (57.6 g, 0.13 mol), dry DMSO (100 mL), dichloromethane (500 mL), and triethylamine (90.6 mL, 0.65 mol) at 0 °C was added pyridine·sulfur trioxide complex (82.8 g, 0.52 mol) in three portions in 5-min intervals. After 2 h, the dark brown reaction mixture was diluted with ether (1.5 L) and washed with H_2O (2 × 200 mL) and brine (50 mL). Drying with $MgSO_4$ followed by solvent removal and flash chromatography (silica, 10% ether in petroleum ether) furnished the aldehyde **13** (54.5 g, 95%, ca. 95% pure by ^1H NMR). **13**: oil; R_f = 0.44 (silica, 10% ether in petroleum ether); IR (neat) ν_{max} 3020, 2970, 2920, 2820 (w, CHO), 1735 (s, CHO), 1455, 1380, 1265, 1255, 1180, 1130, 1110, 1050, 850, 755, 745, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.64 (s, 1 H, *H*C=O), 7.37–7.26 (m, 5 H, Ar), 5.04 (br t, *J* = 9.0 Hz, 1 H, *H*C=C), 4.85, 4.79 (2 × d, *J* = 7.0 Hz, 2 × 1 H, CH_2Ar), 4.71, 4.59 (2 × d, *J* = 12.0 Hz, 2 × 1 H, OCH_2O), 3.60 (dd, *J* = 8.2, 3.2 Hz, 1 H, OC*H*CH_2), 3.43 (t, *J* = 5.6 Hz, 1 H, *H*-epox), 2.11–1.32 (m, 6 H, CH_2), 1.68, 1.60 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.39 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 0.12 (s, 9 H, $(CH_3)_3$Si); MS *m/e* (rel intensity) 466 (M + NH_4, 60), 431 (9), 401 (13), 329 (52), 293 (33), 251 (100), 200 (100), 165 (85), 131 (100), 109 (100); HRMS calcd for $C_{25}H_{44}NO_5Si$ (M + NH_4) 466.2988, found 466.3002.

(1*Z*,3*S*,4*R*,6*S*,7*R*)-6-[(Benzyloxy)methoxy]-1-chloro-3,4-epoxy-3,7,11-trimethyl-7-(trimethylsiloxy)-1,10-dodecadiene (14). A vigorously stirred suspension of (chloromethyl)triphenylphosphonium chloride (83.3 g, 0.24 mol) in dry THF (480 mL) at 0 °C was treated dropwise with sodium bis(trimethylsilyl)amide (240 mL, 1.0 M in THF, 0.24 mol) over a 30-min period. After stirring for an additional 30 min, the bright yellow ylide was treated dropwise with the aldehyde **13** (54.5 g, 0.12 mol) in THF (200 mL) over a 30-min period, and the resulting mixture was stirred at 0 °C for an additional 30 min. The reaction mixture was poured into ether (1 L), washed with H_2O (100 mL) and brine (50 mL), and dried ($MgSO_4$), and the solvent was removed. The residue was triturated with 10% ether in petroleum ether, followed by filtration to remove the triphenylphosphine oxide. The solvents were evaporated from the filtrate and the residue was subjected to flash chromatography (silica, 5–10% ether in petroleum ether) to furnish the allylic epoxide **14** (45.6 g, 79%). **14**: oil; R_f = 0.54 (silica, 20% ether in petroleum ether); $[\alpha]^{21}_D$ −67.5° (*c* 0.60, $CHCl_3$); IR (neat) ν_{max} 3020, 2970, 2920, 1630 (m, C=CCl), 1455, 1380, 1265, 1255, 1170, 1125, 1050, 1030, 840, 760, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5 H, Ar), 6.04, 5.93 (2 × d, *J* = 7.4 Hz, 2 × 1 H, *H*C=C*H*Cl), 5.05 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.91, 4.84 (2 × d, *J* = 7.0 Hz, 2 × 1 H, CH_2Ar), 4.70, 4.61 (2 × d, *J* = 14.5 Hz, 2 × 1 H, OCH_2O), 3.74 (dd, *J* = 8.1, 3.1 Hz, 1 H, OC*H*CH_2), 3.22 (dd, *J* = 5.8, 5.6 Hz, 1 H, *H*-epox), 2.22–2.01 (m, 3 H, CH_2C=C and CH_2), 1.72 (m 2 H, CH_2), 1.66, 1.59 (2 × s,2 ×3 H, $(CH_3)_2$C=C), 1.45 (s, 3 H, CH_3), 1.42 (m, 1 H, CH_2), 1.24 (s, 3 H, CH_3), 0.13 (s, 9 H, $(CH_3)_3$Si); MS *m/e* (rel intensity) 498 (M + NH_4, 14), 463 (44), 433 (16), 391 (100), 345 (100), 285 (100), 255 (100), 143 (100), 121 (100); HRMS calcd for $C_{26}H_{45}ClNO_4Si$ (M + NH_4) 498.2786, found 498.2792.

***cis*-(3*S*,4*R*,6*S*,7*R*)-6-[(Benzyloxy)methoxy]-1-chloro-3,4-epoxy-3,7,11-trimethyldodeca-1,10-dien-7-ol (15).** To a flask containing the silyl ether **14** (45.6 g, 95 mmol) in THF (50 mL) was added tetrabutylammonium fluoride (120 mL, 1 M in THF, 120 mmol). After stirring at ambient temperature for 1.5 h, the THF was evaporated and the residue was chromatographed (silica, 20–50% ether in petroleum ether) to yield the alcohol **15** (36.9 g, 96%). **15**: oil, R_f = 0.40 (silica, 50% ether in petroleum ether); $[\alpha]^{21}_D$ −51.7° (*c* 0.88, $CHCl_3$); IR (neat) ν_{max} 3460, (s, OH), 3030, 2970, 2930, 1630, (m, C=CCl), 1455, 1380, 1170, 1110, 1040, 1030, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5 H, Ar), 6.07, 5.97 (2 × d, *J* = 7.4 Hz, 2 × 1 H, *H*C=C*H*Cl), 4.95, 4.88 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.75, 4.64 (2 × d, *J* = 11.8 Hz, 2 × 1 H, OCH_2O), 3.69 (dd, *J* = 8.1, 3.5 Hz, 1 H, *H*-epox), 2.28–1.80 (m, 4 H, CH_2C=C and CH_2), 1.69, 1.61 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.61 (m, 1 H, CH_2), 1.45 (s, 3 H, CH_3), 1.44 (m, 1 H, CH_2), 1.21 (s, 3 H, CH_3); MS *m/e* (rel intensity) 426 (M + NH_4, 6), 391 (27), 361 (13), 301 (100), 271 (100), 253 (100), 217 (34), 199 (53), 139 (100), 121 (100), HRMS calcd for $C_{23}H_{37}ClNO_4$ (M + NH_4) 426.2411, found 426.2424.

