84731-36-2; **19**, 84731-37-3; **20**, 84731-38-4; **21**, 84731-39-5; **23**, 84731-40-8; **24**, 84731-41-9; **25**, 84731-42-0; **26**, 84731-43-1; **27**, 92346-51-5; **28**, 92346-52-6; **29**, 92346-53-7; **30**, 92346-54-8; **31**, 92346-55-9; **32**, 92346-56-0; **33**, 84731-44-2; **34a**, 84731-45-3; **34b**, 92346-59-3; **35**, 84731-48-6; **36a**, 92346-57-1; **36b**, 92346-58-2; *o*-anisoyl chloride, 21615-34-9; *N*-anisoyl-2-aminoethanol, 88105-15-1; β-bromopropionaldehyde ethylene acetal, 18742-02-4; ethanolamine, 141-43-5; trimethyl phosphonoacetate, 5927-18-4.

Synthesis of Verrucarin B[1]

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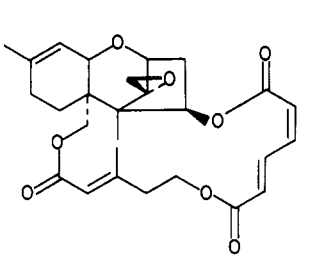
A four-step synthesis of verrucarin B (**3**) from verrucarol (**2**) is described. Coupling of **2** with in situ generated carboxylic acid **5** proceeded with moderate regioselectivity and afforded trichothecene monoester **14** in only 35% yield. It was necessary therefore to block the C(4)-hydroxyl group of verrucarol prior to the coupling reaction with **5**. Selective protection of **2** was accomplished in 54% yield (81% corrected for recovered verrucarol after hydrolysis of the other reaction products) by treatment with [[2-(trimethylsilyl)ethoxy]carbonyl]imidazole (**16**) and DBU in benzene. Esterification of **17** with in situ generated **5** in the presence of BOP-Cl, Et_3N, and catalytic DMAP as the condensing reagents afforded **18** in 64% yield, deprotection of which with KF in wet Me_2SO smoothly afforded seco acid **4** (81%). A number of methods for macrolactonization of **4** via mixed anhydride **21** were examined. Best results were obtained when **21** was treated with stoichiometric 4-pyrrolidinopyridine (4-PP) which afforded verrucarin B in 55% yield along with 34% of the (*E*,*E*)-muconate isomer **19**. Exposure of **19** to I_2 in benzene effected rapid isomerization to verrucarin B (60%) and a new isomer **20** (30%). In this manner the yield of **3** from seco acid **4** was 75% and 35% overall from verrucarol.

The verrucarins, roridins, and baccharinoids are important groups of macrocyclic epoxytrichothecenes which are of considerable interest as a consequence of their potent cytotoxic properties.[4,5] Naturally occurring baccharinoids, for example, typically show T/C values of 160–320 at dose levels of 1–10 mg/kg in the in vivo P388 mouse leukemia assay.[4a] The verrucarins and roridins are generally less active but nonetheless are regarded as promising prototypes for drug development. Indeed, Jarvis has shown that a number of chemically modified verrucarins (e.g., 8β-hydroxy-9β,10β-epoxyverrucarin A) possess very significant activity in the in vivo P388 assay.[6]

For the past several years we have been exploring methodology applicable to the synthesis of a range of macrocyclic epoxytrichothecenes[7,8] and recently described a five-step synthesis of verrucarin J (**1**) from verrucarol (**2**).[7a,b] Although this synthesis was relatively efficient



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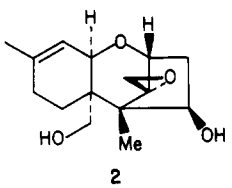

2

(22–24% overall yield), we felt that several aspects of our strategy could be improved. Specifically, we wished to develop a more efficient approach in which the intact macrocyclic "ribbon" would be attached to verrucarol. In principle, this would permit the synthesis of any macrocyclic epoxytrichothecene in as few as three steps from the starting trichothecene (usually **2**). In addition, we hoped to find a solution to the problem of olefin isomerization which we encountered in the macrocyclization of the seco acid intermediate.[7a]

We decided to focus on these problems by using verrucarin B (**3**)[9] as a synthetic target. Based on our experience

(1) Taken in part from the Ph.D. Thesis of T. A. Blizzard, Massachusetts Institute of Technology, Cambridge, MA, 1984.

(2) Holder of the Firmenich Career Development Chair in Natural Products Chemistry; Fellow of the Alfred P. Sloan Foundation, 1982–84.

(3) National Science Foundation Predoctoral Fellow, 1979–82; Fellow of the Whitaker Health Sciences Fund, 1982–84.

(4) (a) Jarvis, B. B.; Eppley, R. M.; Mazzola, E. P. In "Developments in Food Science–Trichothecenes: Chemical, Biological, and Toxicological Aspects"; Ueno, Y., Ed.; Kodansha: Tokyo, 1983; Vol. 4, p 20. (b) Jarvis, B. B.; Mazzola, E. P. *Acc. Chem. Res.* **1982**, *15*, 388. (c) Doyle, T. W.; Bradner, W. T. In "Anticancer Agents Based on Natural Product Models"; Cassidy, J. M., Douros, J., Eds.; Academic Press: New York, 1980; Chapter 2. (d) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63.

(5) The verrucarins and roridins are produced by various *Myrothecium* species whereas the baccharinoids appear to be plant modified roridins. See ref 4a,b and: (a) Jarvis, B. B.; Vrudhula, V. M.; Midiwo, J. O.; Mazzola, E. P. *J. Org. Chem.* **1983**, *48*, 2576. (b) Jarvis, B. B.; Stahly, G. P.; Pavanasasivam, G.; Midiwo, J. O.; De Silva, T.; Holmlund, C. E.; Mazzola, E. P.; Geoghegan, R. F., Jr. *Ibid.* **1982**, *47*, 1117. (c) Jarvis, B. B.; Midiwo, J. O.; Tuthill, D.; Bean, G. A. *Science (Washington, D.C.)* **1981**, *214*, 460. (d) Härri, E.; Loeffler, W.; Sigg, H. P.; Stähelin, H.; Stoll, C.; Tamm, C.; Wiesinger, D. *Helv. Chim. Acta* **1962**, *45*, 839. (e) Böhner, B.; Fetz, E.; Härri, E.; Sigg, H. P.; Stoll, C.; Tamm, C. *Ibid.* **1965**, *48*, 1079.

(6) (a) Jarvis, B. B.; Stahly, G. P.; Pavanasasivam, G.; Mazzola, E. P. *J. Med. Chem.* **1980**, *23*, 1054. (b) Jarvis, B. B.; Midiwo, J. O. Mazzola, E. P. *Ibid.* **1984**, *27*, 239.

