(d, 1 H, J = 10Hz, H-7 or H-6).

Reaction of 5β,6β-Epoxycholest-7-en-3β-ol (12) with Water. 7-Dehydrocholesterol 5β,6β-oxide (**12**, 30 mg) was treated in the manner described above for **2b**. NMR of the crude material, which displayed no UV absorptions in the region of 200-400 nm, indicated the presence of only one component, a triol (**15**): mp 191-195 °C; $[\alpha]_D$ −20° (c 0.18, pyridine); NMR δ 0.66 (s, 3 H, C-18), 1.17 (s, 3 H, C-19), 2.76 (dt, 1 H, J = 4, 14, 14, Hz, H-1β), 3.46 (m, 1 H, H-3), 5.64 (d, 1 H, J = 10 Hz, H-6 or H-7), 5.88 (d, 1 H, J = 10 Hz, H-7 or H-6); MS, m/e (relative intensity) 400 (9), 382 (14), 364 (91), 349 (37), 287 (8), 251 (100), 197 (67); HRMS calcd ($M^+ - H_2O$) 400.3343, found 400.3328.

Reaction of Oxides 2b and 12 with Benzoic Acid. Thirty milligrams of each unsaturated oxide was dissolved in chloroform in separate tubes, benzoic acid (6 mg each) was added, and the reactions were followed by NMR. The α-oxide **2b** gave predominantly the 5α-hydroxy-6α-benzoate (**4c**) after recrystallization from benzene: mp 161–163 °C; NMR δ 0.61 (s, 3 H, C-18), 1.02 (s, 3 H, C-19), 3.93 (m, 1 H, $W_{1/2}$ = 22 Hz, H-3), 5.05 (br s, 1 H, $W_{1/2}$ = 6.5 Hz, H-6), 5.50 (br s, 1 H, $W_{1/2}$ = 6.5 Hz, H-7); MS, m/e (relative intensity) 486 (3), 471 (5), 400 (15), 382 (27), 364 (44), 349 (23), 251 (33), 197 (33), 122 (45), 105 (100). Reaction of the β-oxide **12** with benzoic acid gave exclusively **14**: $[\alpha]_D$ −56.8 (c 1.30, $CHCl_3$); NMR δ 0.59 (s, 3 H, C-18), 1.15 (s, 3 H, C-19), 4.09 (m, 1 H, $W_{1/2}$ = 8 Hz, H-3), 5.11 (br d, 1 H, J = 5.5 Hz, H-6), 5.42 (br d, 1 H, J = 5.5 Hz, H-7); MS, m/e (relative intensity) 504 (3), 486 (8), 471 (13), 400 (68), 382 (29), 364 (61), 287 (39), 122 (64), 105 (100); HRMS calcd ($M^+ - H_2O$) 504.3603, found 504.3567.

6β-[(2-Hydroxyethyl)thio]cholest-7-ene-3β,5α-diol (16). Sodium hydride (20 mg), washed with hexane and dried under nitrogen, was added to deuteriomethanol (1 mL). The α-oxide **2b** (30 mg) was then added, followed by a few drops of deuteriobenzene to aid in solubility. After the NMR spectrum was recorded, 2-mercaptoethanol (10 μL) was added and the spectrum was reobtained at various time intervals. At completion of the reaction, the mixture was dissolved in ether, and the organic phase was washed with water and dried over sodium sulfate to give the thioether **16** in quantitiative yield: mp 157–161 °C; NMR δ 0.59 (s, 3 H, C-18), 1.02 (s, 3 H, C-19), 2.77 (t, 2 H, J = 7 Hz, CH_2S-), 2.91 (m, 1 H, H-6), 3.73 (t, 2 H, J = 7 Hz, CH_2O-), 4.18 (m, 1 H, H-3), 5.30 (m, 1 H, H-7); MS, m/e (relative intensity) 460 (11), 442 (4), 427 (4), 415 (2), 397 (3), 383 (10), 365 (100); HRMS calcd ($M^+ - H_2O$) 460.3375, found 460.3416.

6α-[(2-Hydroxyethyl)thio]cholest-7-ene-3β,5β-diol (17). The β-oxide **12** is treated with 2-mercaptoethanol in the manner described above for the α-oxide **2b** to yield the thioether **17** in nearly quantitative yield: NMR δ 0.55 (s, 3 H, C-18), 0.95 (s, 3 H, C-19), 2.89 (m, 2 H, CH_2S-), 3.59 (br s, 1 H, $W_{1/2}$ = 8 Hz, H-6), 3.82 (m, 2 H, CH_2O-), 4.18 (br s, 1 H, $W_{1/2}$ = 7.5 Hz, H-3), 5.12 (br s, 1 H, $W_{1/2}$ = 6.5 Hz, H-7); MS, m/e (relative intensity) 460 (100), 442 (38), 427 (81), 415 (45), 397 (68), 383 (61), 365 (81); HRMS calcd ($M^+ - H_2O$) 460.3375, found 460.3459.

Registry No. **1b**, 434-16-2; **2b**, 95841-65-9; **3**, 95864-11-2; **4b**, 95841-66-0; **4c**, 63139-17-3; **5a**, 15361-40-7; **6**, 95841-67-1; **7**, 95841-68-2; **8**, 604-32-0; **9**, 26048-46-4; **10**, 95841-69-3; **11**, 95841-70-6; **12**, 95841-71-7; **13**, 4025-59-6; **14**, 95841-72-8; **15**, 95910-37-5; **16**, 95841-73-9; **17**, 95841-74-0; benzoic acid, 65-85-0; 2-mercaptoethanol, 60-24-2; cholesterol oxide oxidase, 55467-47-5.

Acyclic Stereocontrol through the Dianionic Claisen Rearrangement of β-Hydroxy Esters: Synthesis of (±)-Botryodiplodin

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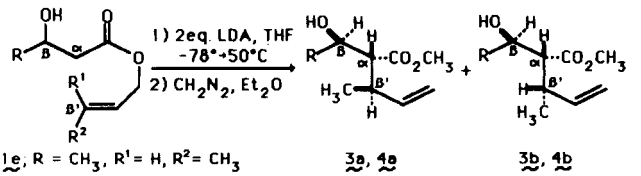
Dianionic Claisen rearrangements of (*E*)- and (*Z*)-butenyl β-hydroxy esters afford moderate stereoselection in the construction of highly functionalized acyclic systems. The reaction proceeds with remote stereocontrol and the resulting products display three contiguous chiral centers, C(α) and C(β′) stereocenters being established in the rearrangement (cf. **1z** → **3b**). Experiments are described which unambiguously establish that each dianionic Claisen proceeds with excellent diastereoface selectivity [C(α),C(β) stereocontrol] and moderate chair/boat selectivity [C(α),C(β′) stereocontrol]. Application of this Claisen protocol to a synthesis of the mycotoxin botryodiplodin is also described (**1z** → **8b**).

Development of methodology for achieving stereocontrol in the construction of acyclic systems is an important objective in current synthetic study.[1] In this regard, the regio- and stereochemically reliable Claisen rearrangement[2] has proven invaluable, particularly in self-immolative[3] transfer of chirality.[4] However, Claisen rearrangement protocols which utilize the asymmetry of a remote stereocenter to induce chirality at the prochiral termini of the rearranging 1,5-diene have received little attention.[5,6]

Scheme I



1e, R = CH_3, R^1 = H, R^2 = CH_3
1z, R = CH_3, R^1 = CH_3, R^2 = H
2e, R = $CH(CH_3)_2$ R^1 = H, R^2 = CH_3
2z, R = $CH(CH_3)_2$, R^1 = CH_3, R^2 = H

3a, **4a**
3a,b, R = CH_3
4a,b, R = $CH(CH_3)_2$

3b, **4b**

In a preliminary communication, we reported the discovery of a dianionic β-hydroxy ester Claisen rearrangement which uses remote stereocontrol to regulate the introduction of three contiguous chiral centers on an acyclic skeleton.[7] While our preliminary work established the

(1) Reviews: (a) Masamune, S.; Choy, W. *Adrichichimica Acta* **1982**, *15*, 47. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (d) Heathcock, C. H. *Science (Washington, D.C.)* **1981**, *214*, 395. (e) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.

