exchange resin (Amberlite IR-45). Concentration of the eluent afforded a residue which was further purified by column chromatography (15% aqueous propanol). The fractions containing the desired amino acid were combined and concentrated to dryness in vacuo to afford a white solid which was recrystallized from water–acetone to give colorless plates (0.022 g, 0.143 mmol, 45.2% yield): mp 221–223 °C dec; R_f 0.40 (*n*-PrOH–H_2O, 7:3, ninhydrin); ^{1}H NMR (250 MHz, D_2O) δ 1.25 (d, 3 H, J = 6.4), 3.85 (d, 1 H, J = 2.6), 5.10 (m, 1 H), 5.43 (m, 1 H), 5.84 (ddd, 1 H, J = 1.7, 2.0, 6.2), 6.17 (ddd, 1 H, J = 2.0, 1.7); IR (KBr) 3430, 3130, 2970, 2925, 2875, 2560, 1630, 1555, 1520, 1400, 1385, 1350, 1105, 1085, 1050 cm^{-1}; HRMS (CI) calcd for $C_7H_{12}O_3N$ (M^+ + 1), 158.0817; found, 158.0819.

(αS,2S,5R)-Furanomycin (2b). A procedure similar to that used to hydrolyze **13a** was used to hydrolyze **13b** (0.085 g, 0.269 mmol). The amino acid was isolated as a white solid which was recrystallized from water–acetone to afford colorless plates (0.021 g, 0.134 mmol, 49.7% yield): mp 222–223 °C dec; R_f 0.43 (*n*-PrOH–H_2O, 7:3, ninhydrin); ^{1}H NMR (250 MHz, D_2O) δ 1.26 (d, 3 H, J = 6.5), 3.99 (d, 1 H, J = 4.0), 5.12 (m, 1 H), 5.43 (m, 1 H), 5.67 (ddd, 1 H, J = 1.7, 1.9), 6.19 (ddd, 1 H, J = 1.7, 6.3, 1.5); IR (KBr) 3430, 3070, 2970, 2880, 2740, 2640, 1610, 1585, 1510, 1410, 1340, 1310, 1085, 1060 cm^{-1}; HRMS (CI) calcd for $C_7H_{12}O_3N$ (M^+ + 1), 158.0817; found, 158.0824.

Acknowledgment. We gratefully acknowledge the generous support of this investigation by the Dow Chemical Company Foundation.

Synthesis of Epoxytrichothecenes: Verrucarin J and Verrucarin J Isomers[1]

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A five-step synthesis of verrucarin J (**1**) from verrucarol (**2**) is described. Esterification of (*E*)-**21** and **2** with DCC in the presence of catalytic DMAP was highly regioselective but afforded a 3–4:1 mixture of (*E*)-**23** and the corresponding *Z* olefin isomer. Two routes from (*E*)-**23** to seco acid **13** are described, the most efficient of which involves the coupling of (*E*)-**24** ("verrol") with muconate ester **28**. Macrolactonization of seco acid **13** via mixed anhydride **31** afforded 55–60% of **1** together with 25–30% of *E,E,E* isomer **32**. Although attempts to suppress the formation of **32** were unsuccessful, treatment of **32** with I_2 in C_6H_6 effected clean isomerization to a 2:1 mixture of **1** and *E,Z,E* isomer **33**. The overall yield of verrucarin J from verrucarol, after a recycle of **32**, was 27–30%. Also described are syntheses of (*Z,E,Z*)-verrucarin (**40**) and *Z,E,E* isomer **41**. Verrucarins **1** and **40** are nearly equipotent in the in vitro L1210 mouse leukemia assay, but the (*E,E*)-muconate isomers **32** and **41** are less active by an order of magnitude. These data may reflect the solvolytic reactivity of **32** and **41**, since these compounds rapidly transesterify in EtOH. Seco acid **13** was essentially inactive in the L1210 assay.

The trichoverroids, verrucarins, and roridins are important groups of epoxytrichothecene mycotoxins produced by various *Myrothecium* species.[4] The macrocyclic verrucarin and roridins, in particular, have attracted considerable attention as a consequence of their potent cytotoxic properties.[5] Thus, for example, in the past three years syntheses of verrucarin A were reported by Still[6] and Tamm,[7] trichoverrin B and verrucarin J by the Fraser-Reid/Jarvis collaborative effort,[8] and roridin E and baccharin B5 by Still.[9] Syntheses of verrucarin J,[1] trichoverrol B,[10] and verrucarin B[11] have been completed in our laboratory. In addition to these, syntheses of verrucarol,[12] anguidine,[13] and calonectrin,[14] which possess the terpene skeleton of the simple trichothecene mycotoxins, have also been reported.[15]

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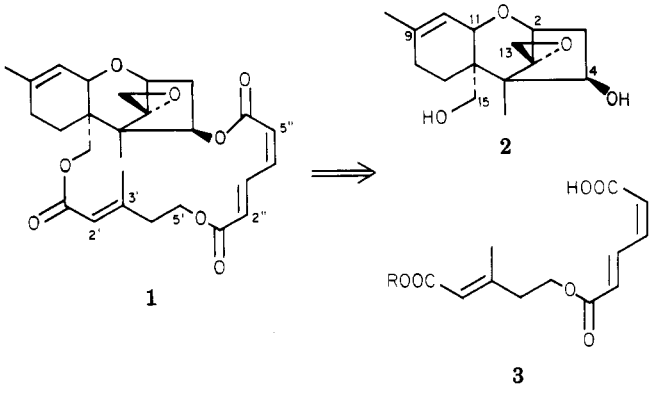
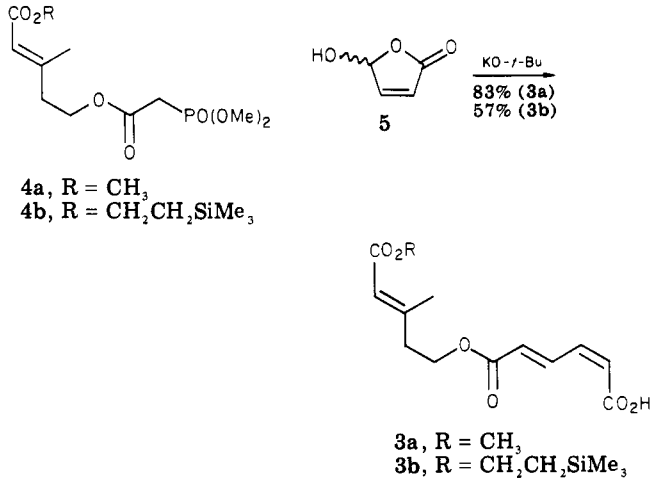
Our attention focused initially on verrucarin J (1) which was first isolated from *M. verrucaria* in 1965.[16] We imagined that **1** would be an ideal target to develop and define strategies suitable for the synthesis of other verrucarins. In particular, we wished from the outset to explore sequences in which the verrucarin would be assembled by coupling of verrucarol **2** to a differentiated diacid **3**.[17]

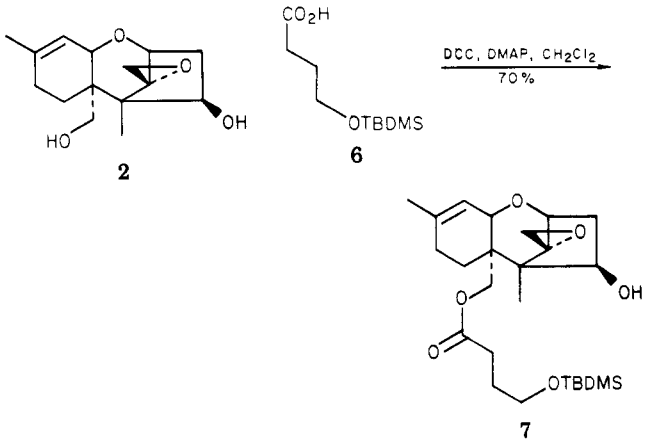


1 2 3

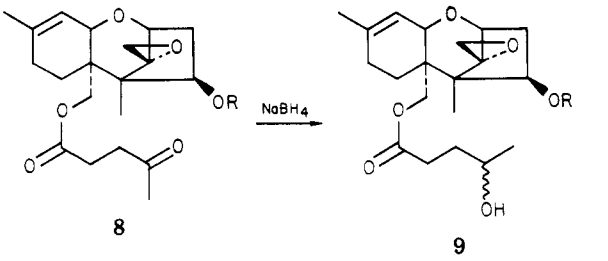
In preliminary studies we showed[15f] that a convenient method for synthesis of **3** involved the Horner–Emmons coupling[18] of a phosphonoacetate such as **4** with maleic aldehydic acid **5**.[19] Application of this procedure to β-(trimethylsilyl)ethyl ester **4b**[20] afforded **3b** which we deemed suitable for use in a synthesis of **1**.[21]



We decided to perform initial coupling experiments of **3** with a C-15 monoprotected verrucarol derivative, even though several selective C-4 acylations of **2** have been reported.[22] These examples may represent special cases since a host of other results suggest that C-15-OH is the most reactive hydroxyl under a range of acylation conditions.[1,6-11,17b] Thus, treatment of verrucarol with carboxylic acid **6**,[23] DCC, and catalytic 4-(dimethylamino)pyridine



(DMAP)[24,25] in CH_2Cl_2 afforded trichothecene **7** in 70% yield. The γ-((*tert*-butyldimethylsilyl)oxy)butyryl residue is a very convenient protecting group for C-15-OH of the trichothecene nucleus and is easily removed by treatment with *n*-Bu_4NF in THF (23 °C, 10 min).[10,26] This group was developed as an alternative to the levulinic ester protecting group[27] after discovering that $NaBH_4$ reduction of **8** did not spontaneously release the free trichothecene.



Indeed, it was necessary to treat alcohol **9** with 1.1 equiv of DBU in benzene for 61 h (23 °C) to complete the deprotection sequence.

With suitably differentiated subunits in hand, we turned to an examination of the coupling sequence which we imagined would complete the synthesis of verrucarin J.[24] Unfortunately, however, all attempts to couple **3a**, **3b**, or other simple (*Z*,*E*)-muconate half esters to trichothecenes **7** or **8** (R = H) were accompanied with substantial isom-

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(17) (a) Verrucarol used in these studies was prepared from natural anguidine by a method developed by Fraser-Reid (described in footnote 8 of ref 8). (b) For an alternative route to verrucarol from anguidine, see: Tulshian, D. B.; Fraser-Reid, B. *Tetrahedron Lett.* **1980**, 4549.
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(20) Phosphonate **4b** was prepared in 50% yield by treatment of acid **15** with 2-(trimethylsilyl)ethanol, DCC, and catalytic 4-pyrrolidinopyridine in Et_2O.
(21) Methyl ester **3a** is unsuited for use in the verrucarin synthesis since selective methods for unblocking the terminal C-1′ carboxylic acid function after esterification of **3a** to verrucarol C-4-OH are unavailable.
(22) (a) Breitenstein, W.; Tamm, C. *Helv. Chim. Acta* **1978**, *61*, 1975. (b) Notegen, E.-A.; Tori, M.; Tamm, C. *Ibid.* **1981**, *64*, 316.
(23) Acid **6** was prepared from 1,4-dihydroxybutane by monosilylation (*n*-BuLi, TBDMS-Cl, 88%) followed by oxidation of the free hydroxyl group (catalytic $RuCl_3$, $NaIO_4$, CH_3CN, H_2O, CCl_4, 53%). For details of the oxidation procedure, see: Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
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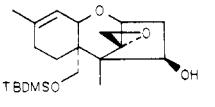
(26) TBDMS ether **i**, which has been described previously by Fraser-Reid (ref 17b), might also have been useful for our purposes. We were not, however, able to prepare **i** by the literature procedure or by a number of alternative methods (including TBDMS-OTf, lutidine). Carboxylic acid **6**, therefore, may be regarded as a "TBDMS equivalent" suitable for protection of sterically hindered alcohols.



i

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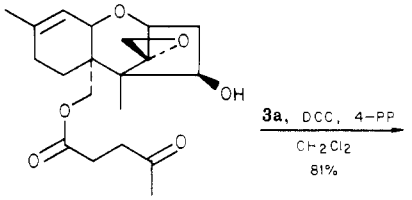

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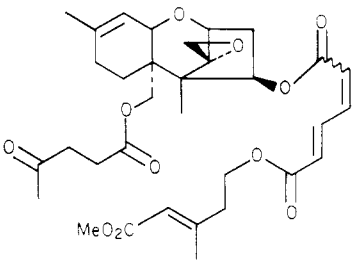
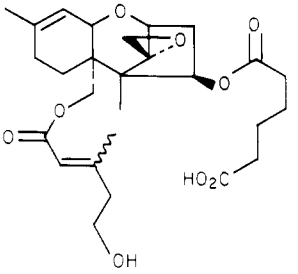


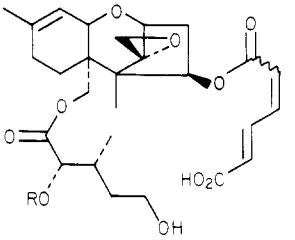
10 (60:40 mixture)

erization to (*E,E*)-muconate diesters. Best results were obtained by using DCC and 4-pyrrolidinopyridine (4-PP) in CH_2Cl_2[6,25] but up to 50% of (*E,E*)-muconates were obtained under these conditions. Similar results were realized by Tamm in his verrucarin A synthesis.[7,28] The Corey pyridine disulfide method[29] afforded exclusively the (*E,E*)-pyridinethiol ester; mixed anhydride procedures (e.g., pivaloyl chloride, Et_3N, CH_2Cl_2 followed by DMAP) and the CDI method,[30] as reported by Still,[6] also led to substantial olefin isomerization.

