Acyclic Stereoselection in the Ortho Ester Claisen Rearrangement

G. William Daub,* James P. Edwards, Carol R. Okada, Jana Westran Allen, Claudia Tata Maxey, Matthew S. Wells, Alexandra S. Goldstein, Michael J. Dibley, Clarence J. Wang, Daniel P. Ostercamp, Steven Chung, Paula Shanklin Cunningham, and Martin A. Berliner

Department of Chemistry, Harvey Mudd College, Claremont, California 91711

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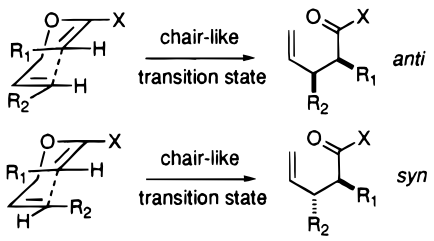
The ortho ester Claisen rearrangement of trisubstituted allylic alcohols exhibits significant levels of diastereoselection. In *E* allylic alcohols, a 1,3-diaxial interaction develops in the chairlike transition state leading to the *anti* isomer, rendering the reaction *syn* selective by a factor of 3−5 to 1. In *Z* allylic alcohols, the 1,3-diaxial interaction develops in the transition state leading to the *syn* isomer, generating an *anti:syn* selectivity of 6−15 to 1. The relative stereochemistry of the *syn* isomer was confirmed independently by the synthesis of the mycotoxin botryodiplodin.

Pericyclic processes have proven to be powerful synthetic tools for the preparation of stereochemically complex materials.[1] This has been especially true when the nature of the transition state for a particular process is well understood and the important nonbonded interactions have been defined. In recent years, work in our laboratory has centered on determining the nature of the nonbonded interactions in the ortho ester Claisen rearrangement and the effect of the substitution pattern of the allylic alcohol on the diastereoselectivity of the reaction.[2]

Acyclic stereoselection in the Claisen rearrangement has been thoroughly studied for some of the Claisen rearrangement variants.[1] The first important observations on this subject are due to Schmid.[3] His studies were modeled on the classic work of Doering and Roth,[4] and they helped to elucidate the preference for the chairlike transition state in acyclic Claisen processes. There are three crucial structural elements in determining the diastereoselectivity of a Claisen rearrangement: (1) the chair- or boatlike nature of the transition state, (2) the geometry about the vinylic double bond, and (3) the geometry about the allylic double bond. A change in any one of these elements leads to a reversal of any diastereoselectivity if the other two elements remain unchanged. This fact has made the Claisen rearrangement very versatile, since a Claisen rearrangement that favors one relative stereochemistry (*e.g. syn*)[5] will usually favor the alternative relative stereochemistry (*e.g. anti*) when the geometry about one of the olefin bonds is reversed, as illustrated in Scheme 1.[6]

By far the most studied and utilized variant of the Claisen rearrangement is the Ireland enolate Claisen rearrangement.[6] Countless examples can be found where the proper choice of enolization conditions allows for the selection of a particular vinyl double bond geometry. After silylation to give an *O*-silyl ketene acetal, subsequent rearrangement with high levels of diastereoselectivity can be realized. Because one can control the geometry of both double bonds in theory, the Ireland enolate Claisen provides the most flexible approach to acyclic stereoselection using the Claisen rearrangement.

Scheme 1



The intermediacy of *N*,*O*-ketene acetals also provides for acyclic stereoselection as illustrated by the work of Sucrow and Richter[7] and Bartlett and Hahne.[8] Sucrow and Richter demonstrated that the amide-acetal Claisen rearrangement of *E* allylic alcohols under thermodynamic control provides for high levels of diastereoselection in favor of the *anti* relative stereochemistry, while the *syn* relationship predominates when *Z* alcohols are employed. Bartlett and Hahne capitalized on the ynamine approach of Ficini[9] and showed that the reverse can be observed under kinetic conditions; the *anti* relationship predominates when a *Z* alcohol is used, and the *syn* relative stereochemistry results from the *E* allylic alcohol.[8]

The related ortho ester[10] and ketal Claisen rearrangements,[11] however, exhibit rather modest levels of acyclic stereoselection when the allylic double bond is disubstituted.[11,12] By introducing a substituent at the 2-position

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1997.

(1) Review articles on the Claisen rearrangement include: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (c) Bennett, G. B. *Synthesis* **1977**, 589.

(2) For a preliminary report on aspects of this study see: Daub, G. W.; Shanklin, P. L.; Tata, C. *J. Org. Chem.* **1986**, *51*, 3402.

(3) Hansen, H. J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959.

(4) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.

(5) All structures, while drawn as a single enantiomer, represent racemates. The *syn/anti* stereostructural notation proposed by Masamune is used in this paper: Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.

(6) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Ireland, R. E., Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155.

(7) Sucrow, W.; Richter, W. *Chem. Ber.* **1971**, *104*, 3679.

(8) Bartlett, P. A.; Hahne, W. F. *J. Org. Chem.* **1979**, *44*, 882.

(9) Ficini, J.; Barbara, C. *Tetrahedron Lett.* **1971**, *104*, 3679.

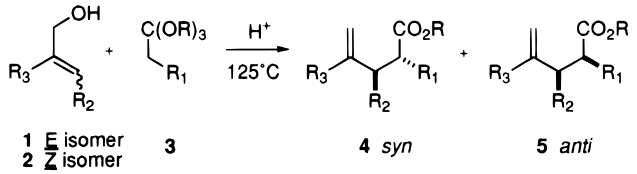
(10) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(11) (a) Daub, G. W.; Sanchez, M. G.; Cromer, R. A.; Gibson, L. G. *J. Org. Chem.* **1982**, *47*, 743. (b) Daub, G. W.; McCoy, M. A.; Sanchez, M. G.; Carter, J. S. *J. Org. Chem.* **1983**, *48*, 3876.

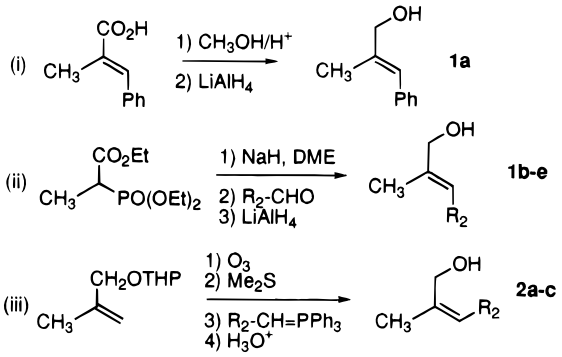
(12) (a) Stork, G.; Raucher, S. *J. Am. Chem. Soc.* **1976**, *98*, 1583. (b) Bolton, I. J.; Harrison, R. G.; Lythgoe, B. *J. Chem. Soc., C* **1971**, 2950. (c) Raucher, S.; Hwang, K. J.; McDonald, J. E. *Tetrahedron Lett.* **1979**, 3057. (d) Raucher, S.; McDonald, J. E.; Lawrence, R. F. *Tetrahedron Lett.* **1980**, 4335. (e) Daub, G. W.; Teramura, D. H.; Bryant, K. E.; Burch, M. T. *J. Org. Chem.* **1981**, *46*, 1485. (f) Daub, G. W.; Lunt, S. R. *Tetrahedron Lett.* **1983**, 4397.

S0022-3263(96)01425-9 CCC: $14.00

Scheme 2



Scheme 3

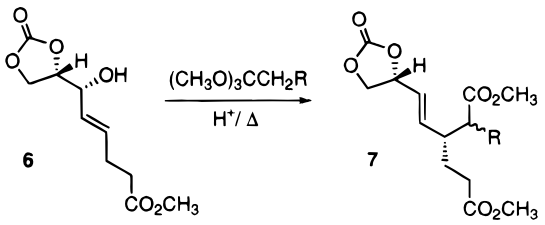


of the allylic alcohol to generate a trisubstituted double bond, an additional nonbonded interaction is created in the transition state that provides for significant levels of diastereoselection.[13−16] Thus, the ortho ester Claisen rearrangement (Scheme 2) of a trisubstituted allylic alcohol (**1** or **2**) and an ortho ester **3** leads to a mixture of the *syn* and *anti* diastereomeric products **4** and **5,** respectively, with significant degrees of diastereoselectivity.[2] This paper documents the observations leading to this conclusion and describes the experimental details associated with the project.