(2) Reviews: (a) Murray, A. W. *Org. React. Mech.* **1980**, Chap, *14*, pp 517. (b) See ref 1e. (c) Bennett, G. B. *Synthesis* **1977**, 589. (d) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (e) Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1.

(3) Mislow, K. "Introduction to Stereochemistry"; W. A. Benjamin: New York, 1965; p 131.

(4) (a) For example, see the Stork-Raucher synthesis of (+)-15(*S*)-PGA_2 from L-erythrose.[4b] (b) Stork, G.; Raucher, S. *J. Am. Chem. Soc.* **1976**, *98*, 1583.

(5) Ziegler, F. E.; Thottathil, J. K. *Tetrahedron Lett.* **1982**, *23*, 3531.

(6) (a) Kurth, M. J.; Decker, O. H. W. *Tetrahedron Lett.* **1983**, *24*, 4535. (b) Kurth, M. J.; Decker, O. H. W. *J. Am. Chem. Soc.*, in press.

0022-3263/85/1950-1840$01.50/0

Table I. Stereoselectivity of Dianionic Claisen Rearrangements

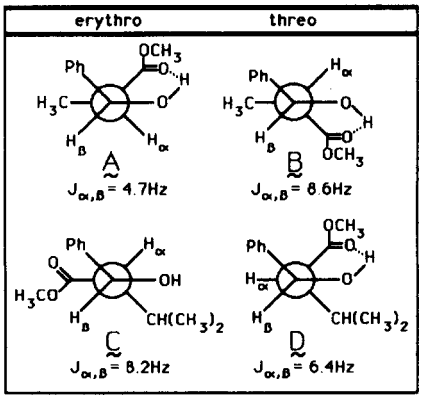
entry	substr.[a]	R	products	a/b ratio[b]	yield, %[c]	$J_{\alpha,\beta}$(Hz)
1	1e	CH_3	3a,3b	81/19	44	4.4
2	1z	CH_3	3a,3b	15/85	36	4.0
3	2e	$CH(CH_3)_2$	4a,4b	84/16	39	3.2
4	2z	$CH(CH_3)_2$	4a,4b	17/83	37	3.4

[a] Cyclization conditions: substrate in THF added to 2 equiv of LDA in THF at −78 °C/warm to 50 °C for 6 h. [b] Determined by ^{1}H NMR of the diazomethane reaction mixture. [c] Overall yield of cyclization/esterification product after medium-pressure liquid chromatography on silica gel.

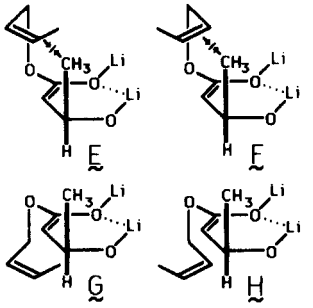
relative stereochemistry at C(α) and C(β), the C(β') stereochemistry was only tentatively assigned on the basis of a presumed chair transition-state preference. Herein we present the details of our previous work, establish unambiguously the stereochemistry at C(β'), expand the scope of our Claisen rearrangement to include (*Z*)-butenyl esters, and demonstrate the synthetic utility of this procedure in a stereocontrolled synthesis of the naturally occuring mycotoxin botryodiplodin.[8]

The starting materials for this work, synthetic (*Z*)-2-buten-1-ol[9] and spinning band distilled commercial (*E*)-2-buten-1-ol,[10] were judged by gas chromatography to be >99% stereochemically pure. Aldol condensation of their acetate esters with either acetaldehyde or isobutyraldehyde produced the required β-hydroxy butenyl esters **1e**, **1z**, **2e**, and **2z** in 78–84% chromatographed yield. The dianions of these esters were prepared by treating a THF solution of the ester with 2 equiv of lithium diisopropylamide at −78 °C. Warming the resulting homogeneous solution to 50 °C for 6 h effected the desired dianionic Claisen rearrangement[11] (Scheme I). After aqueous workup, the crude reaction mixtures were esterified with diazomethane. Purification by medium-pressure liquid chromatography on silica gel produced in each case an inseparable mixture of two β-hydroxy methyl esters (**3a** and **3b** or **4a** and **4b**). Both *E* and *Z* olefin isomers of the starting β-hydroxy butenyl esters (**1e,z** or **2e,z**) were shown to produce the same two rearrangement products. However, the relative ratio of these two products depended on the olefin geometry. These results are summarized in Table I.

The relative stereochemistry of these rearrangement products (**3a,b** or **4a,b**) was not obvious. Erythro–threo stereochemical assignments in β-hydroxy esters are often based on the magnitude of the vicinal coupling constant $J_{\alpha,\beta}$.[1b] This method of assessing relative configuration requires a conformational preference for the intramolecularly hydrogen-bonded rotamer of the C(α),C(β) bond as depicted in *erythro*-A or *threo*-B. However, as steric requirements of the substituents at C(α) and C(β) increase, a nonbonding gauche interaction between these substituents becomes the dominant conformation determining feature and rotamers *erythro*-C or *threo*-D predominate. Consequently, the magnitude of $J_{\alpha,\beta}$ in β-hydroxy esters hinges on the subtle conformational interplay between intramolecular hydrogen bonding and gauche interactions.



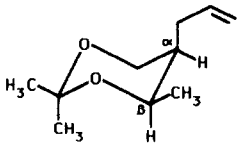
We were surprised to find that $J_{\alpha,\beta}$ for each β-hydroxy methyl ester obtained via our dianionic Claisen rearrangement fell within the "normal" erythro range of $J_{\alpha,\beta}$ = 3–6Hz (Table I). A C(α),C(β) erythro assignment for each Claisen rearrangement product requires that C,C bond formation occurs exclusively from the diastereoface which includes the C(β) methyl substituent as pictured in transition states E and F. In contrast, C,C bond formation



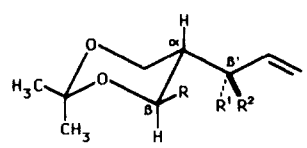
via transition states G and H occurs from the diastereoface which includes the C(β) hydrogen substituent, thus generating C(α),C(β) threo products. Dreiding model analysis of each transition state indicates that conformations G and H are sterically preferred over conformations E and F.

