Stereospecific Total Synthesis of the Cyclohexene Oxide Antibiotic Eupenoxide

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Diels–Alder reaction of the electron-rich (*E,E*)-1,4-bis[(*tert*-butyldimethylsilyl)oxy]butadiene (**4c**), prepared from (*E,E*)-1,4-diacetoxybutadiene, with 4-acetoxybut-2-ynal (**3b**) afforded in good yield the cyclohexadienecarbaldehyde **5e**. Stereospecific epoxidation, development of the heptenyl side chain, and deprotection completed the total synthesis of the racemate of the cyclohexene oxide antibiotic eupenoxide (**1a**).

Eupenoxide (**1a**),[1] an antifungal agent produced by a fungus tentatively assigned to the genus *Eupenicillium*,[2] belongs to an increasing range of highly oxygenated cyclohexanoid metabolites, frequently epoxides, obtained from bacteria, fungi, higher plants, and even molluscs. Other members of the group have diverse biological activities ranging from antifungal, antibacterial, and antitumor to phytotoxic and enzyme inhibitory. Many of these compounds appear to be synthetically accessible via Diels–Alder reactions followed by subsequent adjustment of oxygen functionality, and we illustrate this approach and some of its limitations here with the successful synthesis of racemic eupenoxide (**1a**).

The major problems to be addressed in a synthesis of eupenoxide include the relative configuration of the ring substituents, the *E* configuration of the acyclic olefin, and the instability toward acids, bases, and heat which is to be expected in highly oxygenated hydroaromatic intermediates as well as in the final product itself. The synthetic route should also be versatile and capable of extension to other cyclohexene oxide antibiotics. Retrosynthetic analysis suggested the key intermediate to be a functionalyzed cyclohexenecarbaldehyde of the type **2** carrying protected oxygen functionality. Such an aldehyde could be generated by Diels–Alder addition of an acetylenic aldehyde **3** to an (*E,E*)-1,4-dioxygenated butadiene **4**, followed by epoxidation of the resulting cyclohexadienecarbaldehyde **5**. The cycloaddition process would establish the required cis 1,4-diol system of **5**, the protecting groups of which would then direct electrophilic epoxidation to the rear face of the more reactive, unconjugated olefinic bond. Development of the side chain by a Wittig reaction, with correction of olefin configuration if necessary, and subsequent removal of protecting groups would yield racemic eupenoxide (**1a**). A more convergent process would be achieved by substitution of (*E*)-dec-4-en-2-ynal for the aldehyde **3**, but cycloaddition to the diene **4** might then lack regiospecificity due to competition between the olefinic and acetylenic bonds of the dienophile.[3] Furthermore, extension of the side chain late in the sequence allows the preparation of analogues from the common intermediate **2** if required.

The successful execution of this approach depended upon the choice of protecting groups R^1 and R^2 for the Diels–Alder components **3** and **4**. Two dienophiles **3a,b** and three dienes **4a–c** were studied.

Attempts to prepare 4-(tetrahydropyran-2-yloxy)but-2-ynal (**3a**) by selective acid hydrolysis of the corresponding diethyl acetal[4] led to complex mixtures. However, reaction of the lithium derivative of 3-(tetrahydropyran-2-yloxy)-prop-1-yne with formaldehyde gave the acetylenic alcohol **6a** that was oxidized with manganese dioxide to the required aldehyde **3a**. 4-Acetoxybut-2-ynal (**3b**) was prepared from the same alcohol **6a** via the acetate **6b**, methanolysis of the tetrahydropyranyl ether, and oxidation of the resulting alcohol **6c**. The use of pyridinium chlorochromate[5] or nickel peroxide[6] for oxidation of these alcohols led to extensive decomposition and low yields of the unstable acetylenic aldehydes **3a,b**. Infrared spectra of the pseudosymmetrical diol derivatives **6** lacked typical acetylenic absorption between 2260 and 2190 cm^{-1}, in contrast to the aldehydes **3** which showed the expected stretching frequencies.[7]

Under the forcing conditions (150 °C, 24 h) required to effect cycloaddition between the acetylenic aldehydes **3a** or **3b** and commercially available (*E,E*)-1,4-diacetoxybutadiene (**4a**), the initially formed cyclohexadienecarbaldehydes **5a,b** suffered complete degradation.[8] Phthalaldehyde and 2-(diacetoxymethyl)benzaldehyde (**7**), respectively, were isolated from the two reactions. The benzaldehyde **7**, formed in 25% yield, probably arises by 1,4 elimination of acetic acid from the adduct **5b** and aromatization by allylic rearrangement of the resulting triene **8**. Formation of phthalaldehyde from the adduct **5a** involves the loss of dihydropyran and 2 mol of acetic acid.

To be successful, the cycloaddition step clearly required milder reaction conditions and hence a more reactive diene than **4a**, coupled with increased product stability compared to **5a** and **5b**. Accordingly the 1,4-bis[(trialkylsilyl)oxy]-butadienes **4b,c** were prepared by silylation of the bisenolate anion **4d** formed from (*E,E*)-1,4-diacetoxybutadiene with methyllithium. The expected *E,E* configuration of both dienes was confirmed by their ^1H and ^{13}C NMR spectra, which showed AA'BB' proton spin systems[9] and only two olefinic carbon resonances, respectively.[10]

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(9) Bishop, E. O. In "Nuclear Magnetic Resonance for Organic Chemists"; Mathieson, D. W., Ed.; Academic Press: London, 1967; p 106.
(10) The NMR data are compatible with both *E,E* and *Z,Z* configurations, but the latter can be excluded on mechanistic and steric grounds.

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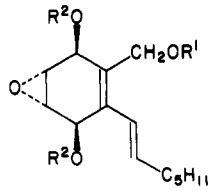
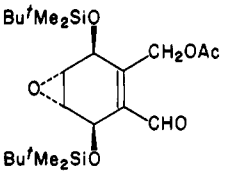


1a: $R^1 = R^2 = H$
b: R^1 = Ac, $R^2 = Bu^tMe_2Si$
c: $R^1 = H$, $R^2 = Bu^tMe_2Si$
d: R^1 = Ac, $R^2 = H$



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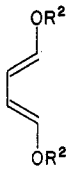
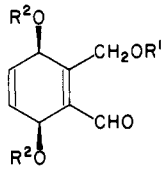
3a: R^1 = Thp
b: R^1 = Ac



4a: R^2 = Ac
b: $R^2 = Me_3Si$
c: $R^2 = Bu^tMe_2Si$
d: $R^2 = \ominus$



5a: R^1 = Thp, R^2 = Ac
b: $R^1 = R^2$ = Ac
c: R^1 = Ac, $R^2 = Me_3Si$
d: R^1 = Ac, $R^2 = H$
e: R^1 = Ac, $R^2 = Bu^tMe_2Si$
f: R^1 = Thp, $R^2 = Bu^tMe_2Si$

6a: R^1 = Thp, $R^2 = H$
b: R^1 = Thp, R^2 = Ac
c: $R^1 = H$, R^2 = Ac

The 1,4-bis[(trimethylsilyl)oxy]butadiene (**4b**) decomposed immediately on contact with moisture. Its reaction with 4-acetoxybut-2-ynal (**3b**) (115 °C, overnight) gave a mixture containing the required cycloadduct **5c** together with its decomposition products, two of which were identified by coupled gas chromatography–mass spectrometry as phthalaldehyde and the substituted benzaldehyde **9**. Attempts to isolate the cyclohexadienecarbaldehyde **5c** by distillation or gas chromatography led to further thermal decomposition, while absorption chromatography resulted in cleavage of the silyl ether groups to give the diol **5d**. The presence of the cyclohexadienecarbaldehydes **5c,d** in these mixtures was established by their ^1H NMR spectra and, in the case of **5c**, by its mass spectrum which showed characteristic retro Diels–Alder fragmentation.[11]

In contrast to the trimethylsilyl derivative **4b**, the 1,4-bis[(*tert*-butyldimethylsilyl)oxy]butadiene (**4c**) was relatively stable and on reaction with 4-acetoxybut-2-ynal (**3b**) (115 °C, 4 days) afforded the corresponding cyclohexadienecarbaldehyde **5e** in 68% yield. The ultraviolet spectrum of **5e** showed λ_{max} (hexane) 227 and 333 nm with ϵ 10900 and 490, respectively, the high extinction coefficient for the $n \rightarrow \pi^*$ transition of the conjugated aldehyde probably reflecting interaction with the homoconjugated double bond.[12a] Reaction of **4c** under similar conditions with the (tetrahydropyranyloxy)butynal **3a** again gave phthalaldehyde, by breakdown of the cycloadduct **5f**, and it is therefore clear that tetrahydropyranyl ethers are not suitable protecting groups for these Diels–Alder processes.