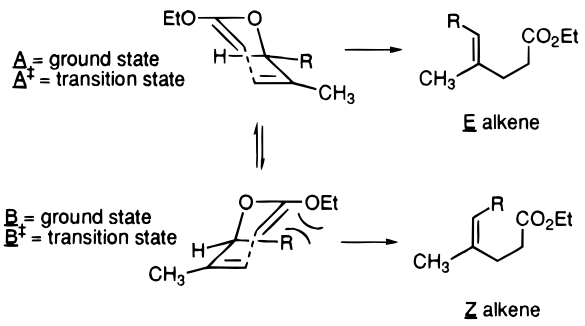
Synthesis of *E* and *Z* Trisubstituted Allylic Alcohols

A number of di- and trisubstituted allylic alcohols of known geometry were required for this project. While a few disubstituted allylic alcohols were available from commercial sources (*E*- and *Z*-**8**, R_2 = Pr), the trisubstituted alcohols needed to be prepared (Scheme 3). The *E* alcohols could be synthesized by the $LiAlH_4$ reduction of *E* trisubstituted acrylic esters. These esters were prepared by two different routes. First, a commerially available *E* trisubstituted acrylic acid could be esterified and reduced (route i), to give alcohol **1a** (R_2 = Ph, R_3 = Me). Alternatively, other *E* trisubstituted alcohols (**1b**−**e**, R_3 = Me, R_2 = Pr, CH_2CH_2Ph, CH_2OBn, $pC_6H_4OCH_3$) were synthesized by the Emmons−Wadsworth modification of the Wittig reaction and reduction (route ii).[17] The *Z* allylic alcohols (**2a**−**c**, R_3 = Me, R_2 = Ph, Pr, CH_2CH_2-Ph) were prepared using Still's modification of the Wittig reaction (route iii).[18]

Scheme 4



Scheme 5



Acyclic Stereoselection in Acid-Catalyzed Claisen Rearrangements

Prior to the investigations described in this paper, ortho ester Claisen rearrangements of α-substituted orthoacetates had exhibited little or no acyclic stereoselection.[12] A typical example produces *syn:anti* ratios of ≈1:1, as shown in Stork's classic synthesis of PGA_2 in Scheme 4.[12a] Other examples can be found in the work of Lythgoe,[12b] Raucher,[12c,d] and our own laboratories.[12e,f] Similarly, little acyclic stereoselection was observed in suitable examples of the ketal Claisen rearrangement.[11]

A potential solution to this problem is suggested in the work of Faulkner,[13] Johnson,[10] and Katzenellenbogen.[19] These reports show that the Claisen rearrangements of secondary allylic alcohols proceed with high *E* selectivity, a result that is ascribed to the development of nonbonded interactions in the transition state leading to the *Z* isomer. The chairlike transition state leading to the *Z* alkene (**B**‡) is destablilized relative to the transition state leading to the *E* alkene (**A**‡) by the 1,3 diaxiallike interaction between R and OEt (Scheme 5). Since conformational changes like **A** ⇌ **B** are rapid relative to the rate of [3,3] rearrangement, the *E* alkene predominates by a factor of 9:1[13] or even higher.[10,19]

Analogous 1,3-diaxial interactions are present in transition states **D**‡ and **F**‡ (Scheme 6), which suggests that *E* trisubstituted allylic alcohols would be expected to select for the *syn* relationship and that *Z* trisubstituted allylic alcohols would be expected to select for the *anti* relationship. To this end, a series of experiments[20] were conducted to determine whether (1) an *E* trisubstituted allylic alcohol exhibited more *syn* diastereoselectivity than a *trans* disubstituted allylic alcohol, (2) a *Z* trisubstituted allylic alcohol exhibited more *anti* diastereoselectivity than a *cis* disubstituted allylic alcohol, and (3) whether there is any evidence for the rapid interconversion of the *E* (ground states of **C**‡ or **E**‡) and *Z* (ground states of **D**‡ or **F**‡) ketene acetals relative to the rate of [3,3] rearrangement.

(13) Faulkner, D. J.; Peterson, M. R. *Tetrahedron Lett.* **1969**, 3243.
(14) The presence of such a 1,3-diaxial interaction in the transition state does not preclude such a pathway from competing, but it does demand that other pathways be sterically more demanding. In the present case, the competing pathway is sterically less demanding and predominates. See Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730.
(15) A similar interaction has been described by Parker, K. A.; Farmar, J. G. *Tetrahedron Lett.* **1985**, 3655.
(16) For examples where selectivity relative to a more distal center is induced by such an interaction, see: (a) White, J. D.; Amedio, J. C. *J. Org. Chem.* **1989**, *54*, 736. (b) Wovkulich, P. M.; Tang, P. C.; Chadha, N. K.; Batcho, A. D.; Barrish, J. C.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1989**, *111*, 2596.
(17) Mori, K; Matsui, M. *Tetrahedron* **1970**, *26*, 2801.
(18) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260.
(19) Katzenellenbogen, J. A.; Christy, K. J. *J. Org. Chem.* **1974**, *39*, 3315.
(20) The detection limits for capillary GC analysis were <±1%.

Scheme 6

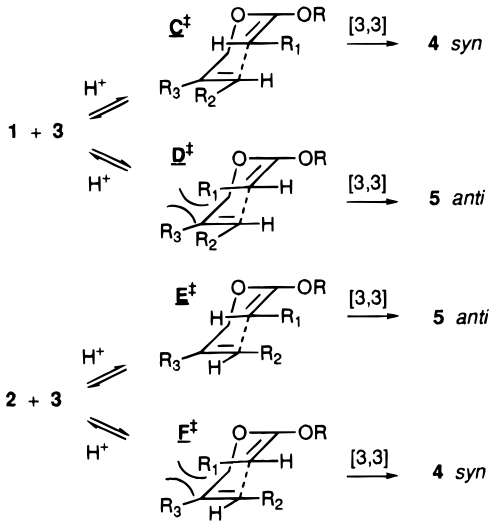
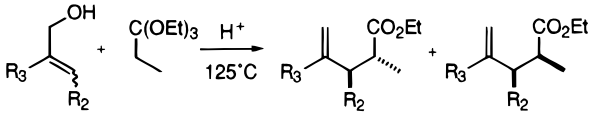


Table 1. Products of Ortho Ester Claisen Rearrangement as a Function of Double Bond Geometry



entry	alkene geometry	R_2	R_3	*syn:anti* ratio[a]	% yield
a	*trans*	Ph	H	60:40	72
b	*E*	Ph	Me	85:15	65
c	*trans*	Pr	H	62:38	49
d	*E*	Pr	Me	79:21	64
e	*cis*	Pr	H	24:76	41
f	*Z*	Pr	Me	9:91	53

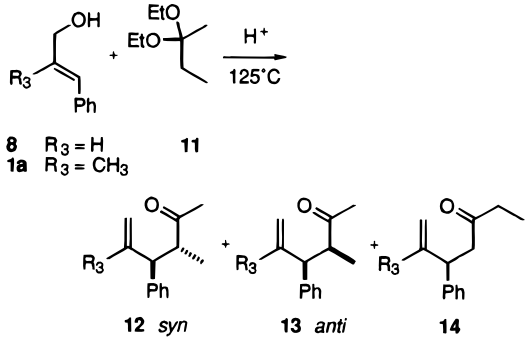
[a] Uncertainties are ±1%.

Table 1 summarizes the selectivities observed for some simple di- and trisubstituted allylic alcohols in both the *E* and *Z* series. Clearly, there is a substantial increase in *syn* selectivity for the *E* trisubstituted alcohol relative to the *trans* disubstituted alcohol and an enhanced *anti* selectivity when a *Z* trisubstituted alcohol is compared to a *cis* disubstituted alcohol. These observations are consistent with the proposition that the added 1,3-diaxial interaction in transition states **D**‡ and **F**‡ render these processes slow relative to the reactions proceeding through transition states **C**‡ and **E**‡.

It is more difficult to establish whether the *E* and *Z* ketene acetals interconvert rapidly on the time scale of the [3,3] reaction rate. Until that fact is adequately demonstrated, it will not be known for certain whether the selectivity reported in Table 1 represents differences in the free energies of the transition states (*e.g.* **C**‡ and **D**‡) or differences in the stabilities of the ground state *E* and *Z* ketene acetals. While the evidence below for the rapid interconversion of the *E* and *Z* ketene acetals in the ortho ester Claisen is only inferential, we have previously shown that the analogous interconversion of *E* and *Z* vinylic double bonds in the ketal Claisen rearrangement is more rapid than the rate of [3,3] rearrangement and that the Curtin−Hammett principle applies to the ketal Claisen rearrangement.[11b]

When one compares the increase in *syn:anti* selectivity in some ketal Claisen rearrangements (Table 2) and the

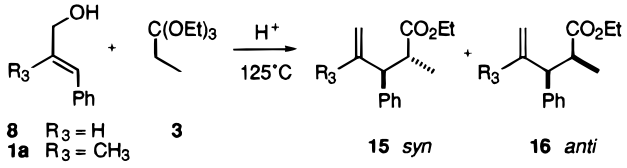
Table 2. *Syn:Anti* Selectivity for Ketal Claisen Rearrangement



R_3	ratio of **12**:**13**:**14**[a]	*syn:anti* ratio (**12**:**13**)[a]	% yield	$\Delta[G^{\ddagger}]$[b]
H	53:45:2	54:46	63	0.1
Me	79:17:4	82:18	78	1.2

[a] Uncertainties are ±1%. [b] In kcal/mol, calculated at 398 K: $\Delta[G^{\ddagger}] = RT \ln (syn/anti)$.

Table 3. *Syn:Anti* Selectivity for Ortho Ester Claisen Rearrangement



R_3	*syn:anti* ratio (**15**:**16**)[a]	% yield	$\Delta[G^{\ddagger}]$[b]
H	60:40	72	0.1
Me	85:15	65	1.2

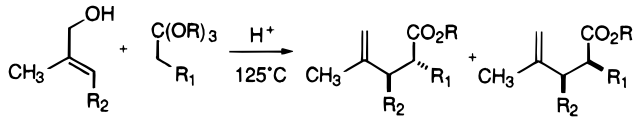
[a] Uncertainties are ±1%. [b] In kcal/mol, calculated at 398 K: $\Delta[G^{\ddagger}] = RT \ln (syn/anti)$.

corresponding ortho ester Claisen rearrangements (Table 3) upon addition of a methyl group at the 2-position of an *E* allylic alcohol, very similar increases in selectivity are exhibited. If one assumes that the Curtin−Hammett principle is operational in the ortho ester Claisen as it is in the ketal Claisen variation, one can calculate the difference in the free energies of the two transition states (one leading to the *syn* relationship, the other leading to the *anti*) for a given reaction. These are included in Tables 2 and 3 as $\Delta G^{\ddagger}$ and are calculated from the *syn:anti* product ratios at 398 K: $\Delta G^{\ddagger} = RT \ln (syn/anti)$. In both reaction examples, the increase in selectivity results from the addition of a single methyl group at the 2-position of the allylic alcohol, and the increase corresponds to an additional 1.1 kcal/mol separation between the relevant transition states. This suggests that, like the ketal Claisen rearrangement, the ortho ester Claisen variation operates under Curtin−Hammett control.