To clarify the apparent contradiction between our transition-state analysis and the observed magnitude of $J_{\alpha,\beta}$ for the rearrangement products, we developed a 1,3-dioxane based method for unambiguously establishing the erythro–threo stereochemistry of the β-hydroxy ester moiety. Relative to these acyclic β-hydroxy esters, the reduced conformational mobility of cyclic 1,3-dioxanes was anticipated to facilitate a $J_{\alpha,\beta}$ based assignment of C-(α),C(β) configuration.[12] To establish the magnitude of $J_{\alpha,\beta}$ in erythro–threo dioxanes, a 3:2 mixture of **5a** and **5b** was prepared starting from methyl acetoacetate. The relative configurations of these model 1,3-dioxanes were readily deduced from the magnitude of $J_{\alpha,\beta}$:[14] erythro-**5a** displaying a 2.0-Hz coupling and *threo*-**5b** displaying a 9.6-Hz coupling. Dioxanes **6a,b** and **7a,b** easily prepared from esters **3a,b** and **4a,b**, all have a 1,2-diaxial relationship between H and H_β as demonstrated by a $J_{\alpha,\beta}$ vicinal cou-

(7) Kurth, M. J.; Yu, C.-M. *Tetrahedron Lett.* **1984**, *25*, 5003.
(8) (a) Arsenault, G. P.; Althaus, J. R.; Divekar, P. V. *J. Chem. Soc. D* **1969**, 1414. (b) Moreau, S.; Lablache-Combier, A.; Biguet, J.; Foulon, C.; Delfosse, M. *J. Org. Chem.* **1982**, *47*, 2358.
(9) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(10) Commercial crotyl alcohol (Aldrich Chemical Co.); (8,600-6) was found to be a 95.5:4.5 *E*/*Z* mixture of isomers which were easily separable by spinning band distillation at ambient pressure [*E* (bp 121 °C); *Z* (bp 123 °C)].
(11) For examples of α-hydroxy ester dianion Claisen rearrangements see: (a) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729. (b) Ayer, D. J.; Cookson, R. C. *Tetrahedron Lett.* **1982**, *23*, 3419. (c) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941.
(12) (a) Seebach, D.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1983**, *105*, 7407. (b) Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*, 2301.
(13) Jackmann, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon Press: Oxford, 1969; p 288.
(14) (a) McCurry, P. M., Jr.; Abe, K. *J. Am. Chem. Soc.* **1973**, *95*, 5824. (b) McCurry, P. M., Jr.; Abe, K. *Tetrahedron Lett.* **1973**, 4103. (c) Wilson, S. R.; Meyers, R. S. *J. Org. Chem.* **1975**, *40*, 3309.



5a



5b; R = CH_3, R^1 = R^2 = H

6a; R = CH_3, R^1 = H, R^2 = CH_3

6b; R = CH_3, R^1 = CH_3, R^2 = H

7a; R = $CH(CH_3)_2$, R^1 = H, R^2 = CH_3

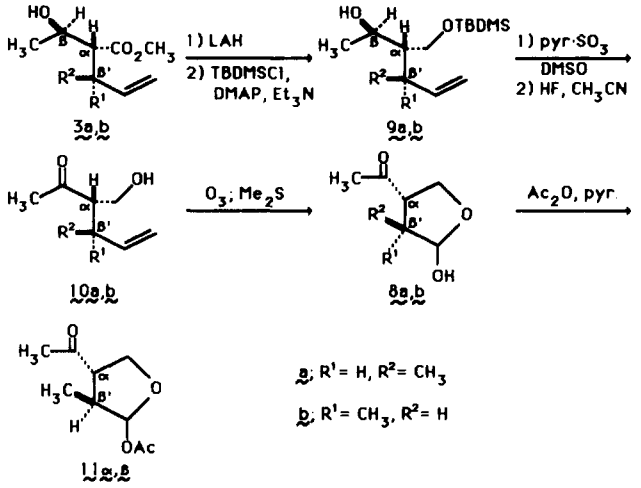
7b; R = $CH(CH_3)_2$, R^1 = CH_3, R^2 = H

pling constant of 9.9 Hz for each dioxane. Therefore, the dianionic Claisen rearrangements of β-hydroxy butenyl esters **1e,z** and **2e,z** yield to the limits of ^1H NMR detection only the C(α),C(β) threo products.

This study clearly demonstrates that the products of each dianionic Claisen rearrangement are derived from C(α),C(β) threo-selective transition states G and H. Since these two transition states are chair/boat conformational isomers, it follows that **3a** differs from **3b** (and **4a** from **4b**) only in the relative stereochemistry at C(β′). This conclusion is supported by the fact that both olefin isomers of the starting butenyl ester produce the same two rearrangement products. To verify these conclusions, we undertook a synthesis of botryodiplodin (**8b**) which employs our dianionic Claisen rearrangement as the key stereodetermining reaction. The structure of botryodiplodin has been determined by X-ray diffraction analysis[8b] and verified by total synthesis.[14] Therefore, a stereocontrolled synthesis of this mycotoxin, which exhibits both antibiotic and antileukemic properties,[15] would unambiguously establish the C(α),C(β′) relative stereochemistry of our Claisen products.

Lithium aluminum hydride reduction of an 81:19 mixture of esters **3a** and **3b** (from **1e**) produced a diol[16] which upon selective protection[17] gave an 84:16 mixture of **9a** and **9b** (Scheme II). Oxidation of this mixture of hexenols follows by desilylation[18] and ozonolysis with reductive workup produced a readily separable 85:15 mixture of 3-epibotryodiplodin (**8a**) and botryodiplodin (**8b**) in 32–35% overall yield from esters **3a** and **3b**. Repeating this sequence with a 15:85 mixture of starting esters **3a** and **3b** (from **1z**) produced **8a** and **8b** in a 26:74 ratio. These results unambiguously establish that **3a** has the threo C(α),C(β′) configuration while **3b** has the erythro C(α),C(β′) configuration.[19] As previously noted by McCurry and Abe,[14a] we find that β-hydroxy ketone **10**, our penultimate precursor to **8**, does not undergo C(α) epimerization under acidic conditions (aqueous HF in CH_3CN). The stereochemistry of **8b** was easily verified by comparison of its spectral data with that published for botryodiplodin.[14a]

Scheme II



Acetylation of **8a** produced the known acetate **11** (3:2 anomeric mixture), thus verifying the relative stereochemistry of 3-epibotryodiplodin.[14b]

These studies unambiguously define the relative stereochemistry of all three contiguous chiral centers in Claisen products **3a,b** and **4a,b**.[20] In each case, the observed products indicate that our dianionic Claisen rearrangement proceeds with excellent diastereoface selectivity [C(α),C(β) stereocontrol] and moderate chair/boat selectivity [C(α),C(β′) stereocontrol]. The resulting stereodefined products are suitably disposed for a variety of synthetic manipulations. Development of a more diastereoselective procedure and application of this reaction to enantioselective syntheses are in progress.

Experimental Section

General Data. Proton magnetic resonance spectra were taken on a Varian EM 390, Nicolet NT-360, or Nicolet NM-500. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Mass spectra were determined by Dr. Ed Larka on an AEI MS-3D instrument (electron impact, EI) at the Mass Spectrometry Service Facility, University of Minnesota, Minneapolis. Elemental analyses were performed by the University of California, Berkeley, analytical laboratories. MPLC refers to chromatography done at 10–50 psi through EM Lobar columns packed with LiChroprep Si60 (40–63 μm) with hexane/EtOAc eluent and monitored by refractive index dtection.

(*E*)-2-Butenyl 3-Hydroxybutanoate (1e). General Procedure A. To a solution of hexamethylsilazane (11.1 g, 69 mmol) in ether (70 mL) at room temperature was added *n*-BuLi (1.6 M in hexanes, 39 mL, 62.0 mmol) in a dropwise fashion via syringe. The solution was heated under reflux for 30 min and then concentrated under vacuo to give solid lithium bis(trimethylsilyl)-amide. Dry THF (70 mL) was added, and the solution was cooled to −78 °C. (*E*)-2-Butenyl acetate (5.92 g, 52 mmol) in dry THF (10 mL) was added dropwise over a period of 5 min, and the solution was stirred for an additional 15 min. Acetaldehyde (3.5 mL, 62 mmol) was then injected, and after 10 min the solution was quenched at −78 °C by injection of 20 mL of 10% hydrochloric acid. The solution was warmed to room temperature and extracted with ethyl acetate (2×). The combined organic phase was washed with water (1×) and brine (1×), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. MPLC (1:1 *n*-hexane/EtOAc) gave β-hydroxy ester **1e** (6.91 g, 84%) [^1H NMR (90 MHz, $CDCl_3$) δ 1.2 (d, 3 H, *J* = 7.5 Hz), 1.7 (d, 3 H, *J* = 6.9 Hz), 2.45 (d, 2 H, *J* = 7.6 Hz), 3.12 (s, 1 H, OH), 3.95–4.3 (m, 1 H), 4.52 (d, 2 H, *J* = 6 Hz), 5.4–6.0 (m, 2 H); IR (CCl_4) 3560, 3050,

(15) Recently Moulé et al. studied the effects of botryodiplodin on mammalian cells in culture[15b] and its mutagenic properties.[15c] (b) Moulé, Y.; Douce, C.; Moreau, S.; Daracq, N. *Chem. Biol. Interact.* **1981**, *37*, 155. (c) Moulé, Y.; Decloitre, D.; Hamon, G. *Environ. Mutagen.* **1981**, *3*, 287.