(7) (a) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, *49*, 1772. (b) Roush, W. R.; Blizzard, T. A. *Ibid.* **1983**, *48*, 758. (c) Roush, W. R.; Spada, A. P. *Tetrahedron Lett.* **1983**, *24*, 3693. (d) Roush, W. R.; Spada, A. P. *Ibid.* **1982**, *23*, 3773. (e) Roush, W. R.; Blizzard, T. A.; Basha, F. Z. *Ibid.* **1982**, *23*, 2331.

(8) For leading references to other studies on the synthesis of macrocyclic epoxytrichothecenes, see ref 7a and: (a) Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242. (b) Mohr, P.; Tori, M.; Grossen, P.; Herold, P.; Tamm, C. *Helv. Chim. Acta* **1982**, *65*, 1412; (c) Herold, P.; Mohr, P.; Tamm, C. *Ibid.* **1983**, *66*, 744. (d) Esmond, R.; Fraser-Reid, B.; Jarvis, B. B. *J. Org. Chem.* **1982**, *47*, 3358. (e) Still, W. C.; Gennari, C.; Noguez, J. A.; Pearson, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 260. (f) Trost, B. M.; McDougal, P. G. *J. Org. Chem.* **1984**, *49*, 458.

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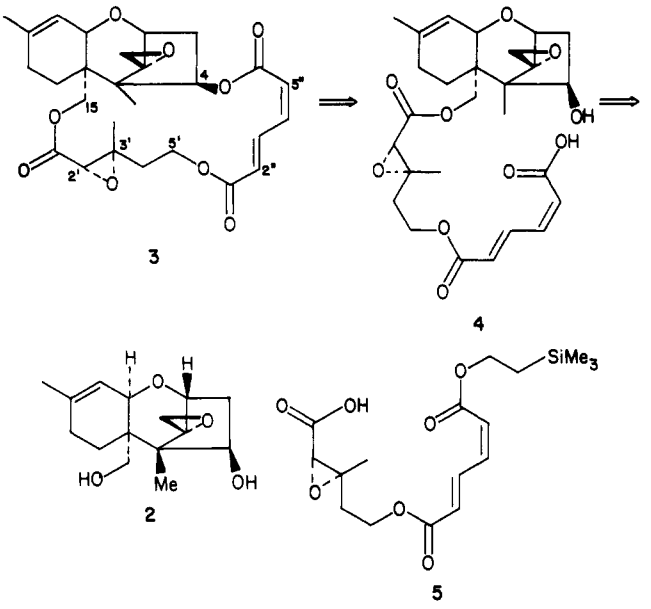
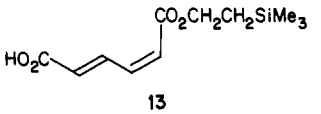


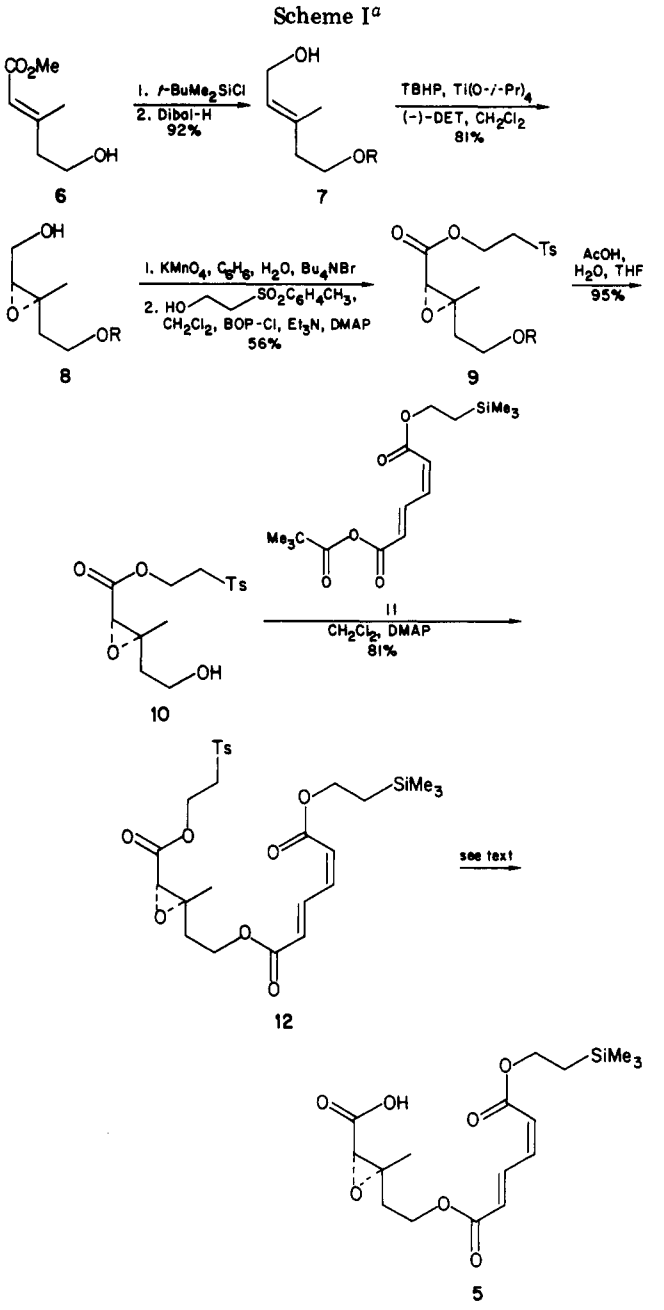
with verrucarin J, we decided to pursue a strategy in which verrucarol C(15)-OH would be selectively esterified with a monoacid such as **5**. Deprotection of the resulting triester would afford seco acid **4** which would be cyclized to give verrucarin B in the final step of the synthesis.