(2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-2-[(*Z*)-2-chlorovinyl]tetrahydro-2,6-dimethyl-6-(4-methyl-3-pentenyl)-2*H*-pyran-3-ol (16). To a stirred solution of the epoxy alcohol **15** (36.9 g, 90.5 mmol) in dry dichloromethane (900 mL) at 0 °C was added in one portion of (1*S*)-(+)-10-camphorsulfonic acid (2.1 g, 9.0 mmol). After stirring at 0 °C for 1 h, the cooling bath was removed, and the reaction mixture was stirred for an additional 1.5 h. The reaction was quenched with triethylamine (2.1 mL, 15.0 mmol), the solvent was evaporated, and the residue was subjected to flash chromatography (silica, 50% ether in petroleum ether) to give the pyran **16** (30.6 g, 83%). **16**: oil; R_f = 0.23 (silica, 50% ether in petroleum ether); $[\alpha]^{21}_D$ +28.2° (*c* 0.17, $CHCl_3$); IR (neat) ν_{max} 3450 (s, OH), 3030, 2960, 2940, 1630 (m, C=CCl), 1455, 1380, 1170, 1130, 1105, 1070, 1035, 1030, 990, 970, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H, Ar), 5.95 (s, 2 H, *H*C=C*H*Cl), 5.02 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.90, 4.74 (2 × d, *J* = 7.3 Hz, 2 × 1 H, CH_2Ar), 4.68 (d, *J* = 1.6 Hz, 2 H, OCH_2O), 4.26 (dt, *J* = 9.5, 4.1 Hz, 1 H, C*H*OH), 3.70 (t, *J* = 4.1 Hz, 1 H, *H*CO–), 3.61 (d, *J* = 9.5 Hz, 1 H, O*H*), 2.13 (t, *J* = 4.2 Hz, 2 H, –OCHCH_2), 2.15–1.92 (m, 2 H, CH_2C=C), 1.76–1.47 (m, 2 H, CH_2), 1.68, 1.60 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.49 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3); MS *m/e* (rel intensity) 409 (M + 1, 10), 391 (18), 261 (5), 301 (24), 271 (21), 253 (48), 166 (20), 121 (17); HRMS calcd for $C_{23}H_{34}ClO_4$ (M + H) 409.2198, found 409.2176.

(2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-3-(acetoxy)-2-[(*Z*)-2-chlorovinyl]tetrahydro-2,6-dimethyl-6-(4-methyl-3-pentenyl)-2*H*-pyran (17). A mixture of the alcohol **16** (20 mg, 0.49 mmol), acetic anhydride (94 μL, 1.0 mmol), 4-(dimethylamino)pyridine (183 mg, 1.5 mmol), and dichloromethane (2 mL) was stirred at 25 °C for 30 min, the solvents were removed in vacuo, and the residue was flash chromatographed (silica, 15% ether in petroleum ether) to furnish the acetate **17** (20 mg, 92%). **17**: oil; R_f = 0.46 (silica, 25% ether in petroleum ether); $[\alpha]^{21}_D$ +4.6° (*c* 0.26, $CHCl_3$); IR (neat) ν_{max} 2960, 2930, 1740 (s, acetate), 1630 (m, C=CCl), 1455, 1375, 1235, 1120, 1040, 730, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5 H, Ar), 6.01, 5.69 (2 × d, *J* = 8.4 Hz, 2 × 1 H, *H*C=C*H*Cl), 5.08 (m, 1 H, *H*C=C$(CH_3)_2$), 5.06 (dd, *J* = 11.8, 4.0 Hz, 1 H, *H*COAc), 4.82, 4.72 (2 × d, *J* = 7.0 Hz, 2 × 1 H, CH_2Ar), 4.63 (s, 2 H, OCH_2O), 3.73 (dd, *J* = 11.8, 4.2 Hz, 1 H, OC*H*–), 2.24 (dt, *J* = 11.0, 4.2 Hz, 1 H, –OCHCH_2), 2.12 (m, 1 H, CH_2), 2.06 (s, 3 H, O_2CCH_3), 1.87 (dt, *J* = 11.0, 11.0 Hz, 1 H, –OCHCH_2), 1.68, 1.58 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.57 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3); MS *m/e* (rel intensity) 468 (M + NH_4, 63), 433 (22), 345 (100), 313 (100), 255 (100), 230 (83), 187 (100), 161 (100), 143 (100), 115 (81); HRMS calcd for $C_{25}H_{39}ClNO_5$ (M + NH_4) 468.2516, found 468.2479.

(2*S*,3*R*,6*R*)-5-[(Benzyloxy)methoxy]-2-[(*Z*)-2-chlorovinyl]-2,6-dimethyl-6-(4-methyl-3-pentenyl)-3-(trimethylsiloxy)tetrahydro-2*H*-pyran (18). A stirred solution of the alcohol **16** (30.6 g, 74.8 mmol) in dichloromethane (75 mL) was treated with 1-(trimethylsilyl)imidazole (13.2 mL, 90 mmol) at 25 °C. After 2 h, the excess 1-(trimethylsilyl)-imidazole was quenched with methanol (1.5 mL) followed by solvent evaporation. The residue was diluted with petroleum ether (150 mL), washed with H_2O (2 × 50 mL) and brine (50 mL), and dried ($MgSO_4$), and the solvent was removed to give the silyl ether **18** (36.0 g, 100%). **18**: oil; R_f = 0.59 (silica, 10% ether in petroleum ether); $[\alpha]^{21}_D$ −17.0° (*c* 1.32, $CHCl_3$); IR (neat) ν_{max} 2960, 2890, 1630 (m, C=CCl), 1455, 1380, 1265, 1255, 1170, 1110, 1050, 1030, 975, 910, 885, 845, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5 H, Ar), 6.01, 5.72 (2 × d, *J* = 8.2 Hz, 2 × 1 H, *H*C=C*H*Cl), 5.07 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.84, 4.75 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.65, 4.58 (2 × d, *J* = 13.0 Hz, 2 × 1 H, OCH_2O), 3.87 (dd, *J* = 11.5, 4.5 Hz, 1 H, OC*H*–), 3.61 (dd, *J* = 11.8, 4.4 Hz, 1 H, OC*H*–), 2.32–2.00 (m, 2 H, CH_2C=C), 2.05 (ddd, *J* = 12.4, 4.6, 4.5 Hz, 1 H, –OCHCH_2), 1.89 (ddd, *J* = 12.4, 12.0, 12.0 Hz, 1 H, –OCHCH_2), 1.66, 1.59 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.75–1.40 (m, 2 H, CH_2), 1.44 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 0.08 (s, 9 H, $(CH_3)_3$Si); MS *m/e* (rel intensity) 481 (M + 1, 100), 433 (100), 397 (53), 375 (100), 283 (100),

261 (100), 235 (100), 192 (100), 161 (100), 138 (90); HRMS calcd for $C_{26}H_{42}ClO_4Si$ (M + 1) 481.2541, found 481.2524.