(16) (a) Attempts at the direct oxidation of this diol to **10** were only marginally successful. For example, upon treatment with silver carbonate on Celite,[16b] **10** was obtained in only 12% yield. The major product was 2-(1-hydroxyethyl)-3-methylpent-4-enal. (b) Fetizon, M.; Golfier, M.; Louis, J.-M. *J. Chem. Soc., Chem. Commun.* **1969**, 1102.

(17) Fráter, G.; Müller, U.; Gunther, W. *Tetrahedron* **1984**, *40*, 1269.

(18) Newton, R. F.; Reynolds, D. P. *Tetrahedron Lett.* **1979**, 3981.

(19) The reactions in Scheme II were performed on diastereomer mixtures since the **a**/**b** products proved inseparable by silica gel chromatography. However, in each reaction sequence the possibility of diastereomer crossover (**3a** → **8b** and **3b** → **8a**) can be rigorously ruled out by considering the starting (**3a**/**3b**) and finishing (**8a**/**8b**; easily separable by MPLC) diastereomer ratios relative to the overall chemical yield for each sequence (**3** → **8**).

(20) (a) Recently, Fujisawa et al. communicated a similar Claisen protocol.[20b] However, Fujisawa's method of establishing the relative stereochemistry of the three contiguous chiral centers and his stereochemical conclusions are very different from ours. (b) Fujisawa, T.; Tajima, K.; Ito, M.; Sato, T. *Chem. Lett.* **1984**, 1169.

3000, 2965, 2910, 1720, 1450, 1405, 1380, 1170, 970, 915, 720 cm^{-1}. Anal. Calcd for $C_8H_{14}O_3$: C, 60.72; H, 8.94. Found: C, 60.92; H, 8.96].

(*Z*)-2-Butenyl 3-Hydroxybutanoate (1z). β-Hydroxy ester **1z** was prepared according to general procedure A. In this way, (*Z*)-2-butenyl acetate (4.8 g, 42.1 mmol) and acetaldehyde were converted to β-hydroxy ester **1z** in 78% yield (5.21 g, 33 mmol) after purification by MPLC (*n*-hexane/EtOAc, 1:1) [^1H NMR (90 MHz, $CDCl_3$) δ 1.21 (d, 3 H, *J* = 6 Hz), 1.67 (d, 3 H, *J* = 6 Hz), 2.46 (d, 2 H, *J* = 6.7 Hz), 3.07 (s, 1 H, OH), 4.07–4.25 (m, 1 H), 4.67 (d, 2 H, *J* = 6.8 Hz), 5.35–5.90 (m, 2 H); IR (CCl_4) 3500, 3055, 2995, 2955, 1720, 1420, 1380, 1320, 1280, 1175, 970, 940 cm^{-1}; MS (EI), *m/e* (relative intensity) 158 (1.0, M^+), 143 (1.0), 130 (6.1), 125 (4.9), 114 (1.6), 105 (2.3), 103 (4.1), 96 (3.0), 89 (11.5), 87 (34.2), 72 (23.9), 71 (98.7), 69 (29.4), 60 (5.0), 57 (14.1), 55 (100); calcd for $C_8H_{14}O_3$, 158.0943; found, 158.0939].

(*E*)-2-Butenyl 3-Hydroxy-4-methylpentanoate (2e). β-Hydroxy ester **2e** was prepared according to general procedure A. In this way, (*E*)-butenyl acetate (2.94 g, 25 mmol) and isobutyraldehyde were converted to β-hydroxy ester **2e** in 79% yield (3.78 g, 20 mmol) after MPLC purification [^1H NMR (90 MHz, $CDCl_3$) δ 0.91 (d, 3 H, *J* = 7.5 Hz), 0.94 (d, 3 H, *J* = 6.3 Hz), 1.70 (m, 1 H), 1.71 (d, 3 H, *J* = 6 Hz), 2.46 (m, 2 H), 2.97 (d, OH, *J* = 4.5 Hz), 3.76 (m, 1 H), 4.53 (d, 2 H, *J* = 6 Hz), 5.4–6.0 (m, 2 H); IR (CCl_4) 3555, 3040, 2983, 2920, 2897, 1725, 1450, 1405, 1380, 1330, 1250, 1170, 1055, 967, 905 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.47; H, 9.76. Found: C, 64.49; H, 9.69].

(*Z*)-2-Butenyl 3-Hydroxy-4-methylpentenoate (2z). β-Hydroxy ester **2z** was prepared according to general procedure A. In this way, (*Z*)-butenyl acetate (1.92 g, 16.8 mmol) and isobutyraldehyde were converted to β-hydroxy ester **2z** in 78% yield (2.44 g, 13.1 mmol) after MPLC purification [^1H NMR (90 MHz, $CDCl_3$) δ 0.91 (d, 3 H, *J* = 7.5 Hz), 0.94 (d, 3 H, *J* = 6.7 Hz), 1.21 (m, 1 H), 1.70 (d, 3 H, *J* = 6 Hz), 2.38 (d, 1 H, *J* = 3.5 Hz), 2.46 (s, 1 H), 2.95 (s, 1 H, OH), 3.63–3.85 (m, 1 H), 3.66 (d, 2 H, *J* = 6.7 Hz), 5.38–6.90 (m, 2 H); IR (CCl_4) 3560, 3050, 2980, 2960, 2910, 1725, 1460, 1440, 1385, 1370, 1275, 1245, 1170, 1045, 960, 875, 735 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.47; H, 9.76. Found: C, 64.16; H, 9.95].

(2*R,3*R**,4*R**)-(±)-3-(Methoxycarbonyl)-4-methyl-5-hexen-2-ol (3a). General Procedure B.** To a solution of LDA [38.1 mmol in THF (35 mL)/hexane (24 mL)] at −78 °C was added (*Z*)-2-butenyl 3-hydroxybutanoate (**1z**, 2.74 g, 17.34 mmol) in dry THF (7 mL). After 30 min at −78 °C, the reaction mixture was allowed to stir for 6 h at room temperature and then warmed to 50 °C for an additional 6 h. The reaction mixture was then poured into 150 mL of 5% aqueous NaOH. This aqueous layer was washed with ether (2 × 20 mL), acidified with concentrated HCl at 0 °C, and extracted repeatedly with methylene chloride. The combined organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. An ethereal solution of the crude carboxylic acid product was esterified with diazomethane. MPLC (1:1 *n*-hexane/EtOAc) gave an inseparable mixture of rearranged β-hydroxy esters **3a** and **3b** (1.31 g, 44%) in a ratio judged by high field ^1H NMR to be 81:19, respectively [**3a**: ^1H NMR (360 MHz, $CDCl_3$) δ 1.1 (d, 3 H, *J* = 6.7 Hz), 1.21 (d, 3 H, *J* = 6.37 Hz), 2.25 (dd, 1 H, *J* = 4.42, 8.72 Hz), 2.64 (m, 1 H), 2.68 (d, OH, *J* = 9.13 Hz), 3.68 (s, 3 H), 3.97 (m, 1 H), 4.94–5.08 (m, 2 H), 5.64–5.76 (m, 2 H); IR (CCl_4) 3540, 3075, 2990, 2960, 2895, 1720, 1630, 1445, 1380, 1365, 1265, 1195, 1165, 1120, 1030, 995, 915 cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.75; H, 9.38. Found: C, 62.66; H, 9.43].