A complete accounting of the various ortho ester Claisen rearrangements of *E* and *Z* trisubstituted allylic alcohols that were examined is given in Table 4. A number of interesting points emerge from these results.

Z Alcohols Show Greater Relative Selectivity. The *Z* alcohols show better selectivity for the *anti* product than the *E* alcohols show for the *syn* product. This generalization means that the difference between the free energies of the two chairlike transition states (Scheme 7) is greater for *Z* alcohols (**21** and **22**) than for *E* alcohols (**19** and **20**). The higher energy transition state is always the one with the 1,3-diaxial interaction (**20** and **22**). The

Table 4. Summary of *Syn*:*Anti* Selectivity for Ortho Ester Claisen Rearrangement

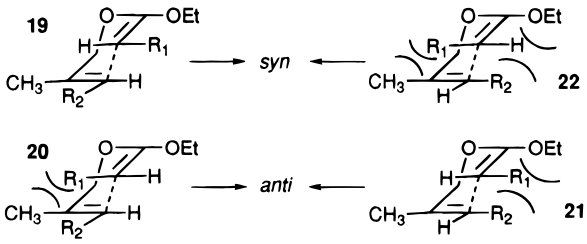


1 E isomer **2** Z isomer **3** **17** *syn* **18** *anti*

entry	R_1	R_2	R	*syn:anti* (*E* isomer)[a]	% yield	*syn:anti* (*Z* isomer)[a]	% yield
a	Me	Ph	Me	84:16	80	–	–
b	Me	Ph	Et	85:15	65	14:86	66
c	Et	Ph	Me	83:17	70	19:81	74
d	Pr	Ph	Me	82:18[b]	60	17:83[b]	41
e	Me	Pr	Et	79:21	64	9:91	53
f	Et	Pr	Me	77:23	68	10:90	68
g	Pr	Pr	Me	72:28	67	9:91	86
h	Me	CH_2CH_2Ph	Et	76:24	60	7:93	67
i	Et	CH_2CH_2Ph	Me	–	–	10:90	58
j	Pr	CH_2CH_2Ph	Me	–	–	8:92	85
k	Me	CH_2OBn	Et	83:17	70	6:94	60
l	Et	CH_2OBn	Me	78:22	61	7:93	67
m	Pr	CH_2OBn	Me	73:27	74	8:92	79
n	Me	*p*-$OMeC_6H_4$	Et	83:17	73[c] 62[d]	–	–
o	Et	*p*-$OMeC_6H_4$	Me	81:19	55	–	–

[a] Uncertainties are ±1%. [b] *Syn* and *anti* isomers did not resolve on GC. Ratio determined by integration of ^1H NMR spectrum at 200 MHz. [c] Acid catalyst was propionic acid. [d] Acid catalyst was mesitoic acid.

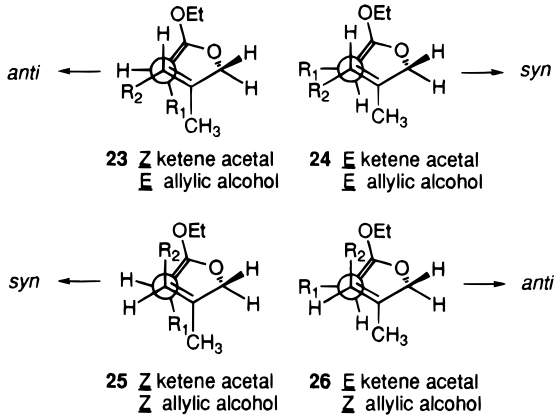
Scheme 7



source of this increased free energy difference is ascribed to the additional 1,3-diaxial interaction present in the transition states involving a *Z* allylic geometry (**21** and **22**). The second 1,3-diaxial interaction "butresses" the original interaction in **20**, leading to an even less stable and earlier transition state with less efficient bond formation. Hence, the free energy gap between transition states **21** and **22** is larger and the selectivity is greater.

Nature of Hybridization of Carbon Attached at R_2. The *syn* selectivity observed for *E* allylic alcohols is greater when the hybridization of the carbon attached at R_2 is sp^2. In contrast, the *anti* selectivity observed for *Z* allylic alcohols is greater when the hybridization of the carbon attached at R_2 is sp^3. Both of these observations are consistent with the increased steric demand of an sp^3 center over an sp^2 center. The chairlike transition state (Scheme 8) contains two sp^2 centers and four centers intermediate in hybridization between sp^2 and sp^3, so one would expect deviations from the classic chair conformation model of cyclohexane. Perrin and Faulkner's model reflects this fact. Models suggest that the newly-forming carbon–carbon single bond is not staggered in the classical sense, but, as structures **23**–**26** suggest, is approaching a "semieclipsed" conformation. If this is the case, then one would expect the $R_1\cdots R_2$ *gauche* interaction in transition state **23** to be somewhat less than the $R_1\cdots R_2$ *gauche* interaction in transition state **24**. Thus, changing the attachment of R_2 to a sterically more

Scheme 8



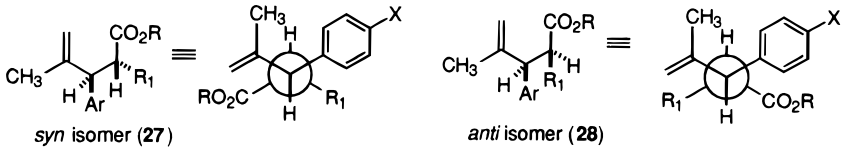
demanding sp^3 hybrid would narrow the free energy gap between transition states **23** and **24** and render the reaction less *syn* selective, in accord with the observations.

The reverse is observed for *Z* allylic alcohols. The $R_2\cdots OEt$ interaction is present in both transition states **25** and **26**. In transition state **25**, note that R_1 engages the CH_3 group in a 1,3-diaxiallike interaction, making this transition state higher in energy than transition state **26**. The $R_1\cdots R_2$ interaction in transition state **26** is expected to be very modest (probably less than a gauche interaction) due to the rather large dihedral angle between the $C-R_2$ and $C-R_1$ bonds. As a result, an increase in steric demand at R_2 makes both transitions states (**25** and **26**) earlier and slows both reactions. Evidently the effect is greater on transition state **25**, probably because the $R_2\cdots OEt$ 1,3-diaxial interaction magnifies the effect of the original $R_1\cdots CH_3$ diaxial interaction and makes carbon–carbon bond formation very inefficient.

Variation in Size of R_1 Has Little Effect. An increase in the bulk of R_1 does not increase the *syn* selectivity of reactions involving *E* alcohols, nor does it increase the *anti* selectivity for reactions involving *Z* alcohols, as one might predict from the analysis given above. In fact, there is a slight decrease in the *syn* selectivity for *E* alcohols. The increase in the steric bulk from methyl to ethyl to propyl may not be sufficient to produce large changes in the $R_1\cdots CH_3$ interaction (see **23** and **25**), or corresponding increases in the nonbonded interactions between R_1 and R_2 in the *syn* transition state (see $R_1\cdots R_2$ interaction in transition state **24**) may cancel out any increase in the 1,3-diaxial interaction generated by changing the size of R_1. The decrease in *syn* selectivity for *E* alcohols may be an indication that the $R_1\cdots R_2$ interaction in transition state **24** is of very real significance.

Enolization Processes Do Not Compete with Overall Reaction Rates. Enolization of the carbon α to the ester carbonyl is not rapid under the reaction conditions, as illustrated by two types of experiments. First, numerous reactions were monitored for changes in the *syn:anti* ratios as a function of reaction time. In all cases, the *syn:anti* ratios were invariant (± 1%) during the course of the reaction. Four additional control experiments were conducted, in which a single pair of racemates (Table 4, **17n**, **17o**, **18n**, and **18o**) were resubjected to the original reaction conditions. In all cases none of the alternative relative stereochemistry (**18n**, **18o**, **17n**, and **17o** respectively) could be detected

Table 5. Chemical Shift Data for Selected *Syn* and *Anti* Isomers



syn isomer (**27**) *anti* isomer (**28**)

entry	R_1	X	R	*syn* isomer: chemical shift (δ) of ester group (group)	*syn* isomer: chemical shift (δ) of α alkyl group (group)	*anti* isomer: chemical shift of ester group (group)	*anti* isomer: chemical shift (δ) of α alkyl group (group)
a	Me	H	Me	3.69 (CH_3)	0.96 (CH_3)	3.41 (CH_3)	1.24 (CH_3)
b	Me	H	Et	4.14 (CH_2)	0.96 (CH_3)	3.85 (CH_2)	1.24 (CH_3)
				1.25 (CH_3)		0.93 (CH_3)	
c	Et	H	Me	3.69 (CH_3)	0.79 (CH_3)	3.39 (CH_3)	0.93 (CH_3)
d	Me	*p*-OCH_3	Et	4.13 (CH_2)	0.93 (CH_3)	3.89 (CH_2)	1.22 (CH_3)
				1.23 (CH_3)		0.95 (CH_3)	
e	Et	*p*-OCH_3	Me	3.67 (CH_3)	0.77 (CH_3)	3.39 (CH_3)	0.89 (CH_3)

by capillary GC.[20] These observations are in contrast to some acid-catalyzed ketal Claisen rearrangements reported previously.[11,21]

The Nature of the Carboxylic Acid Catalyst Does Not Affect the Selectivity. Three different carboxylic acid catalysts, propionic acid, pivalic acid, and mesitoic acid, have been employed, and no differences in selectivity have been observed (±1%). This result is not surprising, but is worth noting nevertheless.