[[(2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-2-ethynyltetrahydro-2,6-dimethyl-6-(4-methyl-3-pentenyl)-2*H*-pyran-3-yl]oxy]trimethylsilane (19). A stirred solution of the vinyl chloride **18** (19.3 g, 43.4 mmol) in dry THF (300 mL) at −78 °C was treated dropwise with *n*-butyllithium (60 mL, 1.6 M in hexanes, 95.5 mmol) over a 20-min period. After an additional 30 min, the reaction was quenched with ether (400 mL) and saturated aqueous solution of NH_4Cl (50 mL). Drying ($MgSO_4$) of the organic phase followed by solvent removal gave the crude product, which was subjected to flash chromatography (5% ether in petroleum ether) to yield the acetylene **19** (16.9 g, 86%). **19**: oil; R_f = 0.49 (silica, 10% ether in petroleum ether); $[\alpha]^{21}_D$ −0.60° (*c* 1.39, $CHCl_3$); IR (neat) ν_{max} 3310 (m, C≡C—H), 2960, 2890, 1455, 1380, 1265, 1255, 1130, 1045, 1030, 975, 885, 845, 750, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5 H, Ar), 5.07 (br t, *J* = 7.0 Hz, *H*C=C), 4.83, 4.72 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.63, 4.57 (2 × d, *J* = 12.0 Hz, 2 × 1 H, OCH_2O), 3.85 (dd, *J* = 11.0, 5.0 Hz, 1 H, −*H*CO), 3.71 (dd, *J* = 10.5 Hz, 1 H, *H*CO), 2.36 (s, 1 H, *H*C≡C), 2.20–2.05 (m, 3 H, CH_2), 1.,82 (m, 1 H, CH_2), 1.65, 1.59 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.65 (m, 2 H, CH_2), 1.49 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 0.13 (s, 9 H, $(CH_3)_3Si$); MS *m/e* (rel intensity): 445 (M + 1, 23), 397 (21), 337 (100), 307 (100), 260 (100), 241 (100), 217 (96), 169 (100), 121 (100); HRMS calcd for $C_{26}H_{41}O_4Si$ (M + 1) 445.2774, found 445.2860. Anal. Calcd for $C_{26}H_{41}O_4Si$: C, 70.22; H, 9.07. Found: C, 70.16; H, 8.86.

(2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]tetrahydro-2,6-dimethyl-6-(4-methyl-3-pentenyl)-3-3-(trimethylsilloxy)-2*H*-pyran-2-acetaldehyde (20). A magnetically stirred solution of borane·THF (50 mL, 1 M in THF, 50 mmol) at 0 °C was treated dropwise with 2-methyl-2-butene (12.7 mL, 120 mmol). After 1.5 **h**, the acetylene **19** (17.8 g, 40 mmol) in THF (37 mL) was added, followed by continued stirring at 0 °C for 45 min and then at ambient temperature for an additional 20 min. The homogeneous mixture was recooled to 0 °C, and the borane was oxidized by slow, dropwise addition of a solution composed of NaOH (50 mL, 3 N in H_2O, 150 mmol) and hydrogen peroxide (18.0 mL, 30% in H_2O, 175 mmol). After 20 min, the heterogeneous mixture was diluted with ether (200 mL), washed with H_2O (2 × 50 mL) and brine (50 mL), and dried ($MgSO_4$), and the solvent removed. The residue was purified through flash chromatography (silica, 8% ether in petroleum ether) to furnish the aldehyde **20** (16.5 g, 89%, ca 95% pure.) **20**: oil; R_f = 0.47 (silica, 10% ether in petroleum ether); IR (neat) ν_{max} 2960, 1730, (s, —CH=O), 1380, 1260, 1110, 1050, 890, 750, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.85 (dd, *J* = 3.3, 2.8 Hz, 1 H, *H*C=O), 7.38–7.30 (m, 5 H, Ar), 5.05 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.83, 4.73 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.64, 4.57 (2 × d, *J* = 12.0 Hz, 2 × 1 H, OCH_2O), 3.56 (m, 2 H, −*H*CO), 2.47 (dd, *J* = 14.3, 3.3 Hz, 1 H, CH_2CHO)8 2.33 (dd, *J* = 14.3, 2.8 Hz, 1 H, CH_2CHO), 2.15–1.80 (m, 4 H, CH_2), 1.68, 1.60 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.65 (m, 2 H, CH_2), 1.33 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 0.13 (s, 9 H, $(CH_3)_3Si$; MS *m/e* (rel intensity) 463 (*M* + 1, 8), 418 (21), 355 (29), 325 (100), 242 (63), 216 (100), 172 (100), 143 (100), 116 (100); HRMS calcd for $C_{26}H_{43}O_5Si$ (M + 1) 463.2879, found 463.2897.

Ethyl 4-[(2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-2,6-dimethyl-2-ethynyl-6-(4-methyl-3-pentenyl)-3-(trimethylsiloxy)tetrahydro-2*H*-pyran-2-yl]-(2*E*)-crotonate (21). A mixture of the aldehyde **20** (16.5 g, 35.6 mmol) and (carbethoxyethylidene)triphenylphosphorane (14.5 g, 40.0 mmol) in dry benzene (70 mL) was stirred at 25 °C for 3 h. The solvent was removed, and the residue was subjected to flash chromatography (silica, 5% ether in petroleum ether) to yield the ester **21** (14.53 g, 75%). **21**: oil; R_f = 0.42 (silica, 10% ether in petroleum ether); $[\alpha]^{21}_D$ −17.0° (*c* 1.15, $CHCl_3$); IR (neat) ν_{max} 2990, 2970, 2890, 1715 (s, CO_2Et), 1655 (m, CH=CCO_2Et), 1455, 1380, 1370, 1255, 1170, 1160, 1125, 1105, 1045, 1030, 980, 910, 885, 835, 740, 700, 650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5 H, Ar), 6.95 (br t, *J* = 7.1 Hz, 1 H, *H*C=CCO_2Et), 5.07 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.82, 4.72 (2 × d, *J* = 7.1 Hz, 2 × 1 Hz, CH_2Ar), 4.62, 4.57 (2 × d, *J* = 11.6 Hz, 2 × 1 H, OCH_2O), 4.16 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 3.55 (dd, *J* = 11.4, 4.3 Hz, 1 H, −*H*CO), 3.49 (dd, *J* = 11.7, 4.5 Hz, 1 H, −*CH*CO), 2.35 (dd, *J* = 15.0, 7.1 Hz, 1 H, CH_2C=CCO_2Et), 2.21 (dd, *J* = 15.0, 7.1 H, 1 H, CH_2C=CCO_2Et), 2.18–1.80 (m, 4 H, CH_2), 1.80 (s, 3 H, C=$C(CH_3)CO_2$), 1.64, 1.56 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.60, 1.45 (s × m, 2 H, CH_2), 1.25 (t, *J* = 7.2 Hz, 3 H, $-OCH_2CH_3$), 1.19 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 0.06 (s, 9 H, $(CH_3)_3Si$); MS *m/e* (intensity) 547 (M + 1, 8), 499 (17), 419 (89), 376 (42), 311 (100), 227 (100), 191 (100), 166 (100); HRMS calcd for $C_{31}H_{51}O_6Si$ (M + 1) 547.3454, found 547.3470.