Carboxylic acid **5** was synthesized as outlined in Scheme I. Silylation of the known alcohol **6**[10] followed by reduction of the ester functionality with Dibal-H afforded allylic alcohol **7** in excellent overall yield. Enantioselective epoxidation of **7** was accomplished by using the extremely powerful Sharpless procedure[11] and afforded >95% optically pure epoxy alcohol **8** in 81% yield. The optical purity of **8** was determined by Mosher ester analysis.[12] The next two steps of the synthesis (oxidation of **8** and esterification of the resulting epoxy acid) proved to be rather troublesome. Best results were obtained when **8** was oxidized with potassium permanganate in a benzene–water mixture in the presence of tetrabutylammonium bromide,[13] followed immediately by esterification of the *crude* acid with 2-(*p*-tolylsulfonyl)ethanol, Et_3N, *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (BOP-Cl),[14] and 4-(dimethylamino)pyridine (DMAP). This procedure afforded ester **9** in 56% overall yield from **8**. Purification of the intermediate acid led to a considerable decrease in the overall yield since the epoxy acid proved to be unstable to chromatography and was obtained in only 36–49% yield after purification. Deprotection of **9** was smoothly accomplished by exposure to aqueous acetic acid in THF (95% yield).[15] Condensation of **10** with mixed anhydride **11**, generated in situ from the corresponding carboxylic acid **13**[7a] by treatment with Et_3N and pivaloyl chloride



led to triester **12** in 81% yield without olefin isomerization. Alternatively, **12** could also be prepared from **10** and **13** via the Mitsunobu procedure,[16] but the yield of **12** was lower in this case (61%) owing to material losses resulting from the repeated chromatography required to obtain product of satisfactory purity.

Scheme I[a]

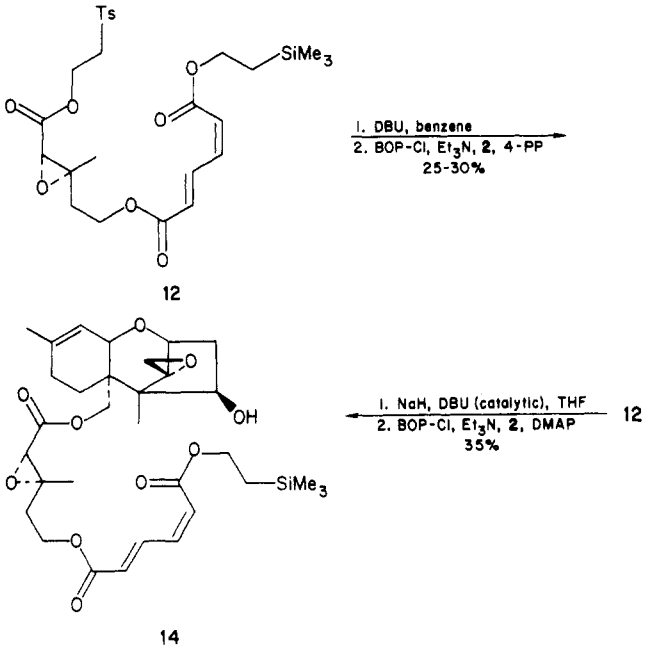


[a] R = *t*-$BuMe_2Si$.

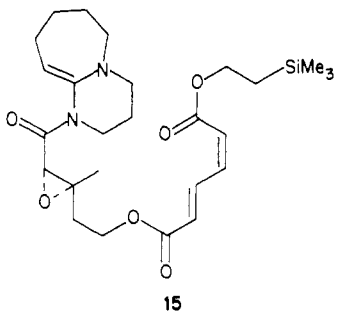
With triester **12** in hand we turned our attention to removal of the 2-(*p*-tolylsulfonyl)ethyl ester protecting group which would complete the synthesis of **5**. We were delighted when our initial attempts to effect this conversion by exposure of **12** to DBU in benzene[17] smoothly afforded **5** in 77% yield after chromatography. We were unable to reproduce this result on a consistent basis, however, in spite of the fact that in each case TLC analysis

(9) (a) Breitenstein, W.; Tamm, C.; Arnold, E. V.; Clardy, J. *Helv. Chim. Acta* **1979**, *62*, 2699. (b) Gutzwiller, J.; Tamm, C. *Ibid.* **1965**, *48*, 177.
(10) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093.
(11) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464. (c) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *Ibid.* **1981**, *103*, 6237.
(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(13) Herriot, A. W.; Picker, D. *Tetrahedron Lett.* **1974**, 1511.
(14) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547.
(15) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(16) Mitsunobu, O. *Synthesis* **1981**, 1.
(17) Colvin, E. W.; Purcell, T. A.; Raphael, R. A. *J. Chem. Soc., Chem. Commun.* **1972**, 1031.

of the reaction mixture indicated that the deprotection had occurred cleanly. Since **5** was apparently decomposing during the isolation and purification steps, we decided to circumvent this problem by esterifying verrucarol (**2**)[18] with crude **5**, or its salts, generated in situ. Thus, a mixture of **12** and DBU in benzene was monitored by analytical TLC. When the deprotection was judged complete BOP-Cl (1.25–1.5 equiv), triethylamine, verrucarol (1.0 equiv), and catalytic 4-pyrrolidinopyridine (4-PP) were added. This procedure afforded C(15)-monoester **14** in 25–30% yield (49–53% corrected for recovered verrucarol). The low



yield of **14** was due in part to relatively modest selectivity (ca. 3:1 (C(15)-OH vs. C(4)-OH) in the acylation step.[19] In addition, a portion of **5** was consumed in an unproductive pathway leading to the formation of a byproduct, tentatively assigned structure **15**, resulting from N-acylation of DBU.



The latter problem was avoided by treatment of **12** with excess sodium hydride (NaH) and 0.1 equiv of DBU in THF which led to smooth elimination of aryl vinyl sulfone. Subsequent esterification of the resulting sodium salt of **5**, as before, afforded **14** in 35% yield (58% corrected for recovered verrucarol), with only a trace of **15** being detected by TLC analysis. It should be noted that deprotection of **12** with NaH in the absence of DBU gave nonreproducible results.

This procedure, although slightly better than initial experiments involving DBU alone, was still unsatisfactory since a substantial amount of material (20–25%) was lost via acylation of verrucarol C(4)-OH. Attempts to suppress C(4)-acylation by using weaker acylation catalysts (e.g., 4-piperidinopyridine, *N*-methylimidazole)[20] were unsuccessful, as this led only to formation of the various products in lower yield without significantly changing the ratio in which they were formed.[21] Other esterification methods (DCC; mixed anhydride with pivaloyl chloride) were more selective for C(15)-OH but afforded **14** in much lower absolute yield and, therefore, were also considered unsatisfactory.

In light of these results, we decided to protect C(4)-OH of the trichothecene nucleus before forming the ester linkage between C(15)-OH and acid **5**. Although several C(4)-protected verrucarol derivatives have been reported in the literature,[22] we desired a protecting group which could be removed under conditions ($KF \cdot 2H_2O$, Me_2SO) suitable for deprotection of a 2-(trimethylsilyl)ethyl ester which we were already using as the blocking group for the C(6″)-acid. We reasoned that a [2-(trimethylsilyl)ethoxy]carbonyl unit[23] would be ideally suited for these purposes.[24]

Thus, treatment of verrucarol (**2**) with [[2-(trimethylsilyl)ethoxy]carbonyl]imidazole (**16**)[25] and DBU in benzene smoothly afforded C(4)-monoprotected derivative **17** in

(18) Verrucarol used in these studies was prepared from natural anguidine by a procedure developed by Fraser-Reid (described in footnote 8 of ref 8d). For an alternative procedure, see ref 22c.