These results prompted us to explore an alternative strategy in which the muconate esterification would be accomplished intramolecularly.[31] We assumed that any acid (or the active ester intermediates) which might isomerize to the *E,E* series would not undergo macrocyclization. This hypothesis was supported by Tamm's observation that only (*E*)-**11** lactonized when the *E,Z* mixture was subjected to the pyridine disulfide procedure.[22a] In addition, Still and Tamm noted that only (*Z*)-**12** cyclized when the (*Z,E*)-muconate mixtures were subjected to the Mitsunobu (**12a**)[6] or the Yamaguchi mixed anhydride protocols (**12b**).[7,32]

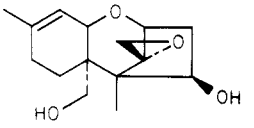


11 (*E,Z* mixture)



12 (*Z,E* mixture)
12a, R = Ac
12b, R = THP

The key intermediate of this revised approach to verrucarin J thus became seco acid **13**. The most concise



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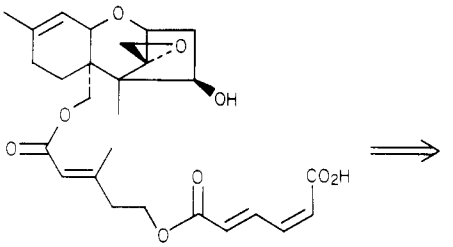
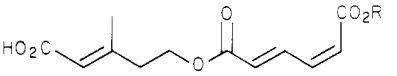


13



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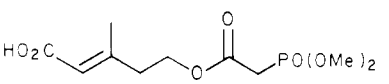
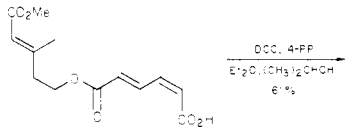


15

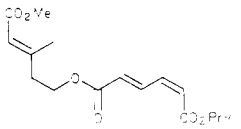
approach to **13**, clearly, would involve the direct coupling of acid **14** to C-15-OH of the trichothecene nucleus. A problem for which an immediate solution was not available, however, was the development of a mutually compatible protecting group scheme for the muconate and acrylic acid units suitable for use in a synthesis of **14**. As will be shown subsequently a synthesis of **14** (R = $CH_2CH_2SiMe_3$) was eventually developed. First, however, we explored an indirect approach wherein most of the side chain, in the form of acid **15**, was attached to the trichothecene before introduction of the muconate by the Horner–Emmons reaction discussed previously.

Treatment of 3-butyn-1-ol with Me_3Al (3.0 equiv) and Cl_2ZrCp_2 (0.25 equiv) followed by trichloroethyl chloroformate (1.1 equiv) according to Negishi's procedure[33] afforded ester **16** in 20–25% yield. Treatment of **16** with 1.2 equiv of the mixed anhydride prepared from trifluoroacetic anhydride and (dimethoxyphosphinyl)acetic acid[34] in CH_2Cl_2 containing pyridine afforded **17** in 94% yield. Deprotection of **17** to give **15** was then accomplished by treatment with Zn in THF buffered with KH_2PO_4 (76% yield).[35]

(28) In contrast, however, Still was able to esterify a (*Z,E*)-muconate derivative to a trichothecene C.4-OH by using the DCC–DMAP procedure (see ref 6). In addition, we were able to esterify **3a** with 2-propanol without olefin isomerization in preliminary studies. Nonetheless, we were unable to suppress the deleterious isomerization in the couplings of **3a** or **3b** with **7** or **8**.



3a



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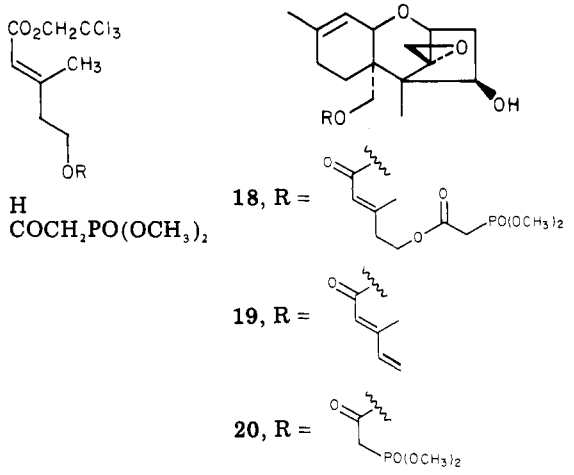
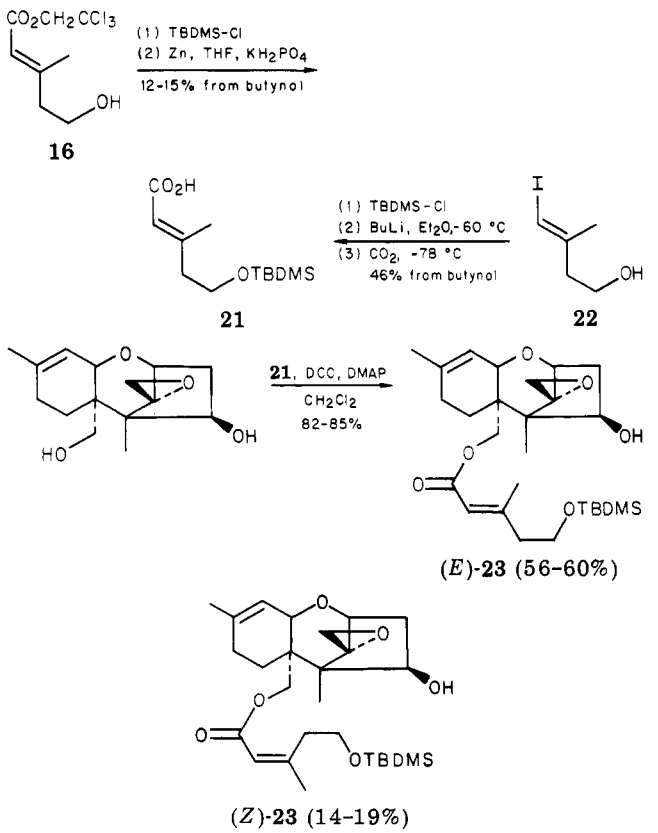
(34) Donovan, S. F.; Avery, M. A.; McMurry, J. E. *Tetrahedron Lett.* **1979**, *3287*.
(35) Just, G.; Grozinger, K. *Synthesis* **1976**, *457*.



Esterification of verrucarol[17a] with 1.5 equiv of **15**, DCC, and DMAP in CH_2Cl_2[25] afforded trichothecene monoester **18** in 34–55% yield as a 3:1 mixture of *E*/*Z* olefin isomers together with up to 19% of diene **19** (ca. 3:1 olefin mixture) and up to 19% of phosphinylacetate **20**. Diene **19** undoubtedly arises from elimination of (dimethoxyphosphinyl)acetic acid from **18** or an activated form of **15**, whereas **20** is obviously the coupling product of verrucarol and the phosphonoacetic acid liberated in the aforementioned elimination reaction. Although a number of coupling methods (DCC, mixed anhydrides, etc.) proved to be highly selective for the primary hydroxyl group of **2**, we were not able to eliminate the formation of **19**, **20**, or (*Z*)-**18**. Moreover, we were unable to separate (*E*)-**18** from its olefin isomer.

A parallel series of coupling experiments was performed by using acid **21**. This intermediate was prepared initially



from **16**, but a higher yielding sequence proceeded from 3-butyn-1-ol via the known vinyl iodide **22**.[33a] Treatment of verrucarol with 1.5 equiv of **21**, DCC, and DMAP afforded ester **23** as a mixture of *E* and *Z* isomers in 82–88% yield. Careful separation of such mixtures by silica gel chromatography afforded pure (*E*)-**23** in 56–60% overall yield along with 14–19% of (*Z*)-**23**.[36] Condensation of **2** and **21** with Mukaiyama's salt[37] afforded *E* esters almost exclusively (>10:1), but in low yield (22%) and with poor regioselectivity (ca. 6:4 C-15 vs. C-4 monoesters). Several other methods (2-pyridylthiol ester; mixed anhydride prepared from CH_3OCOCl, Et_3N, and DMAP; CDI[22a]) also afforded mixtures of olefin isomers, and the Mitsunobu procedure failed altogether. In addition, the mixed anhydride procedure developed in connection with our synthesis of trichoverrol B[10] also failed when applied to **21**.[38] All things considered, the DCC method discussed originally gave the best yield of (*E*)-**23** and was used for all preparation scale experiments.

Deprotection of (*E*)-**23** by treatment with aqueous acetic acid in THF (25 °C, 5 h) smoothly provided (*E*)-**24** in 96% yield. This compound is a known degradation product of verrucarin J[16] and, interestingly, was recently isolated as a minor metabolite of *M. verrucaria* and designated "verrol" by Jarvis.[4a] Acylation of verrol with 1.1 equiv of (dimethoxyphosphinyl)acetic acid, DCC, and DMAP afforded (*E*)-**18** in 53% yield; 33% of **24** was recovered. The use of larger excesses of carboxylic acid did not improve the yield of **18** since diacylation (C-4 and C-5′) was a serious problem under such conditions. Finally, condensation of **18** with malealdehydic acid by using the procedure outlined previously afforded verrucarin J seco acid **13** in 57–58% yield.

Although the quantities of seco acid **13** prepared by the above sequence were sufficient to complete the synthesis of verrucarin J,[1] we were disappointed with the inefficiency of the sequence (17% overall yield for the four steps from verrucarol). Accordingly, we sought an alternative method for introducing the muconate residue. We reasoned that an appropriately differentiated (*Z*,*E*)-muconate half acid could be coupled without complication to C-5′-OH of **24** by the Mitsonubu procedure since C-4-OH is a rather hindered secondary alcohol. This, indeed, proved to be the case.

Muconate **28** was synthesized as outlined in Scheme I. Coupling of (*E*)-**24** with **28** afforded seco acid ester **29** in 87% yield, deprotection[39] of which smoothly afforded seco acid **13** (81%). In this manner **13** was now available in 39% overall yield from verrucarol. In addition, this sequence afforded isomerically pure **13**, whereas **13** prepared from phosphonate (*E*)-**18** contained approximately 10% of the (*Z*,*Z*)-muconate isomer.

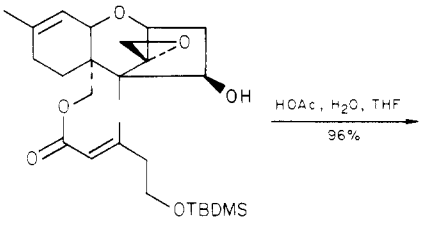
The observation that the muconate unit is stable under acidic reaction conditions (e.g., **27** → **28**) provided the key to the development of a synthesis of acid **14** (Scheme II). Unfortunately, however, we have not been able to separate the mixture of olefin isomers **29** obtained from the coupling

(36) (a) Coupling of verrucarol with (*Z*)-**21** by using the DCC–DMAP procedure afforded 41% of (*Z*)-**23** and 28% of (*E*)-**23** after separation by chromatography. This sequence was used to prepare larger quantities of (*Z*)-**23** required for the synthesis of verrucarin J isomers **40** and **41**. (b) Acid (*Z*)-**21** was prepared in 38% yield from anhydromevalonolactone by a three-step sequence: (i) NaOH, H_2O; (ii) TBDMS–OTf (3 equiv), lutidine, CH_2Cl_2; (iii) LiOH, 3:1 DME–H_2O.

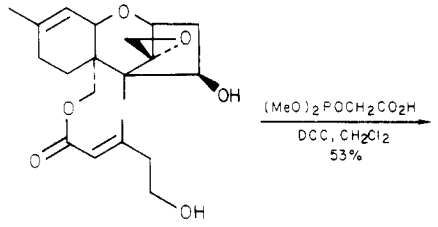
(37) Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045.

(38) No reaction was observed when verrucarol and the mixed anhydride prepared from **21** and pivaloyl chloride were treated with either *n*-BuLi–TMEDA (before addition of mixed anhydride), NaH, or KO-*t*-Bu in THF or DME. Both reaction components were recovered unchanged under these conditions. We thank A.P. Spada for performing these experiments.

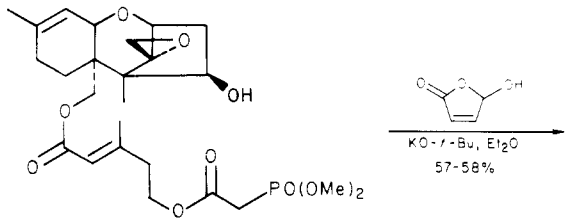
(39) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711.