(2*R,3*R**,4*S**)-(±)-3-(Methoxycarbonyl)-4-methyl-5-hexen-2-ol (3b).** β-Hydroxy ester **1z** (2.21 g, 14.0 mmol) was rearranged and esterified as described in general procedure B. MPLC (1:1 *n*-hexane/EtOAc) gave an inseparable mixture of rearranged β-hydroxy esters **3b** and **3a** (871 mg, 5.06 mmol, 36%) in an 85:15 ratio, respectively [**3b**: ^1H NMR (360 MHz, $CDCl_3$) δ 1.01 (d, 3 H, *J* = 7.2 Hz), 1.19 (d, 3 H, *J* = 7.2 Hz), 2.23 (dd, 1 H, *J* = 9.6, 3.95 Hz), 2.69 (d, OH, *J* = 9.5 Hz), 2.72 (m, 1 H), 3.74 (s, 3 H), 3.96 (m, 1 H), 5.05–5.19 (m, 2 H), 5.63–5.73 (m, 1 H); IR (CCl_4) 3550, 3098, 3000, 2980, 2940, 2905, 1720, 1640, 1440, 1380, 1375, 1270, 1175, 1155, 1115, 1030, 995, 920, 660 cm^{-1}].

(3*R,4*R**,5*R**)-(±)-(Methoxycarbonyl)-2,5-dimethyl-6-hepten-3-ol (4a).** β-Hydroxy ester **2e** (1.82 g, 9.78 mmol) was rearranged and esterified as described in general procedure B. MPLC (1:1 *n*-hexane/EtOAc) gave an inseparable mixture of rearranged β-hydroxy esters **4a** and **4b** (765 mg, 3.83 mmol, 39%) in an 84:16 ratio, respectively [**4a**: ^1H NMR (360 MHz, $CDCl_3$) δ 0.89 (d, 3 H, *J* = 6.7 Hz), 1.0 (d, 3 H, *J* = 6.6 Hz), 1.1 (d, 3 H, *J* = 6.6 Hz), 1.51 (m, 1 H), 2.45 (dd, 1 H, *J* = 9.6, 3.2 Hz), 2.68 (m, 1 H), 2.77 (d, OH, *J* = 10.2 Hz), 3.35 (ddd, 1 H, *J* = 10.18, 8.8, 3.2 Hz), 3.66 (s, 3 H), 4.93–5.03 (m, 2 H), 5.65–5.76 (m, 1 H); IR (CCl_4) 3550, 3095, 2980, 2950, 2895, 1720, 1635, 1434, 1357, 1350, 1270, 1155, 1050, 990, 915, 675 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.95; H, 10.09. Found: C, 66.14; H, 9.99].

(3*R,4*R**,5*S**)-(±)-4-(Methoxycarbonyl)-2,5-dimethyl-6-hepten-3-ol (4b).** β-Hydroxy ester **2z** (1.06 g, 5.7 mmol) was rearranged and esterified as described in general procedure B. MPLC (1:1 *n*-hexane/EtOAc) gave an inseparable mixture of rearranged β-hydroxy esters **4b** and **4a** (422 mg, 2.11 mmol, 37%) in an 83:17 ratio, respectively [**4b**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, 3 H, *J* = 6.9 Hz), 0.99 (d, 3 H, *J* = 6.8 Hz), 1.01 (d, 3 H, *J* = 7.0 Hz), 1.49 (m, 1 H), 2.44 (dd, 1 H, *J* = 10.5, 3.4 Hz), 2.76 (m, 1 H), 2.78 (d, OH, *J* = 9.5 Hz), 3.31 (ddd, 1 H, *J* = 9.5, 9.5, 3.4 Hz), 3.72 (s, 3 H), 5.01–5.18 (m, 2 H), 5.61–5.17 (m, 1 H); IR (CCl_4) 3560, 3100, 2980, 2965, 2890, 1715, 1640, 1435, 1355, 1260, 1190, 1155, 995, 910, 725 cm^{-1}].

***cis*- and *trans*-(±)-2,2,4-Trimethyl-5-(2-propenyl)-1,3-dioxane (5a and 5b). General Procedure C.** The diol (1.01 g, 7.77 mmol) which was prepared by $LiAlH_4$ reduction of 2-allyl acetoacetate was dissolved in benzene (15 mL) along with 2,2-dimethoxypropane (1.2 g, 11.5 mmol) and *p*-toluenesulfonic acid monohydrate (5 mg). The resulting solution was heated at reflux under a Soxhlet extractor containing freshly conditioned 4-Å molecular sieves for 3 h. Anhydrous K_2CO_3 (15 mg) was added to the cooled reaction mixture which was stirred at room temperature for 4 h, filtered, and evaporated. The residue was taken up in ether, washed with water and brine, dried (Na_2SO_4), filtered and evaporated (1.25 g, 7.35 mmol, 94%). Preparative GC (5% SE-30, $^3/_8$ in. × 5 ft, 120 °C) gave an inseparable mixture of **5a** and **5b** in a ratio of 3:2, as determined by 500-MHz ^1H NMR [^1H NMR (500 MHz, $CDCl_3$): **5a**, δ 1.15 (d, 3 H, *J* = 6.5 Hz), 1.27 (m, 1 H), 1.39 (s, 3 H), 1.45 (s, 3 H), 2.24 (m, 1 H), 2.41 (m, 1 H), 3.78 (dd, 1 H, *J* = 12, 1 Hz), 3.95 (dd, 1 H, *J* = 12, 2 Hz), 4.21 (qd, 1 H, *J* = 6, 2 Hz), 5.01–5.12 (m, 2 H), 5.67–5.88 (m, 1 H); **5b**, δ 1.20 (d, 3 H, *J* = 6 Hz), 1.38 (s, 3 H), 1.49 (s, 3 H), 1.57 (m, 1 H), 1.81 (m, 1 H), 2.16 (m, 1 H), 3.55 (dd, 1 H, *J* = 11.5 Hz), 3.69 (qd, 1 H, *J* = 6, 9.6 Hz), 3.76 (dd, 1 H, *J* = 11.5, 5 Hz), 5.01–5.12 (m, 2 H), 5.67–5.74 (m, 1 H). IR (CCl_4); 3090, 2990, 2950, 2900, 1630, 1445, 1380, 1370, 1235, 1245, 1180, 1155, 1090, 1050, 1035, 995, 965, 915, 840 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.68. Found: C, 70.27; H, 10.84].