4-[(2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-2,6-dimethyl-6-(4-methyl-3-pentenyl)-3-(trimethylsiloxy)tetrahydro-2*H*-pyran-2-yl]-(2*E*)-crotyl Alcohol (22). DIBAL (80 mL, 1 M in hexanes, 80 mmol) was added dropwise to a stirring solution of the ester **21** (17.5 g, 32.0 mmol) in dry dichloromethane (200 mL) at −78 °C. After stirring for an additional 1 h, the excess DIBAL was quenched with CH_3OH (2 mL), and the reaction mixture was poured onto a stirring mixture of EtOAc (600 mL) and saturated aqueous potassium sodium tartrate (200 mL). Once the emulsion dissipated, the organic portion was separated, dried ($MgSO_4$), and concentrated to give the allylic alcohol **22** (16.1 g, 100%). **22**: oil; R_f = 0.61 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ −12.2° (*c* 1.60, $CHCl_3$); IR (neat) ν_{max} 3450 (s, OH), 3030, 2990, 2970, 2890, 1500, 1470, 1455, 1380, 1265, 1255, 1210, 1170, 1110, 1050, 980, 890, 845, 750, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5 H, Ar), 5.60 (br t, *J* = 7.1 Hz, 1 H, *H*C=C), 5.07 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.83 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.65, 4.59 (2 × d, *J* = 12.0 Hz, 2 × 1 H, OCH_2O), 4.00 (br d, 2 H, $-CH_2OH$), 3.53 (dd, *J* = 11.5, 4.4 Hz, 1 H, −*H*CO), 3.49 (dd, *J* = 11.4, 4.5 Hz, 1 H, −*H*CO), 2.27 (dd, *J* = 15.0, 7.1 Hz, 1 H, CH_2C=C), 2.20–1.65 (m, 7 H, CH_2 and O*H*), 1.66 (s, 3 H, C=CCH_3CH_2OH), 1.66, 1.58 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.45 (m, 1 H, CH_2), 1.19 (s, 3 H, CH_3), 0.13 (s, 9 H, $(CH_3)_3Si$); MS *m/e* (rel intensity) 505 (M + 1, 19), 419 (100), 389 (26), 367 (23), 282 (100), 214 (100), 191 (100), 161 (100), 135 (100); HRMS calcd for $C_{29}H_{49}O_5Si$ (M + 1) 505.3349, found 505.3281.

(β*R*,γ*R*,2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-β,γ-epoxytetrahydro-β,2,6-trimethyl-6-(4-methyl-3-pentenyl)-3-(trimethylsiloxy)-2*H*-pyran-2-butanol (23) and (2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-2,6-dimethyl-2-[(2*S*,3*S*)-2,3-epoxy-4-hydroxy-3-methylbutyl]-6-(4-methyl-3-pentenyl)-3-(trimethylsiloxy)tetrahydro-2*H*-pyran (24). The preparation of epoxides **23** and **24** from allylic alcohol **22** (16.1 g, 32.0 mmol) was carried out by the same procedure used to convert **11** to **12** described above. Flash chromatography (silica, 15% ether in petroleum ether) afforded the desired epoxide **23** (11.6 g, 70%) along with the diastereomeric epoxide **24** (4.0 g, 24%). **23**: oil; R_f = 0.50 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ +6.8° (*c* 0.16, $CHCl_3$); IR (neat) ν_{max} 3460 (s, OH), 3030, 2960, 2890, 1460, 1385, 1265, 1255, 1110, 1045, 1030, 980, 890, 845, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5 H, Ar), 5.07 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.83, 4.73 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.63, 4.58 (2 × d, *J* = 12.0 Hz, 2 × 1 H, OCH_2O), 3.69 (m, 2 H, CH_2OH and −*H*CO), 5.56 (m, 1 H, $-CH_2OH$), 3.32 (t, *J* = 5.6 Hz, 1 H, *H*-epox), 2.15–1.65 (m, 8 H, CH_2 and O*H*), 1.66, 1.58 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.26 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 0.09 (s, 9 H, $(CH_3)_3Si$); MS *m/e* (rel intensity) 521 (M + H, 16), 413 (54), 383 (100), 300 (100), 247 (100), 217 (100), 191 (100), 165 (100), 139 (100); HRMS calcd for $C_{29}H_{49}O_6Si$ (M + 1) 521.3298, found 521.3214. Anal. Calcd for $C_{29}H_{48}O_6Si$: C, 66.88; H, 9.29. Found: C, 67.01; H, 9.43. **24**: oil; R_f = 0.40 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ −30.0° (*c* 0.59, $CHCl_3$); IR (neat) ν_{max} 3460 (s, OH), 3030, 2960, 2890, 2890, 1460, 1385, 1265, 1255, 1110, 1045, 1030, 980, 890, 845, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5 H, Ar), 5.05 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.85, 4.75 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.63, 4.59 (2 × d, *J* = 13.0 Hz, 2 × 1 H, OCH_2O), 3.69 (br d, *J* = 11.6, 4.5 Hz, 1 H, −*H*CO), 3.40 (dd, *J* = 11.5, 4.4 Hz, 1 H, −*H*CO), 3.36 (dd, *J* = 6.8, 3.8 Hz, 1 H, *H*-epox), 2.15–1.60 (m, 8 H, CH_2 and O*H*), 1.66, 1.55 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.40 (m, 1 H, CH_2), 1.27 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 0.08 (s, 9 H, $(CH_3)_3Si$); HRMS calcd for $C_{29}H_{49}O_6Si$ (M + 1) 521.3298, found 521.3192.

(2*R*,3*R*)-4-[(2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-2,6-dimethyl-6-(4-methyl-3-pentenyl)-3-(trimethylsiloxy)tetrahydro-2*H*-pyran-2-yl]-2,3-epoxy-3-methylbutyraldehyde (25). To a stirred mixture of the epoxy alcohol **23** (11.0 g, 21.8 mmol), dry DMSO (25 mL), dichloromethane (100 mL), and triethylamine (20.5 mL, 150 mmol) at 0 °C was added pyridine·sulfur trioxide complex (13.4 g, 87 mmol) in two portions. The resulting homogeneous solution was stirred for 4 h followed by dilution with ether (500 mL) and sequential washing with H_2O (2 × 50 mL) and brine (50 mL). After drying ($MgSO_4$) and removal of solvents, the resulting crude aldehyde **25** (11.0 g, ca 90% pure) was used directly for the next step. **25**: oil; R_f = 0.83 (silica, 3% ether in petroleum ether); IR (neat) ν_{max} 30030, 2960, 2820, 2720 (w, CHO), 1735, (s, CHO), 1460, 1385, 1260, 110, 1050, 1035, 980, 890, 845, 750, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.85 (s, 1 H, *H*C=O), 7.38–7.30 (m, 5 H, Ar), 5.05 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.85, 4.75 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.63, 4.59 (2 × d, *J* = 12.0 Hz, 2 × 1 H, OCH_2O), 3.74 (dd, *J* = 11.5, 4.5 Hz, 1 H), 3.60 (dd, *J* = 11.6, 4.4 Hz, 1 H, −*HCO*−), 3.49 (dd, *J* = 4.7, 4.6 Hz, 1 H, *H*-epox), 2.15–1.60 (m, 7 H, CH_2), 1.66, 1.56 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.48 (m, 1 H, CH_2), 1.37 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 0.10 (s, 9 H, $(CH_3)_3Si$); MS *m/e* (rel intensity) 519 (M + 1, 14), 471 (17), 411 (18), 381 (54), 298 (83), 272 (100), 228 (100), 181 (100), 139 (100); HRMS calcd for $C_{29}H_{47}O_6Si$ (M + 1) 519.3142, found 519.3116.