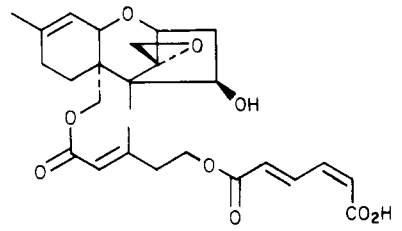
(E)-23



(E)-24



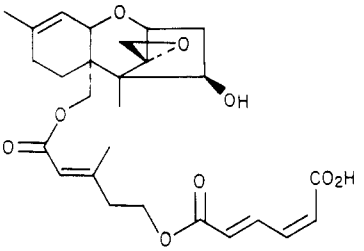
(E)-18



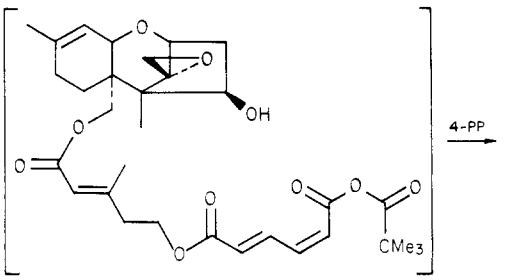
13

of **14** and verrucarol. Even though this sequence constitutes the most direct route to seco acid **13** from verrucarol, this approach is not preparatively useful in the absence of a convenient means of separating the (*E,Z*)-**29** mixture.[40] As a consequence, the transformations summarized in Scheme II have not been optimized; the yields reported are for initial trials only.

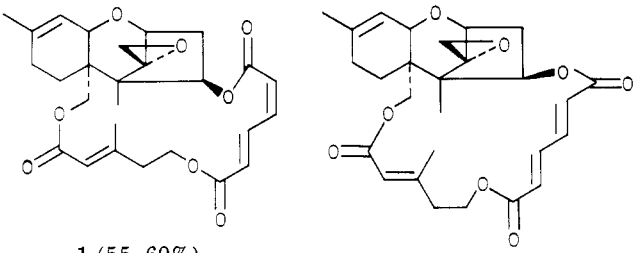
A number of conditions for macrolactonization of seco acid **13** were explored.[41] We were delighted, initially, with the observation that treatment of **13** with DCC and 4-pyrrolidinopyridine (4-PP) effected cyclization without any olefin isomerization. Unfortunately, verrucarin J was isolated in only 33% yield, together with substantial quantities of the *N*-acyl urea derived from N-acylation of DCC. In contrast, the mixed anhydride **31** prepared from **13**, pivaloyl chloride, and Et_3N efficiently cyclized to verrucarin J (55–60%) when treated with 4-pyrrolidinopyridine. Under these conditions, however, an isomer (**32**) possessing an (*E,E*)-muconate linkage was also obtained in 25–30% yield. Although we have not been successful in attempts to increase the yield of **1** by suppressing the formation of **32** (vide infra), the latter could by isomerized to verrucarin J (61%) when treated with I_2 in benzene. Interestingly, a new isomer, (*E,Z,E*)-verrucarin **33**, was also



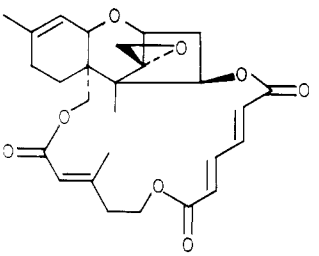
13



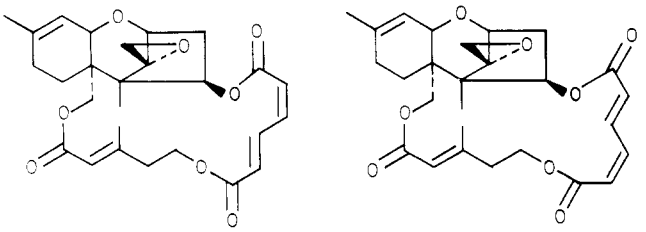
31



1 (55-60%) 32 (25-30%)



32



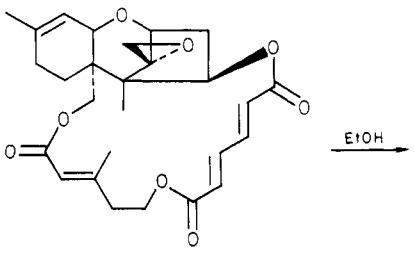
1 (61%) 33 (31%)

obtained under these conditions (31%). Nonetheless, the overall yield of verrucarin J from seco acid **13** was increased to 70–75% by virtue of the facile isomerization of **32**.

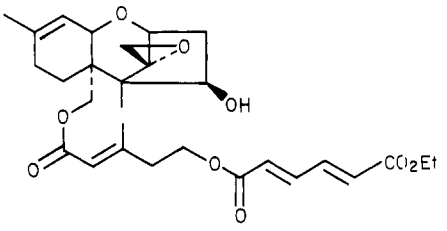
The latter results were most surprising. Prior to our first isolation[1] of **32** we were unaware of any precedent in macrolide chemistry which suggested that isomers of a natural system with unnatural olefin olefin configurations could be formed. The examples cited above (**11** and **12**) from the Still and Tamm laboratories[6,7,22a] certainly supported our (mistaken) assumption that such systems would not be easily produced. Verrucarin **32** is clearly less stable than the natural product, since no **32** remained in the I_2 isomerization experiment (TLC and NMR analysis); verrucarin J did not isomerize when subjected to identical reaction conditions. In addition, **32** undergoes rapid ($t_{1/2} \sim 3$ h) and clean solvolysis in ethanol to (*E,E,E*)-seco acid ethyl

(40) We have also been unsuccessful in attempts to separate mixtures of seco acids **13**/**39** or of verrucarin J/**40** deriving from the (*E,Z*)-**29** mixture.

(41) Macrocyclization did not occur when **13** was treated with Mukaiyama's salt (ref 37) or mesitylenesulfonyl chloride and Et_3N.



32



34

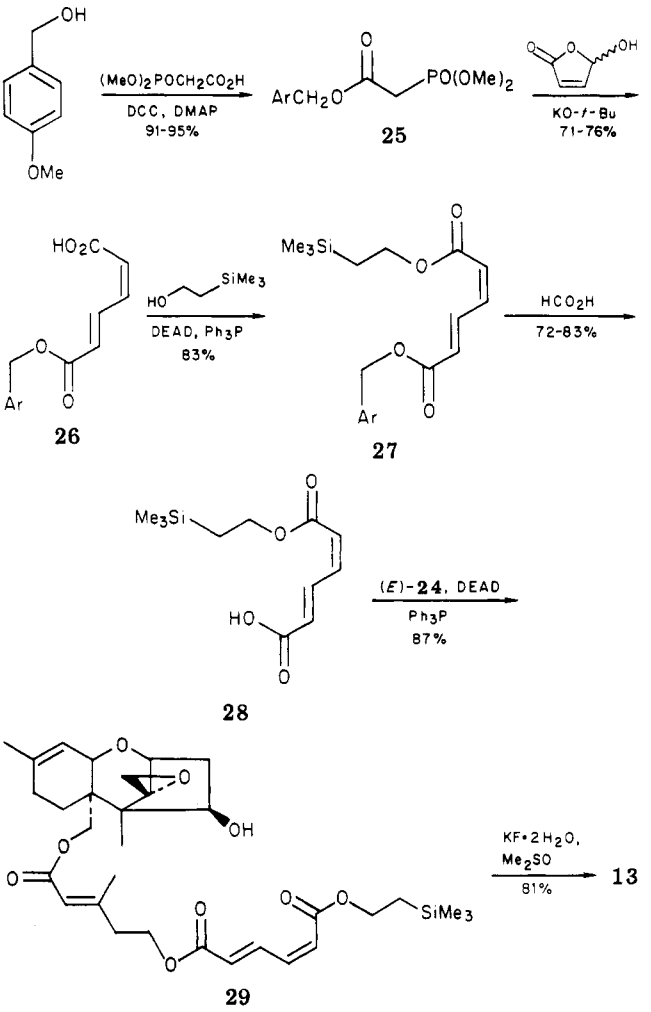
ester **34**.[42] The strain inherent in this ring system, however, is clearly insufficient to prevent the formation of **32** in the macrocyclization step.

Although the aforementioned isomerization of **32** to **1** constitutes compelling evidence of structure, additional evidence is provided by the independent synthesis outlined in Scheme III. In this regard it is interesting to note that some isomerization also occurred in the macrocyclization of (*E*,*E*,*E*)-seco acid **36**. Thus, treatment of **36** with pivaloyl chloride and Et_3N followed by 4-pyrrolidinopyridine afforded 50% of **32** together with 14% of verrucarin J.

We believe that the isomerization observed in the cyclizations of seco acids **13** and **36** occurs at the stage of the active ester intermediate. This conclusion is necessitated by the following evidence. First, control experiments established that verrucarin J (**1**) and isomer **32** do not equilibrate when treated with 4-pyrrolidinopyridine. Second, the mixed anhydride generation step (e.g., **13** → **31**) was followed by 250-MHz NMR spectroscopy in two different solvents ($CDCl_3$ and benzene-d_6). In both instances it was possible to establish that mixed anhydride **31** was generated *without detectable olefin isomerization.* Moreover, no macrocyclization occurred at 23 °C until an acylation catalyst, such as 4-PP, was introduced.[44] Addition of 4-PP initiated a rapid ring closure (~1 h) reaction with the results cited previously.

Several mechanisms for the isomerization of mixed anhydride **31** are possible. One likely candidate is the reversible Michael addition of the acylation catalyst to **31** or to the *N*-acylpyridinium salt[25a] derived from **31**.[45] If

Scheme I

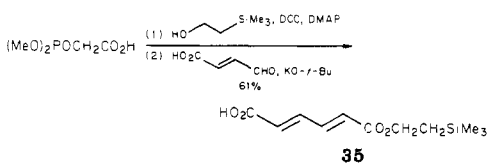


so, it should be possible to suppress the deleterious olefin isomerization by performing the macrocyclization step in the absence of nucleophilic acylation catalysts. This hypothesis led to a highly selective solution to our synthesis of trichoverrol B (**7** + **37** → **38**).[10] Unfortunately, however, attempts to extend this protocol to the synthesis of **1** have thus far met with limited success. For example, treatment of mixed anhydride **31** (generated in benzene) with DBU afforded a complex mixture of products containing, at best, only a trace of verrucarin J. The culprit here is probably the C-2′–C-3′ double bond which facilitates the elimination of the muconic acid unit from C-4′–C-5′ (cf. **17** → **19**). On the other hand, a solution of **31** in $CHCl_3$ maintained at reflux for 27 h in the presence of excess triethylamine afforded verrucarin J in 30% yield; isomer **32** was not detected under these conditions.

We were intrigued by the possibility that other isomers of verrucarin J could also be synthesized. Indeed, isomers **40** and **41** were prepared starting from (*Z*)-**23** which, originally, had been produced as the minor product of the esterification of (*E*)-**21** and verrucarol (see Scheme IV).[36] Several observations are noteworthy. First of all, isomer

(42) The solvolysis of **32** to **34** was discovered during our first attempt to measure the UV spectrum of **32**.

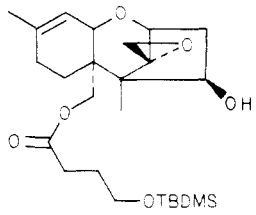
(43) Acid **35** was synthesized as shown below.



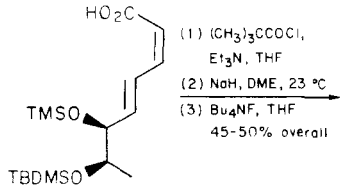
35

(44) This conclusion was also reached by monitoring the cyclization mixture by TLC. No **1** or **32** was detected in the absence of acylation catalysts. All components of this reaction system are easily resolved in 1:1 ether–CH_2Cl_2 containing 1% HCO_2H: **13**, R_f 0.4; **31**, R_f 0.5; **32**, R_f 0.65; **1**, R_f 0.8.

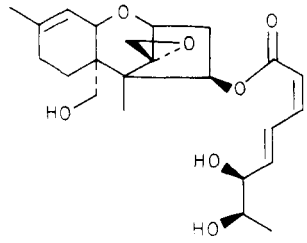
(45) Another possibility is that **31** or the derived *N*-acylpyridinium salt eliminates reversibly to a methylene ketene intermediate. For a review of methylene ketenes, see: Brown, R. F. C.; Eastwood, F. W. In "The Chemistry of Ketenes, Allenes, and Related Compounds"; S. Patai, Ed.; Wiley: New York, 1980; p 757. Olefin isomerization, however, also occurs in the esterification of angelic acid derivatives for which the methylene ketene pathway is not possible (see, for example: Beeby, P. J. *Tetrahedron Lett.* **1977**, 3379). Hence, we favor the reversible Michael addition mechanism discussed in text.