[4*S-[4α,5β(*S**)]]-(±)-2,2,4-Trimethyl-5-(1-methyl-2-propenyl)-1,3-dioxane (6a).** To a stirred suspension of $LiAlH_4$ (82 mg, 2.16 mmol) in ether (15 mL) at −78 °C was added a solution of β-hydroxy ester **3** (**3a**/**3b**, 81:19, 371 mg, 2.16 mmol) in THF (3 mL) over a period of 2–3 min. After an additional 10 min, the reaction mixture was allowed to warm at room temperature and stirred for 12 h. The reaction mixture was sequentially treated with water (1.0 mL) and 15% aqueous NaOH solution (1.0 mL). The resulting suspension was stirred vigorously for 15 min, dried (Na_2SO_4), and filtered. Removal of the solvent under reduced pressure gave the corresponding diol (271 mg, 1.88 mmol, 87%) [^1H NMR (90 MHz, $CDCl_3$) δ 1.10 (d, 3 H, *J* = 7.5 Hz), 1.28 (d, 3 H, *J* = 6.3 Hz), 2.44 (m, 1 H), 3.01 (br, 2 H, OH), 3.57–4.16 (m, 3 H), 4.91–5.09 (m, 2 H), 5.52–5.90 (m, 1 H); IR (CCl_4) 3380, 3095, 2990, 2950, 2910, 1635, 1450, 1415, 1375, 1105, 1050, 1000, 905, 715, 650 cm^{-1}]. This diol (251 mg, 1.74 mmol) was treated with 2,2-dimethoxypropane as described in general procedure C to give an inseparable mixture of acetonides **6a** and **6b** (291 mg, 1.58 mmol, 91%), in a ratio of 81:19 as determined by 500-MHz ^1H NMR [**6a**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.03 (d, 3 H, *J* = 7.0 Hz), 1.20 (d, 3 H, *J* = 6 Hz), 1.37 (s, 3 H), 1.40 (s, 3 H), 1.54 (m, 1 H), 2.40 (m, 1 H), 3.74 (dd, 1 H, *J* = 11.7, 11.7 Hz), 3.79 (dd, 1 H, *J* = 11.7, 5.0 Hz), 3.85 (qd, 1 H, *J* = 6.1, 9.9 Hz), 4.97–5.06 (m, 2 H), 5.69–5.81 (m, 1 H); IR (CCl_4) 3098, 2998, 2960, 2915, 1450, 1435, 1375, 1320, 1260, 1245, 1180, 1155, 1090, 1055, 1000, 980, 910, 845, 720, 670 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.68; H, 10.96. Found: C, 71.41; H, 10.94].

[4*S-[4α,5β(*R**)]]-(±)-2,2,4-Trimethyl-5-(1-methyl-2-propenyl)-1,3-dioxane (6b).** Reduction of β-hydroxy ester **3**

(**3a**/**3b**, 15:85, 382 mg, 2.22 mmol) with $LiAlH_4$ by the procedure described above afforded a diol (275 mg, 1.91 mmol, 86%) [^1H NMR (90 MHz, $CDCl_3$) δ 0.97 (d, 3 H, J = 7.5 Hz), 1.24 (d, 3 H, J = 6.0 Hz), 1.58 (m, 1 H), 2.51 (m, 1 H), 3.08 (br, 2 OH), 3.54–4.17 (m, 3 H), 4.90–5.13 (m, 2 H), 5.57–5.97 (m, 1 H); IR (CCl_4) 3450, 3090, 2985, 2945, 2910, 1420, 1380, 1350, 1260, 1200, 1145, 1120, 1045, 1000, 890, 820 cm^{-1}]. This diol (260 mg, 1.8 mmol) was treated with 2,2-dimethoxypropane as described in general procedure C to give an inseparable mixture of acetonides **6b** and **6a** (286 mg, 1.55 mmol, 86%) in a ratio of 85:15 as determined by 360-MHz ^1H NMR [**6b**: ^1H NMR (360 MHz, $CDCl_3$) δ 1.01 (d, 3 H, J = 7.2 Hz), 1.23 (d, 3 H, J = 6.4 Hz), 1.37 (s, 3 H), 1.43 (s, 3 H), 1.61 (m, 1 H), 2.35 (m, 1 H), 3.67–3.72 (m, 2 H), 3.92 (qd, 1 H, J = 9.9, 6.4 Hz), 4.98–5.04 (m, 2 H), 5.74–5.8 (m, 1 H); IR (CCl_4) 3095, 2995, 2960, 2910, 1450, 1435, 1375, 1260, 1240, 1155, 1090, 1005, 980, 910, 840, 670 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.68; H, 10.96. Found: C, 71.39; H, 11.07].

[4*S-[4α,5β(*S**)]]-(±)-2,2-Dimethyl-4-(1-methylethyl)-5-(1-methyl-2-propenyl)-1,3-dioxane (7a).** Reduction of β-hydroxy ester **4** (**4a**/**4b**, 84:16, 210 mg, 1.05 mmol) with $LiAlH_4$ by the procedure described above afforded a diol (152 mg, 0.88 mmol, 84%) [^1H NMR (90 MHz, $CDCl_3$) δ 0.81 (d, 3 H, J = 7.0 Hz), 0.93 (d, 3 H, J = 7.0 Hz), 1.02 (d, 3 H, J = 7.0 Hz), 1.51 (m, 1 H), 1.72 (m, 1 H), 2.45 (m, 1 H), 3.13 (br s, 2 OH), 3.45–4.15 (m, 3 H), 4.92–5.17 (m, 2 H), 5.57–5.97 (m, 1 H); IR (CCl_4) 3370, 3090, 2990, 2960, 2940, 2910, 1645, 1455, 1385, 1370, 1260, 1160, 1045, 1000, 915 cm^{-1}]. This diol (145 mg, 0.84 mmol) was treated with 2,2-dimethoxypropane as described in general procedure C to give an inseparable mixture of acetonides **7a** and **7b** (157 mg, 0.74 mmol, 88%) in a ratio of 84:16 as determined by 500-MHz ^1H NMR [^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, 3 H, J = 7.0 Hz), 0.93 (d, 3 H, J = 7.0 Hz), 1.02 (d, 3 H, J = 7.1 Hz), 1.33 (s, 3 H), 1.35 (s, 3 H), 1.74 (m, 1 H), 1.92 (m, 1 H), 2.36 (m, 1 H), 3.56 (dd, 1 H, J = 9.9, 3.3 Hz), 3.71 (dd, 1 H, J = 10.8, 10.8 Hz), 3.78 (dd, 1 H, J = 10.8, 5.8 Hz), 5.01–5.03 (m, 2 H), 5.74–5.79 (m, 1 H); IR (CCl_4) 3090, 2985, 2960, 2935, 2895, 1410, 1380, 1370, 1260, 1230, 1200, 1180, 1150, 1075, 1005, 915, 875 cm^{-1}. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.52; H, 11.41. Found: C, 73.52; H, 11.53].

(2*R,3*S**,4*R**)-(±)-3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4-methyl-5-hexen-2-ol (9a).** The diol (476 mg, 3.3 mmol) obtained by $LiAlH_4$ reduction of **3** (**3a**/**3b**, 81:19) was added slowly to a CH_2Cl_2 (10 mL) solution of *tert*-butyldimethylchlorosilane (550 mg, 3.6 mmol), triethylamine (0.51 mL, 3.6 mmol), and 4-(dimethylamino)pyridine (17 mg, 0.14 mmol) at room temperature. After 12 h, the reaction mixture was heated to reflux for 1 h, cooled, washed with water (1×) and saturated ammonium chloride (1×), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. MPLC (84:15 *n*-hexane/EtOAc) gave an inseparable mixture of alcohols **9a** and **9b** (656 mg, 2.5 mmol, 77%) [**9a**: ^1H NMR (90 MHz, $CDCl_3$) δ 0.10 (s, 6 H), 0.93 (s, 9 H), 1.08 (d, 3 H, J = 6.9 Hz), 1.25 (d, 3 H, J = 7.0 Hz), 1.54 (m, 1 H), 2.57 (m, 1 H), 3.55 (d, OH, J = 8 Hz), 3.67–4.03 (m, 3 H), 4.89–5.06 (m, 2 H), 5.47–5.85 (m, 1 H); IR (CCl_4) 3540, 3095, 2997, 2965, 2910, 2890, 1637, 1465, 1410, 1390, 1380, 1370, 1255, 1080, 1035, 965, 910, 840, 760, 670 cm^{-1}. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.11; H, 11.62. Found: C, 65.29; H, 11.88].