(19) In an experiment in which verrucarol (**2**) was esterified with purified **5** (BOP-Cl, Et_3N, DMAP), ester **14** was obtained in 47% yield along with 9% of C(4)-monoacylated trichothecene, 8% of diacylated product, and 24% of recovered verrucarol.

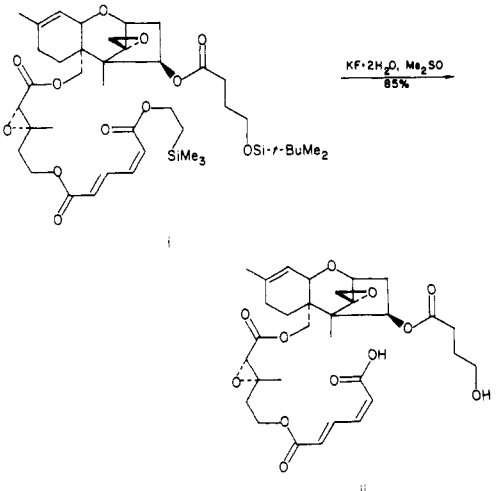
(20) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.

(21) These experiments are summarized in Table II.

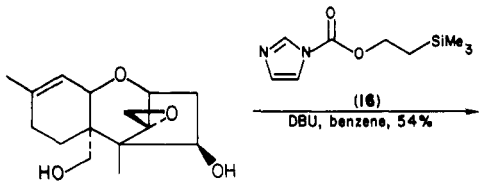
(22) (a) Breitenstein, W.; Tamm, C. *Helv. Chim. Acta* **1978**, *61*, 1975. (b) Notegen, E.-A.; Tori, M.; Tamm, C. *Ibid.* **1981**, *64*, 316. (c) Tulshian, D. B.; Fraser-Reid, B. *Tetrahedron Lett.* **1980**, *21*, 4549.

(23) Gioelli, C.; Balgobin, N.; Josephson, S.; Chattopadhyaya, J. B. *Tetrahedron Lett.* **1981**, *22*, 969.

(24) During the course of these studies we also prepared i in which the C(4)-hydroxyl group is blocked with the γ-[(*tert*-butyldimethylsilyl)oxy]butyryl residue used previously in these laboratories as a protecting group for C(15)-OH (see ref 7a,c). Treatment of i with 10 equiv of KF in wet Me_2SO effected cleavage of the 2-(trimethylsilyl)ethyl ester and the *t*-$BuMe_2$ ether. Unfortunately, however, spontaneous loss of butyrolactone to liberate C(4)-OH did not occur under these conditions. In addition, the γ-hydroxybutyrate residue remained attached to C(4) even after exposure to DBU in THF. These totally unexpected results may be due to the hindered environment of C(4) (possibly steric deceleration of tetrahedral intermediate formation or unfavorable stereoelectronics for participation of C(4)-OH as a leaving group in the decomposition of the tetrahedral intermediate).



(25) In principle, **17** might also have been prepared by treating verrucarol with 2-(trimethylsilyl)ethyl chloroformate (see ref 23). However, this reagent is unstable and phosgene is used in its preparation. In contrast, imidazolide **16** is a crystalline, apparently stable compound which can be easily prepared from 2-(trimethylsilyl)ethanol and CDI (see Experimental Section). It seems likely, therefore, that **16** could become a useful reagent for the protection of alcohols and amines.



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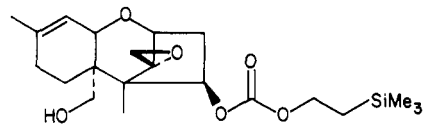
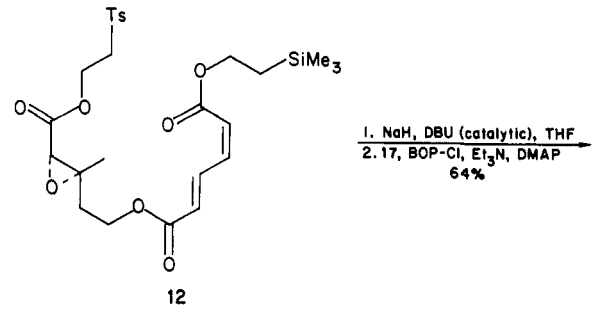


17

54% yield (81% yield corrected for verrucarol recovered after hydrolysis of the other reaction products (see Experimental Section)). Esterification of 17 and in situ generated 5 by using the sequence described earlier smoothly afforded trichothecene 18 in 64% yield. Finally,



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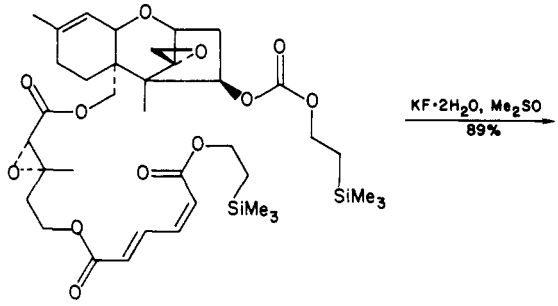

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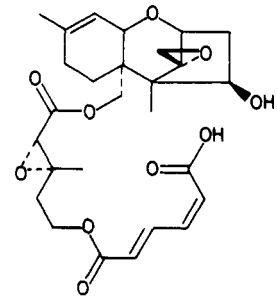
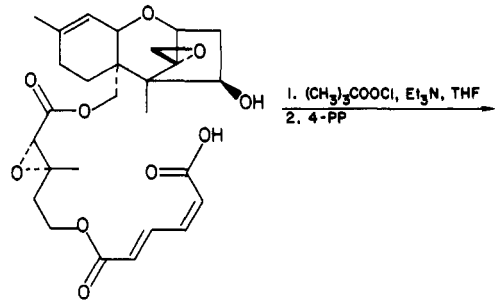


4

treatment of 18 with potassium fluoride in wet Me_2SO completed the synthesis of seco acid 4.[26] The overall yield of 4 from verrucarol was 46%.[27]

With a convenient synthesis of seco acid 4 in hand we turned to the final remaining problem, the macrolactonization which would complete the synthesis. We decided to perform the initial cyclization by using the conditions worked out in our verrucarin J synthesis. Thus, treatment of 4 with pivaloyl chloride and triethylamine followed by stoichiometric 4-pyrrolidinopyridine (4-PP) resulted in rapid macrocyclization and afforded verrucarin B (3) in 55% yield along with 34% of the (*E,E*)-muconate isomer 19. This result was essentially identical with that