Although the substitution in the cyclohexadienecarbaldehyde **5e** was expected to direct electrophilic epoxidation to the disubstituted olefinic bond, this too was found to be unreactive due to the inductive effect of the flanking allylic ether functions.[13] No oxidation occurred with *m*-chloroperoxybenzoic acid under normal conditions while forcing conditions in the presence of a radical scavenger[14] gave only traces of the epoxide **2** together with considerable unreacted material. Benzonitrile/hydrogen peroxide,[15] a reactive system known to be capable of epoxidizing a disubstituted olefin carrying three allylic oxygen substituents,[16] gave numerous oxidation products but not the required epoxide **2**. However, reaction with *tert*-butyl hydroperoxide catalyzed by molybdenum hexacarbonyl,[17] or with *p*-nitroperoxybenzoic acid,[18] yielded 20% and 30%, respectively, of the epoxide **2**, with the latter reagent being preferred. The yields in these reactions reflect the instability of the starting material and products under the severe conditions required for epoxidation, and aromatic products arising from **5e** by dehydrogenation and by elimination of *tert*-butyldimethylsilanol were identified in both reactions.

The crucial stereospecific trans epoxidation of **5e** from the rear face of the molecule was confirmed by consideration of vicinal proton coupling constants. Dreiding models of **2** indicated approximate dihedral angles between H-3 and H-4 and H-5 and H-6 of 50° or 120° for trans stereochemistry and of 0° or 70° for cis stereochemistry. The Karplus equations[19] predict corresponding J values of 3.2 or 2.1 Hz for trans and 8.2 or 0.8 Hz for cis stereochemistry, while the Tori equation[20] predicts values of 2.1 or 1.3 Hz for trans and 5.1 or 0.6 Hz for cis stereochemistry. The observed value of 2.3 Hz for $J_{3,4}$ and $J_{5,6}$ establishes the expected trans relationship of the introduced epoxide to both silyl ether groups.

Wittig reaction of the cyclohexenecarbaldehyde **2** with *n*-hexylidenetriphenylphosphorane gave in 70% yield the olefin **10a**, in which the *Z* configuration of the side chain was indicated by the coupling constant of 11.5 Hz between the olefinic protons.[21] In view of the base sensitivity of the cyclohexene ring substituents, the possibility of obtaining the *E* olefin by α-metalation and inversion of the intermediate betaine[22] was rejected in favor of photochemical isomerization. Irradiation of the *Z* olefin with visible light in the presence of iodine catalyst[23] afforded in 70% conversion the thermodynamically more stable *E* olefin **1b**. The *E* and *Z* isomers were inseparable by

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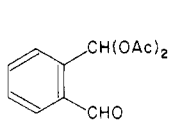
thin-layer chromatography, but crystallization afforded the required isomer **1b**, the only crystalline intermediate encountered in the synthesis. The *E* configuration of **1b** was confirmed by the coupling constant of 15 Hz between the olefinic protons,[21] by the lower chemical shifts (δ 6.24 and 6.02) of these protons relative to those of the *Z* isomer **10a** (δ 5.76 and 5.67), and by an ultraviolet absorption maximum at 243 nm compared to the end absorption of **10a**.[24]



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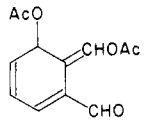

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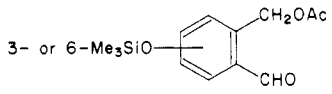

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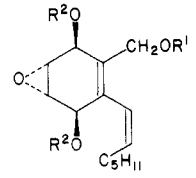


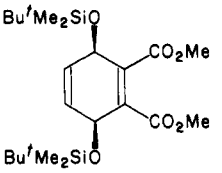
10a: R^1 = Ac, R^2 = Bu^tMe_2Si
b: R^1 = Ac, R^2 = H
c: R^1 = R^2 = H

Removal of the protecting groups from the sensitive oxygenated hydroaromatic system was first studied with the *Z* isomer **10a**. Desilylation with acetic acid gave in 57% yield the diol **10b**, which was deacetylated in 90% yield with methanolic ammonia. The resulting *Z* isomer **10c** of eupenoxide resembled the natural product **1a** spectroscopically but showed the expected differences in olefinic proton resonances (δ 5.85–5.27 (J = 11.5 Hz), δ 6.29 and 6.11 (J = 15 Hz)) and ultraviolet absorption (end absorption; λ_{max} 240.3 nm).

The deprotection of the *E* isomer **1b** was carried out in the reverse order, initiated by ammonolysis (98% yield) of the acetate in order to provide the alcohol **1c** as a more soluble substrate for subsequent desilylation. Desilylation with aqueous acetic acid gave eupenoxide (**1a**) but was accompanied by acetylation to the primary allylic acetate **1d** (10%) and some decomposition. Natural eupenoxide behaved similarly under these conditions, and it is clear that if acidic desilylation is used, it should precede alkaline deacetylation as in the case of the *Z* isomer **10a**. Desilylation of the alcohol **1c** was subsequently achieved under nonacidic conditions with tetrabutylammonium fluoride,[25] affording in 87% yield racemic eupenoxide (**1a**) identical with natural material.

As a model substrate for several reactions in this synthesis, the cyclohexadiene **11** was prepared in 75% yield from 1,4-bis[(*tert*-butyldimethylsilyl)oxy]butadiene (**4c**) and dimethyl acetylenedicarboxylate. Like the cyclohexadienecarbaldehyde **5e**, the cyclohexadiene **11** was decomposed by benzonitrile/hydrogen peroxide but gave the trans epoxide **12a** with *p*-nitroperoxybenzoic acid[18] or *tert*-butyl hydroperoxide in the presence of molybdenum hexacarbonyl.[17] The product **12a** could be desilylated with aqueous acetic acid to the diol **12b**.

Although the model cyclohexadiene **11** on reaction with *o*-nitroperoxybenzoic acid[26] yielded the expected epoxide



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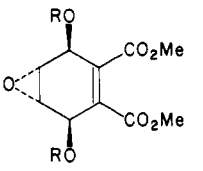
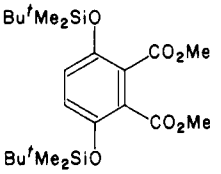


12a: R = Bu^tMe_2Si
b: R = H
c: R, R = H, Bu^tMe_2Si



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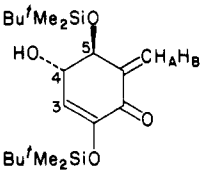

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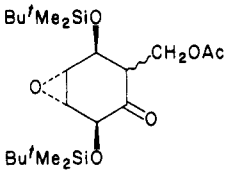

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12a (together with the dehydrogenation product **13**), the cyclohexadienecarbaldehyde **5e** gave only a trace of the required epoxide **2**, together with a product formulated as the cross-conjugated dienone **14**. This compound $C_{19}H_{36}O_4Si_2$ showed hydroxyl, conjugated carbonyl, and olefinic absorption in its IR spectrum at 3700–3200, 1680, and 1630 cm^{-1}, and ultraviolet absorption at 279 nm[12b] which was removed by the addition of sodium borohydride. ^{13}C NMR spectra indicated four appropriately substituted olefinic carbon atoms at δ 152.7 (s), 149.0 (s), 131.3 (d), and 125.2 (t), a ketonic carbonyl at δ 189.9, and two oxygen-carrying methine carbons at δ 82.1 and 76.8. The ^1H NMR spectrum showed two-proton multiplets at δ 4.34 and 6.08 and a one-proton multiplet at δ 5.65, assigned from decoupling experiments to H-4 and H-5, H-3 and H-B, and H-A, respectively. These signals were separated and reduced to first-order patterns by the lanthanide shift reagent $Eu(fod)_3$, enabling measurement of the coupling constants $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ = 7.5 Hz, and $J_{5,A} = J_{5,B} = J_{A,B}$ = 2.0 Hz, in agreement with the structure and configuration proposed. The dienone **14** probably arises by Baeyer–Villiger oxidation of the aldehyde **5e** to an enol formate, hydrolysis to the cyclohexanone **15**, and subsequent β-elimination of both the acetoxy and epoxide substituents.

Experimental Section

General Methods. Melting points were determined on a Kofler stage and are uncorrected. IR spectra were measured on a Perkin-Elmer 257 or a Jasco IRA-1 spectrometer and UV spectra on a Cary 118C spectrometer. NMR spectra were recorded on Varian HA-100 (^1H), JEOL Minimar 100-MHz (^1H), and JEOL JNM-FX60 (^1H and ^{13}C) spectrometers, with tetramethylsilane as internal reference. Coupling constants in certain ^1H NMR spectra were analyzed by using exact solutions[27] where possible, assisted by homonuclear decoupling if necessary, and the parameters were refined with the LAOCN-4A program.[28]

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Mass spectra were run on GEC-AEI MS902 or Varian MAT CH-7 spectrometers operating at 70 eV. Combined GLC–MS analyses were carried out on a Varian MAT 111 instrument fitted with a 180 cm × 3 mm i.d. glass column containing 2% OV-17 on 80-100 Chromosorb Q. GLC analyses and preparative separations were performed on Varian Aerograph 1400 and 90-P instruments, respectively, using glass columns containing 2% OV-17 on 80-100 Chromosorb Q.