7



37



38

40 possesses the structure originally proposed for verrucarin J by Tamm.[16] Although verrucarin J and **40** are not distinguishable by TLC, the two structures are easily differentiated, as expected, by ^{1}H NMR analysis (see Experimental Section).[15e,f,46] Second, isomer **41**, but not **40**, shares with **32** the property of undergoing rapid transesterification in ethanol.[47] These data suggest that the verrucarin ring system is more tolerant of structural variation in the acrylic acid terminus than in the muconate region, an observation which is borne out in nature.[4,5]

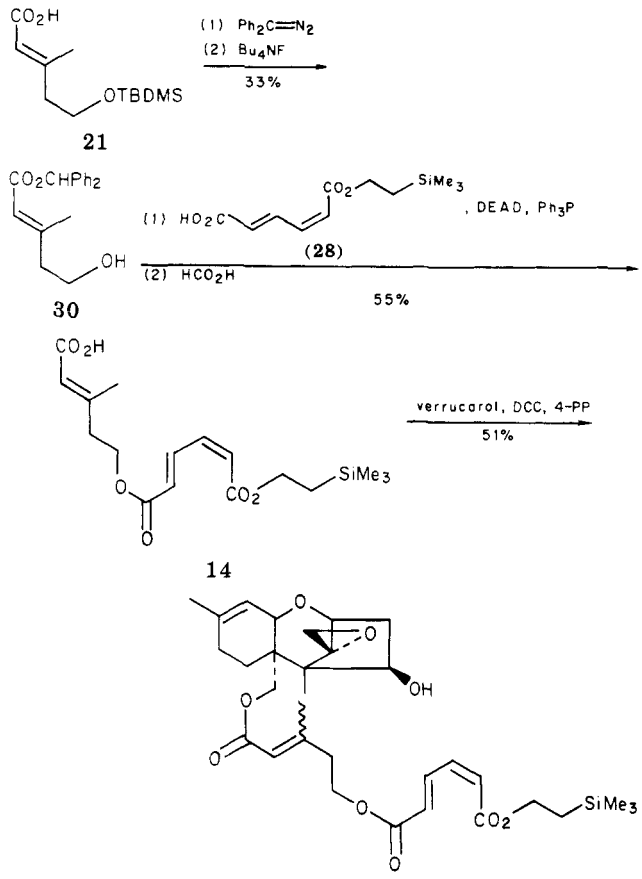
The biological properties of these verrucarin isomers are also sensitive to the nature of the macrocyclic ring system (see Table I). It is noteworthy that the in vitro activities of **1** and *Z,E,Z* isomer **40** in the L1210 mouse leukemia assay are nearly equivalent whereas the two (*E,E*)-muconate isomers (**32** and **41**, respectively) are less active by an order of magnitude. The lower activity of **32** and **41** may reflect the solvolytic sensitivity of these systems, since the expected solvolysis products (e.g., seco acid **36** in the case of **32**) would be expected to be essentially biologically inactive based on the very low activity measured for seco acid **13**.[48]

In conclusion, it is clear that the verrucarin ring system can accomodate a variety of isomeric arrangements. It is probable that our experiences with verrucarin J will not prove unique and that a rich array of unnatural macrocyclic trichothecene analogues will become available for detailed biological evaluation.[49]

Experimental Section

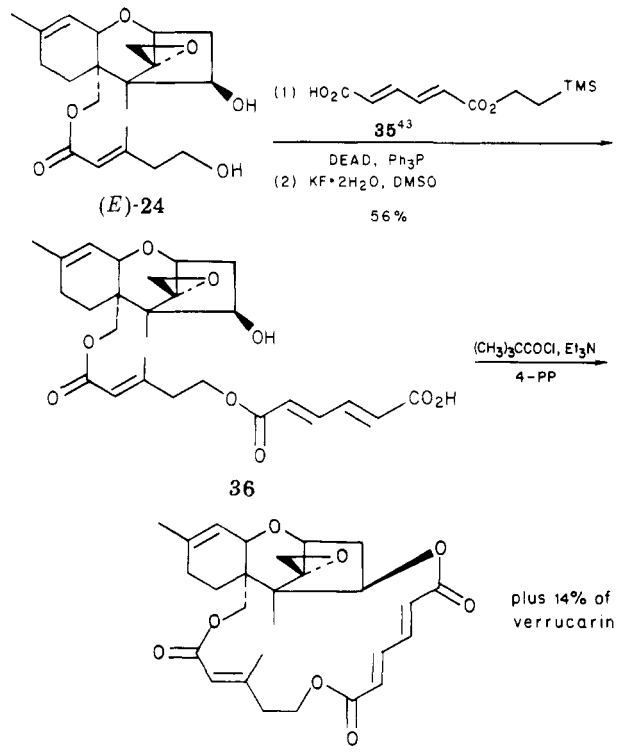
Proton (^{1}H) NMR spectra were measured at 60 MHz on a Varian T-60 or a Perkin-Elmer R-24B instrument, and at 250 or 270 MHz on Bruker WM250 and 270 instruments. Chemical shifts are reported in δ units using tetramethylsilane or the 7.27 ppm resonance of residual chloroform as internal reference. Carbon (^{13}C) NMR spectra were measured at 67.9 MHz on a Bruker WM 270 instrument or at 22.6 MHz on a JEOL FX90Q instrument. Carbon chemical shifts are reported in δ_c units using the 77.0 ppm resonance of $CDCl_3$ as internal reference. Infrared spectra were

Scheme II



29 (2:1 mixture)

Scheme III



32 (50%)

(46) Jackman, L. M.; Wiley, R. H. *J. Chem. Soc.* **1960**, 2886.

(47) A UV sample of **41** in absolute ethanol underwent clean, rapid transesterification to the (*E,E*)-seco acid ethyl ester corresponding to **39**. Isomer **40** was recovered unchanged after measurement of the UV spectrum in ethanol. In addition, **40** did not isomerize when subjected to I_2 in C_6H_6 (23 °C, 5 h).

(48) The ID_{50} values for several other trichothecenes in the L1210 in vitro assay are summarized in ref 5a. The low activity of seco acid **13** is fully consistent with previous observations that the intact macrocycle is essential for full biological activity (e.g., trichoverrins A,B).

(49) For example, while this manuscript was in preparation we learned that Still has prepared several isomers of roridin E among which are substances possessing (*E,E*)-diene units within the macrocycle (ref 9). We have also recently synthesized the (*E,E*)-muconate isomer of verrucarin B (ref 11).

Scheme IV

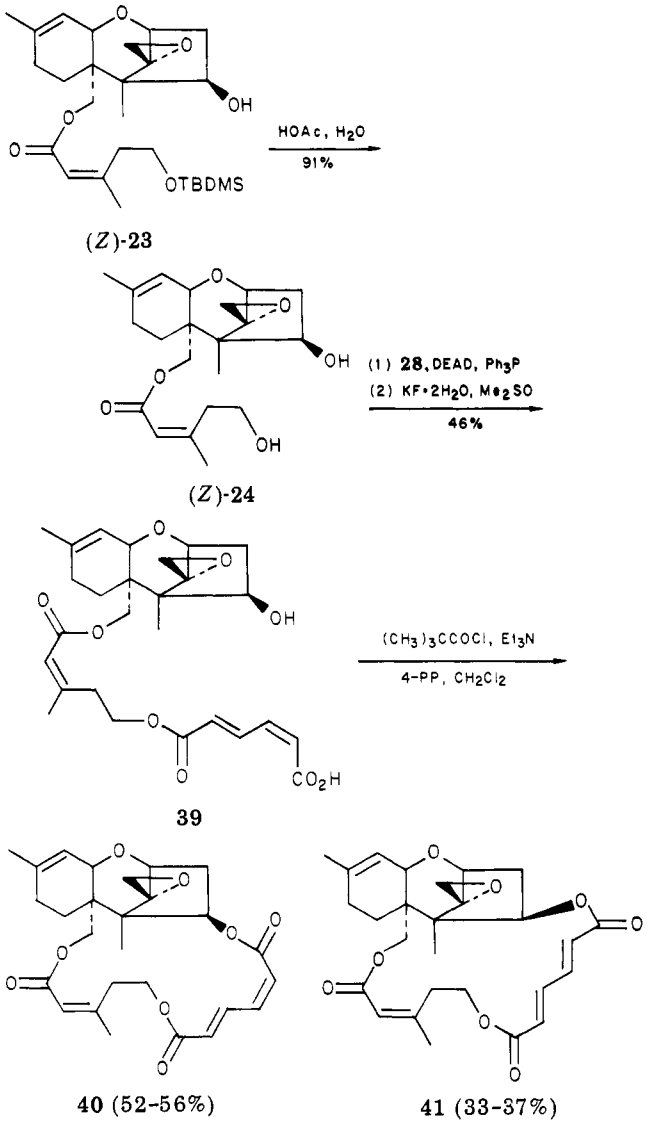


Table I[a]

compd	ID_{50} vs. L1210 cells, ng/mL
verrucarin J (1)	2.7[b]
Z,E,Z isomer 40	3.1[b]
E,E,E isomer 32	35
Z,E,E isomer 41	26
seco acid 13	247

[a] The in vitro L1210 mouse leukemia assays were performed at the Warner-Lambert/Parke-Davis Laboratories by K. Hamelehle and M. Havlick. [b] Average of two runs.

measured on a Perkin-Elmer Model 283B Infrared Spectrophotometer calibrated with the 1601 cm^{-1} absorption of polystyrene. IR spectra are reported in wave numbers (cm^{-1}). Ultraviolet spectra were measured on a Perkin-Elmer 330 UV-Visible Spectrophotometer. Wavelengths are reported in nanometers (nm). Optical rotations were measured on a Rudolph Autopol III Automatic Polarimeter using a 1 cm^3 capacity quartz cell (10 cm path length). Mass spectra were measured on a Varian MAT 44 instrument. Elemental analyses were performed by Robertson Laboratory, Inc. of Florham Park, New Jersey. Melting points were obtained on a Fisher-Johns hot stage melting point apparatus and are uncorrected.

All reactions were conducted in oven-dried (125 °C) glassware with magnetic stirring under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, THF, and DME were distilled from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2), acetonitrile, *tert*-butyl alcohol, diisopropylamine, and Me_2SO (reduced pressure) were distilled from CaH_2. Benzene and toluene were distilled from sodium metal. DMF was dried over molecular sieves and then distilled (reduced pressure). Triethylamine was predried over $CaSO_4$ and then distilled from P_2O_5. Pyridine was distilled from sodium hydroxide.

Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm × 10 cm plates coated with 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin-layer chromatography (PTLC) was performed by using 20 cm × 20 cm plates coated with 0.25, 0.5, and 1.5 mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were visualized with shortwave UV light, or by staining with either iodine vapor or by charring with ethanolic H_2SO_4. Compounds containing the trichothecene nucleus or a phosphonate group were eluted from the adsorbents with ethyl acetate; all other compounds were eluted with ether. Flash chromatography was performed as described by Still.[50] All chromatography solvents were distilled prior to use.

2,2,2-Trichloroethyl 5-Hydroxy-3-methyl-2(*E*)-pentenoate (16). Trimethylaluminum (7.5 mL of 2 M toluene solution, 15 mmol) was added to a solution of 370 mg (1.27 mmol) of bis(cyclopentadienyl)zirconium dichloride (Cp_2ZrCl_2) in 25 mL of CH_2Cl_2. The yellow solution was cooled to 0 °C and then a solution of 350 mg (5 mmol) of 3-butyn-1-ol in 3 mL of CH_2Cl_2 was added dropwise (gas evolution) at 0 °C. The solution was stirred for 19.5 h at 25 °C and then 0.75 mL (5.5 mmol) of 2,2,2-trichloroethyl chloroformate was added. The solution was stirred for 1.25 h at 25 °C and then cooled (10 °C) as 10 mL of water was added very slowly dropwise (caution: vigorous reaction). Enough 6 N HCl to dissolve the voluminous precipitate was then added. The aqueous layer was extracted with ether (3 × 15 mL) and the combined extracts dried (Na_2SO_4), filtered, and evaporated. The residue was purified by flash chromatography (60 mm column, 1:1 hexane:ether, R_f 0.28) to afford 273 mg (21%) of trichloroethyl ester **16**. The yield of **16** was 32% when this procedure was performed on a 1 mmol scale.

16: ^1H NMR (270 MHz, $CDCl_3$) δ 5.87 (br s, 1 H, H_2), 4.76 (s, 2 H, CH_2CCl_3), 3.83 (t, J = 6 Hz, 2 H, H_5), 2.47 (t, J = 6 Hz, 2 H, H_4), 2.24 (br s, 3 H, H_6), 1.75 (br s, 1 H, OH); IR (film) 3440, 2956, 1730, 1646, 1132, 1040 cm^{-1}.

5-((*tert*-Butyldimethylsilyl)oxy)-3-methyl-2(*E*)-pentenoic Acid ((*E*)-21). Method A. Imidazole (137 mg, 2.0 mmol) and 145 mg (0.96 mmol) of *tert*-butyldimethylsilyl chloride were added to a solution of 210 mg (0.80 mmol) of **16** in 1 mL of DMF. The solution was stirred for 22 h at 25 °C, then diluted with 20 mL of water, and extracted with hexane (8 × 50 mL). The combined extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated. The crude silyl ether was dissolved in 10 mL of THF and treated with zinc dust (523 mg, 8.0 mmol) and 2 mL of 1 M aqueous KH_2PO_4 (note that the 5:1 THF:buffer ratio is important).[35] The resulting slurry was stirred for 16 h at 25 °C. The mixture was then filtered and the filtrate acidified to pH 1 by addition of 6 N HCl saturated with NaCl. The mixture was extracted with ethyl acetate (6 × 10 mL) and the combined extracts dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed on a 1.5 mm silica gel plate (1% formic acid in 3:1 hexane:ether, R_f 0.43) to afford 115 mg (59%) of pure (*E*)-21.