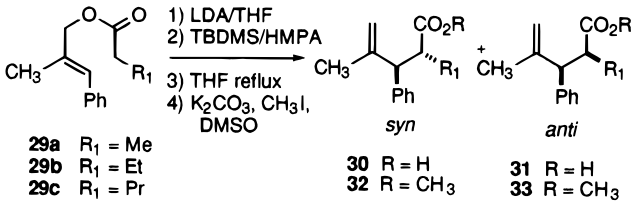
Determination of Relative Stereochemistry

The accurate determination of the relative stereochemistry of the Claisen products is essential to the validity of this work. The relative stereochemistry was established in three independent ways: (1) inference from ^{1}H NMR spectroscopy, (2) confirmation by independent synthesis via enolate Claisen rearrangement, and (3) by the synthesis of the mycotoxin botryodiplodin, a known compound whose relative stereochemistry is firmly established.

(1) ^{1}H NMR spectroscopy aided in the assignment of relative stereochemistry since there were significant differences in the spectra of *syn* and *anti* isomers. One of the most striking effects was in the series where R_2 was an aromatic substituent (entries a, b, c, n, and o in Table 4). In such cases, the anisotropy introduced by the aromatic ring led to specific upfield shifts of the α alkyl group (R_1) in the *syn* isomer **27**, and corresponding upfield shifts in the ester alkoxy group in the *anti* isomer **28**. These spectral correlations are presented in Table 5.

(2) The enolate Claisen rearrangement variation has exhibited strong selectivity for either the *syn* or *anti* isomer depending on the enolization conditions as discussed previously. We used this fact to help confirm the *syn* and *anti* assignments of the products obtained in our own Claisen studies by preparing mixtures of the same products according to the work of Ireland.[6] We chose to prepare mixtures under conditions in which the *anti* isomer was expected to predominate for stereochemical correlations as described in Table 6. Enolization of esters **29a**−**c** with lithium diisopropylamide in THF followed by silylation with *tert*-butyldimethylsilyl chloride in HMPA afforded mixtures of the *E* and *Z* silyl ketene acetals in which the *E* isomer should predominate.[6] Sigmatropic rearrangement was conducted at THF reflux, and workup provided 3:1 *anti:syn* mixtures of carboxylic acids **31a**−**c** and **30a**−**c**, respectively. The carboxylic acids **31a**−**c** and **30a**−**c** were then converted into the corresponding methyl esters (**33a**−**c** and **32a**−**c**) using potassium carbonate and iodomethane in DMSO. In all three cases, both the *syn* and *anti* isomers prepared in this fashion (**32a**−**c**, **33a**−**c**) proved identical to the compounds assigned as the *syn* and *anti* isomers prepared using the ortho ester Claisen by capillary GC and NMR spectroscopy (200 MHz ^{1}H and 50 MHz ^{13}C).

Table 6. Enolate Claisen Rearrangements to Confirm *Syn*:*Anti* Correlations



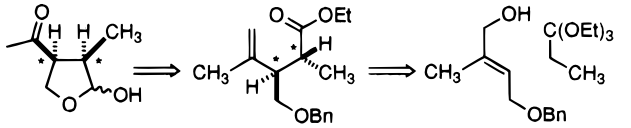
29a R_1 = Me
29b R_1 = Et
29c R_1 = Pr

30 R = H
32 R = CH_3

31 R = H
33 R = CH_3

ester	*anti:syn* ratio (**31:30**)	% yield	*anti:syn* ratio (**33:32**)	% yield
29a	3:1	23	3:1	42
29b	3:1	30	3:1	61
29c	3:1	24	3:1	63

Scheme 9



45 **35** **34**

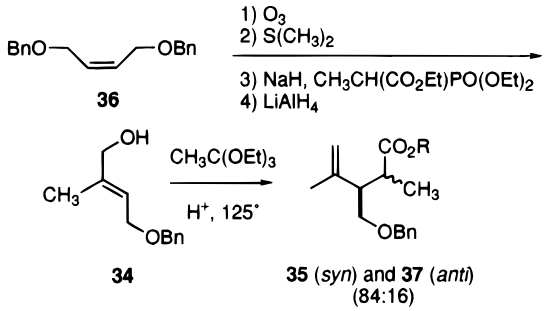
(3) In an effort to confirm the assignments of relative stereochemistry on a chemical basis, we have synthesized the mycotoxin botryodiplodin (**45**)[22,23] using the ortho ester Claisen rearrangement (Scheme 9). The results described in the following section demonstrate the utility of the diastereoselective ortho ester Claisen rearrangement and clearly establish the *syn* relationship present in the major product **35** of the ortho ester Claisen rearrangement of the *E* trisubstituted alcohol **34**.

(21) Daub, G. W., Griffith, D. A. *Tetrahedron Lett.* **1986**, 6311.

(22) (a) Arsenault, G. P.; Althaus, J. R.; Divekar, P. V. *J. Chem. Soc., D* **1969**, 1414. (b) Moreau, S.; Lablanche-Combier, A.; Biguet, J.; Foulon, C.; Delfosse, M. *J. Org. Chem.***1982**, *47*, 2358.

(23) For other syntheses of botryodiplodin see: (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) Mukaiyama, T.; Wada, M.; Hanna, J.; *Chem. Lett.* **1974**, *94*, 1181. (d) Wilson, S. R.; Myers, R. S. *J. Org. Chem.* **1975**, *40*, 3309. (e) Kurth, M. J.; Yu, C.-M. *J. Org. Chem.***1985**, *50*, 1840. (f) Rehnberg, N.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, 3589.

Scheme 10



A Synthesis of Botryodiplodin

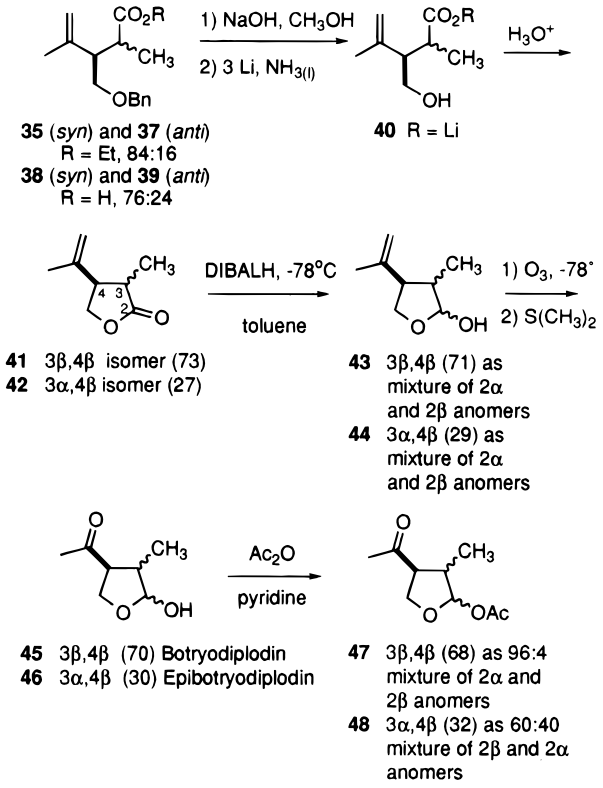
Scheme 10 summarizes the synthetic route to the key intermediate **35**. Allylic alcohol **34** was prepared from the dibenzyl ether of *cis* 2-buten-1,4-diol (**36**)[24] by ozonolysis (76%),[25] Emmons−Wadsworth olefination of the resulting aldehyde with triethyl 2-phosphonopropionate (to give an 84:16 mixture of *E* and *Z* isomers in 72% yield),[17] and $LiAlH_4$ reduction. Allylic alcohol **34** was obtained in 53% yield after purification by medium pressure liquid chromatography on silica as a 98:2 mixture of *E* and *Z* isomers. Ortho ester Claisen rearrangement of alcohol **34** with triethyl orthopropionate afforded an 84:16 mixture of the desired *syn* (**35**) and *anti* (**37**) unsaturated esters in 88% yield after flash chromatography. Independent confirmation of this *syn* selectivity would await the sucessful synthesis of botryodiplodin (**45**). In all cases, the isomeric ratios were determined by ^1H NMR and capillary gas chromatography.

The completion of the synthesis is shown in Scheme 11. Saponification of esters **35** and **37** afforded a 76:24 mixture[26] of carboxylic acids **38** (*syn*) and **39** (*anti*) in 98% yield. The small change in the ratio of *syn* and *anti* diastereomers is presumably due to enolization under the basic reaction conditions. Reductive removal of the benzyl ether moiety in **38**/**39** was accomplished using 3 equiv of lithium in liquid ammonia.[27] Acidification of the crude reaction mixture afforded an 87% yield of the γ-lactones (IR: 1772 cm^{-1}) as a 73:27 mixture[26] of the 3β,4β (**41**) and 3α,4β (**42**) isomers. Lactones **41** and **42** presumably result from lactonization of the carboxylic acid salts **40** upon acidic workup.

The syntheses of botryodiplodin and epibotryodiplodin were completed by diisobutylaluminum hydride reduction[28] to the lactol and oxidative cleavage of the terminal alkene by ozonolysis. Lactols **43** and **44** could be prepared in 75−85% yields as a 71:29 mixture[26] of the 3β,4β (**43**, mixture of 2α and 2β anomers) and the 3α,4β (**44,** mixture of 2α and 2β anomers) isomers. Ozonolysis of **43** and **44** with a reductive workup (Me_2S) afforded a 70:30 mixture of botryodiplodin (**45**) and epibotryodiplodin (**46**) in 55% yield after chromatography.