Microanalyses were carried out by the A.N.U. Analytical Services Unit.

Materials. Low boiling solvents were fractionated through a vacuum-jacketed glass column (100 × 2 cm) packed with glass helices. Anhydrous ether and tetrahydrofuran were distilled from sodium benzophenone ketyl immediately before use. Chloroform used in epoxidation reactions was washed with aqueous sodium carbonate and water, dried (K_2CO_3), and distilled from phosphorus pentoxide before use. For preparative TLC, the petroleum ether used had a boiling point of 30–40 °C and the absorbent was Merck Kieselgel GF_{254}.

o- and *p*-nitroperoxybenzoic acids were prepared after Silbert et al.[26a] from hydrogen peroxide concentrated according to the method of Hurd and Puterbaugh.[29]

3-(Tetrahydropyran-2-yloxy)prop-1-yne. The ether was prepared by acid-catalyzed condensation of 2,3-dihydropyran and propargyl alcohol according to the known procedure:[4] IR (neat) 2120 cm^{-1} (C≡C); MS, *m/z* (relative intensity) 139 (13), 101 (7), 85 (100); ^1H NMR ($CDCl_3$) δ 4.8 (br s, CHO), 4.23 (d, ^4J = 2.4 Hz, OCH_2≡C), 3.96–3.68 and 3.62–3.38 (m, each 1 H, CH_2O), 2.46 (t, ^4J = 2.4 Hz, C≡CH), 2.0–1.4 (m, 3 CH_2).

4-(Tetrahydropyran-2-yloxy)but-2-yn-1-ol (6a). To a stirred solution of 3-(tetrahydropyran-2-yloxy)prop-1-yne (140 g) in tetrahydrofuran (800 mL), cooled to −78 °C and maintained under a nitrogen atmosphere, was added dropwise *n*-butyllithium in hexane (1 mol, 600 mL). The mixture was allowed to warm to room temperature with continuous stirring. Paraformaldehyde (90 g) was heated to 180–200 °C and the resulting formaldehyde bubbled through the stirred reaction mixture in a stream of nitrogen. After the mixture was stirred overnight at room temperature, the solvent was removed under reduced pressure and water (600 mL) was added. The mixture was extracted with ether and the ether phase dried (K_2CO_3). Removal of ether and vacuum distillation of the residue gave the alcohol **6a** (85 g, 80% based on unrecovered starting material): bp 110–120 °C (0.05 mm); IR (neat) 3700–3030 cm^{-1} (OH); MS, *m/z* (relative intensity) 169 (1.5), 115 (2), 112 (3), 111 (3), 101 (17), 100 (5), 97 (6), 85 (60), 41 (100); ^1H NMR ($CDCl_3$) δ 4.83 (br s, OCHO), 4.27 (s, OCH_2C≡CCH_2O), 3.98–3.70 and 3.68–3.41 (m, each 1 H, CH_2O), 3.23 (br s, exchanged in D_2O, OH), 2.0–1.4 (m, 3 CH_2); ^{13}C NMR ($CDCl_3$) δ 96.75 (d, OCHO), 84.93 and 81.03 (br s, C≡C), 61.94 (t, CH_2O), 54.41 and 50.65 (t, OCH_2C≡CCH_2O), 30.26, 25.45, and 19.09 (t, C-3, C-5, and C-4). Anal. Calcd for $C_9H_{14}O_3$: C, 63.5; H, 8.29. Found: C, 63.1; H, 8.45.

4-(Tetrahydropyran-2-yloxy)but-2-ynal (3a). To a solution of the alcohol **6a** (2.5 g) in benzene (470 mL) was added manganese dioxide (30 g), and the mixture was heated under reflux with stirring for 4 h. The catalyst was removed by filtration and washed with benzene. The filtrate and the washings were combined and concentrated under reduced pressure, and the residue was purified by preparative TLC on silica gel in ether/petroleum ether (1:1). Further purification by vacuum distillation gave the aldehyde **3a** (800 mg, 32%), bp 80 °C (0.1 mm), from which an analytical sample was purified by preparative GLC operating at 185 °C isothermally: MS, *m/z* 167.0710 (M^+ − H, calcd for $C_9H_{11}O_3$ *m/z* 167.0708); UV max (hexane) 375.5 nm (ε 6), 357 (45.6), 342 (22), 329.5 (25.1), 319 (23.8), 310 (sh, 21.7), 258 (sh, 160.5), 228.4 (7250), 220.6 (7440), 213 (5430); IR (neat) 2240, 2200 (C≡C), 1670 cm^{-1} (CHO); MS, *m/z* (relative intensity) 167 (4), 125 (0.5), 113 (4), 111 (1), 110 (4), 101 (15), 100 (20), 97 (3), 85 (33), 84 (40), 83 (25), 70 (15), 69 (17), 68 (58), 56 (90), 55 (100), 39 (100^+); ^1H NMR ($CDCl_3$) δ 9.24 (s, CHO), 4.80 (br s, OCHO), 4.45 (s, OCH_2C≡C), 4.0–3.68 and 3.68–3.4 (m, each 1 H, CH_2O), 2.0–1.20 (m, 3 CH_2); ^{13}C NMR ($CDCl_3$) δ 176.22 (d, CHO), 97.27 (d, OCHO), 92.46 (s, C≡C), 85.19 (s, C≡C), 61.81 (t, CH_2O), 53.76 (t, OCH_2C≡$CCHO$), 30.13, 25.32, and 18.83 (t, C-3, C-5, and C-4). Anal. Calcd for $C_9H_{12}O_3$: C, 64.3; H, 7.19. Found: C, 63.9; H, 7.06.

1-Acetoxy-4-(tetrahydropyran-2-yloxy)but-2-yne (6b). To a stirred solution of the alcohol **6a** (85 g) in anhydrous pyridine (124 mL) cooled to 0 °C was added acetic anhydride (75.5 mL). The mixture was stirred at room temperature overnight, ice (200 g) was added, and the mixture was extracted with dichloromethane. The extracts were combined and dried (K_2CO_3), and the solvent was removed under reduced pressure. Vacuum distillation of the residue gave the acetate **6b** (98 g, 92.5%): bp 110–112 °C (0.05 mm); IR (neat) 1740 cm^{-1} (CO); MS, *m/z* (relative intensity) 169 (1), 168 (1.6), 139 (1.4), 111 (39), 101 (17), 97 (7), 86 (32), 85 (100), 84 (95), 83 (47), 82 (30), 79 (30), 55 (100), 43 (100^+); ^1H NMR ($CDCl_3$) δ 4.76 (br s, OCHO), 4.66 (t, ^4J = 1.9 Hz, CH_2OAc), 4.26 (br s, OCH_2C≡C), 3.96–3.68 and 3.62–3.18 (m, each 1 H, CH_2O), 2.06 (s, $OCOCH_3$), 2.0–1.4 (m, 3 CH_2); ^{13}C NMR ($CDCl_3$) δ 169.86 (s, $OCOCH_3$), 96.75 (d, OCHO), 82.85 and 79.87 (m, C≡C), 61.81 (t, CH_2O), 54.02 and 52.20 (t, OCH_2C≡CCH_2OAc), 20.65 (q, $OCOCH_3$), 30.26, 25.45, and 18.96 (t, C-3, C-5, and C-4). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.1; H, 7.72.

4-Acetoxybut-2-ynol (6c). A solution of the acetate **6b** (98 g) in 1.0 M acetic acid in methanol (500 mL) was heated under reflux for 3 days. Toluene (500 mL) was added, and the mixture was evaporated under reduced pressure. Vacuum distillation of the residue gave the alcohol **6c** (53 g, 90%): bp 93–95 °C (0.08 mm); IR (neat) 3700–3100 (OH), 1740 cm^{-1} (CO); MS, *m/z* (relative intensity) 128 (0.2), 127 (0.2), 111 (2), 97 (4), 86 (24), 85 (4), 82 (21), 71 (6), 68 (19), 61 (9), 57 (7), 55 (14), 53 (3), 52 (5), 51 (15), 50 (9), 43 (100); ^1H NMR ($CDCl_3$) δ 4.68 (t, ^5J = 1.7 Hz, CH_2OAc), 4.27 (t, ^5J = 1.7 Hz, CH_2OH), 2.50–2.24 (m, exchanged in D_2O, OH), 2.06 (s, $OCOCH_3$); ^{13}C NMR ($CDCl_3$) δ 170.90 (s, $OCOCH_3$), 85.58 and 79.22 (br s, C≡C), 52.46 and 50.26 (t, CH_2OAc and CH_2OH), 20.65 (q, $OCOCH_3$). Anal. Calcd for $C_6H_8O_3$: C, 56.2; H, 6.29. Found: C, 56.5; H, 6.38.