Method B. *n*-Butyllithium (0.53 mL of 2.9 M hexane solution, 1.54 mmol) was added dropwise to a solution of 4-((*tert*-butyldimethylsilyl)oxy)-2-methyl-(*E*)-butenyl iodide (500 mg, 1.53 mmol)[33a] in 20 mL of ether at −78 °C. The solution was allowed to warm to −60 °C, stirred for 1.25 h at −60 °C, and then recooled to −78 °C. A stream of dry CO_2 gas was passed over the solution for 1 h at −78 °C. The solution was then allowed to warm to 0 °C with the CO_2 gas flow being continued for another 1 h at 0 °C. Ether (10 mL) and water (5 mL) were added and the mixture acidified to pH 2 by careful addition of 3 N HCl. The layers were separated and the aqueous layer extracted with ether (7 × 10 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to afford 403 mg of crude acid. The crude product was

(50) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

purified by flash chromatography (30 mm column, 1% formic acid in 3:1 hexane:ether) to give 281 mg (75%) of pure (*E*)-**21**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.72 (br s, 1 H, H_2), 3.77 (t, J=6 Hz, 2 H, H_5), 2.38 (t, J=6 Hz, 2 H,H_4), 2.20 (d, J=1 Hz, 3 H, H_6), 0.89 (s, 9 H, *t*-Bu), 0.05 (s, 6 H, $SiMe_2$); IR (film) 3400–2500 (br OH), 2954, 2926, 2860, 1692, 1640, 1250, 1100, 832, 772 cm^{-1}; mass spectrum, *m/e* 229 ($M^+ - CH_3$), 187 (M^+ – *t*-Bu). Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 58.74; H, 9.87.

12,13-Epoxytrichothec-9-ene-4β,15-diol 15-[5′-[(1,1-Dimethylethyl)dimethylsilyloxy]-3′-methyl-2′(*E*)-pentenoate] ((*E*)-23). A solution of 112 mg (0.55 mmol) of dicyclohexylcarbodiimide (DCC) and 10 mg (0.08 mmol) of 4-(dimethylamino)pyridine (DMAP) in 0.40 mL of CH_2Cl_2 was added to a solution of 58 mg (0.22 mmol) of verrucarol and 75 mg (0.31 mmol) of (*E*)-**21** in 0.40 mL of CH_2Cl_2. The resulting mixture (white precipitate) was stirred for 6 h at 25 °C. The mixture was then filtered and the filtrate chromatographed on a 1.5 mm silica gel plate (1:1 ether:CH_2Cl_2, R_f 0.51) to give 88 mg (82%) of a 3:1 mixture of product isomers. This mixture was separated by careful chromatography on a 1.5 mm silica gel plate (1:1 hexane:ether, 8 developments) to give 64 mg (60%) of (*E*)-**23** from the band centered at R_f 0.53 and 22 mg (19%) of (*Z*)-**23** from the faster moving band (R_f 0.62). Esterification of verrucarol with (*Z*)-**21**[36b] under analogous conditions afforded 41% of (*Z*)-**23** and 28% of (*E*)-**23**.

(*E*)-**23**: $[\alpha]^{22}_D$ –42° (*c* 1.4, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.70 (br s, 1 H, $H_{2'}$), 5.41 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.50 (m, 1 H, H_4), 4.17 (d, *J* = 12 Hz, 1 H, H_{15a}), 3.90 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.84 (d, *J* = 5 Hz, 1 H, H_2), 3.76 (t, *J* = 6 Hz, 2 H, $H_{5'}$), 3.61 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.12 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.82 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.59 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.35 (t, *J* = 6 Hz, 2 H, $H_{4'}$), 2.20 (d, *J* = 1 Hz, 3 H, $H_{6'}$), 2.05–1.75 (m, 6 H, H_7, H_8, $H_{3\beta}$, and OH), 1.65 (br s, 3 H, H_{16}), 0.89 (s, 9 H, *t*-Bu), 0.87 (s, 3 H, H_{14}), 0.05 (s, 6 H, $SiMe_2$); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 166.1, 158.2, 140.8, 118.2, 116.5, 74.2, 66.5, 65.4, 62.4, 60.8, 48.9, 47.3, 43.8, 42.6, 39.7, 27.9, 25.8, 23.1, 21.0, 19.1, 18.1, 7.0, –5.5; IR ($CHCl_3$) 3580, 3004, 2952, 2930, 2860, 1709, 1648, 1146, 1060, 962, 832 cm^{-1}; mass spectrum, *m/e* 492 (M^+), 435 (M^+ – *t*-Bu), 265 (M^+ – side chain).

(*Z*)-**23**: $[\alpha]^{22}_D$ –37° (*c* 2.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.70 (br s, 1 H, $H_{2'}$), 5.42 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.53 (m, 1 H, H_4), 4.14 (d, *J* = 12 Hz, 1 H, H_{15a}), 3.90 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.84 (d, *J* = 5 Hz, 1 H, H_2), 3.78 (t, *J* = 7 Hz, 2 H, $H_{5'}$), 3.62 (br d, *J* = 5 Hz, 2 H, H_{11}), 3.12 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.85 (t, *J* = 7 Hz, 2 H, $H_{4'}$), 2.81 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.60 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 1.98 (br s, 3 H, $H_{6'}$), 1.95–1.75 (m, 6 H, H_7, H_8, $H_{3\beta}$, and OH), 1.70 (br s, 3 H, H_{16}), 0.88 (br s, 12 H, *t*-Bu and H_{14}), 0.05 (s, 6 H, $SiMe_2$); IR (CH_2Cl_2) 3576, 2934, 2858, 1710, 1642, 1142, 1070, 832 cm^{-1}.

12,13-Epoxytrichothec-9-ene-4β,15-diol 15-(5′-Hydroxy-3′-methyl-2′(*E*)-pentenoate) ((*E*)-24). A solution of 86.0 mg (0.17 mmol) of (*E*)-**23** in 5 mL of 3:1:1 acetic acid–water–THF was stirred for 5 h at 25 °C. Heptane (20 mL, MCB reagent grade) was then added, and the mixture concentrated in vacuo. This procedure was repeated several times until the azeotropic removal of acetic acid and water was complete. The residue was purified by chromatography on a 1.5 mm silica gel plate (ethyl acetate, R_f 0.35) to give 64.1 mg (97%) of (*E*)-**24** (verrol)[4a] as a crystalline solid: mp 55–60 °C; $[\alpha]^{20}_D$ –42° (*c* 0.29, $CHCl_3$) (lit.[16] $[\alpha]_D$ –41°); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.74 (br s, 1 H, $H_{2'}$), 5.42 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.54 (m, 1 H, H_4), 4.16 (d, *J* = 12 Hz, 1 H, H_{15a}), 3.94 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.87–3.77 (br s, 2 H, $H_{5'}$), 3.84 (d, *J* = 5 Hz, H_2), 3.65 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.12 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.82 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.60 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.43 (t, *J* = 6 Hz, 2 H, $H_{4'}$), 2.21 (br s, 3 H, $H_{6'}$), 2.10–1.75 (m, 5 H, H_7, H_8 and $H_{3\beta}$), 1.71 (br s, 3 H, H_{16}), 0.88 (s, 3 H, H_{14}); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 166.0, 157.4, 140.7, 118.3, 116.9, 74.1, 66.5, 65.4, 62.7, 59.9, 48.8, 47.4, 43.6, 42.6, 39.5, 27.9, 23.1, 21.1, 18.7, 7.0; IR (CH_2Cl_2) 3600, 3060, 2960, 1712, 1650, 1224, 1150, 1074, 966, 690 cm^{-1}; mass spectrum, *m/e* 378 (M^+), 265 (M^+ – side chain), 113 (side chain).

12,13-Epoxytrichothec-9-ene-4β,15-diol 15-(5′-Hydroxy-3′-methyl-2′(*Z*)-pentenoate) ((*Z*)-24). Silyl ether (*Z*)-**23** (19.0 mg, 0.039 mmol) was deprotected by using the procedure described above for the preparation of (*E*)-**24**. The crude product was chromatographed on a 0.5 mm silica gel plate (ethyl acetate, R_f 0.34) to give 13.3 mg (91%) of pure (*Z*)-**24** as a colorless solid: mp 128.5–130 °C (recrystallized from 1:1 benzene–hexane); $[\alpha]^{22}_D$ –49° (*c* 1.33, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.82 (br s, 1 H, $H_{2'}$), 5.41 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.52 (br s, 1 H, H_4), 4.16 (d, *J* = 12 Hz, 1 H, H_{15a}), 3.93 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.83 (d, *J* = 6 Hz, 1 H, H_2), 3.82 (t, *J* = 6 Hz, 2 H, $H_{5'}$), 3.63 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.12 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.87 (t, *J* = 6 Hz, 2 H,$H_{4'}$), 2.81 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.59 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.1–1.8 (m, 7 H, H_7, H_8, $H_{3\beta}$, and 2-OH's), 1.97 (d, *J* = 1 Hz, 3 H, $H_{6'}$), 1.71 (br s, 3 H, H_{16}), 0.87 (s, 3 H, H_{14}); IR ($CHCl_3$) 3580, 3460, 3006, 2974, 1700, 1648, 1168, 1070, 964 cm^{-1}; mass spectrum, *m/e* 348 (M^+ – CH_2OH).

12,13-Epoxytrichothec-9-ene-4β,15-diol 15-[5′-([Dimethoxyphosphinylacetyl]oxy)-3′-methyl-2′(*E*)-pentenoate] ((*E*)-18). A solution of 26.2 mg (0.13 mmol) of dicyclohexylcarbodiimide and several small crystals of 4-(dimethylamino)-pyridine (DMAP) in 0.60 mL of CH_2Cl_2 was added to a solution of 23 mg (0.061 mmol) of (*E*)-**24** and 11.2 mg (0.067 mmol) of dimethylphosphonoacetic acid in 0.40 mL of CH_2Cl_2. The mixture was stirred for 5 h at 25 °C and then filtered. The filtrate was concentrated and chromatographed on a 0.5 mm silica gel plate (97:3) ethyl acetate–methanol, R_f 0.25) to give 17.1 mg (53%) of phosphonate (*E*)-**18** and 7.5 mg (33%) of recovered (*E*)-**24** (R_f 0.50).

(*E*)-**18**: $[\alpha]^{21}_D$ –33° (*c* 0.32, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.73 (br s, 1 H, $H_{2'}$), 5.43 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.63 (m, 1 H, H_4), 4.33 (t, *J* = 6 Hz, 2 H, $H_{5'}$), 4.15 (d, *J* = 12 Hz, 1 H, H_{15a}), 3.96 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.84 (d, *J* = 5 Hz, 1 H, H_2), 3.81 (d, *J* = 11 Hz, 3 H, –OMe), 3.80 (d, *J* = 11 Hz, 3 H, –OMe), 3.70 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.12 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.98 (d, *J* = 21 Hz, 2 H, $H_{2''}$), 2.81 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.59 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.52 (t, *J* = 6 Hz, 2 H, $H_{5'}$), 2.26 (d, *J* = 9 Hz, 1 H, OH), 2.21 (d, *J* = 2 Hz, 3 H, $H_{6'}$), 2.15–1.75 (m, 5 H, H_7, H_8, and $H_{3\beta}$), 1.71 (br s, 3 H, H_{16}), 0.88 (s, 3 H, H_{14}); IR (CH_2Cl_2) 3580, 2964, 1738, 1714, 1650, 1260, 1040, 690 cm^{-1}; mass spectrum, *m/e* 528 (M^+).

***p*-Methoxybenzyl (Dimethoxyphosphinyl)acetate (25).** A solution of 1.85 g (9.0 mmol) of dicylohexylcarbodiimide in 5 mL of CH_2Cl_2 was added to a cooled (ice bath) solution of 1.00 g (5.95 mmol) of dimethylphosphonoacetic acid, 0.82 mL (6.5 mmol) of p-methoxybenzyl alcohol, and 75 mg (0.61 mmol) 4-(dimethylamino)pyridine in 7 mL of CH_2Cl_2. The mixture (white precipitate) was stirred for 17 h at 25 °C and then filtered. The filtrate was concentrated and the residue purified by flash chromatography (50 mm column, 1:1 ether–CH_2Cl_2, R_f 0.36) to afford 1.63 g (95%) of pure **25**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (d, *J* = 9 Hz, 2 H), 6.89 (d, *J* = 9 Hz, 2 H), 5.12 (br s, 2 H, benzylic), 3.81 (s, 3 H, $ArOCH_3$), 3.76 (d, *J* = 11 Hz, 6 H, $-POCH_3$), 3.01 (d, *J* = 21 Hz, 2 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 165.2 (d, *J* = 6 Hz), 159.5 (s), 129.9 (s), 127.1 (s), 113.6 (s), 66.9 (s), 55.0 (s), 52.8 (d, *J* = 6 Hz, 2 C, $POCH_3$), 33.1 (d, *J* = 135 Hz, CH_2P); IR (film) 2960, 2840, 1734, 1614, 1586, 1516, 1250, 1030 cm^{-1}; mass spectrum, *m/e* 288 (M^+). Anal. Calcd. for $C_{12}H_{17}O_6P$: C, 50.00; H, 5.94. Found C, 50.23; H, 6.04.