Compounds **45** and **46** exhibited ^1H NMR spectral features consistent with published data.[23] Further characterization was accomplished after conversion of **45**/**46** to the mixture of acetates **47**/**48** with acetic anhydride

Scheme 11



and pyridine (84%). Acetates **47** and **48** each existed as a pair of α and β anomers consistent with published observations.[29]

While the individual lactone isomers **41** and **42** could not be separated in sufficient quantities to be individually carried on to the final products, there is no doubt in the stereochemical correlation of the *cis* isomer **41** with **45** and the *trans* isomer **42** with **46**. Stoichiometry precludes the possibility that the product obtained is a 30:70 mixture of **45** and **46**. Further, epimerization of lactol **43** to **44** proved to be rapid and complete in the presence of acid or base, most certainly through the open chain aldehyde form. This shows that **43** and **44** possess *cis* (less stable) and *trans* (more stable) relationships between the isopropenyl and methyl groups at positions 4 and 3, respectively. Thus, the major lactol **43** has the *less* stable stereochemical relationship and is thus expected to have a *cis* relative stereochemistry between the isopropenyl and methyl groups.

In this fashion we have prepared the mycotoxin botryodiplodin (**45**) and its epimer, epibotryodiplodin (**46**). The successful completion of the synthesis confirms that the relative stereochemistry of the major product **35** of ortho ester Claisen rearrangement of alcohol **34** with triethyl orthopropionate is *syn*.

Conclusion

The ortho ester Claisen rearrangement of trisubstituted allylic alcohols exhibits significant levels of diastereoselection, especially when the *Z* allylic alcohol is employed. We ascribe the increased selectivity over

(24) Prepared from *cis*-2-butene-1,4-diol according to Czernecki, S.; Georgoulis, C.; Proveloenghiou, C. *Tetrahedron Lett.* **1976**, 3535.

(25) The authors would like to thank the Chemistry Departments of the University of California, Irvine, and Pomona College for the use of their ozone generators.

(26) Isomer ratios were determined using ^1H NMR at 200 MHz.

(27) Reist, E. J.; Bartuska, V. J.; Goodman, L.; Johnson, E. *J. Org. Chem.* **1964**, *29*, 3725.

(28) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

(29) Capillary GC analysis of the mixture of acetates indicated the presence of 4 materials in a 65:3:19:13 ratio. ^1H NMR revealed these to be the α-anomer of botryodiplodin acetate (2α-**47**), the β-anomer of botryodiplodin acetate (2β-**47**), the β-anomer of epibotryodiplodin acetate (2β-**48**), and the α-anomer of epibotryodiplodin acetate (2α-**48**), respectively.

disubstituted allylic alcohols to the presence of a 1,3-diaxiallike interaction that develops in one of the transition states. In the case of *E* allylic alcohols, the new diaxial interaction develops in the transition state leading to the *anti* isomer, rendering the reaction *syn* selective. In a complementary fashion, *Z* allylic alcohols exhibit *anti* selectivity because the new diaxial interaction develops in the transition state leading to the *syn* isomer. We have taken advantage of this selectivity to synthesize the mycotoxin botryodiplodin.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were determined at 200 MHz (FT) and 50 MHz, respectively, in $CDCl_3$. Vapor-phase chromatograms were obtained on a 30 m DB-1 capillary column (J and W Scientific). Integrations were not corrected for varying detector responses. Combustion microanalyses were performed by Atlantic Microlab, Inc. Flash and MPLC chromatography were performed on silica gel [0.040−0.063 mm]. Ethylene glycol dimethyl ether (DME), diisopropylamine, and pyridine were distilled from CaH_2, tetrahydrofuran was distilled from sodium/benzophenone ketyl, and hexamethylphosphoric triamide (HMPA) was distilled from sodium under reduced pressure; all other reagents were reagent grade as supplied by the vendor.

Synthesis of Allylic Alcohols. (*E*)-Methyl 2-Methyl-3-phenyl-2-propenoate. (*E*)-2-Methyl-3-phenyl-2-propenoic acid (10.00 g, 61.66 mmol, Aldrich), trimethyl orthoformate (7.20 g, 67.9 mmol), and $TsOH\cdot H_2O$ (0.619 g, 3.25 mmol) were dissolved in MeOH and heated at reflux for 48 h. The reaction mixture was concentrated under reduced pressure and dissolved in ether. The organic layer was extracted with saturated $NaHCO_3$, and the resulting aqueous layer was back extracted with additional ether. The combined ether layers were extracted with water and saturated brine and dried over $MgSO_4$. Concentration under reduced pressure afforded a low-melting, colorless liquid (10.45 g, 96%) suitable for subsequent use. A sample of the ester was purified by recrystallization from hexane (mp 26−27 °C) to provide a sample suitable for combustion analysis. IR (KBr): 3050, 1711, 1633 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.12 (s, 3H), 3.82 (s, 3H), 7.4 (m, 5H), 7.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0, 52.0, 128.3, 128.4 (2 carbons), 129.6, 136.0, 138.9, 169.1. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.08; H, 6.81.

(*E*)-2-Methyl-3-phenyl-2-propen-1-ol (1a). A solution of (*E*)-methyl 2-methyl-3-phenyl-2-propenoate (8.01 g, 45.2 mmol) in anhydrous ether (50 mL) was added dropwise over 30 min to a solution of $LiAlH_4$ (1.806 g, 45.2 mmol) in anhydrous ether (250 mL) at 0 °C under nitrogen, and the reaction mixture was allowed to stir at 0 °C for an additional 1 h. The excess $LiAlH_4$ was destroyed by the addition of saturated Na_2SO_4. The aluminum salts were removed by filtration, and the salts were extracted with hot ether. The combined organic layers were concentrated, and the resulting liquid was and purified by bulb-to-bulb distillation (185 °C, 0.8 mm Hg) to afford colorless product (6.42 g, 95%). IR (neat): 3050, 1711, 1633 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.82 (s, 3H), 3.3 (br s, 1H), 4.10 (s, 2H), 6.48 (s, 1H), 7.2−7.3 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.2, 68.8, 125.0, 126.3, 128.1, 128.8, and 137.6. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.21; H, 8.21.

2-Methyl-2-propen-1-yl Tetrahydropyranyl Ether. Over a period of 15 min, $TsOH\cdot H_2O$ (34.80 g, 0.202 mol) was added to a solution of 2-methyl-2-propen-1-ol (14.44 g, 0.200 mol) and 3,4-dihydro-2*H*-pyran (16.83 g, 0.200 mol) in CH_2Cl_2 (300 mL) while keeping the reaction temperature at 20 °C. After 3 h, the reaction mixture was extracted with saturated $NaHCO_3$, water, and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the resulting material was distilled (53 °C, 5 mmHg) to give 2-methyl-2-propen-1-yl tetrahydropyranyl ether (16.97 g, 54%). IR (neat): 1640 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.5−2.0 (m, 9H) including 1.76 (s), 3.53 (m, 1H), 3.8−4.0 (m, 2H) including 3.9 (m) and 3.90 (d, J = 12.7 Hz), 4.14 (d, 1H, J = 12.8 Hz), 4.64 (t, 1H, J = 3.4 Hz), 4.89 (s, 1H), 5.00 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.3, 19.4, 25.4, 30.5, 61.9, 70.6, 97.6, 111.4, 142.1.

Acetonyl Tetrahydropyranyl Ether. Ozone was vigorously bubbled through a 0.15 M solution of 2-methyl-2-propen-1-yl tetrahydropyranyl ether (5.00 g, 0.032 mol) in 50/50 (v/v) $MeOH/CH_2Cl_2$ (215 mL total) at −78 °C until a blue color persisted (≈1 h). The ozone flow was stopped, oxygen gas was bubbled through the reaction mixture for 15 min to remove any excess ozone, excess Me_2S (6 mL, 0.082 mol) was added to the solution, and the reaction mixture was allowed to warm to 25 °C over a 2 h period. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure and vacuum distillation (68−72 °C, 5.0 mmHg) afforded acetonyl tetrahydropyranyl ether (2.94 g, 58%) as a colorless liquid. IR (neat): 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.5−2.0 (m, 6H), 2.18 (s, 3H), 3.54 (m, 1H), 3.84 (m, 1H), 4.11 (d, 1H, J = 17.3 Hz), 4.26 (d, 1H, J = 17.3 Hz), 4.65 (t, 1H, J = 3.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.1, 25.2, 26.4, 30.2, 62.3, 72.3, 98.7, 206.6.

(*Z*)-2-Methyl-3-phenyl-2-propen-1-ol (2a, R_2 = Ph). The following procedure is a modification of the method of Still.[18] Butyllithium (42.0 mmol, 20.0 mL of 2.1 M solution in hexane) was added via syringe to a mixture of benzyltriphenylphosphonium bromide (19.54 g, 45.1 mmol) and THF (130 mL) at 25 °C, and the reaction mixture was allowed to stir for 10 min and then cooled to −78 °C. Acetonyl tetrahydropyranyl ether (5.100 g, 32.2 mmol) in THF (20 mL) was added, and the solution was allowed to warm to 25 °C over a 45 min period. The reaction was quenched by the addition of hexane (150 mL), and the resulting slurry was promptly subjected to flash chromatography on silica gel (3% ethyl acetate/97% hexane). Fractions were pooled and concentrated under reduced pressure to give a 60:40 mixture (by GC) of (*Z*)- and (*E*)-2-methyl-3-phenyl-2-propen-1-yl tetrahydropyranyl ethers (2.634 g, 35%).

This mixture of THP ethers was deprotected without further purification. The mixture of (*Z*)- and (*E*)-2-methyl-3-phenyl-2-propen-1-yl tetrahydropyranyl ethers (2.634 g, 11.4 mmol), $TsOH\cdot H_2O$ (0.507 g, 2.67 mmol), and MeOH (250 mL) were allowed to react at 25 °C for 30 min. The reaction mixture was diluted with ether and washed with saturated $NaHCO_3$, water, and saturated brine. After drying over $MgSO_4$, the solution was concentrated under reduced pressure. The crude product consisted of a 60:40 mixture (1.397 g, 80%) of the *Z* and *E* isomers of 2-methyl-3-phenyl-2-propen-1-ol, respectively. Medium pressure chromatography on silica gel (1% 2-propanol/14% ethyl acetate/85% hexane) afforded a pure sample (>99%) of (*Z*)-2-methyl-3-phenyl-2-propen-1-ol (0.098 g) plus an additional mixture of *E* and *Z* alcohols. IR (neat): 3300 (br), 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): *Z* isomer: δ 1.92 (s, 3H), 2.45 (br s, 1H), 4.20 (s, 2H), 6.39 (s, 1H), 7.2−7.3 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.7, 62.2, 126.5, 128.1, 128.3, 128.9, 137.2, 137.5. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.17; H, 8.25.