4-Acetoxybut-2-ynal (3b). To a solution of the alcohol **6c** (8 g) in dichloromethane (1 L) was added manganese dioxide (80 g), and the mixture was stirred at room temperature for 4 days. The catalyst was removed by filtration and washed with dichloromethane. The filtrate and washings were concentrated under reduced pressure, and the residue was purified by preparative TLC on silica gel in ether/petroleum ether (1:1). Further purification by molecular distillation gave the aldehyde **3b** (3 g, 38%), bp 30–40 °C (0.001 mm), from which an analytical sample was obtained by preparative GLC operating at 125 °C isothermally: MS, *m/z* 126.0319 (M^+, calcd for $C_6H_6O_3$ *m/z* 126.0317); UV max (hexane) 375.0 nm (ε 5.2), 357.5 (13.2), 342.3 (20.3), 329.5 (22.6), 319.0 (21.5), 309.5 (sh, 18.6), 276.5 (sh, 13.3), 258 (sh, 98.7), 226 (6570), 217.8 (7487), 215 (sh, 5108); IR (neat) 2270, 2200 (C≡C), 1750 (CO), 1675 cm^{-1} (CHO); MS, *m/z* (relative intensity) 126 (1.5), 125 (1), 111 (38), 98 (2), 97 (1.5), 84 (100), 70 (4.5), 67 (3), 66 (18), 55 (18), 53 (13), 50 (5), 44 (9.4), 43 (100^+); ^1H NMR ($CDCl_3$) δ 9.20 (s, CHO), 4.84 (s, CH_2OAc), 2.10 (s, $OCOCH_3$); ^{13}C NMR ($CDCl_3$) δ 175.83 (d, CHO), 169.73 (s, $OCOCH_3$), 89.47 (m, C≡C), 51.30 (t, CH_2OAc), 20.39 (q, $OCOCH_3$). Anal. Calcd for $C_6H_6O_3$: C, 57.1; H, 4.80. Found: C, 57.1; H, 4.65.

***(E,E)*-1,4-Diacetoxybuta-1,3-diene (4a).** Diene **4a** was prepared by the method of Hill and Carlson[8b] and also purchased from Fluka Chemical Co: ^1H NMR ($CDCl_3$) δ 5.37 (m, H-1 and H-4), 4.95 (m, H-2 and H-3) (refined coupling constants $^3J_{1,2}$ = 12.9 Hz, $^4J_{1,3}$ = 0.9 Hz, $^3J_{2,3}$ = 11.5 Hz, $^5J_{1,4}$ = 0.9 Hz, error ±0.4 Hz), 2.12 (s, 2 $OCOCH_3$); ^{13}C NMR ($CDCl_3$) δ 167.39 (2 $OCOCH_3$), 137.91 (br d, C-1 and C-4), 110.12 (br d, C-2 and C-3), 20.52 (q, 2 $OCOCH_3$).

***(E,E)*-1,4-Bis[(trimethylsilyl)oxy]buta-1,3-diene (4b).** To a stirred solution of the diene **4a** (210 mg) in tetrahydrofuran (5 mL), cooled to 0 °C and maintained under a dry nitrogen atmosphere, was added dropwise methyllithium in ether (1.7 M, 4.2 mL). The mixture was stirred at room temperature for 2 h, then trimethylsilyl chloride (1.1 mL) was added, and stirring was continued for 1 h. The mixture was allowed to settle, and the supernatant was distilled under reduced pressure to give the diene **4b** (150 mg, 53%), bp 120 °C (0.01 mm), from which an analytical sample was obtained by preparative GLC operating at 180 °C isothermally: MS, *m/z* 230.1160 (M^+, calcd for $C_{10}H_{22}O_2Si$ *m/z*

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230.1159); MS, m/z (relative intensity) 230 (65), 215 (1), 156 (1.5), 75 (25), 73 (100), m* 105.8 (230 → 156); ^{1}H NMR ($CHCl_3$) δ 6.34 (m, H-1 and H-4), 5.56 (m, H-2 and H-3) (refined coupling constants $^3J_{1,2}$ = 11.9 Hz, $^4J_{1,3}$ = 0.6 Hz, $^3J_{2,3}$ = 11.3 Hz, $^5J_{1,4}$ = −0.5 Hz, error ±0.2 Hz), 0.18 (s, 2 $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 139.86 (d, C-1 and C-4), 109.47 (d, C-2 and C-3), −0.39 (q, 2 $OSi(CH_3)_3$). Anal. Calcd for $C_{10}H_{22}O_2Si_2$: C, 52.1; H, 9.62. Found: C, 51.7; H, 9.44.

This compound decomposes immediately on contact with moisture.

(*E*,*E*)-1,4-Bis[(*tert*-butyldimethylsilyl)oxy]buta-1,3-diene (4c). To a stirred solution of the diene **4a** (800 mg) in tetrahydrofuran (10 mL), cooled to 0 °C and maintained under a nitrogen atmosphere, was added dropwise methyllithium in ether (1.7 M, 14 mL). The mixture was heated to reflux and a solution of *tert*-butyldimethylsilyl chloride in tetrahydrofuran (10 mL) was added. Refluxing was continued for 1 h, and then half of the solvent was allowed to distill off. The residue was cooled to room temperature, and, with stirring, ether (20 mL) was added, followed by slow addition of water (15 mL). The mixture was extracted with ether and the extract dried (K_2CO_3). Solvent was removed under reduced pressure, and other volatile components were removed under reduced pressure at approximately 100 °C. Vacuum distillation of the residue gave the diene **4c**, a pale yellow oil (1.25 g, 85%), bp 170 °C (0.01 mm), which crystallized in the refrigerator but liquefied at room temperature. The analytical sample was purified by preparative GLC operating at 120–220 °C, Δ 10 °C/min: MS, m/z 314.2098 (M^+, calcd for $C_{16}H_{34}O_2Si_2$ m/z 314.2098); UV max (hexane) 210 nm (ϵ 8300); IR (neat) 1695 cm^{-1}; MS, m/z (relative intensity) 314 (26), 75 (22), 73 (100); ^{1}H NMR ($CHCl_3$) δ 6.34 (m, H-1 and H-4), 5.56 (m, H-2 and H-3) (refined coupling constants $^3J_{1,2}$ = 12 Hz, $^4J_{1,3}$ = 0.7 Hz, $^5J_{1,4}$ = −0.6 Hz, $^3J_{2,3}$ = 11.3 Hz), 0.90 (s, 2 $SiC(CH_3)_3$), 0.12 (s, 2 $Si(CH_3)_2$). Anal. Calcd for $C_{16}H_{34}O_2Si_2$: C, 61.1; H, 10.9. Found: C, 61.3; H, 10.8.

Cycloaddition Reactions of the Diene 4a. (a) With the Aldehyde 3a. The diene **4a** (130 mg) and the aldehyde **3a** (130 mg) in *m*-xylene (15 mL) were refluxed under nitrogen for 4 days. Concentration of the mixture, chromatography on Sephadex LH20 in chloroform/methanol (1:1), and then PLC in ether/petroleum ether (1:1) gave recovered starting materials as major components, together with phthalaldehyde (5 mg) identified by UV, MS, and ^{1}H NMR.

(b) With the Aldehyde 3b. The diene **4a** (34 mg) and the aldehyde **3b** (252 mg) in benzene (0.3 mL) were heated at 150 °C for 24 h in an evacuated sealed tube. Extraction of the mixture with dichloromethane, concentration of the extracts, and PLC in ether/petroleum ether (1:1) gave 2-(diacetoxymethyl)benzaldehyde (**7**) (12 mg, 25%) as an oil: UV max (EtOH) 321 nm (sh, ϵ 165), 290 (sh, 1410), 283 (1621), 245.5 (8607); IR (neat) 1750 ($OCOCH_3$), 1700 cm^{-1} (CHO); MS, m/z 177.0549 ($M^+ - OCOCH_3$, calcd for $C_{10}H_9O_3$ m/z 177.0552), 165.0552 ($M^+ - CH_2CO - CHO$, calcd for $C_9H_9O_3$ m/z 165.0552), 151.0394 ($M^+ - CH_2CO - CH_3CO$, calcd for $C_8H_7O_3$ m/z 151.0395); MS, m/z (relative intensity) 177 (2.5), 176 (20), 165 (1.5), 151 (2), 149 (1.5), 135 (47), 134 (100), 133 (40), 105 (34), 77 (20), 43 (95); ^{1}H NMR ($CDCl_3$) δ 10.38 (s, CHO), 7.95–7.86 and 7.70–7.46 (m, 2 H and 3 H, H-3, H-4, H-5, H-6, and $CH(OAc)_2$), 2.07 (s, 2 $OCOCH_3$).