(2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-2-[(2*R*,3*R*)-2,3-epoxy-3-methyl-4-pentenyl]tetrahydro-2,6-dimethyl-6-(4-methyl-3-pentenyl)-2*H*-pyran-3-ol (26). To a vigorously stirred suspension of methyltri-

phenylphosphonium bromide (18.0 g, 50.4 mmol) in dry THF (100 mL) at 0 °C was added sodium bis(trimethylsilyl)amide (50.0 mL, 1 M in THF, 50.0 mmol) dropwise over a 10-min period. After stirring for 30 min, the orange ylide was treated dropwise with a solution of the crude aldehyde **25** (11.0 g, ca 21.0 mmol) in THF (50 mL) and the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with ether (200 mL) and then washed with H_2O (2 × 50 mL) and brine (50 mL). Drying ($MgSO_4$) and concentration followed by flash chromatography (silica, 5% ether in petroleum ether) gave the allylic epoxide **26** (8.6 g, 79%). **26**: oil; R_f = 0.55 (silica, 10% ether in petroleum ether); $[\alpha]^{21}_D$ −21.9° (*c* 0.36, $CHCl_3$); IR (neat) ν_{max} 2990, 2960, 1455, 1385, 1255, 1110, 1045, 1030, 980, 965, 890, 845, 750, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H, aromatic), 5.64 (dd, *J* = 17.4, 10.7 Hz, 1 H, *H*C=CH_2), 5.30 (dd, *J* = 17.4, 1.1 Hz, 1 H, HC=CH_2), 5.17 (dd, *J* = 10.7, 1.1 Hz, 1 H, C=CH_2), 5.07 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.86, 4.76 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.66, 4.60 (2 × d, *J* = 12.0 Hz, 2 × 1 H, OCH_2O), 3.70 (dd, *J* = 11.4, 4.5 Hz, 1 H, −*H*CO), 3.12 (dd, *J* = 6.6, 5.7 Hz, 1 H, *H*C–C), 2.15–1.60 (m, 7 H, CH_2), 1.67, 1.57 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.45 (m, 1 H, CH_2), 1.37 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 0.10 (s, 9 H, $(CH_3)_3$Si); MS *m/e* (rel intensity) 517 (M + 1, 100), 469 (63), 409 (100), 380 (100), 319 (100), 289 (100), 243 (87), 191 (100), 137 (100); HRMS calcd for $C_{30}H_{49}O_5Si$ (M + 1) 517.3349, found 517.3305. Anal. Calcd for $C_{30}H_{48}O_5Si$: C, 69.72; H, 9.36. Found: C, 69.92; H, 9.19.

(2*S*,3*R*,5*S*,6*R*)-5-[(Benzyloxy)methoxy]-3-[(2*R*,3*R*)-2,3-epoxy-3-methyl-4-pentenyl]tetrahydro-2,6-dimethyl-6-(4-methyl-3-pentenyl)-2*H*-pyran-3-ol (27). Tetrabutylammonium fluoride (18.0 mL, 1 M in THF, 18.0 mmol) was added to a solution of the silyl ether **26** (7.6 g, 14.8 mmol) in THF (15 mL) at 25 °C. After stirring for 3 h, the solvent was removed, and the residue was flash chromatographed (silica, 30–80% ether in petroleum ether) to afford the pure alcohol **27** (6.4 g, 97%). **27**: oil; R_f = 0.31 (silica, 6% ether in petroleum ether); $[\alpha]^{21}_D$ +11.1° (*c* 0.91, $CHCl_3$); IR (neat) ν_{max} 3450 (s, OH), 2990, 2950, 1455, 1380, 1210, 1170, 1140, 1070, 1045, 1030, 960, 925, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5 H, Ar), 5.63 (dd, *J* = 17.3, 10.6 Hz, 1 H, *H*C=CH_2), 5.30 (dd, *J* = 17.3, 1.1 Hz, 1 H, C=CH_2), 5.17 (dd, *J* = 10.6, 1.1 Hz, 1 H, C=CH_2), 5.07 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 3.86, 3.76 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.83 (br s, 2 H, OCH_2O), 3.84 (m, 1 H, −*H*CO), 3.64 (dd, *J* = 11.6, 4.3 Hz, 1 H, −*H*CO), 3.11 (dd, *J* = 7.6, 3.4 Hz, 1 H, *H*-epox), 2.34 (d, *J* = 5.5 Hz, 1 H, O*H*), 2.20–1.60 (m, 7 H, CH_2), 1.68, 1.58 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.45 (m, 1 H, CH_2), 1.38 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3); MS *m/e* (rel intensity) 445 (M + 1, 8), 347 (13), 389 (66), 263 (69), 233 (56), 209 (73), 161 (100), 141 (100), 121 (95); HRMS calcd for $C_{27}H_{41}O_5$ (M + 1) 445.2953, found 445.2913.

(2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-[(Benzyloxy)methoxy]octahydro-2,4a,6-trimethyl-6-(4-methyl-3-pentenyl)-2-vinylpyrano[3,2-*b*]pyran-3-ol (28). Pyridinium *p*-toluenesulfonate (2.9 g, 11.4 mmol) was added to a stirring solution of the epoxide **27** (6.4 g, 14.3 mmol) in dry dichloromethane (140 mL) at 0 °C. After 2 h, the cooling bath was removed, and stirring was continued for an additional 2 h. The reaction mixture was diluted with ether (600 mL) and washed sequentially with H_2O (2 × 50 mL) and brine (50 mL) and dried ($MgSO_4$). Concentration followed by flash chromatography (silica, 30% ether in petroleum ether) of the residue afforded the bicycle **28** (5.4 g, 85%). **28**: oil; R_f = 0.62 (silica, 60% ether in petroleum ether); $[\alpha]^{21}_D$ −55.8° (*c* 0.36, $CHCl_3$); IR (neat) ν_{max} 3460 (s, OH), 2980, 2940, 1455, 1380, 1210, 1155, 1120, 1040, 980, 925, 890, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H, Ar), 5.95 (dd, *J* = 17.5, 10.9 Hz, 1 H, *H*C=CH_2), 5.32 (dd, *J* = 17.5, 1.2 Hz, 1 H, C=CH_2), 5.17 (dd, *J* = 10.9, 1.2 Hz, 1 H, C=CH_2), 5.07 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.85, 4.73 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.61 (br d, 2 H, OCH_2O), 3.74 (dd, *J* = 11.2, 4.7 Hz, 1 H, −*H*CO), 3.73 (m, 1 H, −*H*COH), 3.31 (dd, *J* = 12.6, 3.2 Hz, 1 H, −*H*CO– ring juncture), 2.20–2.14 (m, 3 H, CH_2), 2.00 (d, *J* = 4.2 Hz, 1 H, O*H*), 1.85–1.45 (m, 5 H, CH_2), 1.66, 1.59 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.31 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3); MS *m/e* (rel intensity) 445 (M + 1, 100), 397 (84), 379 (63), 361 (46), 337 (100), 319 (100), 289 (100), 239 (100), 161 (100), 125 (100); HRMS calcd for $C_{27}H_{41}O_5$ (M + 1) 445.2953, found 445.3034.