(*E*)- and (*Z*)-Ethyl 2-Methyl-5-phenyl-2-pentenoate. The following procedure is a modification of the method of Mori.[17] A solution of triethyl 2-phosphonopropionate (8.40 g, 35.3 mmol) in DME (30 mL) was added to a slurry of NaH (1.72 g of 50% oil disp, 35.8 mmol, washed free of oil) and DME (30 mL). A solution of 3-phenylpropanal (4.77 g, 35.5 mmol) in DME (30 mL) was then added, and the resulting mixture was stirred for 3 h at 25 °C and then heated at reflux for 30 min. The reaction mixture was poured into ice−water and extracted with ether. The combined organic layers were washed with water and brine and dried over $MgSO_4$. Concentration under reduced pressure yielded a 6:1 mixture of the *E* and *Z* isomers of ethyl 2-methyl-5-phenyl-2-pentenoate (5.96 g, 77%) by capillary GC.

Flash chromatography of a sample of (*E*)- and (*Z*)-ethyl 2-methyl-5-phenyl-2-pentenoate (1.5 g) on silica gel (4% ethyl acetate/96% hexane) provided samples of (*E*)-ethyl 2-methyl-5-phenyl-2-pentenoate (0.656 g), *Z* ethyl 2-methyl-5-phenyl-2-pentenoate (0.089 g), and a mixture of the two isomers (0.535 g, 85% recovery). IR (neat): 1707, 1644 cm^{-1}. *E* isomer: ^{1}H

NMR ($CDCl_3$, 200 MHz): δ 1.29 (t, 3H, J = 7.1 Hz), 1.78 (s, 3H), 2.48 (q, 2H, J = 8.0 Hz), 2.76 (t, 2H, J = 8.0 Hz), 4.18 (q, 2H, J = 7.1 Hz), 6.80 (t, 1H, J = 8.0 Hz), 7.2−7.3 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.0, 14.0, 30.3, 34.5, 60.0, 125.8, 128.1, 128.2, 128.3, 140.5, 141.0, 167.7. *Z* isomer: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.29 (t, 3H, J = 7.2 Hz), 1.89 (s, 3H), 2.74 (m, 2H), 4.19 (q, 2H, J = 7.2 Hz), 5.96 (t, 1H, J = 7.9 Hz), 7.2−7.3 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.3, 20.5, 31.1, 35.5, 60.0, 125.9, 128.0, 128.3, 128.4, 141.3, 141.6, 168.1. Mixture of *E* and *Z* isomers: Mass spectrum: 218 (M^+), 91 (100). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.25; H, 8.20.

Claisen Rearrangements. General Procedure for Ketal Claisen Rearrangement. An allylic alcohol (1 mmol), a ketal (3 mmol), and a carboxylic acid (0.1 equiv) were combined in a round-bottom flask equipped with magnetic stirring and a short-path distillation apparatus, and the mixture was heated at 125 °C for 20 h.[11] The reaction mixture was diluted with ether and extracted with 10% HCl, saturated $NaHCO_3$, water, and saturated brine. The resulting organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Capillary gas chromatography of the crude reaction mixture revealed the composition of the reaction mixture as a ratio of the less substituted product, the *syn* isomer of the more highly substituted product, and the *anti* isomer of the more highly substituted product. Flash chromatography on silica (5% ethyl acetate/hexane) afforded samples of the three isomers. These materials were characterized by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis.

Ketal Claisen Rearrangement between (*E*)-2-Methyl-3-phenyl-2-propen-1-ol and 2,2-Diethoxybutane. (*E*)-2-Methyl-3-phenyl-2-propen-1-ol and 2,2-diethoxybutane were allowed to react in the presence of propionic acid to give a 4:79:17 ratio of 6-methyl-5-phenyl-6-hepten-3-one (**14**, $R_3 = CH_3$): *syn* 3,5-dimethyl-4-phenyl-5-hexen-2-one (**12**, $R_3 = CH_3$):*anti* 3,5-dimethyl-4-phenyl-5-hexen-2-one (**13**, $R_3 = CH_3$). Flash chromatography on silica gel (3% ethyl acetate/hexane) afforded the products in 78% combined yield. 6-Methyl-5-phenyl-6-hepten-3-one: IR (neat): 1711, 1642 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.97 (t, 3H, J = 7.3 Hz), 1.62 (s, 3H), 2.3 (m, 2H), 2.79 (dd, 1H, J = 7.6 Hz, 16.1 Hz), 2.95 (dd, 1H, J = 7.4 Hz, 16.1 Hz), 3.63 (t, 1H, J = 7.5 Hz), 4.84 (s, 1H), 4.86 (s, 1H), 7.3 (s, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 7.6, 21.6, 36.6, 47.0, 47.7, 110.1, 126.5, 127.7, 128.4, 142.6, 147.2, 209.7. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.96; H, 8.78. *syn*- and *anti*-3,5-Dimethyl-4-phenyl-5-hexen-2-one: IR (neat): 1710, 1644 cm^{-1}. ^{1}H NMR (60 MHz): *syn* isomer: δ 0.86 (d, 3H, J = 6.9 Hz), 1.62 (s, 3H), 2.20 (s, 3H), 3.15 (dq, 1H, J_d = 11.5 Hz, J_q = 6.9 Hz), 3.39 (d, 1H, J = 11.5 Hz), 4.82 (s, 1H), 4.90 (s, 1H), 7.3 (s, 5H); *anti* isomer δ 1.15 (d, 3H, J = 6.7 Hz), 1.58 (s, 3H), 1.91 (s, 3H), 3.1 (m, 1H), 3.50 (d, 1H, J = 11.6 Hz), 4.89 (s, 1H), 5.00 (s, 1H), 7.3 (s, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): *syn* isomer δ 16.2, 22.5, 28.2, 50.4, 55.4, 110.1, 126.7, 128.4 (2 carbons), 140.8, 147.6, 211.9; *anti* isomer δ 16.2, 19.8, 28.9, 48.5, 56.3, 112.4, 126.6, 127.9, 128.4, 141.5, 145.2, 213.7. Mass spectrum: 202 (M^+), 187, 159, 131 (100), 129, 117, 115, 91. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.24; H, 8.80.

General Procedure for Ortho Ester Claisen Rearrangement. An allylic alcohol (1 mmol), an ortho ester (10 mmol), and a carboxylic acid (0.1 equiv) were combined in a round-bottom flask equipped with magnetic stirring and a short-path distillation apparatus, and the mixture was heated at 125 °C for 2 h.[2,10] The reaction mixture was diluted with ether and extracted with 10% HCl, saturated $NaHCO_3$, water, and saturated brine. The resulting organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Capillary gas chromatography of the crude reaction mixture provided *syn*:*anti* ratios of the products, and flash chromatography on silica (5% ethyl acetate/hexane) afforded samples of the *syn* and *anti* isomers. These materials were characterized by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis.

***syn*- and *anti*-Ethyl 2,4-Dimethyl-3-phenyl-4-pentenoate (17 and 18, R_2 = Ph, R_1 = Me).** (*E*)-2-Methyl-3-phenyl-2-propen-1-ol and triethyl orthopropionate were allowed to react in the presence of propionic acid to give an 85:15 mixture of *syn* and *anti* products. Flash chromatography afforded the *syn* and *anti* products in 65% overall yield. IR (neat): 1735, 1644 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): *syn* isomer: δ 0.96 (d, 3H, J = 6.9 Hz), 1.25 (t, 3H, J = 7.2 Hz), 1.62 (s, 3H), 2.99 (dq, 1H, J_d = 11.8 Hz, J_q = 7.2 Hz), 3.38 (d, 1H, J = 11.8 Hz), 4.14 (q, 2H, J = 7.2 Hz), 4.79 (m, 1H), 4.97 (m, 1H), 7.2 (m, 5H); *anti* isomer: δ 0.93 (t, 3H, J = 7.2 Hz), 1.24 (d, 3H, J = 6.8 Hz), 1.57 (s, 3H), 3.06 (dq, 1H, J_d = 11.5 Hz, J_q = 6.8 Hz), 3.48 (d, 1H, J = 11.5 Hz), 3.85 (q, 2H, J = 7.2 Hz), 4.84 (m, 1H), 4.99 (m, 1H), 7.2 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): *syn* isomer: δ 14.2, 16.7, 22.1, 43.2, 56.2, 60.2, 110.1, 126.7, 128.4, 128.5, 140.7, 147.3, 176.1; *anti* isomer: δ 13.8, 16.7, 19.9, 41.9, 56.9, 60.0, 112.3, 126.5, 128.0, 128.1, 141.5, 145.2, 175.7. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.46; H, 8.70.

In a separate experiment, the *Z* isomer of 2-methyl-3-phenyl-2-propen-1-ol and triethyl orthopropionate were allowed to react in the presence of pivalic acid to give a 14:86 mixture of *syn* and *anti* products in 66% yield after flash chromatography. The products exhibited identical spectral characteristics to the corresponding products obtained from the *E* alcohol.