(±)-(3*R,6*S**)-2-(Acetoxymethyl)-3,6-bis[(trimethylsilyl)oxy]cyclohexa-1,4-dienecarbaldehyde (5c).** A mixture of the diene **4b** (200 mg) and the dienophile **3b** (100 mg) was heated in an evacuated sealed tube at 110–120 °C overnight. A portion of this mixture was distilled at 110–120 °C (0.03 mm) to give a partially purified cycloadduct, **5c**: ^{1}H NMR ($CDCl_3$) δ 10.02 (s, CHO), 5.79 (d, J = 1 Hz, H-4 and H-5), 5.32 and 4.82 (each 1 H, d, J = 11 Hz, CH_2OAc), 4.96 (d, J = 2 Hz, H-3 and H-6), 2.07 (s, $OCOCH_3$), 0.12 and 0.09 (s, 2 $Si(CH_3)_3$), with impurities. GLC–MS at 130–280 °C, Δ10 °C/min, showed *inter alia* phthalaldehyde, the benzaldehyde **9** [MS, m/z (relative intensity) 266 (M^+, 6), 251 (2), 224 (44), 223 (50), 209 (44), 207 (60), 206 (57), 135 (100^+), 134 (100^+), 105 (50), 75 (100), 73 (100^+)], and the aldehyde **5c**, a small portion of which was purified by preparative GLC: MS, m/z (relative intensity) 356 (M^+, 0.08), 341 (0.1), 296 (0.5), 281 (2), 266 (3), 251 (2.5), 231 (10), 230 (46), 224 (15), 223 (22), 209 (14), 207 (18), 206 (25), 163 (10), 135 (29), 134 (53), 133 (20), 177 (22), 106 (11), 105 (28), 77 (26), 75 (55), 73 (97), 43 (100).

Portion of the reaction mixture was dissolved in methanol, concentrated, and subjected to PLC in dichloromethane/methanol (20:1) to give the partially purified diol **5d**: ^{1}H NMR ($CDCl_3$) δ 10.02 (s, CHO), 6.02 (d, J = 1 Hz, H-4 and H-5), 5.36 and 5.06 (each 1 H, d, J = 11 Hz, CH_2OAc), 4.87 and 4.64 (each 1 H, m, H-3 and H-6), 2.12 (s, $OCOCH_3$).

Cycloaddition of the Diene 4c and the Aldehyde 3a. The diene **4c** (35.7 mg) and the aldehyde **3a** (30 mg) in benzene (25 μL) were heated in an evacuated sealed tube at 110–120 °C for 3 days. PLC of the resulting mixture in ether/petroleum ether (1:2) gave phthalaldehyde (8.5 mg) as the major product, identified by UV, MS, and ^{1}H NMR.

(±)-(3*R,6*S**)-2-(Acetoxymethyl)-3,6-bis[(*tert*-butyldimethylsilyl)oxy]cyclohexa-1,4-dienecarbaldehyde (5e).** A solution of the diene **4c** (105 mg) and the dienophile **3b** (190 mg) in benzene (1.5 mL) was heated in an evacuated sealed tube at 115 °C for 4 days. The mixture was subjected to PLC in ether/petroleum ether (2:1) to give the aldehyde **5e** (93 mg, 68%): MS, m/z 440.2414 (M^+, calcd for $C_{22}H_{40}O_5Si_2$ m/z 440.2414); UV max (hexane) 332.5 nm (ϵ 490), 226.5 (10 900); IR (neat) 1745 ($OCOCH_3$), 1694 cm^{-1} (CHO); MS, m/z (relative intensity) 440 (0.5), 383 (3), 381 (4), 365 (4), 351 (3), 341 (7), 325 (20), 324 (31), 323 (100), 315 (10), 314 (28), 251 (100^+), 209 (100^+), 207 (18), 181 (13), 177 (13), 151 (12), 117 (100^+), 75 (100^+), 43 (100^+), m* 272.4 (383 → 323), 174.0 (251 → 209), 156.8 (209 → 181), 135.2 (323 → 209), 109.1 (209 → 151), 54.5 (251 → 117), 48.1 (117 → 75); ^{1}H NMR ($CHCl_3$) δ 10.04 (s, CHO), δ_A 5.88 and δ_B 5.86 (H-4 and H-5), δ_C 4.99 and δ_D 4.72 (H-3 and H-6) (refined coupling constants $^3J_{AB}$ = 10.2 Hz, $^3J_{AC}$ = 1.5 or 3.3 Hz, $^4J_{AD}$ = −3.3 or −1.5 Hz, $^4J_{BC}$ = −3.1 or −1.6 Hz, $^3J_{BD}$ = 1.6 or 3.1 Hz, $^5J_{CD}$ = 5.3 Hz), 5.37 and 4.83 (each 1 H, d, J = 11 Hz, CH_2OAc), 2.04 (s, $OCOCH_3$), 0.91 and 0.86 (s, 2 $SiC(CH_3)_3$), 0.13 and 0.15 (s, 2 $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 191.42 (d, CHO), 170.24 (s, $OCOCH_3$), 144.80 (s, C-1), 137.13 (s, C-2), 128.43 and 127.52 (d, C-4 and C-5), 61.68 and 63.89 (d, C-3 and C-6), 59.22 (t, CH_2OAc), 25.71 (q, $OCOCH_3$), 20.78 (q, 2 $SiC(CH_3)_3$), 18.05 (s, 2 $SiC(CH_3)_3$), −4.29 and −3.90 (q, 2 $Si(CH_3)_2$). Anal. Calcd for $C_{22}H_{40}O_5Si_2$: C, 60.0; H, 9.15. Found: C, 60.1; H, 9.04.

***meso*-Dimethyl 3,6-Bis[(*tert*-butyldimethylsilyl)oxy]-cyclohexa-1,4-diene-1,2-dicarboxylate (11).** A solution of the diene **4c** (314 mg) and dimethyl acetylenedicarboxylate (280 mg) in benzene (0.8 mL) was heated in an evacuated sealed tube at 115 °C for 20 h. The mixture was evaporated under reduced pressure and distilled to give the cyclohexadiene **11** (335 mg, 75%), bp 180 °C (0.01 mm), which could be further purified by preparative TLC on silica gel in ether/petroleum ether (1:1): UV max (hexane) 306.5 nm (ϵ 588), 282.5 (578), 273.5 (sh, 488); IR (neat) 1730 cm^{-1} ($COOCH_3$); MS, m/z (relative intensity) 441 (4), 425 (0.5), 424 (0.4), 409 (0.5), 401 (14), 400 (31), 399 (100), 397 (5), 393 (1), 381 (1), 367 (12), 341 (4), 340 (10), 339 (34), 314 (3), 75 (28), 73 (46), m* 228.0 (399 → 339); ^{1}H NMR ($CHCl_3$) δ_{AA} 5.83 (m, H-4 and H-5), δ_{XX} 4.87 (m, H-3 and H-6) (refined coupling constants $^3J_{AA}$ = 5.2 Hz, $^3J_{AX}$ = 2.3 Hz, $^4J_{AX}$ = −0.7 Hz, $^5J_{XX}$ = 0 Hz), 3.78 (s, 2 CO_2CH_3), 0.87 (s, 2 $SiC(CH_3)_3$), 0.14 and 0.08 (s, 2 $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 167.13 (s, 2 CO_2CH_3), 135.58 (s, C-1 and C-2), 127.78 (d, C-4 and C-5), 63.37 (d, C-3 and C-6), 52.07 (q, 2 CO_2CH_3), 25.71 (q, 2 $SiC(CH_3)_3$), 18.05 (s, 2 $SiC(CH_3)_3$), −4.54 and −4.16 (q, 2 $Si(CH_3)_2$). Anal. Calcd for $C_{22}H_{40}O_6Si_2$: C, 57.9; H, 8.83. Found: C, 57.5; H, 8.69.

(±)-(3*S,4*S**,5*R**,6*R**)-2-(Acetoxymethyl)-3,6-bis[(*tert*-butyldimethylsilyl)oxy]-4,5-epoxycyclohex-1-enecarbaldehyde (2). Method a.** The aldehyde **5e** (44 mg), molybdenum hexacarbonyl (4.5 mg), 4,4′-thiobis(6-*tert*-butyl-3-methylphenol) (0.5 mg), and *tert*-butyl hydroperoxide (47 mg) in benzene (5 mL) were heated under reflux in a nitrogen atmosphere for 6 h. The mixture was concentrated under reduced pressure and purified by preparative TLC, first on silica gel in ether/petroleum ether (1:2) and second on neutral alumina using the same solvent, to give the epoxide **2** (9 mg, 20%).