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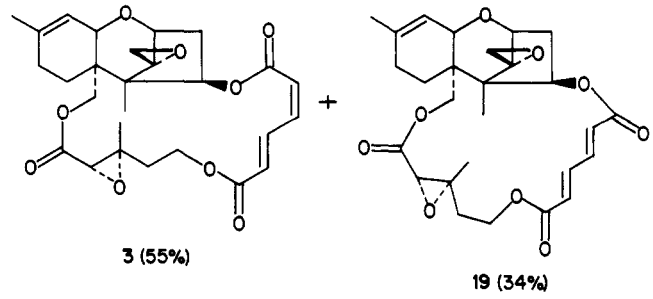
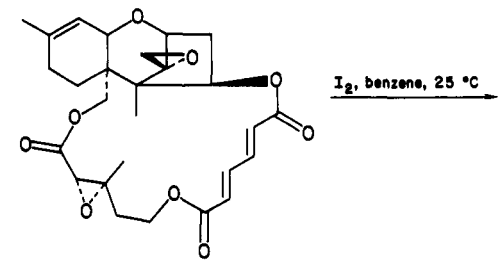


3 (55%) 19 (34%)

realized in the verrucarin J series.[7a] Exposure of *E,E* isomer 19 to I_2 in benzene effected rapid olefin isomerization and afforded a mixture of verrucarin B (60%) and a new isomer (*Z,E*)-verrucarin 20 (30%). Hence, the



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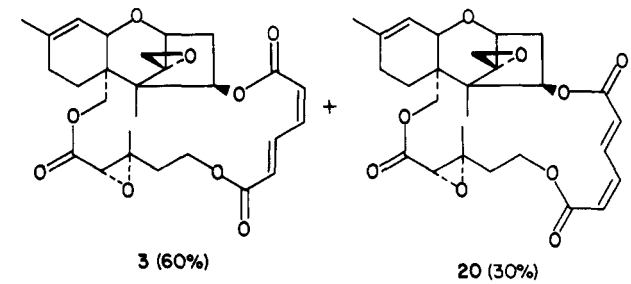


3 (60%) 20 (30%)

overall yield of verrucarin B from seco acid 4 was increased to 75% by virtue of the facile isomerization of 19. Synthetic verrucarin B so obtained was identical in all respects with an authentic sample kindly provided by Professor C. Tamm.

Table I summarizes our efforts to minimize the production of *E,E* isomer 19 in the macrocyclization of 4. We previously speculated that the olefin isomerizations observed in macrolactonizations and esterifications of α,β-unsaturated carboxylic acids may be the consequence of reversible Michael addition of nucleophilic reagents to the active ester intermediate (mixed anhydride 21 in the case of 4 → 3).[7a,c] If so, it should be possible to suppress this

(26) It is interesting to note that the deprotection of 18 with KF actually proceeds somewhat more rapidly than the deprotection of 14. Furthermore, TLC analysis of the reaction mixture suggested that the C(4)-protecting group is cleaved faster than the C(6″) ester. Thus, it may be that the C(4)-alkoxide generated in the case of 18 somehow assists in the cleavage of the 2-(trimethylsilyl)ethyl ester at C(6″).

(27) Yield based on verrucarol consumed in the preparation of 17.

Table I.[a] Macrocyclizations Leading to Verrucarins B (3) and J (1)

entry	cyclization substrate[a]	cyclization conditions	products, % 3/1	products, % 19/24[b]
1	21	CH_2Cl_2, 4-PP (1.0 equiv), 1.5 h	55	34
2	21	CH_2Cl_2, 4-PP (0.15 equiv), 17 h	54	10
3	21	CH_2Cl_2, 4-PP (0.05 equiv), 65 h	40	6
4	21	DBU, THF	24–58	trace
5	21	KO-*t*-Bu, THF	38	trace
6	21	NaH, THF	20[c]	0
7	22[d]	DCC, 4-PP[e]	33	0
8	23[d]	CH_2Cl_2, 4-PP,[e] 2 h	55–60	25–30
9	23[d]	DBU, benzene	(extensive decomposition)	
10	23[d]	Et_3N, $CHCl_3$, reflux	30	0

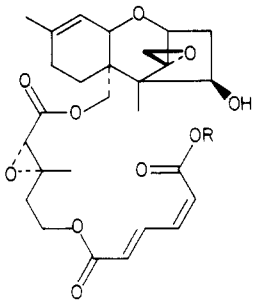
[a] Mixed anhydrides 21 and 23 were generated in situ by treatment of seco acids 4 and 22, respectively, with excess pivaloyl chloride and triethylamine. [b] Compounds 19 and 24 are the (*E,E*)-muconate isomers corresponding to verrucarins B (3) and J (1), respectively. [c] TLC analysis indicated extensive hydrolysis had occurred to give verrucarol. [d] See ref 7a. [e] Amount of catalyst not determined, but probably stoichiometric.

Table II

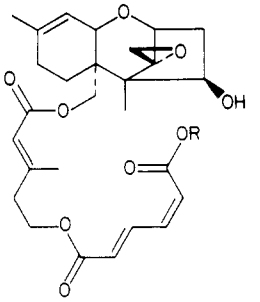
acylation catalyst	products, % C(15)-acylated (14)	products, % C(4)-acylated	products, % diacylated	recovered verrucarol, %
4-pyrrolidinopyridine[a]	47	9	8	24
4-dimethylaminopyridine	41	4	17	28
4-piperidinopyridine	30	7	17	32
1-methylimidazole	26	6	11	44

[a] This experiment was performed using purified acid 5.

isomerization process by limiting the amount of acylation catalyst, or by omitting altogether such nucleophilic species from the reaction medium.



21 (R=COCMe$_3$)
4 (R=H)



23 (R=COCMe$_3$)
22 (R=H)

The data summarized in entries 1–3 of Table I clearly show that the amount of acylation catalyst is one variable which must be controlled in order to minimize the production of olefin isomers. Conditions which gave the best yield of 3 (54%) while limiting the production of 19 (10%) involved treatment of in situ generated mixed anhydride 21 with a total of 0.15 equiv of 4-PP in CH_2Cl_2 over a 17-h reaction period (entry 2). It is possible that further improvement in selectivity may be realized by using acylation catalysts less reactive than 4-PP.[20] Indeed, a preliminary TLC-scale cyclization of 21 catalyzed with 0.1 equiv of *N*-methylimidazole led to slow macrolactonization with no detectable olefin isomerization. This, then, is a possible area for future work on this problem.