Mono(*p*-methoxybenzyl) (*E,Z*)-Muconate (26). A solution of 586 mg (5.85 mmol) of malealdehydic acid[19] in 40 mL of ether and solution of 1.29 g (11.5 mmol) of potassium *tert*-butoxide in 40 mL of *tert*-butyl alcohol were added dropwise via separate addition funnels to a cooled (ice bath) solution of 1.58 g (5.47 mmol) of phosphonate **25** in 50 mL of ether. The mixture (white precipitate) was stirred for 3 h at 25 °C and then poured into 50 mL of water. Ether (100 mL) was added and the cooled (ice bath) mixture acidified to pH 2 by careful addition of 3 N HCl. The layers were separated and the aqueous phase extracted with ether (5 × 100 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give 1.82 g of white solid. The crude muconate was purified by flash chromatography (60 mm column, 1% formic acid in 2:1 hexane:ether, R_f 0.21 for **26** and R_f 0.3 for the *Z,Z* isomer; mixed fractions were rechromatographed) to give 0.10 g (7%) of the Z,Z isomer and 1.1 g (76%) of **26**: mp 118.5–120 °C (recrystallized from CH_2Cl_2–hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 12, 16 Hz, 1 H), 7.35 (d, *J* = 9 Hz, 2 H, aromatic), 6.91 (d, *J* = 9 Hz, 2 H, aromatic), 6.75 (t, *J* = 12 Hz, 1 H), 6.18 (d, *J* = 16 Hz, 1 H), 6.00 (d, *J* = 12 Hz, 1 H), 5.18 (br s, 2 H, benzylic), 3.82 (s, 3 H, OMe); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 170.4, 165.8, 159.6, 142.5, 138.5, 130.1, 129.5, 127.8, 123.8, 113.9,

66.4, 55.1; IR (CH_2Cl_2) 3500–2400 (br OH), 1716, 1696, 1612, 1602, 1514, 1230 cm^{-1}; mass spectrum, m/e 262 (M^+); UV (EtOH) 262 (ϵ 21 600), 227 (ϵ 15 500). Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found C, 63.96; H, 5.68.

p-Methoxybenzyl 2-(Trimethylsilyl)ethyl (*E*,*Z*)-Muconate (27). Diethyl azodicarboxylate (0.19 mL, 1.21 mmol) was added to a cooled (10–15 °C) solution of 161 mg (0.61 mmol) of **26**, 0.11 mL (0.77 mmol) of 2-(trimethylsilyl)ethanol, and 322 mg (1.22 mmol) of triphenylphosphine in 10 mL of THF. The yellow solution was stirred for 2.5 h at 25 °C and then the solvent was removed in vacuo. The crude product was purified by flash chromatography (60 mm column, 10:1 hexane:ethyl acetate, R_f 0.24, mixed fractions were rechromatographed) to give 185 mg (83%) of pure crystalline diester **27**: mp 42–43 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.42 (dd, J = 12, 16 Hz, 1 H), 7.34 (d, J = 9 Hz, 2 H, aromatic), 6.90 (d, J = 9 Hz, 2 H, aromatic), 6.61 (t, J = 12 Hz, 1 H), 6.12 (d, J = 16 Hz, 1 H), 5.95 (d, J = 12 Hz, 1 H), 5.16 (s, 2 H, benzylic), 4.30–4.24 (m, 2 H, OCH_2), 3.82 (s, 3 H, $-OCH_3$), 1.08–1.02 (m, 2 H, CH_2Si), 0.06 (s, 9 H, $SiMe_3$); IR (CH_2Cl_2) 2960, 2900, 2840, 1710, 1612, 1602, 1516, 1242, 1162, 836 cm^{-1}; mass spectrum, m/e 362 (M^+); UV (EtOH) 264 (ϵ 30 500), 227 (ϵ 17 400). Anal. Calcd for $C_{19}H_{26}O_5Si$: C, 62.95; H, 7.23. Found: C, 62.84; H, 7.05.

Mono-2-(trimethylsilyl)ethyl (*E*,*Z*)-Muconate (28). A solution of 490 mg (1.35 mmol) of diester **27** in 3 mL of formic acid was stirred for 2 h at 25 °C. Carbon tetrachloride was added and the solution concentrated in vacuo. This procedure was repeated several times to remove the formic acid (HCO_2H–CCl_4 azeotrope). Purification of the resulting white solid by flash chromatography (50 mm column, 1% formic acid in 3:1 hexane–ether, R_f 0.21, mixed fractions were rechromatographed) afforded 251 mg (76%) of pure **28**: mp 70–72 °C (recrystallized from CH_2Cl_2–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 8.52 (dd, J = 12, 16 Hz, 1 H), 6.62 (t, J = 12 Hz, 1 H), 6.11 (d, J = 16 Hz,1 H), 6.00 (d, J = 12 Hz, 1 H), 4.32–4.25 (m, 2 H, OCH_2), 1.10–1.03 (m, 2 H, CH_2Si), 0.07 (s, 9 H, $SiMe_3$); IR (CH_2Cl_2) 3300–2500 (br OH), 3050, 2958, 2900, 1712, 1696, 1682, 1646, 1602, 1254, 1176, 858, 836 cm^{-1}; mass spectrum, m/e 242 (M^+), UV (EtOH) 261 (ϵ 21 600). Anal. Calcd for $C_{11}H_{18}O_4Si$: C, 54.52; H, 7.49. Found: C, 54.29; H, 7.48.

Verrucarin J Seco Acid 2-(Trimethylsilyl)ethyl Ester (29). Diethyl azodicarboxylate (0.025 mL, 0.158 mmol) was added to a solution of 42 mg (0.158 mmol) of triphenylphosphine, 22 mg (0.091 mmol) of acid **28** and 30.0 mg (0.079 mmol) of (*E*)-**24** in 1.5 mL of THF. The light yellow solution was stirred for 1 h at 25 °C. The solvent was evaporated leaving 148 mg of clear yellow syrup which was chromatographed on a 1.5 mm silica gel plate (1% HCO_2H in 1:1 hexane:ether, 3 developments, R_f 0.09–0.18) to give 42 mg (87%) of pure **29**: mp 42–46 °C; $[\alpha]^{20}_D$ −28° (c 4.2, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.41 (dd, J = 11, 16 Hz, 1 H, $H_{3''}$), 6.61 (t, J = 11 Hz, 1 H, $H_{4''}$), 6.07 (d, J = 16 Hz, 1 H, $H_{2''}$), 5.95 (d, J = 11 Hz, 1 H, $H_{5''}$), 5.68 (br s, 1 H, $H_{2'}$), 5.39 (br d, J = 5 Hz, 1 H, H_{10}), 4.48 (m, 1 H, H_4), 4.33 (t, J = 7 Hz, 2 H, $H_{5'}$), 4.26 (m, 2 H, $-OCH_2$), 4.15 (d, J = 12 Hz, 1 H, H_{15a}), 3.90 (d, J = 12 Hz, 1 H, H_{15b}), 3.81 (d, J = 5 Hz, 1 H, H_2), 3.60 (br d, J = 5 Hz, 1 H, H_{11}), 3.09 (d, J = 4 Hz, 1 H, H_{13a}), 2.79 (d, J = 4 Hz, 1 H, H_{13b}), 2.57 (dd, J = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.52 (t, J = 7 Hz, 2 H, $H_{4'}$), 2.21 (d, J = 1 Hz, 3 H, $H_{6'}$), 2.0–1.7 (m, 6 H, H_7, H_8, $H_{3\beta}$, and OH), 1.69 (br s, 3 H, H_{16}), 1.04 (m, 2 H, CH_2Si), 0.84 (s, 3 H, H_{14}), 0.05 (s, 9 H, $SiMe_3$); IR ($CHCl_3$) 3580, 3004, 2960, 1712, 1650, 1602, 1171, 1148 cm^{-1}; UV (EtOH) 263 nm (ϵ 24 800), 218 nm (ϵ 18 800).

Verrucarin J Seco Acid (13). Method A. A solution of potassium *tert*-butoxide in *tert*-butyl alcohol (0.30 mL of 0.26 M solution, 0.08 mmol) was added dropwise to a solution of 5.0 mg (0.05 mmol) of malealdehydic acid and 13.0 mg (0.025 mmol) of phosphonate (*E*)-**18** in 0.40 mL of *tert*-butyl alcohol. The solution was stirred for 3 h at 25 °C. Analytical TLC still showed some starting material remaining so an additional 0.050 mL (0.015 mmol) of potassium *tert*-butoxide solution was added. A few minutes later a considerable amount of yellow precipitate began to form. The reaction was then quenched by addition of 1 mL of water and 3 mL of ether. The pH was adjusted to 2 by careful addition of 1 N HCl. The layers were separated and the aqueous phase extracted with ether (3 × 3 mL) and ethyl acetate (4 × 3 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give 14.5 mg of a colorless syrup. This crude product was chromatographed on a 0.25 mm silica gel plate (1% HCO_2H in 1:1 ether:CH_2Cl_2, R_f 0.37) to give 7.1 mg (57%) of verrucarin J seco acid **13** which contained approximately 10% of a muconate isomer.

Method B. Water (0.016 mL, 0.98 mmol) was added to a solution of 27 mg (0.46 mmol) of anhydrous potassium fluoride and 39.5 mg (0.0655 mmol) of ester **29** in 3 mL of Me_2SO. The resulting mixture was stirred for 42.5 h at 25 °C. The reaction mixture (white precipitate) was then cooled in an ice bath as 25 mL of water and 15 mL of ethyl acetate were added. The pH was lowered to 1.5 by careful addition of 3 N HCl. The layers were separated and the aqueous phase extracted with ethyl acetate (5 × 15 mL) and CH_2Cl_2 (2 × 15 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give 398 mg of yellow liquid. The crude product (containing a large amount of Me_2SO) was chromatographed on a 1.5 mm silica gel plate (1% formic acid in 1:1 ether–CH_2Cl_2) to give 30 mg of impure product. This material was rechromatographed on a 0.25 mm silica gel plate (1% formic acid in 1:1 ether:CH_2Cl_2, R_f 0.42) to afford 26.8 mg (81%) of isomerically pure crystalline seco acid **13**: mp 63–66 °C; $[\alpha]^{20}_D$ −26° (c 0.81, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.35 (dd, J = 11, 16 Hz, 1 H, $H_{3''}$), 6.64 (t, J = 11 Hz, 1 H, $H_{4''}$), 6.02 (d, J = 16 Hz, 1 H, $H_{2''}$), 5.97 (d, J = 11 Hz, 1 H, $H_{5''}$), 5.87 (br s, 1 H, $H_{2'}$), 5.43 (br d, J = 6 Hz, 1 H, H_{10}), 4.84 (dd, J = 2, 8 Hz, 1 H, H_4), 4.34 (m, 2 H, $H_{5'}$), 4.07 (m, 2 H, H_{15}), 3.87 (d, J = 6 Hz, 1 H, H_2), 3.78 (br d, J = 6 Hz, 1 H, H_{11}), 3.16 (d, J = 4 Hz, 1 H, H_{13a}), 2.85 (d, J = 4 Hz, 1 H, H_{13b}), 2.68 (dd, J = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.57 (t, J = 6 Hz, 2 H, $H_{4'}$), 2.21 (d, J = 2 Hz, 3 H, $H_{6'}$), 2.1–1.8 (m, 5 H, H_7, H_8, and $H_{3\beta}$), 1.72 (br s, 3 H, H_{16}), 0.98 (s, 3 H, H_{14}); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 167.3, 166.0, 165.8, 156.2, 141.1, 140.7, 139.0, 128.4, 124.9, 118.3, 117.6, 78.5, 74.7, 66.3, 65.7, 62.9, 61.3, 49.1, 47.7, 42.4, 39.7, 39.4, 27.8, 23.2, 21.2, 18.0, 7.1; IR ($CHCl_3$) 3004, 2974, 1710, 1650, 1601, 1438, 1148 cm^{-1}; mass spectrum, m/e 360 (M^+ − muconic acid); UV (EtOH) 263 (ϵ 33 500), 221 (ϵ 29 100).

Verrucarin J (1) and (*E*,*E*,*E*)-Verrucarin (32). Pivaloyl chloride (0.0048 mL, 0.039 mmol) was added to a solution of triethylamine (0.009 mL, 0.065 mmol) and 12.9 mg (0.026 mmol) of verrucarin J seco acid (**13**) in 30 mL of CH_2Cl_2.[51] The solution was stirred for a few minutes at 25 °C and then two small crystals of 4-pyrrolidinopyridine were added. The solution was stirred for 2.5 h at 25 °C. Analytical TLC still showed some seco acid remaining so an additional 0.009 mL (0.065 mmol) of triethylamine was added followed by 0.0048 mL (0.039 mmol) of pivaloyl chloride. The solution was stirred for an additional 1.5 h at 25 °C and then the solvent was evaporated. The residue was chromatographed on a 0.5 mm silica gel plate (1:1 ether–CH_2Cl_2) to afford 6.7 mg (54%) of synthetic verrucarin J (R_f 0.70) and 4.0 mg (32%) of *E*,*E*,*E* isomer **32** (R_f 0.53), both of which were obtained as crystalline solids. The cyclization was complete within 1 h at 25 °C when **13** was treated 3–4 equiv of pivaloyl chloride and 5 equiv of Et_3N at the start of the reaction.