Method b. The aldehyde **5e** (500 mg), finely powdered *p*-nitroperoxybenzoic acid (500 mg), and 4,4′-thiobis(6-*tert*-butyl-3-methylphenol) (4 mg) in chloroform were heated under reflux for 3 days. The mixture was cooled to 0 °C and filtered, and the precipitate was washed with cold chloroform. The filtrate and the washings were concentrated under reduced pressure and subjected to preparative TLC on silica gel in ether/petroleum

ether (1:2) to give the epoxide **2** (136 mg, 26%): UV max (hexane) 229.5 nm (ϵ 8100); IR (neat) 1745 ($OCOCH_3$), 1690 cm^{-1} (CHO); MS, m/z 399.1653 ($M^+ - 57$, calcd for $C_{18}H_{31}O_6Si_2$ m/z 399.1658); MS, m/z (relative intensity) 399 (4), 381 (5), 339 (82), 327 (5), 311 (8), 267 (15), 265 (20), 207 (44), 179 (42), 147 (36), 117 (74), 75 (100), 73 (100^+), 43 (45); ^1H NMR ($CDCl_3$) δ 10.10 (s, CHO), δ_A 5.04 (m, H-6), δ_B 4.73 (m, H-3), δ_X 3.32 and δ_Y 3.26 (symmetrical m, H-4 and H-5) (refined coupling constants $^5J_{AB} = \pm 1.6$ or ± 1.3 Hz, $^3J_{AX} = +2.3$ or $+1.0$ Hz, $^4J_{AY} = -1.0$ or -2.3 Hz, $^4J_{BX} = -1.0$ or -2.3 Hz, $^3J_{BY} = +2.3$ or $+1.0$ Hz, $^3J_{XY} = \pm 3.6$ or ± 3.6 Hz), 5.35 and 4.73 (each 1 H, d, J = 13 Hz, CH_2OAc), 2.08 (s, $OCOCH_3$), 0.91 and 0.86 (s, 2 $SiC(CH_3)_3$), 0.20 and 0.10 (s, 9 H and 3 H, 2 $Si(CH_3)_2$). Anal. Calcd for $C_{22}H_{40}O_6Si_2$: C, 57.9; H, 8.43. Found: C, 58.2; H, 8.98.

***meso*-Dimethyl *r*-3,*c*-6-Bis[(*tert*-butyldimethylsilyl)oxy]-*t*-4,5-epoxycyclohex-1-ene-1,2-dicarboxylate (12a). Method a.** The cyclohexadiene **11** (46 mg), molybdenum hexacarbonyl (5 mg), 4,4'-thiobis(6-*tert*-butyl-3-methylphenol) (0.5 mg) and *tert*-butyl hydroperoxide (60 mg) in benzene (5 mL) were heated under reflux for 8 h. The mixture was concentrated under reduced pressure and subjected to preparative TLC on neutral alumina in ether/petroleum ether (1:2) to give the epoxide **12a** (10 mg, 21%) and dimethyl 3-[(*tert*-butyldimethylsilyl)oxy]-phthalate (12 mg, 25%).

Method b. The cyclohexadiene **11** (76 mg), *p*-nitroperoxybenzoic acid (60 mg), and 4,4'-thiobis(6-*tert*-butyl-3-methylphenol) (2 mg) in chloroform (10 mL) were heated under reflux for 5 days. The mixture was cooled to 0 °C and filtered, and the precipitate was washed with cold chloroform. The filtrate and the washings were concentrated under reduced pressure and subjected to preparative TLC on neutral alumina in ether/petroleum ether (1:2) to give the epoxide **12a** (17 mg, 22%).

Method c. The cyclohexadiene **11** (100 mg), *o*-nitroperoxybenzoic acid (120 mg), and 4,4'-thiobis(6-*tert*-butyl-3-methylphenol) (2 mg) in chloroform (10 mL) were heated under reflux for 3 days. The mixture was cooled to 0 °C and filtered, and the precipitate was washed with cold chloroform. The filtrate and the washings were concentrated under reduced pressure and subjected to preparative TLC on silica gel in ether/petroleum ether (1:2) to give the epoxide **12a** (15 mg, 14%) and dimethyl 3,6-bis[(*tert*-butyldimethylsilyl)oxy]phthalate (**13**) (24 mg, 25%). The epoxide **12a** was a colorless oil: IR (neat) 1730 cm^{-1} (CO_2CH_3); MS, m/z 457.2081 ($M^+ - CH_3$, calcd for $C_{21}H_{37}O_7Si_2$ m/z 457.2077); MS, m/z (relative intensity) 457 (3.5), 417 (14), 416 (30), 415 (100), 399 (7), 397 (11), 267 (10), 127 (16), 89 (27), 75 (24), 73 (53); ^1H NMR ($CHCl_3$) δ 4.65 (t, J = 1.5 Hz, H-3 and H-6), 3.28 (t, J = 1.5 Hz, H-4 and H-5) ($^3J_{3,4} = {}^4J_{3,5} = \pm 1.5$ Hz, $^5J_{3,6} = {}^3J_{4,5}$ unknown but the same magnitude and sign), 3.76 (s, 2 CO_2CH_3), 0.89 (s, 2 $SiC(CH_3)_3$), 0.16 and 0.10 (s, 2 $Si(CH_3)_2$). Anal. Calcd for $C_{22}H_{40}O_7Si_2$: C, 55.9; H, 8.53. Found: C, 56.3; H, 8.55.

(±)-(4*S,5*S**)-2,5-Bis[(*tert*-butyldimethylsilyl)oxy]-4-hydroxy-6-methylenecyclohex-2-en-1-one (14).** The aldehyde **5e** (440 mg), *o*-nitroperoxybenzoic acid (550 mg), and 4,4'-thiobis(6-*tert*-butyl-3-methylphenol) (4 mg) in chloroform (50 mL) were heated under reflux for 4 h. The mixture was cooled to 0 °C and filtered, and the residue was washed with cold chloroform. The filtrate and the washings were eluted through a short column of Florisil with ether. The eluant was concentrated under reduced pressure and subjected to preparative TLC, first on silica gel in ether/petroleum ether (1:2) and second on neutral alumina in ether/petroleum ether (1:3), to give the epoxide **2** (10 mg, 2%) and the dienone **14** (50 mg, 13%): MS, m/z 384.2151 (M^+, calcd for $C_{19}H_{36}O_4Si_2$ m/z 384.2152); UV max (hexane) 279 nm (ϵ 1930), 244 (sh, 1300); IR ($CHCl_3$) 3700–3200 (OH), 1680 (CO), 1630 cm^{-1} (C=C); MS, m/z (relative intensity) 384 (1), 369 (5), 227 (100), 196 (4), 195 (9), 167 (11), 75 (22), 73 (57); ^1H NMR ($CHCl_3$) δ 6.08 and 5.65 (m, 2 H and 1 H, H-3 and C=CH_2), 4.34 (m, H-4 and H-5), 2.64–2.28 (m, exchanged in D_2O, OH), 0.96 and 0.94 (s, 2 $SiC(CH_3)_3$), 0.19, 0.18, 0.16, and 0.12 (s, 2 $Si(CH_3)_2$). Irradiation at δ 4.34 reduced the signal at δ 5.65 to a doublet and the multiplet centered at δ 6.08 to a doublet at δ 6.11 (1 H) and a singlet at δ 6.06 (1 H). Irradiation at δ 5.65 or 6.08 reduced the multiplet at δ 4.34 into a simpler multiplet. ^1H NMR [$CDCl_3$ + Eu(fod)$_3$] δ 6.90 (d, $^3J_{3,4}$ = 2.7 Hz, H-3), 6.53 and 5.99 ($^2J_{AB}$ = 2 Hz, $^4J_{1',5}$ = 2 Hz, C=CH_2), 4.80–4.62 (m, $^3J_{4,3}$ = 2.7 Hz, $^3J_{4,5}$ = 7.5 Hz, H-4), 4.46–4.30 (m, $^3J_{5,4}$ = 7.5 Hz, $^4J_{5,1'}$ =2 Hz, H-5), 1.06 and 0.99 (s, 2 $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 189.86 (s, CO), 152.72 and 148.95 (s, C-2 and C-6), 131.30 (d, C-3), 125.19 (t, C=CH_2), 82.07 and 76.75 (d, C-4 and C-5), 30.26 (q, 2 $SiC(CH_3)_3$), 22.86 (s, 2 $SiC(CH_3)_3$), 4.76 (q, 2 $Si(CH_3)_2$). Anal. Calcd for $C_{19}H_{36}O_4Si_2$: C, 59.3; H, 9.43. Found: C, 59.7; H, 9.26.

Dimethyl 3-[(*tert*-Butyldimethylsilyl)oxy]phthalate. The phthalate byproduct obtained from the preparation of the epoxide **12a** by method a was vacuum distilled (bp 160 °C (0.001 mm)) to give a pale yellow liquid: UV max (hexane) 292.3 nm (ϵ 22600), 242 (sh, 47500); IR (neat) 1730 cm^{-1} (CO_2CH_3); MS, m/z 267.0691 ($M^+ - 57$, calcd for $C_{12}H_{15}O_5Si$ m/z 267.0688); MS, m/z (relative intensity) 309 (5), 293 (12), 267 (100), 237 (3), 235 (2), 75 (1.5), 73 (7), m* 210.4 (267 → 237), 206.8 (267 → 235); ^1H NMR ($CDCl_3$) δ_A 7.57, δ_B 7.28 and δ_C 7.01 ($^3J_{AB}$ = 7.7 Hz, $^3J_{BC}$ = 8.0 Hz, $^4J_{AC}$ = 1.2 Hz, H-4, H-5, and H-6), 3.92 and 3.88 (s, 2 CO_2CH_3), 0.98 (s, $SiC(CH_3)_3$), 0.20 (s, $Si(CH_3)_2$). Anal. Calcd for $C_{16}H_{24}O_5Si$: C, 59.2; H, 7.46. Found: C, 58.9; H, 7.54.