(2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-[(Benzyloxy)methoxy]octahydro-2,4a,6-trimethyl-3-acetoxy-6-(4-methyl-3-pentenyl)-2-vinylpyrano[3,2-*b*]pyran (29). A mixture of the alcohol **28** (30 mg, 0.067 mmol), acetic anhydride (20 μL, 0.20 mmol), 4-(dimethylamino)pyridine (22 mg, 0.2 mmol), and dichloromethane (500 μL) was stirred at 25 °C for 30 min. The solvents were removed in vacuo, and the residue was flash chromatographed (silica, 15% ether in petroleum ether) to afford the acetate **29** (28 mg, 93%). **29**: oil; R_f = 0.66 (silica, 30% ether in petroleum ether); $[\alpha]^{21}_D$ +13.2° (*c* 0.28, $CHCl_3$); IR (neat) ν_{max} 3000, 2950, 2860, 1750 (s, OAc), 1455, 1380, 1240, 1165, 1120, 1090, 1030, 990, 930, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5 H, Ar), 5.83 (dd, *J* = 17.3, 10.8 Hz, 1 H, *H*C=CH_2), 5.25 (dd, *J* = 17.3, 10.8 Hz, 1 H, C=CH_2), 5.13 (dd, *J* = 10.8, 1.0 Hz, 1 H, C=CH_2), 5.07 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.94 (dd, *J* = 11.8, 5.2 Hz, 1 H, −*H*COAc), 4.85, 4.73 (2 × d, *J* = 7.2 Hz, 2 × 1 H, CH_2Ar), 4.61 (br s, 2 H, OCH_2O), 3.71 (dd, *J* = 11.1, 4.6 Hz, 1 H, −*H*CO), 3.36 (dd, *J* = 12.3, 3.1 Hz, 1 H, −*H*CO ring juncture), 2.15–2.05 (m, 3 H, CH_2), 2.01 (s, 3 H, CH_3CO_2), 1.90–1.40 (m, 5 H, CH_2), 1.66, 1.59 (2 × s, 2 × 3 H, $(CH_3)_2$ C=C), 1.36 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3); MS *m/e* (rel intensity) 487 (M + 1, 12), 457 (10), 427 (10), 404 (15), 379 (100), 289 (100), 266 (65), 197 (100), 124 (100); HRMS calcd for $C_{29}H_{43}O_6$ (M + 1) 487.3048, found 487.3005.

(2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-Hydroxyoctahydro-2,4a,6-trimethyl-3-acetoxy-6-(4-methyl-3-pentenyl)-2-vinylpyrano[3.2-*b*]pyran-3-ol (30). To a stirred solution of the alcohol **28** (44 mg, 0.1 mmol) and ethanethiol (75 μL, 1.0 mmol) in dichloromethane (1 mL) at −20 °C was added BF_3·Et_2O (37 μL, 0.3 mmol), and stirring was continued at that temperature for 1 h. Dilution with ether (5 mL) followed by washing with saturated $NaHCO_3$ (1 mL) and brine (1 mL), drying ($MgSO_4$), and concentration gave a yellow oil. Flash chromatography (silica, 50% ether in petroleum ether) gave pure diol **30** (30 mg, 92%). **30**: colorless needles, mp 134–135 °C (from ether/hexane); R_f = 0.25 (silica, 50% ether in petroleum ether); $[\alpha]^{21}_D$ +36.0° (*c* 0.25, $CHCl_3$); IR (neat) ν_{max} 3400 (s, OH), 3010, 2990, 2950, 1465, 1455, 1385, 1270, 1135, 1120, 1060, 1060, 1030, 970, 930, 890, 750, 705 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.96 (dd, *J* = 17.5, 10.8 Hz, 1 H, *H*C=CH_2), 5.33 (dd, *J* = 17.5, 1.0 Hz, 1 H, HC=CH_2), 5.18 (dd, *J* = 10.8, 1.0 Hz, 1 H, C=CH_2), 5.11 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 3.73 (m, 2 H, −*H*CO), 3.34 (dd, *J* = 12.1, 3.3 Hz, 1 H, −*H*CO ring juncture), 2.20–1.45 (m, 10 H, CH_2 and O*H*), 1.68, 1.62 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.33 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3); MS *m/e* (rel intensity) 325 (M + 1, 69), 307 (43), 289 (46), 242 (86), 224 (42), 197 (36), 185 (25), 141 (100), 109 (100); HRMS calcd for $C_{19}H_{33}O_4$ (M + 1) 325.2370, found 325.2385.

(2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-[(Benzyloxy)methoxy]octahydro-2,4a,6-trimethyl-3-(trimethylsiloxy)-6-(4-)methyl-3-pentenyl)-2-vinylpyrano-[3,2-*b*]pyran (31). The alcohol **28** (3.1 g, 7.0 mmol) in dichloromethane (14 mL) at 25 °C was treated with 1-(trimethylsilyl)imidazole (1.3 mL, 9.0 mmol). After 2 h, the excess 1-(trimethylsilyl)imidazole was quenched with methanol (1.0 mL), and the solvents were removed by evaporation. The residue was diluted with petroleum ether (50 mL) and washed with H_2O (2 × 10 mL) and brine (10 mL). Drying ($MgSO_4$) and concentration gave essentially pure silyl ether **31** (3.6 g, 100%). **31**: oil; R_f = 0.41 (silica, 5% ether in petroleum ether); $[\alpha]^{21}_D$ +28.7° (*c* 2.0, $CHCl_3$); IR (neat) ν_{max} 3030, 2990, 2950, 1465, 1455, 1385, 1270, 1135, 1120, 1060, 1030, 970, 930, 890, 750, 705 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50–7.28 (m, 5 H, Ar), 5.89 (dd, *J* = 17.4, 10.8 Hz, 1 H, *H*C=CH_2), 5.37 (dd, *J* = 17.4, 1.0 Hz, 1 H, C=CH_2), 5.09 (dd, *J* = 10.8, 1.0 Hz, 1 H, C=CH_2), 5.08 (m, 1 H, *H*C=C), 4.85, 4.72 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.65, 4.69 (2 × d, *J* = 15.0 Hz, 2 × 1 H, OCH_2O), 3.74 (dd, *J* = 11.4, 6.4 Hz, −*H*CO), 3.67 (dd, *J* = 11.5, 4.2 Hz, 1 H, −*H*CO), 3.32 (dd, *J* = 12.3, 3.0 Hz, 1 H, −*H*CO ring juncture), 2.20–2.05 (m, 3 H, CH_2), 1.95–1.45 (m, 5 H, CH_2), 1.66, 1.59 (2 × s, 2 × 3 H, $(CH_3)_2$C=C), 1.29 (s, 3 H, CH_3), (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 0.07 (s, 9 H, $(CH_3)_3$Si); MS *m/e* (rel intensity) 517 (M + 1, 5), 409 (21), 379 (22), 343 (9), 289 (13), 269 (11), 213 (63); HRMS calcd for $C_{30}H_{49}O_5Si$ (M + 1) 517.3336, found 517.3356.