Synthetic verrucarin J so obtained[51] was identical in all respects with an authentic sample provided by Professor B. Jarvis: mp >290 °C (recrystallized from $CHCl_3$–Et_2O) (lit.[16] mp >315 °C); $[\alpha]^{20}_D$ +40° (c 0.33, C_6H_6) (lit.[16] $[\alpha]^{23}_D$ +41°); ^1H NMR (270 MHz, $CDCl_3$) δ 8.07 (dd, J = 11, 16 Hz, 1 H, $H_{3''}$), 6.63 (t, J = 11 Hz, 1 H, $H_{4''}$), 6.11 (d, J = 11 Hz, 1 H, $H_{5''}$), 6.01 (d, J = 16 Hz, 1 H, $H_{2''}$), 6.01 (dd, J = 4, 8 Hz, 1 H, H_4), 5.84 (br s, 1 H, $H_{2'}$), 5.46 (br d, J = 5 Hz, 1 H, H_{10}), 4.47 (m, 1 H, $H_{5'a}$), 4.44 (d, J = 13 Hz, 1 H, H_{15a}), 4.15 (m, 1 H, $H_{5'b}$), 3.97 (d, J = 13 Hz, 1 H, H_{15b}), 3.86 (d, J = 5 Hz, 1 H, H_2), 3.76 (br d, J = 5 Hz, 1 H, H_{11}), 3.15 (d, J = 4 Hz, 1 H, H_{13a}), 2.84 (d, J = 4 Hz, 1 H, H_{13b}), 2.53 (m, 3 H, $H_{4'}$, and $H_{3\alpha}$), 2.29 (br s, 3 H, $H_{6'}$), 2.2–1.8 (m, 5 H, H_7, H_8, and $H_{3\beta}$), 1.72 (br s, 3 H, H_{16}), 0.84 (s, 3 H, H_{14}); IR (CH_2Cl_2) 3022, 2962, 1712, 1650, 1224, 1182 cm^{-1}; mass spectrum, m/e 484 (M^+);

(51) Seco acid **13** prepared from phosphonate (*E*)-**18** contains approximately 10% of the (*Z*,*Z*)-muconate isomer. Macrocyclization of such mixtures afforded verrucarin J containing the corresponding amount of a verrucarin isomer (probably the (*Z*,*Z*)-muconate derivative) which was removed by crystallization from $CHCl_3$–ether (see footnote 17a of ref 1). The latter isomer was not detected when isomerically pure **13** (prepared as outlined in Scheme I) served as the substrate for the macrocyclization step.

UV (EtOH) 262 (ε 20 400), 218 (ε 27 600).

32: mp 136–142 °C; $[\alpha]^{20}_D$ +64° (*c* 0.36, C_6H_6); ^{1}H NMR (270, $CDCl_3$) δ 7.41 (dd, *J* = 12, 14 Hz, 1 H, $H_{3''}$ or $H_{4''}$), 7.26 (dd, *J* = 12, 15 Hz, 1 H, $H_{4''}$ or $H_{3''}$), 6.46 (d, *J* = 14 Hz, 1 H, $H_{2''}$ or $H_{5''}$), 6.16 (d, *J* = 15 Hz, 1 H, $H_{5''}$ or $H_{2''}$), 5.78 (br s, 1 H, $H_{2'}$), 5.43 (br d, *J* = 6 Hz, 1 H, H_{10}), 5.39 (dd, *J* = 3, 7 Hz, 1 H, H_4), 4.57–4.47 (m, 1 H, $H_{5'a}$), 4.44 (d, *J* = 13 Hz, 1 H, H_{15a}), 4.34–4.25 (m, 1 H, $H_{5'b}$), 3.95 (d, *J* = 13 Hz, 1 H, H_{15b}), 3.89 (d, *J* = 6 Hz, 1 H, H_2), 3.70 (br d, *J* = 6 Hz, 1 H, H_{11}), 3.12 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.83 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.68 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.5–2.3 (m, 3 H, $H_{4'}$ and $H_{3\beta}$), 2.29 (d, *J* = 1 Hz, 3 H, $H_{6'}$), 2.10–1.90 (m, 4 H, H_7 and H_8), 1.74 (br s, 3 H, H_{16}), 0.94 (s, 3 H, H_{14}); IR (CH_2Cl_2) 3060, 2980, 1720, 1650, 1228, 1144, 1080, 690 cm^{-1}; mass spectrum, *m/e* 484 (M^+); UV (decomposes in EtOH to give **34**); high-resolution mass spectrum, calcd for $C_{27}H_{32}O_8$ *m/e* 484.210, found *m/e* 484.210.

34: Prepared by ethanolysis of **32** ($t_{1/2}$ ~ 3 h, TLC analysis); R_f 0.45 (1:1 ether–CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.4–7.2 (m, 2 H, $H_{3''}$ and $H_{4''}$), 6.3–6.15 (m, 2 H, $H_{4''}$ and $H_{5''}$), 5.70 (br s, 1 H, $H_{2'}$), 5.41 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.50 (m, 1 H, H_4), 4.35 (t, *J* = 7 Hz, 2 H, $H_{5'}$), 4.25 (q, *J* = 7 Hz, 2 H, OCH_2CH_3), 4.17 (d, *J* = 13 Hz, 1 H, H_{15a}), 3.93 (d, *J* = 13 Hz, 1 H, H_{15b}), 3.84 (d, *J* = 5 Hz, 1 H, H_2), 3.65 (br s, 1 H, OH), 3.62 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.12 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.81 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.57 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.54 (t, *J* = 7 Hz, 2 H, $H_{4'}$), 2.22 (br s, 3 H, $H_{6'}$), 2.1–1.8 (m, 5 H, H_7, H_8, and $H_{3\beta}$), 1.71 (br s, 3 H, H_{16}), 1.32 (t, *J* = 7 Hz, 3 H, OCH_2CH_3), 0.87 (s, 3 H, H_{14}); UV (EtOH) 263 (ε 24 500), 217 (ε 20 700).

Isomerization of 32 to Verrucarin J and *E,Z,E* Isomer 33. One small crystal of I_2 was added to a solution of 1.3 mg of **32** in 1 mL of dry benzene. The resulting red solution was stirred at 25 °C for 90 min and then was diluted with 10 mL of benzene. Solid sodium sulfite (Na_2SO_3) was added and the mixture stirred at 25 °C until the iodine color had disappeared. The mixture was filtered and the filtrate concentrated in vacuo. The residue was chromatographed on a 0.25 mm silica gel plate (1% methanol in CH_2Cl_2, 5 developments) to afford 0.8 mg (61%) of verrucarin J (R_f 0.60) and 0.4 mg (31%) of the *E,Z,E* isomer **33** (R_f 0.63).

33: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 12, 16 Hz, 1 H, $H_{4''}$), 6.71 (t, *J* = 12 Hz, 1 H, $H_{3''}$), 6.33 (dd, *J* = 5, 8 Hz, 1 H, H_4), 6.20 (d, *J* = 16 Hz, 1 H, $H_{5''}$), 5.93 (d, *J* = 12 Hz, 1 H, $H_{2''}$), 5.90 (br s, 1 H, $H_{2'}$), 5.52 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.39–4.43 (m, 2 H, $H_{5'}$), 4.22 (d, *J* = 13 Hz, 1 H, H_{15a}), 4.11 (d, *J* = 5 Hz, 1 H, H_{11}), 4.02 (d, *J* = 13 Hz, 1 H, H_{15b}), 3.88 (d, *J* = 5 Hz, 1 H, H_2), 3.19 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.86 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.8–2.5 (m, 3 H, $H_{4'}$ and $H_{3\alpha}$), 2.23 (br s, 3 H, $H_{6'}$), 2.2–1.8 (m, 5 H, H_7, H_8, and $H_{3\beta}$), 1.72 (br s, 3 H, H_{16}), 0.75 (s, 3 H, H_{14}); mass spectrum, *m/e* 484 (M^+).

Mono-2-(trimethylsilyl)ethyl (*E,E*)-Muconate (35). A solution of 479 mg (2.3 mmol) of dicyclohexylcarbodiimide in 1 mL of CH_2Cl_2 was added to a cooled (10 °C) solution of 260 mg (1.55 mmol) of dimethoxyphosphinylacetic acid, 0.24 mL (1.7 mmol) of 2-(trimethylsilyl)ethanol, and 19 mg (0.155 mmol) of 4-(dimethylamino)pyridine in 1 mL of CH_2Cl_2. The mixture (white precipitate) was stirred for 16 h at 25 °C and then filtered. The crude product was purified by flash chromatography (50 mm column, 1:1 ether:CH_2Cl_2, R_f 0.45) to give 429 mg of phosphonate ester which was distilled (Kugelrohr, 160–163 °C (0.35 mmHg)) to afford 381 mg (92%) of pure phosphonate: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.25–4.21 (m, 2 H, OCH_2), 3.80 (d, *J* = 11 Hz, 6 H, OMe), 2.96 (d, *J* = 21 Hz, 2 H, PCH_2), 1.05–0.98 (m, 2 H, CH_2Si), 0.03 (s, 9 H, $SiMe_3$); IR (film) 2954, 2900, 2856, 1732, 1450, 1400, 1260, 1054, 1030, 834 cm^{-1}; mass spectrum, *m/e* 268 (M^+). Anal. Calcd for $C_9H_{21}O_5PSi$: C, 40.29; H, 7.89. Found: C, 40.68; H, 8.09.

A solution of 22.0 mg (0.22 mmol) of fumaraldehydic acid[52] in 3 mL of ether and a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (1.65 mL of 0.28 M solution, 0.46 mmol) were added dropwise simultaneously, but separately, to a solution of 59 mg (0.22 mmol) of the above phosphonate in 3 mL of ether. The cloudy yellow mixture was stirred for 6 h at 25 °C and then 5 mL of water was added. The mixture was acidified to pH 1.5 by slow addition of 3 N HCl and then extracted with ether (5 × 100 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to afford 65 mg of crude product. The crude material was chromatographed on a 0.5 mm silica gel plate (1% formic acid in 3:1 hexane–ether, R_f 0.22) to afford 35 mg (66%) of a 5:1 mixture of **35** and its *Z,E* isomer. Recrystallization of this mixture from hexane–CH_2Cl_2 afforded pure (*E,E*)-**35**: mp 135.5–137 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47–7.30 (m, 2 H), 6.26–6.18 (m, 2 H), 4.32–4.25 (m, 2 H, OCH_2), 1.09–1.02 (m, 2 H, CH_2Si), 0.07 (s, 9 H, $SiMe_3$); IR (CH_2Cl_2) 3400–2400 (br OH), 2958, 2900, 1708, 1695, 1612, 1002, 908, 856, 836 cm^{-1}; mass spectrum, *m/e* 227 ($M^+ - CH_3$), 199 ($M^+ - CH_3 - C_2H_4$); UV (EtOH) 261 (ε 24 500).

(*E,E,E*)-Verrucarin J Seco Acid (36). Diethyl azodicarboxylate (0.015 mL, 0.095 mmol) was added to a solution of 25.0 mg (0.095 mmol) of triphenylphosphine, 15.0 mg (0.062 mmol) of acid **35**, and 18.0 mg (0.0475 mmol) of (*E*)-**24** in 1 ml of THF. The solution was stirred for 1.5 h at 25 °C, and the all volatile components were removed in vacuo. The residue was chromatographed on a 1.5 mm silica gel plate (1% HCO_2H in 1:1 hexane–ether, 3 developments, R_f 0.15–0.25) to afford 23 mg (80%) of the seco acid β-(trimethylsilyl)ethyl ester: mp 59–62 °C; $[\alpha]^{20}_D$ −31° (*c* 1.89, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.2 (m, 2 H, $H_{3''}$ and $H_{4''}$), 6.25–6.15 (m, 2 H, $H_{2''}$ and $H_{5''}$), 5.69 (br s, 1 H, $H_{2'}$), 5.4 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.49 (m, 1 H, H_4), 4.34 (t, *J* = 7 Hz, 2 H, $H_{5'}$), 4.27 (m, 2 H, OCH_2), 4.16 (d, *J* = 12 Hz, 1 H, H_{15a}), 3.91 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.83 (d, *J* = 5 Hz, 1 H, H_2), 3.61 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.11 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.80 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.59 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.53 (t, *J* = 7 Hz, 2 H, $H_{4'}$), 2.21 (br s, 3 H, $H_{6'}$), 2.05–1.7 (m, 6 H, H_8, H_7, $H_{3\beta}$, and OH), 1.70 (br s, 3 H, H_{16}), 1.04 (m, 2 H, CH_2Si), 0.86 (s, 3 H, H_{14}), 0.04 (s, 9 H, $SiMe_3$); IR ($CHCl_3$) 3580, 3480, 3010, 2958, 2904, 1710, 1242, 1150, 1072 cm^{-1}; UV (EtOH) 264 (ε 32 800), 219 (ε 19 700).

Water (0.0095 mL, 0.528 mmol) was added to a solution of 15.4 mg (0.264 mmol) of potassium fluoride and 20.0 mg (0.033 mmol) of the above (trimethylsilyl)ethyl ester in 2 mL of Me_2SO. The mixture was stirred for 44 h at 25 °C. The reaction mixture (white precipitate) was cooled in an ice bath as 25 mL of water and 15 mL of ethyl acetate were added. The pH was lowered to 1.5 by careful addition of 3 N HCl. The layers were separated and the aqueous phase extracted with ethyl acetate (5 × 15 mL) and CH_2Cl_2 (2 × 15 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give 33 mg of a yellow residue. The crude product was chromatographed on a 0.5 mm silica gel plate (1% HCO_2H in 1:1 ether–CH_2Cl_2, R_f 0.30) to give 11.7 mg (70%) of (*E,E,E*)-seco acid **36**: $[\alpha]^{19}_D$ −19° (*c* 0.80, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.4–7.25 (m, 2 H, $H_{3''}$ and $H_{4''}$), 6.3–6.15 (m, 2 H, $H_{2''}$ and $H_{5''}$), 5.70 (br s, 1 H, $H_{2'}$), 5.41 (br d, 1 H, H_{10}), 4.52 (br d, 1 H, H_4), 4.35 (t, *J* = 6 Hz, 2 H, $H_{5'}$), 4.17 (d, *J* = 13 Hz, 1 H, H_{15a}), 3.92 (d, *J* = 13 Hz, 1 H, H_{15b}), 3.84 (d, *J* = 5 Hz, 1 H, H_2), 3.62 (d, *J* = 5 Hz, 1 H, H_{11}), 3.13 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.81 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.57 (dd, *J* = 9, 16 Hz, 1 H, $H_{3\alpha}$), 2.54 (t, *J* = 6 Hz, 2 H, $H_{4'}$), 2.22 (br s, 3 H, $H_{6'}$), 2.1–1.75 (m, 5 H, H_8, H_7, and $H_{3\beta}$), 1.70 (br s, 3 H, H_{16}), 0.86 (s, 3 H, H_{14}); IR (CH_2Cl_2) 3570, 3480, 3400–2500 (acid OH), 2980, 1715, 1695, 1648, 1612, 1220, 1142, 1070 cm^{-1}; mass spectrum, *m/e* 360 (M^+ – muconic acid), 265 (M^+ – side chain); UV (EtOH) 262 (ε 21 700), 219 (ε 15 800).