Dimethyl 3,6-Bis[(*tert*-butyldimethylsilyl)oxy]phthalate (13). The phthalate byproduct from the preparation of the epoxide **12a** by method c was isolated as a colorless waxy solid: MS, m/z 454.2199 (M^+, calcd for $C_{22}H_{38}O_6Si_2$ m/z 454.2207), 397.1506 ($M^+ - 57$, calcd for $C_{18}H_{29}O_6Si_2$ m/z 397.1502); UV max (hexane) 306.5 nm (ϵ 3500); IR (CCl_4) 1740 cm^{-1} (CO_2CH_3); MS, m/z (relative intensity) 454 (0.15), 453 (0.12), 439 (3), 423 (5), 397 (100), 325 (2.5), 89 (9), 75 (2), 73 (15), 59 (3); ^1H NMR ($CDCl_3$) δ 6.75 (s, H-4 and H-5), 3.76 (s, 2 CO_2CH_3), 0.95 (s, 2 $SiC(CH_3)_3$), 0.16 (s, 2 $Si(CH_3)_2$). Anal. Calcd for $C_{22}H_{38}O_6Si_2$: C, 58.1; H, 8.42. Found: C, 58.1; H, 8.24.

(±)-(1*R,4*S**,5*S**,6*R**)-3-(Acetoxymethyl)-1,4-bis[(*tert*-butyldimethylsilyl)oxy]-2-[(*Z*)-hept-1'-enyl]-5,6-epoxycyclohex-2-ene (10a).** To a suspension of finely powdered *n*-hexyltriphenylphosphonium bromide (300 mg) in anhydrous ether (25 mL) cooled to 0 °C was added *n*-butyllithium (1.7 M in hexane, 0.4 mL), and the resulting orange mixture was stirred at room temperature for 3 h. The stirred mixture was cooled to −78 °C, the aldehyde **2** (126 mg) was added, and the mixture was allowed to warm to room temperature. Ether (20 mL) was added and the mixture filtered. The filtrate was diluted with water (20 mL) and extracted with ether. The extract was washed with water until the aqueous phase became neutral, dried ($MgSO_4$), and then concentrated under reduced pressure to give a yellow oil. Purification by preparative TLC on silica gel in ether/petroleum ether (1:3) gave the olefin **10a** (90 mg, 70%): MS, m/z 524.3350 (M^+, calcd for $C_{28}H_{52}O_5Si_2$ m/z 524.3353); UV max (hexane) end absorption from 270 nm; IR (neat) 1745 cm^{-1} ($OCOCH_3$); MS, m/z (relative intensity) 524 (0.2), 509 (0.3), 506 (0.2), 495 (0.2), 467 (20), 465 (2), 451 (3.5), 449 (5), 407 (25), 393 (2), 389 (4), 335 (13), 328 (18), 305 (4.5), 304 (3), 293 (6), 275 (22), 259 (15), 191 (14), 149 (20), 147 (33), 117 (68), 75 (68), 73 (100); ^1H NMR ($CDCl_3$) δ 5.76 and 5.67 (m, H-1' and H-2', $^3J_{1',2'}$ = 11.5 Hz, $^3J_{2',3'}$ = 7 Hz), 4.67 and 4.47 (each 1 H, d, J = 12 Hz, CH_2OAc), 4.64 and 4.31 (br s, H-1 and H-4), 3.26 (br s, H-5 and H-6), 2.28–1.75 (m, CH=$CHCH_2$), 2.04 (s, $OCOCH_3$), 1.27 (m, 3 CH_2), 0.84–0.86 (2 $SiC(CH_3)_3$ and CH_2CH_3); ^1H NMR ($CHCl_3$) δ 0.14, 0.12, 0.10, and 0.08 (s, 2 $Si(CH_3)_2$). Anal. Calcd for $C_{28}H_{52}O_5Si_2$: C, 64.1; H, 9.99. Found: C, 64.3; H, 9.94.

(±)-(1*R,4*S**,5*S**,6*R**)-3-(Acetoxymethyl)-1,4-bis[(*tert*-butyldimethylsilyl)oxy]-2-[(*E*)-hept-1'-enyl]-5,6-epoxycyclohex-2-ene (1b).** A solution of the olefin **10a** (80 mg) in iodine/hexane (0.1 mg/mL, 25 mL) was cooled to 0 °C and irradiated with a Pyrex-filtered medium-pressure mercury lamp for 7 h. The solution was concentrated under reduced pressure and subjected to preparative TLC on silica gel in ether/petroleum ether (1:3) to give a mixture of *E* and *Z* isomers in the ratio of 3:1 as indicated by the ^1H NMR spectrum. Crystallization of the mixture from methanol/water (9:1) gave colorless needles of the olefin **1b** (40 mg, 50%): mp 60 °C; MS, m/z 524.3352 (M^+, calcd for $C_{28}H_{52}O_5Si_2$ m/z 524.3353); UV max 243 nm (ϵ 20650); IR (CCl_4) 1745 ($OCOCH_3$), 1650 cm^{-1} (C=C); MS, m/z (relative intensity) 524 (0.2), 509 (0.1), 506 (0.15), 495 (0.8), 467 (0.5), 464 (6), 451 (3.5), 449 (3), 446 (2), 415 (3), 407 (29), 393 (4), 379 (4), 335 (9), 305 (15), 293 (7), 275 (20), 247 (3), 219 (5), 205 (7), 201 (8), 191 (18), 149 (11), 147 (32), 117 (60), 75 (78), 73 (100), 59 (8); ^1H NMR ($CHCl_3$) δ 6.19 and 6.01 (m, H-1' and H-2', $^3J_{1',2'}$ = 15 Hz, $^3J_{2',3'}$ = 6 Hz), 4.83 and 4.58 (each 1 H, d, J = 12.2 Hz, CH_2OAc), 4.75 and 4.63 (br s, H-1 and H-4), 3.31 and 3.24 (br,

$^3J_{5,6}$ = 3.8 Hz, H-5 and H-6), 2.26–1.94 (m, CH=CHCH$_2$), 2.04 (s, OCOCH$_3$), 1.54–1.10 (m, 3 CH$_2$), 0.90–0.86 (2 SiC(CH$_3$)$_3$ and CH$_2$CH$_3$); ^{1}H NMR ($CHCl_3$) δ 0.16, 0.14, 0.13, and 0.06 (s, 2 Si(CH$_3$)$_2$). Anal. Calcd for $C_{28}H_{52}O_5Si_2$: C, 64.1; H, 9.9. Found: C, 64.1; H, 9.70.

***meso*-Dimethyl *r*-3,*c*-6-Dihydroxy-*t*-4,5-epoxycyclohex-1-ene-1,2-dicarboxylate (12b).** The epoxide **12a** (19 mg) in acetic acid/tetrahydrofuran/water (3:2:1, 6 mL) was heated under reflux for 2 days. Toluene (10 mL) was added, and the mixture was concentrated under reduced pressure and purified by preparative TLC on silica gel in dichloromethane/methanol (95:5) to give the diol **12b** (6 mg, 48%): mp 144–145 °C sublimation; IR (neat) 3500–3200 (OH), 1730 cm^{-1} (CO_2CH_3); MS, *m/z* (relative intensity) 213 (100), 197 (47), 194 (87), 169 (96) 165 (85), 143 (99), 142 (60), 141 (85), 139 (85), 59 (91); ^{1}H NMR (CD_3OD) δ 4.72 (t, *J* = 1.5 Hz, H-3 and H-6), 3.38 (t, *J* = 1.5 Hz, H-4 and H-5) ($^3J_{3,4} = {}^4J_{4,6}$ = ±1.5 Hz, $^5J_{3,6} = {}^3J_{4,5}$ unknown, but the same sign and magnitude), 3.78 (s, 2 CO_2CH_3). Anal. Calcd for $C_{10}H_{12}O_7$: C, 49.2; H, 5.07. Found: C, 49.0; H, 5.07.

A monodesilylated alcohol, **12c** (3 mg, 19%), was also isolated: MS, *m/z* (relative intensity) 343 (3), 327 (6), 301 (100), 75 (62), 73 (25); ^{1}H NMR ($CHCl_3$) δ 4.85 (t, *J* = 1.5 Hz, H-3 and H-6), 3.27 (t, *J* = 1.5 Hz, H-4 and H-5) ($^3J_{3,4} = {}^4J_{4,6}$ = 1.5 Hz, $^5J_{3,6} = {}^3J_{4,5}$ unknown, but same magnitude and sign), 3.76 (s, 2 CO_2CH_3), 1.54 (br s, exchanged in D_2O, OH), 0.90 (s, SiC(CH$_3$)$_3$), 0.16 and 0.10 (s, Si(CH$_3$)$_2$).