Other attempts to suppress the formation of 19 by performing the macrocyclization in the absence of acylation catalysts were less successful. Treatment of mixed anhydride 21 with DBU in THF led to verruarin B in 24–58% yield (entry 4). Only a trace of *E,E* isomer 19 was observed under these conditions. Unfortunately, the lower yields were obtained from the larger scale experiments. Attempts to effect the cyclization of 21 by using other bases (e.g., KO-*t*-Bu or NaH) afforded verrucarin B in yields no greater than 38% (entries 5 and 6). Considerable hydrolysis to verrucarol occurred in the NaH experiment. For comparison, several cyclization experriments involving verrucarin J seco acid 22 and the corresponding mixed anhydride 23 are summarized in entries 7–10 of Table I.

One of our objectives in undertaking this synthesis of verrucarin B was to develop an efficient solution to this olefin isomerization problem. It is ironic, therefore, that the best yield of 3 realized to date derives from experiments in which the mixed anhydride derived from seco acid 4 is cyclized with stoichiometric acylation catalyst, conditions which promote maximal levels of olefin isomerization. Although a solution to this problem is clearly desirable for aesthetic reasons, the present protocol involving the cyclization of mixed anhydride 21 with stoichiometric 4-PP and the facile iodine-catalyzed isomerization of the (*E,E*)-muconate isomer (e.g., 19 → 3) constitutes a very efficient indirect method. Indeed, this synthesis of verrucarin B, which proceeds in 35% overall yield from verrucarol,[27] ranks as the most efficient verrucarin synthesis on record.

Experimental Section

Proton (^{1}H) NMR spectra were measured 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 measured on a Perkin-Elmer Model 283B infrared spectrophotometer calibrated with the 1601-cm^{-1} absorption of polystyrene. IR spectra are reported in wavenumbers (cm^{-1}). Ultraviolet spectra were measured on a Perkin-Elmer 330 UV–vis 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 or a Finnegan MAT 8200 instrument. Elemental analyses were performed by Robertson Laboratory, Inc. of Florham Park, NJ. 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 distilled from P_2O_5. Pyridine was distilled from sodium hydroxide. 4-Pyrrolidinopyridine (4-PP) was recrystallized from hexane. Pivaloyl chloride, (−)-diethyl tartrate ((−)-DET), titanium tetraisopropoxide, and DBU were distilled.

Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm × 10 cm plates coated with a 0.25-mm layer 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 were eluted from the adsorbents with ethyl acetate; all other compounds were eluted with ether. Flash chromatography was performed as described by Still.[28] All chromatography solvents were distilled prior to use.

5-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2(*E*)-penten-1-ol (7). Imidazole (2.60 g, 38.2 mmol) and 2.63 g (17.4 mmol) of *tert*-butyldimethylsilyl chloride were added to a solution of 2.19 g (15.2 mmol) of **6**[10] in 20 mL of DMF. The solution was stirred for 13 h at 25 °C, then diluted with 100 mL of water, and extracted with hexane (8 × 100 mL). The combined hexane extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated. The crude silyl ether was dissolved in 100 mL of ether and the solution cooled to −78 °C. Dibal-H (50 mL of 1 M hexane solution, 50 mmol) was then added. The solution was stirred at −78 °C for 10 min and then at 25 °C for 1.5 h. The solution was cooled in an ice bath as 15 mL of water was added cautiously (white precipitate) followed by slow addition of 3 N HCl to lower the pH to 4 (precipitate dissolved). The layers were separated and the aqueous phase was extracted with ether (7 × 75 mL). The combined extracts were dried, filtered, and evaporated to afford 4.07 g of crude product which was distilled (Kugelrohr, 140–150 °C, 10–15 mmHg) to give 3.22 g (92%) of pure **7**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.43 (br t, J = 7 Hz, 1 H, H_2), 4.14 (br d, J = 7 Hz, 2 H, H_1), 3.69 (t, J = 7 Hz, 2 H, H_5), 2.24 (t, J = 7 Hz, 2 H, H_4), 1.69 (br s, 3 H, H_6), 1.52 (br s, 1 H, OH), 0.88 (s, 9 H, *t*-Bu), 0.04 (s, 6 H, $SiMe_2$); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 135.6, 125.4, 62.0, 58.7, 42.6, 25.7, 18.0, 16.4, −5.5; IR (film) 3340, 2950, 2926, 2858, 1664, 1470, 1460, 1254, 1092, 832 cm^{-1}; mass spectrum, m/e 213 (M^+ − OH). Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.85; H, 11.49.

5-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2(*R*),3(*R*)-epoxypentan-1-ol (8). Freshly distilled (−)-diethyl tartrate (3.6 mL, 20.6 mmol) was added to a −20 °C solution of 4.13 mL (13.8 mmol) of titanium(IV) isopropoxide in 60 mL of CH_2Cl_2. The solution was stirred for 20 min at −20 °C. A solution of 3.02 g (13.1 mmol) of allylic alcohol **7** in 50 mL of CH_2Cl_2 was then added dropwise followed by *tert*-butyl hydroperoxide solution (6.6 mL of 3.98 M toluene solution, 26.2 mmol). The mixture was left in a −20 °C freezer for 17 h before being quenched with 5 mL of saturated aqueous Na_2SO_4. The mixture was stirred vigorously and then filtered through Celite and evaporated. The residue was partitioned between 80 mL of ether and 80 mL of saturated aqueous NaCl and then cooled to 0 °C. Aqueous NaOH (10 mL of 5 N solution) was added and the mixture stirred vigorously for 1.5 h at 0 °C until analytical TLC showed complete disappearance of (−)-diethyl tartrate. The layers were separated and the aqueous phase washed with 50 mL of ether. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The crude epoxide was purified by flash chromatography (50-mm column, 1:1 hexane–ether, R_f 0.26) to afford 2.63 g (81%) of >95% optically pure epoxy alcohol **8** as a colorless liquid: $[\alpha]^{19}_D$ +2.1° (*c* 1.59, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.91–3.63 (m, 4 H, H_1 and H_5), 3.06 (dd, J = 4, 7 Hz, 1 H, H_2), 1.90 (dt, J = 14, 6 Hz, 1 H, H_{4a}), 1.71 (t, J = 7 Hz, 1 H, OH), 1.65 (dt, J = 14, 6 Hz, 1 H, H_{4b}), 1.34 (s, 3 H, H_6), 0.90 (s, 9 H, *t*-Bu), 0.06 (s, 6 H, $SiMe_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 63.2, 61.3, 59.8, 59.5, 41.4, 25.8, 18.1, 17.2, −5.5; IR (film) 3340, 2950, 2926, 2858, 1470, 1256, 1098, 832, 772 cm^{-1}; mass spectrum, m/e 246 (M^+). Anal. Calcd for $C_{12}H_{26}O_3Si$: C, 58.49; H, 10.63. Found: C, 58.28; H, 10.89.