Enolate Claisen Rearrangements. (*E*)-2-Methyl-3-phenyl-2-propenyl Propanoate (29a). Propionic anhydride (2.60 g, 20.0 mmol) was added via syringe to a solution of 2-methyl-3-phenyl-2-propen-1-ol (1.48 g, 10.0 mmol) in anhydrous pyridine (10 mL) at 0 °C, and the resulting solution was allowed to warm to 25 °C over 2 h and stirred for 24 h at 25 °C. The excess anhydride was quenched by the addition of water, and the reaction mixture was stirred an additional 30 min. The reaction mixture was poured into saturated $NaHCO_3$, and the mixture was extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$, water, saturated $CuSO_4$, and brine. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and purified by bulb-to-bulb distillation (160 °C, 0.15 mmHg) to give the desired ester (1.850 g, 91%). IR (neat): 1726, 1662 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.18 (t, 3H, J = 7.6 Hz), 1.89 (s, 3H), 2.40 (q, 2H, J = 7.6 Hz), 4.64 (s, 2H), 6.53 (s, 1H), 7.3 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 9.1, 15.4, 27.6, 69.9, 126.7, 128.1, 128.9, 132.9, 137.1, 174.1 (one peak is 2 carbons). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.24; H, 7.96.

***syn*- *and anti*-2,4-Dimethyl-3-phenyl-4-pentenoic Acid (30 and 31, R_1 = Me) via Enolate Claisen.** The following procedure is a modification of the method of Ireland.[6] Butyllithium (0.56 mL of 1.95 M solution in hexane, 1.1 mmol) was added to a solution of diisopropylamine (0.252 g, 1.5 mmol) in THF (3 mL) at 0 °C under dry nitrogen. The resulting pale yellow solution was cooled to −78 °C and (*E*)-2-methyl-3-phenyl-2-propenyl propanoate (0.204 g, 1.0 mmol) in THF (0.2 mL) was added dropwise over 4 min and stirred an additional 3 min to produce a red solution. A solution of *tert*-butyldimethylsilyl chloride (0.166 g, 1.1 mmol) in HMPA (0.5 mL) was added, and the now brown reaction mixture was stirred an additional 2 min at −78 °C, warmed to 25 °C, and heated at reflux for 1 hr. Aqueous HCl (1 mL of 10% solution) was added, and the reaction mixture was stirred for 45 min at 25 °C. The resulting mixture was poured into aqueous 5% NaOH and extracted with ether. Concentrated HCl and ice were added to the aqueous layer until the solution was cloudy, and the mixture was extracted with ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Removal of volatiles under vacuum (0.3 mmHg) afforded an orange waxy residue (23%). This solid was shown to be a 3:1 *anti*:*syn* mixture of the desired pentenoic acids by ^{1}H NMR spectroscopy. IR (KBr): 3300−2800, 1697 cm^{-1}. *Anti* isomer: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25 (d, 3H, J = 6.8 Hz), 1.54 (s, 3H), 2.9−3.1 (m), 3.49 (d, 1H, J = 11.0 Hz), 4.84 (s, 1H), 4.98 (s, 1H), 7.3 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 16.8, 19.6, 41.3, 56.2, 112.7, 126.6, 127.8, 128.2, 141.2, 144.9, 181.2. *Syn* isomer: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.96 (d, 3H, J = 6.8 Hz), 1.60 (s, 3H), 2.9−3.1 (m), 3.33 (d, 1H, J = 11.6 Hz), 4.80

(s, 1H), 4.98 (s), 7.3 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 16.8, 22.2, 43.0, 55.8, 110.2, 126.8, 127.8, 128.9, 140.3, 147.0, 181.2.

***syn*- and *anti*-Methyl 2,4-Dimethyl-3-phenyl-4-pentenoate (32 and 33, R_1 = Me).** A 3:1 mixture of *the syn* and *anti* isomers of 2,4-dimethyl-3-phenyl-4-pentenoic acid (0.090 g, 0.44 mmol), iodomethane (0.160 g, 1.13 mmol), and K_2CO_3 (0.157 g, 1.14 mmol) were dissolved in DMSO (2 mL) and allowed to stir at 25 °C for 10 h. The reaction mixture was diluted with ether and washed with water, 5% HCl, 50% saturated $NaHCO_3$, water, and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a pale yellow liquid (0.040 g, 42%). The major and minor isomers (3:1) in this mixture exhibited NMR spectral data (^{1}H and ^{13}C) identical with those of the minor and major isomers, respectively, produced in the ortho ester Claisen rearrangement described previously.

Synthesis of Botryodiplodin. (Benzyloxy)ethanal. A magnetically stirred solution of *cis*-1,4-bis(benzyloxy)-2-butene[24] (**36**, 14.40 g, 53.6 mmol) in 50% (v/v) MeOH−CH_2Cl_2 (200 mL) was cooled to −78 °C, and ozone was bubbled through until TLC indicated the complete disappearance of starting material (2 h). The reaction mixture was purged with oxygen, and dimethyl sulfide (17.8 g, 285 mmol) was added. After stirring overnight at 23 °C, the reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure and vacuum distillation (75 °C, 0.25 mm Hg) afforded the desired aldehyde as a colorless liquid (12.16 g, 76%). ^{1}H NMR δ 4.07 (d, 2H, J = 0.7 Hz), 4.60 (s, 2H), 7.3 (m, 5H), 9.67 (t, 1H, J = 0.7 Hz). ^{13}C NMR δ 73.5, 75.2, 127.9, 128.0, 128.4, 136.8, 200.2.

***(E)*- and *(Z)*-Ethyl 4-(Benzyloxy)-2-methyl-2-butenoate.** (*E*)- and (*Z*)-Ethyl 4-(benzyloxy)-2-methyl-2-butenoate was prepared according to the method used to make (*E*)-ethyl 2-methyl-5-phenyl-2-pentenoate. Triethyl 2-phosphonopropionate (30.0 g, 126 mmol), NaH (6.00 g of 50% oil disp, 126 mmol), and (benzyloxy)ethanal (18.96 g, 126 mmol) afforded a 5.3:1 mixture of (*E*)- and (*Z*)-ethyl 4-(benzyloxy)-2-methyl-2-butenoate as a colorless liquid (21.2 g, 72%). IR (neat) 1709, 1655 cm^{-1}. The *E* and *Z* isomers were separated in another experiment and characterized individually. *E* isomer: ^{1}H NMR δ 1.29 (t, 3H, J = 7.1 Hz), 1.81 (s, 3H), 4.17 (q, 2H, J = 7.1 Hz), 4.17 (d, 2H, J = 6.0 Hz), 4.51 (s, 2H), 6.87 (t, 1H, J = 6.0 Hz), 7.3 (m, 5H). ^{13}C NMR: δ 12.6, 14.1, 60.5, 66.7, 72.7, 127.6 (2 carbons), 128.3, 129.4, 137.7, 137.8, 167.3. *Z* isomer: ^{1}H NMR δ 1.27 (t, 3H, J = 7.1 Hz), 1.91 (s, 3H), 4.17 (q, 2H, J = 7.1 Hz), 4.48 (dm, 2H, J_d = 6.0 Hz), 4.51 (s, 2H), 6.14 (t, 1H, J = 6.0 Hz), 7.3 (m, 5H). ^{13}C NMR: δ 14.1, 19.7, 60.3, 68.7, 72.7, 127.6, 127.7 (2 carbons), 128.3, 138.2, 141.3, 167.2. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.68; H, 7.74.

***(E)*-4-(Benzyloxy)-2-methyl-2-buten-1-ol** (**34**). (*E*)-4-(Benzyloxy)-2-methyl-2-butenoate (10.11 g, 43.2 mmol) was reduced with $LiAlH_4$ according to the procedure used to prepare (*E*)-2-methyl-3-phenyl-2-propen-1-ol. Medium pressure chromatography on silica gel (12:1:87 ethyl acetate:2-propanol:hexane) afforded alcohol (**36**, 4.54 g, 53%) as a 98:2 *E*:*Z* mixture by capillary GC. In a separate experiment, selected fractions provided small samples of (*Z*)-4-(benzyloxy)-2-methyl-2-buten-1-ol for spectral and reaction studies. IR (neat) 3397, 1675 cm^{-1}. *E* isomer: ^{1}H NMR δ 1.65 (s, 3H), 2.2 (br s, 1H), 3.99 (s, 2H), 4.06 (d, 2H, J = 6.7 Hz), 4.51 (s, 2H), 5.65 (t, 1H, J = 6.7 Hz), 7.3 (m, 5H). ^{13}C NMR δ 13.7, 66.3, 68.1, 72.4, 121.6, 127.6, 127.8, 128.4, 138.4, 139.2. *Z* isomer: ^{1}H NMR δ 1.80 (s,3H), 2.4 (br s, 1H), 4.03 (d, 2H, J = 6.9 Hz), 4.06 (s, 2H), 4.50 (s, 2H), 5.55 (t, 1H, J = 6.9 Hz), 7.3 (m, 5H). ^{13}C NMR δ 21.4, 61.8, 65.7, 72.4, 123.6, 127.7, 127.8, 128.4, 138.0, 140.7. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.57; H, 8.11.