(*E,E,E*)-Verrucarin (32) from Seco Acid 36. Pivaloyl chloride (0.0060 mL, 0.048 mmol) was added to a solution of 0.0112 mL (0.080 mmol) of triethylamine and 8.1 mg (0.016 mmol) of seco acid **36** in 5 mL of CH_2Cl_2. The solution was stirred for 30 min at 25 °C then 25 mL of CH_2Cl_2 and two small crystals of 4-pyrrolidinopyridine were added. The solution was stirred for 3.5 h at 25 °C. Analytical TLC still showed some seco acid remaining so additional quantities of triethylamine (0.11 mL, 0.079 mmol) and pivaloyl chloride (0.006 mL, 0.048 mmol) were added. The solution was stirred for an additional 2.5 h at 25 °C and then the solvent was evaporated. The residue was chromatographed on a 0.5 mm silica gel plate (1:1 ether–CH_2Cl_2) to afford 3.9 mg (50%) of *E,E,E* isomer **32** (R_f 0.53) and 1.1 mg (14%) of synthetic verrucarin J (R_f 0.70).

(*Z,E,Z*)-Verrucarin J Seco Acid (39). Diethyl azodicarboxylate (0.011 mL, 0.066 mmol) was added to a solution of 17.3 mg (0.066 mmol) of triphenylphosphine, 9.0 mg (0.036 mmol)

(52) Fumaraldehydic acid was prepared by isomerization of malealdehydic acid (I_2, C_6H_6, reflux, 12–40 h, 12–18% yield; 51–67% of malealdehydic acid was recovered). For an alternative isomerization procedure, see: Grove, M. D.; Weisleder, D. *J. Org. Chem.* **1973**, *38*, 815.

of acid **28**, and 12.5 mg (0.033 mmol) of (*Z*)-**24** in 1 mL of THF. The solution was stirred for 35 min at 25 °C, and then the solvent was evaporated leaving a residual yellow liquid. This material was chromatographed on a 0.5 mm silica gel plate (ethyl acetate, R_f 0.63) to give 26 mg of impure product. This impure material was rechromatographed on a 0.5 mm silica gel plate (1% formic acid in 1:1 hexane–ether, 2 developments, R_f 0.09) to afford 13.3 mg (66%) of pure seco acid ester as a waxy solid: mp 30–35 °C; $[\alpha]^{22}_D$ −36° (*c* 1.33, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 12, 16 Hz, 1 H, $H_{3''}$), 6.62 (t, *J* = 12 Hz, 1H, $H_{4''}$), 6.08 (d, *J* = 16 Hz, 1 H, $H_{2''}$), 5.95 (d, *J* = 12 Hz, 1 H, $H_{5''}$), 5.76 (br s, 1 H, $H_{2'}$), 5.40 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.51 (br s, 1 H, H_4), 4.34 (t, *J* = 7 Hz, 2 H, $H_{5'}$), 4.27 (m, 2 H, OCH_2), 4.15 (d, *J* = 12 Hz, 1 H, H_{15a}), 3.92 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.83 (d, *J* = 5 Hz, 1 H, H_2), 3.63 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.11 (d, *J* = 4 Hz, 1H, H_{13a}), 3.02 (t, *J* = 7 Hz, 2 H, $H_{4'}$), 2.81 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.59 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 1.99 (br s, 3 H, $H_{6'}$), 2.0–1.7 (m, 6 H, H_8, H_7, $H_{3\beta}$, and OH), 1.71 (br s, 3 H, H_{16}), 1.05 (m, 2 H, CH_2Si), 0.87 (s, 3 H, H_{14}), 0.06 (s, 9 H, $SiMe_3$); IR (CH_2Cl_2) 3580, 3050, 2955, 1712, 1648, 1602, 1170, 1146, 1072, 964, cm^{-1}; UV (EtOH) 263 (ε 23 100), 218 (ε 16 800).

The *Z,E,Z* ester prepared as described in the preceding paragraph (12.3 mg, 0.0204 mmol) was deprotected by using a procedure analogous to the one described for the synthesis of **13**. The crude product was chromatographed on a 0.5 mm silica gel plate (1% formic acid in 1:1 ether–CH_2Cl_2, R_f 0.42) to afford 7.2 mg (70%) of seco acid **39**: mp 90–93 °C (with softening at 40–45 °C); $[\alpha]^{21}_D$ +32° (*c* 0.72, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 12, 16 Hz, 1 H, $H_{3''}$), 6.63 (t, *J* = 12 Hz, 1 H, $H_{4''}$), 6.03 (d, *J* = 16 Hz, 1 H, $H_{2''}$), 5.96 (d, *J* = 12 Hz, 1 H, $H_{5''}$), 5.86 (br s, 1 H, $H_{2'}$), 5.40 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.67 (m, 1 H, H_4), 4.34 (m, 2 H, $H_{5'}$), 4.20 (d, *J* = 12 Hz, 1 H, H_{15a}), 3.98 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.86 (d, *J* = 5 Hz, 1 H, H_2), 3.85–3.65 (m, 1 H, $H_{4'a}$), 3.62 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.16 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.87 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.7–2.55 (m, 2 H, $H_{4'b}$ and $H_{3\alpha}$), 2.1–1.7 (m, 5 H, H_8, H_7, and $H_{3\beta}$), 1.95 (br s, 3 H, $H_{6'}$), 1.71 (br s, 3 H, H_{16}), 0.99 (s, 3 H, H_{14}); IR (CH_2Cl_2) 3560, 3400–2800 (acid OH), 2970, 1712, 1650, 1194, 1148, 1072 cm^{-1}; mass spectrum, *m/e* 265 (M^+ − side chain); UV (EtOH) 261 (ε 18 600), 220 (ε 17 600).

(*Z,E,Z*)-Verrucarin Isomer 40 and (*Z,E,Z*)-Verrucarin Isomer 41. Pivaloyl chloride (0.0061 mL, 0.049 mmol) was added to a solution of 0.0086 mL (0.061 mmol) of triethylamine and 6.2 mg (0.0123 mmol) of seco acid **39** in 7 mL of CH_2Cl_2. The solution was stirred for 35 min at 25 °C. Two crystals of 4-pyrrolidinopyridine were then added and the solution stirred for an additional 70 min at 25 °C. The solvent was evaporated and the residue chromatographed on a 0.25 mm silica gel plate (1:1 ether:CH_2Cl_2) to give 3.1 mg (52%) of *Z,E,Z* isomer **40** (R_f 0.70) and 2.2 mg (37%) of *Z,E,Z* isomer **41** (R_f 0.54).

40: mp 118–121 °C; $[\alpha]^{21}_D$ +124° (*c* 0.31, C_6H_6); ^1H NMR (250 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 12, 16 Hz, 1 H, $H_{3''}$), 6.66 (t, *J* = 12 Hz, 1 H, $H_{4''}$), 6.10 (d, *J* = 12 Hz, 1 H, $H_{5''}$), 6.02–5.94 (m, 2 H, $H_{2''}$ and H_4), 5.78 (br s, 1 H, $H_{2'}$), 5.44 (br d, *J* = 5 Hz, 1 H, H_{10}), 5.05 (d, *J* = 12 Hz, 1 H, H_{15a}), 4.66–4.46 (m, 2 H, $H_{5'}$), 4.18–4.12 (m, 1 H, $H_{4'a}$), 3.87 (d, *J* = 5 Hz, 1 H, H_2), 3.65 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.65 (d, *J* = 5 Hz, 1 H, H_{11}), 3.15 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.84 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.45 (dd, *J* = 8, 15 Hz, 1 H, $H_{3\alpha}$), 2.35–1.7 (m, 6 H, $H_{4'b}$, H_7, H_8, and $H_{3\beta}$), 1.89 (br s, 3 H, $H_{6'}$), 1.73 (br s, 3 H, H_{16}), 0.65 (s, 3 H, H_{14}); IR (CH_2Cl_2) 2960, 2920, 1712, 1650, 1188, 1148, 1080, 966 cm^{-1}; mass spectrum, *m/e* 484 (M^+); UV (EtOH) 262 (ε 14 700), 217 (ε 19 800); high-resolution mass spectrum, calcd for $C_{27}H_{32}O_8$ *m/e* 484.2097, found *m/e* 484.210.

41: mp 185–187 °C; $[\alpha]^{21}_D$ +110° (*c* 0.22, C_6H_6); ^1H NMR (250 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 12, 14 Hz, 1 H, $H_{3''}$ or $H_{4''}$), 7.25 (dd, *J* = 12, 15 Hz, 1 H, $H_{4''}$ or $H_{3''}$), 6.43 (d, *J* = 14 Hz, 1 H, $H_{2''}$ or $H_{5''}$), 6.08 (d, *J* = 15 Hz, 1 H, $H_{5''}$ or $H_{2''}$), 5.83 (br s, 1 H, $H_{2'}$), 5.42 (br d, *J* = 5 Hz, 1 H, H_{10}), 5.27 (dd, *J* = 3, 8 Hz, 1 H, H_4), 4.61–4.56 (m, 1 H, $H_{5'a}$), 4.4–4.2 (m, 2 H, $H_{5'b}$ and $H_{4'a}$), 4.29 (d, *J* = 13 Hz, 1 H, H_{15a}), 3.94 (d, *J* = 13 Hz, 1 H, H_{15b}), 3.89 (d, *J* = 5 Hz, 1 H, H_2), 3.55 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.12 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.84 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.63 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.46–2.36 (m, 1 H, $H_{4'b}$), 2.2–1.8 (m, 5 H, H_8, H_7, and $H_{3\beta}$), 1.94 (br s, 3 H, $H_{6'}$), 1.73 (br s, 3 H, H_{16}), 0.88 (s, 3 H, H_{14}); IR (CH_2Cl_2) 2960, 2940, 1714, 1642, 1142, 1088, 910 cm^{-1}; mass spectrum, *m/e* 484 (M^+); UV (**41** decomposes in EtOH to give the corresponding (*E,E,E*)-seco acid ethyl ester); high-resolution mass spectrum, calcd for $C_{27}H_{32}O_8$ *m/e* 484.2097, found *m/e* 484.211.

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Registry No. **1**, 4643-58-7; **2**, 2198-92-7; **3a**, 80514-96-1; **3b**, 88968-92-7; **4b**, 80515-01-1; **5**, 14032-66-7; **6**, 69171-62-6; **7**, 88245-09-4; **8**, 88980-77-2; (*E*)-**10**, 88968-93-8; (*Z*)-**10**, 89015-88-3; **13**, 84303-92-4; **15**, 88968-94-9; **16**, 88968-95-0; **17**, 88969-03-3; (*E*)-**18**, 84303-84-4; (*Z*)-**18**, 84303-85-5; (*E*)-**19**, 89103-57-1; (*Z*)-**19**, 89015-96-3; **20**, 84303-87-7; **21**, 88968-96-1; **22**, 78592-73-1; **22** (TBDMS ether), 78592-77-5; (*E*)-**23**, 84303-90-2; (*Z*)-**23**, 84303-91-3; (*E*)-**24**, 84412-91-9; (*Z*)-**24**, 84412-92-0; **25**, 88968-97-2; **26**, 88968-98-3; **27**, 88968-99-4; **28**, 87729-23-5; (*E*)-**29**, 89016-44-4; **32**, 89015-89-4; **33**, 89015-90-7; **34**, 88969-00-0; **35**, 88969-01-1; **36**, 89015-91-8; **36** (β-(trimethylsilyl)ethyl ester), 88969-02-2; **39**, 89015-92-9; **39** (β-(trimethylsilyl)ethyl ester), 89015-95-2; **40**, 89015-93-0; **41**, 89015-94-1; $(MeO)_2P(O)CH_2CO_2H$, 34159-46-1; $4\text{-}MeOC_6H_4CH_2OH$, 105-13-5; $(MeO)_2P(O)CH_2CO_2(CH_2)_2SiMe_3$, 89121-12-0; (*E*)-$HO_2CCH{=}CHCHO$, 4437-06-3; $HO(CH_2)_4OH$, 110-63-4; $TBDMSO(CH_2)_4OH$, 87184-99-4; 3-butyn-1-ol, 927-74-2; 2,2,2-trichloroethyl chloroformate, 17341-93-4.