(±)-(1*R,4*S**,5*R**,6*S**)-3-(Acetoxymethyl)-2-[(*Z*)-hept-1′-enyl]-5,6-epoxycyclohex-2-ene-1,4-diol (10b).** The olefin **10a** (8 mg) in acetic acid/tetrahydrofuran/water (3:2:1, 12 mL) was heated under reflux for 2 days. After azeotropic removal of the solvent with toluene, the residue was subjected to preparative TLC on silica gel in dichloromethane/methanol (97:3) to give the diol **10b** (2.5 mg, 57%): UV max (EtOH) end absorption from 270 nm; MS, *m/z* (relative intensity) 296 (5), 279 (10), 254 (5), 249 (10), 236 (45), 218 (37), 207 (47), 190 (20), 189 (25), 177 (33), 165 (85), 161 (40), 149 (50), 147 (100); ^{1}H NMR ($CDCl_3$) δ 5.89–5.78 (m, $^3J_{1',2'}$ = 11.5 Hz, H-1′ and H-2′), 4.71, 4.62, and 4.58 (br s, CH_2OAc, H-1 and H-4 and 2 OH), 3.46 (br s, H-5 and H-6), 2.09 (s, OCOCH$_3$), 1.92–1.52 (m, CH=CHCH$_2$), 1.25 (m, 3 CH$_2$), 0.88 (m, CH_2CH_3).

(±)-(1*R,4*S**,5*R**,6*S**)-2-[(*Z*)-Hept-1′-enyl]-3-(hydroxymethyl)-5,6-epoxycyclohex-2-ene-1,4-diol [(±)-*Z* Isomer of Eupenoxide] (10c).** A stirred solution of the diol **10b** (2.5 mg) in methanol (2 mL) was cooled to 0 °C and then saturated with ammonia. The mixture was stirred at room temperature overnight and then evaporated to dryness. Preparative TLC on silica gel in dichloromethane/methanol (93:7) gave the *Z* isomer **10c** of eupenoxide (2 mg, 90%): MS, *m/z* 254.1517 (M$^+$, calcd for $C_{14}H_{22}O_4$ 254.1518); UV max (EtOH) end absorption from 265 nm; MS, *m/z* (relative intensity) 254 (4), 236 (6), 223 (21), 207 (35), 189 (25), 177 (100), 165 (62), 149 (55), 147 (43), 137 (49), 133 (58), 123 (84), 107 (80), 91 (86); ^{1}H NMR ($CDCl_3$) 5.85–5.27 (m, $^3J_{1',2'}$ = 11.5 Hz, H-1′ and H-2′), 4.75, 4.47, 4.32, 4.18, and 3.82 (m, C^{1}H$_2$OH, H-1 and H-4), 3.44 (br s, H-5 and H-6), 1.95–1.92 (m, CH=CHCH$_2$, 3 OH), 1.26 (m, 3 CH$_2$), 0.89 (m, CH_2CH_3).

(±)-(1*R,4*S**,5*S**,6*R**)-1,4-Bis[(*tert*-butyldimethylsilyl)oxy]-2-[(*E*)-hept-1′-enyl]-3-(hydroxymethyl)-5,6-epoxycyclohex-2-ene (1c).** A stirred solution of the olefin **1b** (40 mg) in methanol (4 mL) was cooled to 0 °C and saturated with ammonia. The mixture was allowed to warm to room temperature, and stirring was continued overnight. Removal of the solvent under reduced pressure and preparative TLC on silica gel in ether/petroleum ether (1:3) gave the alcohol **1c** as a colorless oil (27 mg, 98% based on recovered starting material): UV max (hexane) 242.5 nm (ϵ 19 200); IR (neat) 3650–3100 (OH), 1650 cm^{-1} (C=C); MS, *m/z* 451.3066 (M$^+$ – CH_2OH, calcd for $C_{25}H_{47}O_3Si_2$ *m/z* 451.3064), 425.2542 (M$^+$ – C_4H_9, calcd for $C_{22}H_{41}O_4Si_2$ *m/z* 425.2543); MS, *m/z* (relative intensity) 482 (1.5), 467 (0.5), 464 (0.3), 451 (9), 425 (11), 407 (4.5), 397 (5), 395 (2), 333 (6), 320 (3), 305 (4), 293 (31), 265 (8), 263 (5), 179 (6), 177 (2), 173 (3), 149 (16), 147 (28), 75 (60), 73 (100); ^{1}H NMR ($CDCl_3$) δ 6.24 and 6.02 (m, H-1′ and H-2′, $^3J_{1',2'}$ = 15.5 Hz, $^3J_{2',3'}$ = 6 Hz), 4.79 and 4.69 (br s, H-1 and H-4), 4.26 and 4.18 ($^2J_{AB}$ = 12 Hz, CH_2OH), 3.31 and 3.24 (m, $^3J_{5,6}$ = 3.6 Hz, H-5 and H-6), 2.28–2.0 (m, CH=CHCH$_2$), 1.40–1.20 (m, exchanged in D_2O, OH), 1.5–1.1 (m, 3 CH$_2$), 0.91–0.86 (m, 2 SiC(CH$_3$)$_3$ and CH_2CH_3); ^{1}H NMR ($CHCl_3$) δ 0.21, 0.13, and 0.08 (s, 6 H, 3 H, 3 H, 2 Si(CH$_3$)$_2$). Anal. Calcd for $C_{26}H_{50}O_4Si_2$: C, 64.7; H, 10.4. Found: C, 64.5; H, 10.5.

(±)-(1*R,4*S**,5*R**,6*S**)-2-[(*E*)-Hept-1′-enyl]-3-(hydroxymethyl)-5,6-epoxycyclohex-2-ene-1,4-diol [(±)-Eupenoxide] (1a). Method a.** To a solution of the alcohol **1c** (34 mg) in acetic acid (8 mL) was added water (2 mL), and the mixture was stirred at 43 °C overnight. After azeotropic removal of the solvent with toluene, the residue was subjected to preparative TLC on silica gel in dichloromethane/methanol (93:7) to give (±)-eupenoxide acetate (**1d**) and (±)-eupenoxide (**1a**) (17 mg): MS, *m/z* 254.1514 (M$^+$, calcd for $C_{14}H_{22}O_4$ *m/z* 254.1518); UV max (EtOH) 240.7 nm; MS, *m/z* (relative intensity) 254 (27), 236 (70), 223 (15), 218 (14), 207 (8), 189 (22), 183 (42), 177 (30), 165 (92), 147 (65), 137 (67), 123 (86), 107 (65), 91 (100). A stirred solution of this product (4 mg) in methanol (4 mL) cooled to 0 °C was saturated with ammonia. The mixture was allowed to warm to room temperature, and stirring was continued overnight. The mixture was concentrated under reduced pressure, and the residue was subjected to preparative TLC on silica gel in dichloromethane/methanol (93:7) to give (±)-eupenoxide (2.5 mg); ^{1}H NMR (CD_3OD) except for signals due to approximately 5% impurities was superimposable with that of natural eupenoxide.

Method b. To the alcohol **1c** (35 mg) in tetrahydrofuran (6 mL) at 0 °C was added tetrabutylammonium fluoride in tetrahydrofuran (0.4 M, 0.6 mL). After 2 h at 0 °C the reaction was diluted with water (30 mL) and extracted with ether. The extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a pale yellow oil. Preparative TLC on silica gel in dichloromethane/methanol (10:1) gave (±)-eupenoxide (**1a**) (16 mg, 87%), identical by IR, MS, and ^{1}H NMR with natural eupenoxide.

Eupenoxide Monoacetate 1d. Treatment of natural eupenoxide (**1a**, 18 mg) with acetic acid (8 mL) and water (2 mL) as described above for the alcohol **1c** gave recovered eupenoxide (8 mg, 44%) and the monoacetate **1d** (2 mg, 10%): IR (CCl_4) 3600–3100 (OH), 1740 (OCOCH$_3$), 1670 cm^{-1} (C=C); MS, *m/z* (relative intensity) 296 (5), 278 (8), 249 (16), 236 (28), 218 (49), 207 (37), 190 (21), 189 (22), 177 (18), 165 (63), 161 (27), 147 (100), 119 (62); ^{1}H NMR (CD_3OD) δ 6.36 and 6.14 (m, H-1′ and H-2′, $^3J_{1',2'}$ = 16 Hz, $^3J_{2',3'}$ = 6 Hz), 4.90, 4.64, and 4.46 (br s, CH_2OAc, H-1 and H-4), 2.40–1.80 (m, CH=CHCH$_2$), 2.03 (s, OCOCH$_3$), 1.36 (m, 3 CH$_2$), 0.90 (t, CH_2CH_3); ^{1}H NMR (C_6D_6) 6.54–5.90 (m, H-1′ and H-2′), 4.72, 4.55, and 4.40–3.60 (m, CH_2OAc, H-1, H-4, and 2 OH), 3.36 (m, H-5 and H-6), 2.30–1.90 (m, CH=CHCH$_2$), 1.67 (s, OCOCH$_3$), 1.24 (m, 3 CH$_2$), 0.88 (t, CH_2CH_3).

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