2-(*p*-Tolylsulfonyl)ethyl 5-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2(*S*),3(*R*)-epoxypentanoate (9). A solution of 640 mg (4.0 mmol) of potassium permanganate in 8 mL of water containing 200 mg (0.6 mmol) of tetrabutylammonium bromide was cooled (10–15 °C) and stirred vigorously (mechanical stirrer) as a solution of 400 mg (1.6 mmol) of epoxy alcohol **8** in 8 mL of benzene was added. The resulting purple mixture was stirred vigorously for 28 h at 25 °C. The reaction mixture (brown at this point) was then cooled in an ice bath as 10 mL of saturated aqueous $NaHSO_3$ and 10 mL of benzene were added. The mixture was stirred at 0 °C until the color changed from brown to white (~5 min), and then the pH was lowered to 3 by *careful* addition of 3 N HCl. The aqueous phase was saturated with NaCl and extracted with ethyl acetate (6 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to afford the crude epoxy acid: $[\alpha]^{18}_D$ +14.4° (*c* 0.84, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.74 (t, J = 6 Hz, 2 H, H_5), 3.53 (s, 1 H, H_2), 1.98 (dt, J = 14, 6 Hz, 1 H, H_{4a}), 1.74 (dt, J = 14, 6 Hz, 1 H, H_{4b}), 1.44 (s, 3 H, H_6), 0.89 (s, 9 H, *t*-Bu), 0.06 (s, 6 H, $SiMe_2$); IR (film) 3600–2500 (acid OH), 2956, 2928, 2858, 1752, 1732, 1472, 1254, 1104, 832, 774 cm^{-1}.

The crude acid, prepared as described in the preceding paragraph, was dissolved in 10 mL of CH_2Cl_2. Triethylamine (0.57 mL, 4.1 mmol) was added followed by 496 mg (1.95 mmol) of *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (BOP-Cl),[14] 455 mg (2.3 mmol) of 2-(*p*-tolylsulfonyl)ethanol and 10 mg (0.08 mmol) of 4-(dimethylamino)pyridine. The mixture (white precipitate) was stirred for 16 h at 25 °C and then cooled in an ice bath as 10 mL of 0.5 N HCl and 10 mL of CH_2Cl_2 were added. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were filtered through cotton and evaporated. The crude product was purified by flash chromatography (50-mm column, 1:1 hexane-ether, R_f 0.23) to afford 399 mg (56%) of pure **9** as a colorless liquid: $[\alpha]^{21}_D$ +17° (*c* 1.54, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.81 (d, J = 8 Hz, 2 H, Ar), 7.39 (d, J = 8 Hz, 2 H, Ar), 4.54 (dt, J = 12, 6 Hz, 1 H, H_a of $-CO_2CH_2-$), 4.42 (dt, J = 12, 6 Hz, 1 H, H_b of $-CO_2CH_2-$), 3.69 (t, J = 6 Hz, 2 H, H_5), 3.47 (t, J = 6 Hz, 2 H, CH_2SO_2Ar), 3.23 (s, 1 H, H_2), 2.46 (br s, 3 H, Ar-CH_3), 1.89 (dt, J = 14, 6 Hz, 1 H, H_{4a}), 1.68 (dt, J = 14, 6 Hz, 1 H, H_{4b}), 1.33 (s, 3 H, H_6), 0.89 (s, 9 H, t-Bu), 0.05 (s, 6 H, $SiMe_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 167.9, 145.2, 136.1, 130.0, 128.1, 61.5, 58.9, 58.2, 58.1, 54.8, 40.5, 25.8, 21.6, 18.1, 16.5, −5.5; IR ($CHCl_3$) 3020, 2958, 2936, 2870, 1754, 1652, 1600, 1324, 1142, 834 cm^{-1}; mass spectrum, m/e 385 (M^+ − *t*-Bu). Anal. Calcd for $C_{21}H_{34}O_6SSi$: C, 56.98; H, 7.74. Found: C, 57.00; H, 7.81.

2-(*p*-Tolylsulfonyl)ethyl 5-Hydroxy-3-methyl-2(*S*),3-(*R*)-epoxypentanoate (10). A solution of 250 mg (0.56 mmol) of silyl ether **9** 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 flash chromatography (30-mm column, ether, R_f 0.23) to afford 177 mg (95%) of pure **10** as a colorless syrup: $[\alpha]^{20}_D$ −3° (*c* 1.1, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.80 (d, J = 9 Hz, 2 H, Ar), 7.32 (d, J = 9 Hz, 2 H, Ar), 4.61 (dt, J = 12, 5 Hz, 1 H, H_a of $-CO_2CH_2-$), 4.45 (dt, J = 12, 5 Hz, 1 H, H_b of $-CO_2CH_2-$), 3.75 (br t, J = 6 Hz, 2 H, H_5), 3.46 (t, J = 6 Hz, 2 H, $-CH_2SO_2Ar$), 3.37 (s, 1 H, H_2), 2.47 (br s, 3 H, Ar-CH_3), 2.09 (br s, 1 H, OH), 1.95 (dt, J = 15, 5 Hz, 1 H, H_{4a}), 1.84 (dt, J = 15, 5 Hz, 1 H, H_{4b}), 1.39 (s, 3 H, H_6); IR (CH_2Cl_2) 3596, 3540, 3052, 2954, 2930, 1756, 1598, 1408, 1320, 1188, 1142, 1084 cm^{-1}; mass spectrum, m/e 310 ($M^+ - H_2O$). Anal. Calcd for $C_{15}H_{20}O_6S$: C, 54.86; H, 6.14. Found: C, 54.99; H, 6.33.

Triester 12. Triethylamine (0.18 mL, 1.29 mmol) and 0.078 mL (0.63 mmol) of pivaloyl chloride were added to a solution of 137 mg (0.57 mmol) of acid **13**[7a] in 3 mL of CH_2Cl_2. The mixture was stirred for 1.5 h at 25 °C and then transferred via syringe to another flask containing 158 mg (0.48 mmol) of alcohol **10** and 6 mg (.049 mmol) of 4-(dimethylamino)pyridine (DMAP). The solution was stirred for 13 h at 25 °C. The solvent was evaporated