(2*S*,3*R*,5a*S*,6*R*,7*S*,8a*R*)-7-[(Benzyloxy)methoxy]octahydro-2,4a,6-trimethyl-6-(4-methyl-3-pentenyl)-3-(trimethylsiloxy)pyrano[3,2-*b*]-pyran-2-ethanol (32). A stirred solution of borane·THF (9.1 mL, 1 M in THF, 9.1 mmol) at 0 °C was treated dropwise with 2-methyl-2-butene (2.3 mL, 21.8 mmol). After 1.5 h at 0 °C, the olefin **31** (3.6 g, 7.0 mmol) in dry THF (30 mL) was added, followed by continued stirring at 0 °C for 45 min, then removal of the cooling, and further stirring for an additional 20-min period. The homogeneous solution was recooled to 0 °C, and the borane was oxidized by slow addition of a solution of 3 N NaOH (10.6 mL, 32 mmol) and hydrogen peroxide (4.1 mL, 30% in H_2O, 36 mmol). After 20 min, the heterogeneous mixture was diluted with ether (100 mL) followed by washing with H_2O (2 × 25 mL) and brine (25 mL), drying ($MgSO_4$), and concentration. The residue was purified by flash chromatography (silica, 30–50% ether in petroleum ether) to afford the alcohol **32** (3.2 g, 87%). **32**: oil; R_f = 0.68 (silica, 60% ether in petroleum ether); $[\alpha]^{21}_D$ −15.7° (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 3510 (s, OH), 3030, 2990, 2960, 1470, 1460, 1385, 1270, 1260, 1215, 1140, 1100, 1050, 980, 895, 850, 750, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5 H, Ar), 5.06 (br s, *J* = 7.0 Hz, 1 H, *H*C=C), 4.83, 4.71 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.658 4.58 (2 × d, *J* = 13.0 Hz, 2 × 1 H, OCH_2O), 3.78 (m, 3 H, CH_2OH and −*H*CO), 3.71 (dd, *J* = 11.2, 4.8 Hz, 1 H, −*H*CO), 3.25 (dd, *J* = 12.4, 3.3 Hz, 1 H, −*H*CO ring juncture), 3.16 (t, *J* = 5.3 Hz, 1 H, O*H*), 2.15–1.45 (m, 10 H, CH_2), 1.66, 1.59 (2 × s, 2 × 3 H, $(CH_3)_2$C=C),

1.29 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 0.09 (s, 9 H, $(CH_3)_3Si$); MS *m/e* (rel intensity) 535 (M + 1, 90), 504 (8), 452 (12), 396 (100), 344 (51), 317 (70), 287 (54), 182 (100), 136 (100); HRMS calcd for $C_{30}H_{51}O_6Si$ (M + 1) 535.3455, found 535.3419.

(2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-[(Benzyloxy)methoxy]-2-(2-iodoethyl)-6-(4-methyl-3-pentenyl)-2,4a,6-trimethyl-3-(trimethylsiloxy)perhydropyrano[3,2-*b*]pyran (33). To a stirred heterogeneous mixture of alcohol **32** (2.6 g, 4.9 mmol), triphenylphosphine (3.8 g, 14.7 mmol), imidazole (1.0 g, 14.7 mmol), and dry benzene (50 mL) at 10 °C was added, in one portion, iodine (2.4 g, 9.8 mmol). After 20 min, the iodine color dissipated, and the clear benzene solution was decanted from the orange residue. The residue was washed with benzene (2 × 2 mL), and the benzene fractions were combined. Concentration and flash chromatography (silica, 3% ether in petroleum ether) gave the iodide **33** (2.8 g, 89%). **33**: oil; R_f = 0.61 (silica, 5% ether in petroleum ether); $[\alpha]^{21}_D$ +36.7° (*c* 1.65, $CHCl_3$); IR (neat) ν_{max} 3030, 2990, 2960, 2900, 1460, 1385, 1270, 1260, 1180, 1140, 1100, 1050, 990, 920, 890, 750, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5 H, Ar), 5.08 (br t, *J* = 7.0 Hz, 1 H, *H*C=C), 4.85, 4.72 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.61 (br s, 2 H, OCH_2O), 3.72 (dd, *J* = 11.3, 4.7 Hz, 1 H, -*H*CO), 3.65 (dd, *J* = 1.3, 5.2 Hz, 1 H, -*H*CO), 3.23 (dd, *J* = 7.7, 7.5 Hz, 2 H, CH_2I), 3.18 (dd, *J* = 12.0, 3.1 Hz, 1 H, -*H*CO ring juncture), 2.30-1.45 (m, 10 H, CH_2), 1.66, 1.58 (2 × s, 2 × 3 H, $(CH_3)_2C$=C), 1.26 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 0.10 (s, 9 H, $(CH_3)_3Si$); MS *m/e* (intensity) 644 (M, 7), 506 (57), 424 (32), 397 (74), 284 (100); HRMS calcd for $C_{30}H_{49}O_5SiI$ (M) 644.2394, found 644.2369.