***syn*- and *anti*-Ethyl 3-[(Benzyloxy)methyl]-2,4-dimethyl-4-pentenoate (35 and 37).** A mixture of alcohol **34** (0.330 g, 1.7 mmol), triethyl orthopropionate (6.0 g, 35 mmol), and propionic acid (0.038 g, 0.5 mmol) were allowed to react at 110 °C in a round bottom flask equipped with magnetic stirring and a microdistillation head. After 60 min TLC indicated the absence of starting material, and the reaction mixture was cooled and diluted with ether. The ether solution was extracted with 5% HCl, saturated $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration under reduced pressure and flash chromatography on silica with 5% ethyl acetate/hexane afforded esters **35** and **37** (0.425 g, 88%) as an 84:16 mixture of *syn* and *anti* isomers by capillary GC. IR (neat) 1727, 1643 cm^{-1}. *Syn* isomer: ^{1}H NMR δ 1.14 (d, 3H, J = 6.5 Hz), 1.20 (t, 3H, J = 7.1 Hz), 1.75 (s, 3H), 2.67 (m, 2H), 3.53 (d, 2H, J = 5.7 Hz), 4.06 (q, 2H, J = 7.1 Hz), 4.45 (d, 1H, J = 11.5 Hz), 4.53 (d, 1H, J = 11.5 Hz), 4.75 (m, 1H), 4.84 (m, 1H), 7.3 (m, 5H). ^{13}C NMR δ 14.1, 14.5, 21.2, 40.6, 49.2, 60.0, 70.1, 73.1, 112.7, 127.5 (2 carbons), 128.3, 138.4, 145.1, 175.6. *Anti* isomer: ^{1}H NMR δ 1.07 (d, 3H, J = 6.8 Hz), 1.19 (t, 3H, J = 7.1 Hz), 1.65 (s, 3H), 2.52 (dq, 1H, J_q = 6.9 Hz, J_d = 10.7 Hz, 6.9 Hz), 2.73 (dt, 1H, J_d = 10.7 Hz, J_t = 8.0 Hz), 4.09 (dd, 1H, J = 8.0 Hz, 9.8 Hz), 3.50 (dd, 1H, J = 8.0 Hz, 9.8 Hz), 4.04 (q, 2H, J = 7.1 Hz), 4.45 (d, 1H, J = 11.6 Hz), 4.53 (d, 1H, J = 11.6 Hz), 4.83 (m, 1H), 4.91 (m, 1H), 7.3 (m, 5H). ^{13}C NMR δ 14.1, 15.7, 19.7, 40.1, 50.0, 60.2, 71.5, 72.9, 114.3, 127.4, 127.6, 128.2, 138.5, 143.5, 176.1. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.88; H, 8.77.

***syn*- and *anti*-3-[(Benzyloxy)methyl]-2,4-dimethyl-4-pentenoic Acid (38 and 39).** A sample of **35** and **37** (2.987 g, 10.8 mmol), MeOH (250 mL), and 10% aqueous NaOH (100 mL) were heated at reflux for 90 min at which time TLC indicated the absence of the ester. The reaction mixture was cooled and acidified with 5% HCl to pH 1 and extracted with ether. The combined organic layers were extracted with water and brine and dried over $MgSO_4$. Concentration under reduced pressure afforded carboxylic acids **38** and **39** (2.60 g, 98%) as a 76:24 mixture of *syn* and *anti* isomers by capillary GC. The crude products were sufficiently pure to be carried on to the next step without purification. IR (neat) 3400−2400 (vbr), 1701, 1641 cm^{-1}. ^{1}H NMR δ 1.06(*anti*)/1.11(*syn*) (d/d, 3H, J = 6.5 Hz), 1.60(*anti*)/1.71(*syn*) (s/s, 3H), 2.67 (m, 2H), 3.45(*anti*)/3.51(*syn*) (m/d, 2H, J = 5.7 Hz), 4.45 (m, 2H), 4.71(*syn*)/4.78(*anti*) (s/s, 1H), 4.82(*syn*)/4.87(*anti*) (s/s, 1H), 7.3 (m, 5H). ^{13}C NMR (*syn* isomer) δ 14.0, 21.6, 40.5, 48.6, 69.9, 73.0, 112.8, 127.5 (2 carbons), 128.3, 138.3, 144.7, 181.2; (*anti* isomer) δ 15.5, 20.0, 39.9, 49.6, 71.4, 72.8, 114.4, 127.5 (2 carbons), 128.3, 138.3, 143.2, 182.0.

***cis*- and *trans*-2-Methyl-3-(2-propenyl)butyrolactone (41 and 42).** The following procedure is a modification of Reist.[27] Ammonia (100 mL) was distilled from lithium into a three-necked round-bottom flask equipped with magnetic stirring, a dry-ice condenser, and a drying tube. The solution was maintained at −78 °C, and a sample of carboxylic acids **38** and **39** (0.996 g, 4.03 mmol) in anhydrous ether (20 mL) was added via syringe. Lithium wire was added as small pieces to the reaction mixture until the characteristic blue color persisted for 2 min (90 mg, 13 mmol). Solid NH_4Cl (≈5 g) was added to quench the reaction, and the dry-ice bath was replaced with a water bath. The ammonia was allowed to evaporate under N_2 until a white solid remained. The white residue was dissolved in water and acidified with HCl to a pH of 2, and the aqueous solution was extracted with ether. The combined extracts were dried over $MgSO_4$. The solvent was removed by distillation at ambient pressure, and the resulting liquid was purified by bulb-to-bulb distillation (135 °C, 15 mmHg) to afford lactones **41** (*cis*) and **42** (*trans*) (0.491 g, 87%) in a 73:27 ratio by VPC. IR (neat) 1772, 1640 cm^{-1}. Small amounts of the *cis* and *trans* isomers were separated in another experiment and characterized individually: *cis* isomer: ^{1}H NMR δ 1.02 (d, 3H, J = 7.3 Hz), 1.70 (s, 3H), 2.75 (5-plet, 1H), 3.12 (m, 1H), 4.26 (dd, 1H, J = 4.1, 9.3 Hz), 4.35 (dd, 1H, J = 6.2, 9.3 Hz), 4.78 (s, 1H), 4.94 (s, 1H); ^{13}C NMR δ 10.1, 20.9, 37.2, 46.6, 69.8, 114.1, 141.5, 179.3; *trans* isomer: ^{1}H NMR δ 1.25 (d, 3H, J = 7.0 Hz), 1.76 (s, 3H), 2.53 (dq, 1H, J_d = 11.0 Hz, J_q = 6.9 Hz), 2.81 (ddd, 1H, J = 7.7, 10.6, 11.0 Hz), 3.95 (dd, 1H, J = 8.9, 10.5 Hz), 4.37 (dd, 1H, J = 7.8, 8.9 Hz), 4.90 (s, 1H), 4.96 (s, 1H); ^{13}C NMR δ 13.6, 19.6, 38.1, 51.1, 69.4, 113.6, 140.7, 179.1. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.32; H, 8.66.

***cis*- and *trans*-2-Hydroxy-3-methyl-4-(2-propenyl)tetrahydrofuran (43 and 44**, each as a mixture of α and β

anomers). The following procedure is a modification of Corey.[28] A 73:27 *cis*/*trans* mixture of lactones **41** and **42** (96 mg, 0.681 mmol) was dissolved in anhydrous toluene under N_2 and cooled to −78 °C. Diisobutylaluminum hydride (0.55 mL of 1.5 M solution in toluene, 0.817 mmol) was added and the reaction mixture was allowed to stir for 1.5 h at which time TLC indicated the absence of starting material. The reaction was quenched by the addition of sufficient 1 M H_2SO_4 to redissolve the precipitated salts. The reaction mixture was allowed to warm to room temperature and was partitioned between ether and water. The organic layer was washed with saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. Concentration under reduced pressure and flash chromatography on silica with 40% ethyl acetate/hexane afforded lactols **43** (*cis*) and **44** (*trans*) (82 mg, 85%) in a 71:29 ratio by VPC. IR (neat) 3390, 1642 cm^{-1}. Small amounts of the *cis* isomer could be separated and characterized individually; the *trans* isomer could only be characterized as part of a *cis*−*trans* mixture: *cis* isomer (**43**, >92% α-anomer): ^1H NMR δ 0.81 (d, 3H, $J = 7.2$ Hz), 1.76 (s, 3H), 2.31 (5-plet, 1H), 3.10 (br s, 1H), 3.16 (q, 1H, $J = 8.2$ Hz), 3.96 (t, 1H, $J = 8.3$ Hz), 4.12 (t, 1H, $J = 8.3$ Hz), 4.62 (s, 1H), 4.88 (s, 1H), 5.18 (s, 1H); ^{13}C NMR δ 11.3, 23.2, 42.3, 46.2, 68.9, 104.4, 111.3, 141.9; *trans* isomer (**44**, ≈1:1 mixture of α and β anomers): ^1H NMR δ distinctive signals included 1.03/1.09 (d/d, 3H, $J = 6.9$ Hz), 1.69/1.74 (s/s, 3H), 5.12/5.37 (t/t, 1H, $J = 4.4$ Hz). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.48; H, 8.96.

Botryodiplodin and Epibotryodiplodin (45 and 46). A 71:29 mixture of lactols **43** and **44** (122 mg, 0.859 mmol) was dissolved in CH_2Cl_2 and treated with O_3 at −78 °C for 7 min. The solution was purged with O_2 (5 min), $(CH_3)_2S$ (0.5 mL) was added, and the reaction mixture was allowed to warm to 25 °C over 30 min. The mixture was poured into water and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure and flash chromatography on silica with 50% ethyl acetate/hexane afforded **45** and **46** (68 mg, 55%) as a 70:30 mixture by VPC. The ^1H NMR spectra of **45** and **46** agreed with published data.

Botryodiplodin Acetate and Epibotryodiplodin Acetate (47 and 48). A 70:30 mixture of **45** and **46** (39 mg, 0.273 mmol) was dissolved in anhydrous pyridine (2 mL) and treated with acetic anhydride (0.2 g, 2 mmol) for 20 h at 25 °C. The mixture was diluted with CH_2Cl_2, washed with saturated $CuSO_4$, water, saturated $NaHCO_3$, and brine, and dried over Na_2SO_4. Concentration under reduced pressure afforded **47** and **48** (43 mg, 84%) as a 68:32 mixture by ^1H NMR. Acetate **47** existed as a 96:4 mixture of α and β anomers while **48** was a 60:40 mixture of β and α anomers. The ^1H NMR spectra of **47** and **48** agreed with published data.[29]

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Supporting Information Available: Experimental descriptions and spectral and analytical data for other compounds described in this paper (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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