(2*R,3*S**,4*S**)-(±)-3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4-methyl-5-hexen-2-ol (9b).** The primary hydroxyl of the diol (260 mg, 1.8 mmol) obtained by $LiAlH_4$ reduction of **3** (**3a**/**3b**, 15:85) was selectively protected as described above for **9a**. MPLC (85:15 *n*-hexane/ethyl acetate) gave an inseparable mixture of alcohols **9b** and **9a** (355 mg, 1.37 mmol, 76%) [**9b**: ^1H NMR (90 MHz) δ 0.1 (s, 6 H), 0.91 (s, 9 H), 0.98 (d, 3 H, J = 6.8 Hz), 1.23 (d, 3 H, J = 7.0 Hz), 1.57 (m, 1 H), 2.51 (m, 1 H), 3.61 (br d, OH), 3.82–4.03 (m, 3 H), 4.93–5.05 (m, 2 H), 5.62–6.05 (m, 1 H); IR (CCl_4) 3550, 3095, 2995, 2970, 2910, 2890, 1640, 1460, 1380, 1370, 1255, 1080, 965, 840 cm^{-1}. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.11; H, 11.62. Found: C, 65.16; H, 11.77].

(3*S,4*R**)-(±)-3-(Hydroxymethyl)-4-methyl-5-hexen-2-one (10a).** Sulfur trioxide pyridine complex (890 mg, 5.6 mmol) in Me_2SO (3.5 mL, 49.3 mmol) was added in one-portion to a room-temperature Me_2SO (3.5 mL, 49.3 mmol) solution of trimethylamine (1.4 mL, 10 mmol) and protected alcohol **9** (84:16 **9a**/**9b**, 360 mg, 1.39 mmol). After 4 h, water was added and the mixture extracted with ether (3×). The combined organic layers were washed with 10% HCl (1×), water (1×), and brine (2×) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. MPLC (85:15 *n*-hexane/EtOAc) gave a mixture of β-siloxy ketones (84:16 erythro/threo, 308 mg, 1.2 mmol, 86%) [^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (s, 6 H), 0.92 (s, 9 H), 0.97 (d, 3 H, J = 6 Hz), 2.20 (s, 3 H), 2.56 (m, 1 H), 2.58 (m, 1 H), 3.73 (d, 2 H, J = 6.8 Hz), 4.93–5.12 (m, 2 H), 5.48–5.87 (m, 1 H); IR (CCl_4) 3094, 2975, 2955, 2903, 2880, 1712, 1635, 1465, 1415, 1375, 1353, 1253, 1160, 1095, 1045, 990, 913, 835, 665 cm^{-1}]. This β-siloxy ketone (291 mg, 1.13 mmol) was dissolved in acetonitrile (10 mL) containing 48% aqueous hydrofluoric acid (0.55 mL). After 1 h at room temperature, chloroform and water were added and the layers separated. The organic layer was washed with water (1×) and brine (1×), then dried (Na_2SO_4), filtered, and concentrated under reduced presure to give β-hydroxy ketone **10** (84:16 **10a**/**10b**, 154 mg, 1.08 mmol, 96%) [**10a**: ^1H NMR (90 MHz, $CDCl_3$) δ 1.01 (d, 3 H, J = 6.8 Hz), 2.24 (s, 3 H), 2.46 (d, OH, J = 6 Hz), 2.53–2.74 (m, 2 H), 3.71–3.83 (m, 2 H), 4.95–5.13 (m, 2 H), 5.50–5.86 (m, 1 H); IR (CCl_4) 3480, 3105, 2990, 2985, 2965, 2940, 2905, 1705, 1640, 1455, 1415, 1380, 1355, 1160, 1050, 1045, 920 cm^{-1}].

(3*S,4*S**)-(±)-3-(Hydroxymethyl)-4-methyl-5-hexen-2-one (10b).** Protected alcohol **9** (75:25 **9b**/**9a**, 384 mg, 1.48 mmol) was oxidized by sulfur trioxide pyridine complex according to the procedure described above to give a mixture of β-siloxy ketones (75:25 threo/erythro, 331 mg, 1.27 mmol, 86%) [^1H NMR (90 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.91 (s, 9 H), 1.01 (d, 3 H, J = 6.8 Hz), 2.13 (s, 3 H), 2.33–2.76 (m, 2 H), 3.66–3.81 (m, 2 H), 4.88–5.07 (m, 1 H), 5.53–5.92 (m, 1 H); IR (CCl_4) 3097, 2980, 2950, 2880, 2900, 1710, 1635, 1460, 1415, 1380, 1345, 1250, 1085, 905, 835 cm^{-1}]. This β-siloxy ketone (301 mg, 1.17 mmol) was deprotected by HF as described above to give β-hydroxy ketone **10** (75:25 **10b**/**10a**, 166 mg, 1.17 mmol, ~100%) [**10b**: ^1H NMR (90 MHz, $CDCl_3$) δ 1.03 (d, 3 H, J = 6.8 Hz), 2.21 (s, 3 H), 1.36 (br, OH), 2.57–2.80 (m, 2 H), 3.66–3.90 (m, 2 H), 4.97–5.13 (m, 2 H), 5.62–5.98 (m, 1 H); IR (CCl_4) 3480, 3100, 2990, 2985, 2970, 2945, 2905, 1705, 1635, 1450, 1415, 1380, 1150, 1050, 920 cm^{-1}].

(±)-3-Epibotryodiplodin (8a). A solution of β-hydroxy ketone **10** (**10a**/**10b**, 84:16, 301 mg, 2.11 mmol) in methanol (2 mL) and dichloromethane (6 mL) was cooled to −78 °C and treated with ozone for 10 min. Dimethyl sulfide (0.3 mL, 4.1 mmol) and sodium bicarbonate (35 mg) were added, and the mixture was allowed to stir at room temperature overnight. Water (5 mL) was added and the mixture extracted with CH_2Cl_2 (2×), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **8a** and **8b** in a ratio of 85:15 as judged by 90-MHz ^1H NMR of crude products. MPLC (1:1 *n*-hexane/EtOAc) gave, in order of elution; **8a** (195 mg, 1.35 mmol, 64%) [^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, 3 H, 8 Hz), 2.20, 2.27 (s, 1 H, ca 1:4), 2.36, 2.42 (m, 1 H, ca 1:4), 2.90, 3.13 (m, 1 H), 3.91, 4.17, 4.28 (m, 3 H), 4.02 (br, OH), 5.03, 5.31 (s, d, 1 H); IR (CCl_4) 3420, 2980, 2950, 2900, 1710, 1440, 1380, 1360, 1230, 1180, 1150, 1080, 980, 920 cm^{-1}] and **8b** (34 mg, 0.24 mmol, 11%).

(±)-Botryodiplodin (8b). β-Hydroxy ketone **10** (**10b**/**10a**, 76:24, 80 mg, 0.56 mmol) was converted to **8b** and **8a** by ozonolysis as described above. MPLC (1:1 *n*-hexane/EtOAc) gave, in order of elution, **8a** (12 mg, 0.05 mmol, 15%) and **8b** (34 mg, 0.27 mmol, 42%) [**8b**: ^1H NMR (500 MHz, CCl_4) δ 0.83 (d, 3 H × $^4/_5$, J = 7.3 Hz, β-anomer), 1.02 (d, 3 H × $^1/_5$, J = 7.3 Hz, α-anomer), 2.15 (s, 3 H × $^4/_5$, β-anomer), 2.24 (s, 3 H × $^1/_5$, α-anomer), 2.35 (m, 1 H × $^1/_5$, α-anomer), 2.49 (m, 1 H × $^4/_5$, β-anomer), 2.91 (br s, 1 H), 3.26 (m, 1 H × $^1/_5$, α-anomer), 3.56 (q, 1 H, J = 7.5 Hz), 3.92 (t, 1 H, J = 8.0 Hz), 4.18 (t, 1 H, J = 8.0 Hz), 5.05 (s, 1 H); IR (CCl_4) 3405, 2990, 2950, 2910, 1715, 1345, 1175, 1095, 1065, 980, 905 cm^{-1}].