(2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-[(Benzyloxy)methoxy]-6-(3-hydroxypropyl)-2-(2-iodoethyl)-2,4a,6-trimethyl-3-(trimethylsiloxy)perhydropyrano[3,2-*b*]pyran (34). Ozone was passed through a solution of the olefin **33** (1.0 g, 1.6 mmol) in dichloromethane (20 mL) at -78 °C until a blue coloration persisted. The excess ozone was removed with a stream of oxygen, followed by addition of BH_3·SMe_2 (3.0 mL, 2 M in THF, 6.0 mmol). The cooling bath was removed and the reaction mixture was stirred for 30 min. The excess BH_3·SMe_2 was carefully quenched at 25 °C by dropwise addition of H_2O (2.0 mL). Dilution with ether (60 mL) followed by washing with H_2O (50 mL) and brine (20 mL), drying ($MgSO_4$), and concentration gave a crude oil. Flash chromatography (silica, 35% ether in petroleum ether) furnished the alcohol **34** (0.85 g, 86%). **34**: oil; R_f = 0.37 (silica, 50% ether in petroleum ether); $[\alpha]^{21}_D$ +46.6° (*c* 0.60, $CHCl_3$); IR (neat) ν_{max} 3450 (s, OH), 2990, 2960, 2900, 1470, 1460, 1385, 1270, 1260, 1180, 1100, 1050, 990, 890, 850, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5 H, Ar), 4.87, 4.75 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.62 (br s, 2 H, OCH_2O), 3.71-3.50 (m, 4 H, $-CH_2O$ and -*H*CO), 3.24 (dd, *J* = 10.3, 7.3 Hz, 1 H, CH_2I), 3.20 (m, 1 H, -*H*CO ring juncture), 2.57 (br s, 1 H, O*H*), 2.30-1.96 (m, 3 H, CH_2), 1.89-1.50 (m, 7 H, CH_2), 1.29 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 0.09 (s, 9 H, $(CH_3)_3Si$); MS *m/e* (rel intensity) 621 (M + 1, 68), 573 (20), 513 (85), 483 (80), 387 (42), 354 (100), 284 (64), 215 (100); HRMS calcd for $C_{27}H_{46}O_6ISi$ (M) 621.2051, found 621.2022. Anal. Calcd for $C_{27}H_{46}O_6ISi$: C, 52.17; H, 7.46. Found: C, 52.31; H, 7.24.

(2*S*,3*R*,4a*S*,6*R*,7*S*,8a*R*)-7-[(Benzyloxy)methoxy]-6-[3-(*tert*-butyldimethylsiloxy)propyl]-2-(2-iodoethyl)-2,4a,6-trimethyl-3-(trimethylsiloxy)perhydropyrano[3,2-*b*]pyran (35). A stirred mixture of alcohol **34** (0.85 g, 1.4 mmol), imidazole (380 mg, 4.2 mmol), and dry DMF (5 mL) at 0 °C was treated with *tert*-butyldimethylsilyl chloride (310 mg, 2.1 mmol). After 1 h the reaction mixture was diluted with ether (20 mL) and washed with H_2O (2 × 5 mL) and brine (5 mL). Drying ($MgSO_4$) and concentration followed by flash chromatography (silica, 3% ether in petroleum ether) gave the bis silyl ether **35** (1.0 g, 98%). **35**: oil; R_f = 0.23 (silica, 5% ether in petroleum ether); $[\alpha]^{21}_D$ +34.1° (*c* 0.51, $CHCl_3$); IR (neat) ν_{max} 3000, 2960, 2900, 2870, 1480, 1470, 1385, 1270, 1260, 1180, 1100, 1050, 1035, 890, 845, 780, 735, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5 H, Ar), 4.83, 4.72 (2 × d, *J* = 7.1 Hz, 2 × 1 H, CH_2Ar), 4.61 (br s, 2 H, OCH_2O), 3.75-3.53 (m, 4 H, CH_2O and -*H*CO), 3.28-3.12 (m, 3 H, CH_2I, -O*CH*- ring juncture), 2.30-1.42 (m, 10 H, CH_2), 1.26 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3), 0.88 (s, 9 H, $(CH_3)_3CSi$), 0.03 (s, 6 H, $(CH_3)_2Si$); MS *m/e* (rel intensity) 735 (M + 1, 4), 647 (43), 597 (37), 539 (15), 449 (17), 354 (100), 284 (100), 215 (100); HRMS calcd for $C_{33}H_{60}IO_6Si_2$ (M + 1) 735.2912, found 735.2973.

3,7:6,10-Dianhydro-9-*O*-[(benzyloxy)methyl]-13-*O*-(*tert*-butyldimethylsilyl)-1,2,5,8,11,12-hexadeoxy-3,6,10-tri-*C*-methyl-4-*O*-(trimethylsilyl)-1-(triphenylphosphonio)-D-*erythro*-D-*allo*-tridecitol Iodide (1). A stirred mixture of iodide **35** (1.0 g, 1.3 mmol), triphenylphosphine (2.7 g, 10.4 mmol), and dry CH_3CN (3.0 mL) was heated at 90 °C for 24 h. After cooling, the excess triphenylphosphine was removed by washing with hexanes (10 × 15 mL). The remaining solvents were removed in vacuo to afford the phosphoinium salt **1** (1.3 g, 100%). **1**: amorphous solid; R_f = 0.31 (silica, 10% methanol in EtOAc); $[\alpha]^{21}_D$ +33.6° (*c* 0.99, $CHCl_3$); IR (neat) ν_{max} 3060, 3040, 3000, 2960, 2900, 2870, 1595, 1470, 1460, 1445, 1390, 1270, 1260, 1220, 1190, 1160, 1110, 1040, 1000, 890, 845, 780, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.90-7.22 (m, 20 H, Ar), 4.84, 4.72 (2 × d, *J* = 7.0 Hz, 2 × 1 H, CH_2Ar), 4.61 (s, 2 H, OCH_2O), 3.68 (dd, *J* = 11.3, 4.7 Hz, 1 H, -*H*CO), 3.58 (m, 3 H, CH_2O and CH_2P), 3.45 (dd, *J* = 11.2, 5.2 Hz, 1 H, -*H*CO), 3.32 (m, 1 H, CH_2P), 3.20 (dd, *J* = 11.0, 3.0 Hz, 1 H, -*H*CO ring juncture), 2.13-1.45 (m, 10 H, CH_2), 1.27 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 0.86 (s, 9 H, $(CH_3)_3CSi$), 0.10 (s, 6 H, $(CH_3)_2Si$), -0.08 (s, 9 H, $(CH_3)_3Si$); HRMS calcd for $C_{51}H_{74}O_6PSi_2$ (M - 1) 869.476, found 869.481. Anal. Calcd for $C_{51}H_{74}O_6PSi_2$: C, 61.43; H, 7.48. Found: C, 61.62; H, 7.27.

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Supplementary Material Available: ORTEP drawing and X-ray crystallographic analysis data for compound **30** (7 pages). Ordering information is given on any current masthead page.

Synthesis of the Brevetoxin B IJK Ring System

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Abstract: A stereoselective synthesis of a functionalized system representing the IJK ring framework of brevetoxin B is reported. The synthesis begins with D-mannose pentaacetate and proceeds through intermediates **24** and **38**, which serve as key cyclization precursors. The stereochemistry of the optically active target molecule **1** was confirmed by an X-ray crystallographic analysis of the crystalline derivative **42**.

In a preceding paper,[2] we described a retrosynthetic analysis of brevetoxin B in which three fragments containing the tetrahydropyran rings, ABC, FG, and IJK (**1**) were defined as subtargets for an eventual total synthesis. We also described stereoselective syntheses of fragments ABC[2] and FG.[3] In this article, we report a stereocontrolled construction of the IJK ring framework of brevetoxin B as the dithio ketal aldehyde **1** (Scheme

(1) Taken in part from the Ph.D. Thesis of C.-K. H., Department of Chemistry, University of Pennsylvania, 1986.

(2) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.*, first of three papers in this issue.

(3) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.*, second of three papers in this issue.

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