(±)-(2α,3β,4α)- and (±)-(2β,3β,4α)-2-Acetoxy-3-methyl-4-acetyltetrahydrofuran (11α and 11β). 3-Epibotryodiplodin (**8a**, 90 mg, 0.63 mmol), acetic anhydride (200 μL, 2.1 mmol), and dry pyridine (5 mL) were stirred at room temperature for 12 h. After concentration under reduced pressure, the mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ (1×) and water (1×), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. MPLC gave a mixture of anomeric acetate **11α** and **11β** (69 mg, 0.37 mmol, 59%) in a ratio of 3:2, respectively [^1H NMR (500 MHz, $CDCl_3$) **11α**, δ 1.22 (d, 3 H, J = 7.6 Hz), 2.07 (s, 3 H), 2.22 (s, 3 H), 2.66 (m, 1 H), 2.80 (m, 1 H), 4.18–4.25 (m, 2 H), 5.87 (s, 1 H), **11β**, δ 1.07 (d, 3 H, J = 6.3 Hz), 2.02 (s, 3 H), 2.22 (s, 3 H), 2.57 (m, 1 H), 3.10 (m, 1 H), 3.96 (t, 1 H, J = 9.0

Hz), 4.28 (t, 1 H, J = 9.0 Hz), 6.24 (d, 1 H, J = 4.9 Hz); IR (CCl_4) 2990, 2950, 2905, 1740, 1715, 1370, 1360, 1230, 1170, 1125, 1005, 945, 895 cm^{-1}].

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Registry No. (±)-**1e**, 95976-00-4; (±)-**1z**, 95976-01-5; (±)-**2e**, 95865-60-4; (±)-**2z**, 95865-61-5; (±)-**3a**, 95976-02-6; (±)-**3a** (acid), 95976-09-3; (±)-**3b**, 95976-03-7; (±)-**3b** (acid), 95976-14-0; (±)-**4a**, 95976-04-8; (±)-**4b**, 95976-05-9; (±)-**5a**, 95865-62-6; (±)-**5a** (diol), 95865-70-6; (±)-**5b**, 95865-63-7; (±)-**5b** (diol), 95865-75-1; (±)-**6a**, 95865-64-8; (±)-**6a** (diol), 95976-10-6; (±)-**6b**, 95865-65-9; (±)-**6b** (diol), 95976-11-7; (±)-**7a**, 95865-66-0; (±)-**7a** (diol), 95976-12-8; (±)-**7b**, 95865-67-1; (±)-**7b** (diol), 95976-13-9; **8**, 27098-03-9; (±)-**9a**, 95865-68-2; (±)-**9b**, 95976-06-0; (±)-**10a**, 95865-69-3; (±)-**10a** (TBDMS ether), 95865-72-8; (±)-**10b**, 51552-44-4; (±)-**10b** (TBDMS ether), 95865-73-9; (±)-**11a**, 95976-07-1; (±)-**11b**, 95976-08-2; (*E*)-$CH_3CH{=}CHCH_2OH$, 7204-29-7; (*Z*)-$CH_3CH{=}CHCH_2OH$, 7204-36-6; CH_3CHO, 75-07-0; $(CH_3)_2CHCHO$, 78-84-2; 2-(1-hydroxyethyl)-3-methylpent-4-enal, 95865-74-0; methyl 2-allylacetoacetate, 95865-71-7.

A Study of the Reaction of 2-Haloacyl Halides with Trialkyl Phosphites. Synthesis of (2-Substituted acyl)phosphonates[1]

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Reactions of triethyl and trimethyl phosphites with chloroacetyl chloride (1), which give phosphinylethenyl phosphates, formally 2:1 adducts, have been reinvestigated. From observed characteristics of the reactions, it has been deduced that a 2:1 adduct precursor forms before dealkylation occurs and that by hindering formation of the precursor, either by using a sterically bulky trialkyl phosphite or a dialkyl trimethylsilyl phosphite, (chloroacetyl)phosphonates may be obtained directly from 1. The effect of the nature of the 2-leaving group in 2-substituted acetyl chlorides on the formation of the phosphinylethenyl phosphate and/or the (2-substituted acetyl)phosphonate is also reported.

The reaction of phosphorus III nucleophiles bearing at least one alkoxy group with organic electrophiles is one of the oldest and best-known preparative methods in organophosphorus chemistry (the Michaelis–Arbuzov reaction).[2] Acyl halides function normally in this reaction, leading to acylphosphonates. In the case of chloroacetyl chloride, it has long been known that the reaction leads to a 2:1 product **3** (Scheme I), even when conducted with 1:1 stoichiometry.[3]

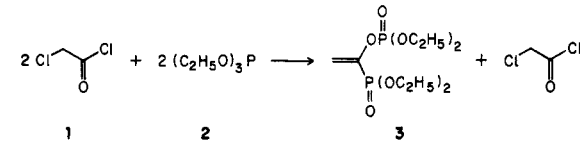
This has been interpreted to mean that the reactants initially react in the Michaelis–Arbuzov manner to give the (chloroacetyl)phosphonate **4**, with a subsequent Perkow[2] reaction of **4** forming **3** (Scheme II).[4,5] This scheme requires that k_2 be much faster that k_1, or only **4** would be formed with this stoichiometry.

We doubted this mechanistic picture, in particular finding it hard to accept the notion that **4** would be more reactive than acid chloride **1** toward phosphite **2**.

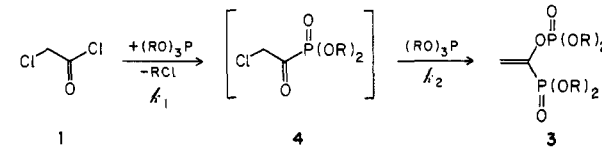
We have reinvestigated this reaction and have reached an understanding of the mechanism and structure-reactivity relationships which have allowed us to develop syntheses of compounds of type **4**.

Initially, the reaction of **1** with **2** in a 1:1 molar ratio was investigated at low temperature to see if the reaction could be halted at the supposed first step and **4** isolated. Even with addition of **2** to **1** at −78 °C and subsequent warmup, the 2:1 product **3** and none of **4** is produced. The reaction of trimethyl phosphite (**5**) and **1** at 10 °C evolved no chloromethane (bp −24 °C), suggesting for the first time that some type of 2:1 adduct forms even before the dialkylation in the putative first Michaelis–Arbuzov process

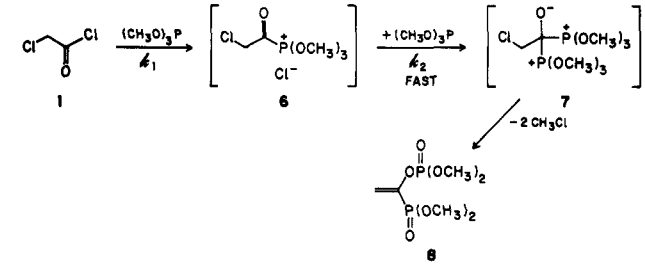
Scheme I



Scheme II



Scheme III



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