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

and the residue partitioned between 20 mL of ethyl acetate and 10 mL of 0.1 N HCl. The aqueous layer was extracted with ethyl acetate (5 × 15 mL). The combined organic solutions were dried (Na_2SO_4), filtered, and evaporated. The crude product was purified by flash chromatography (40-mm column, 2:1 ether–hexane, R_f 0.28) to afford 217 mg (81%) of pure triester **12** as a colorless syrup: $[\alpha]^{20}_D$ +22° (*c* 1.01, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$)[29] δ 8.44 (dd, *J* = 12, 15 Hz, 1 H, $H_{3''}$), 7.80 (d, *J* = 9 Hz, 2 H, Ar), 7.38 (d, *J* = 9 Hz, 2 H, Ar), 6.66 (dd, *J* = 12, 12 Hz, 1 H, $H_{4''}$), 6.13 (d, *J* = 15 Hz, 1 H, $H_{2''}$), 5.98 (d, *J* = 12 Hz, 1 H, $H_{5''}$), 4.55–4.44 (m, 2 H, $H_{5'a}$ and H_a of $CO_2CH_2CH_2SO_2Ar$), 4.38–4.18 (m, 4 H, $H_{5'b}$, H_b of $CO_2CH_2CH_2SO_2Ar$, and $CO_2CH_2CH_2SiMe_3$), 3.45 (t, *J* = 6 Hz, 2 H, CH_2SO_2Ar), 3.18 (s, 1 H, $H_{2'}$), 2.46 (br s, 3 H, Ar-CH_3), 2.06 (dt, *J* = 15, 6 Hz, 1 H, $H_{4'a}$), 1.91 (dt, *J* = 15, 6 Hz, 1 H, $H_{4'b}$), 1.37 (s, 3 H, $H_{6'}$), 1.08–1.02 (m, 2 H, CH_2Si), 0.06 (s, 9 H, $SiMe_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 167.4, 165.7, 165.3, 145.1, 140.0, 139.1, 130.0, 128.1, 128.0, 125.2, 62.8, 60.7, 60.4, 58.3, 57.7, 54.7, 36.6, 21.5, 17.3, 16.2, -1.6; IR ($CHCl_3$) 3018, 2958, 1756, 1712, 1684, 1598, 1174, 858, 834 cm^{-1}; mass spectrum, *m/e* 552 (M^+); UV (EtOH) 263 (ε 26 300), 226 (17 650). Anal. Calcd for $C_{26}H_{36}O_9SSi$: C, 56.50; H, 6.57. Found: C, 56.33; H, 6.64.

Carboxylic Acid 5. A solution of 16.0 mg (0.029) of triester **12** and 0.0052 mL (0.0348 mmol) of DBU in 1 mL of benzene was stirred for 1 h at 25 °C. A small amount of **12** remained (TLC analysis) so an additional 0.0025 mL (0.017 mmol) of DBU was added and the solution stirred for an extra 1 h at 25 °C. The reaction was quenched by the addition of 1 mL of acidic (pH 2) saturated aqueous NaCl. The pH of the mixture was adjusted to 2 by careful addition of 3 N HCl. The mixture was extracted with ethyl acetate (7 × 2 mL), and the combined extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a 0.25-mm silica gel plate (1% formic acid in 1:1 hexane–ethyl acetate, R_f 0.39) to afford 8.3 mg (77%) of acid **5** as a colorless syrup which decomposed slowly upon storage. It should be noted that we were unable to consistently reproduce this procedure (see text).

5: ^1H NMR (250 MHz, $CDCl_3$)[29] δ 8.46 (dd, *J* = 12, 16 Hz, 1 H, $H_{3''}$), 6.64 (dd, *J* = 12, 12 Hz, 1 H, $H_{4''}$), 6.12 (d, *J* = 16 Hz, 1 H, $H_{2''}$), 5.98 (d, *J* = 12 Hz, 1 H, $H_{5''}$), 4.40–4.24 (m, 4 H, $H_{5'}$, and $-CO_2CH_2CH_2SiMe_3$), 3.47 (s, 1 H, $H_{2'}$), 2.19–1.98 (m, 2 H, $H_{4'}$), 1.48 (s, 3 H, $H_{6'}$), 1.09–1.02 (m, 2 H, CH_2Si), 0.06 (s, 9 H, $SiMe_3$).

Verrucarin B Seco Acid 2-(Trimethylsilyl)ethyl Ester (14). Verrucarol (52.0 mg, 0.195 mmol)[18] was acylated with the sodium salt of **5** (generated in situ from 72 mg (0.13 mmol) of triester **12**) by using the procedure described for the preparation of **18**. The crude product was chromatographed on a 1.5-mm silica gel plate (1% formic acid in 1:1 ether–CH_2Cl_2, R_f 0.51) to afford 28.5 mg (35% based on **12**) of pure **14** as a colorless syrup along with 32 mg of recovered verrucarol (**2**).[19]

14: $[\alpha]^{20}_D$ -8.5° (*c* 2.4, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 11, 16 Hz, 1 H, $H_{3''}$), 6.64 (dd, *J* = 11, 11 Hz, 1 H, $H_{4''}$), 6.11 (d, *J* = 16 Hz, 1 H, $H_{2''}$), 5.98 (d, *J* = 11 Hz, 1 H, $H_{5''}$), 5.40 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.48–4.40 (m, 1 H, H_4), 4.38–4.22 (m, 4 H, $H_{5'}$ and $-CO_2CH_2-$), 4.27 (d, *J* = 12 Hz, 1 H, H_{15a}), 4.02 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.83 (d, *J* = 5 Hz, 1 H, H_2), 3.57 (d, *J* = 5 Hz, 1 H, H_{11}), 3.41 (s, 1 H, $H_{2'}$), 3.11 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.79 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.58 (dd, *J* = 7, 16 Hz, 1 H, $H_{3\alpha}$), 2.2–1.7 (m, 8 H, $H_{4'}$, H_7, H_8, $H_{3\beta}$, and OH), 1.71 (br s, 3 H, H_{16}), 1.44 (s, 3 H, $H_{6'}$), 1.09–1.02 (m, 2 H, CH_2Si), 0.85 (s, 3 H, H_{14}), 0.06 (s, 9 H, $SiMe_3$); IR ($CHCl_3$) 3570, 3006, 2954, 1744, 1714, 1600, 1412, 1172, 1070, 964 cm^{-1}; mass spectrum, *m/e* 618 (M^+); UV (EtOH) 263 (ε 21 800).

1-[[2-(Trimethylsilyl)ethoxy]carbonyl]imidazole (16). Carbonyldiimidazole (CDI, 195 mg, 1.2 mmol) was added to a solution of 118 mg (1 mmol) of 2-(trimethylsilyl)ethanol in 2 mL of benzene. The resulting mixture (white precipitate) was stirred for 1 h at 25 °C and then was diluted with 20 mL of CH_2Cl_2. The solution was washed quickly with ice-cold water, filtered through a cotton plug and evaporated. The crude product was chromatographed on a 1.5-mm silica gel plate (1:1 hexane–ether, R_f 0.35) to give 205 mg (97%) of imidazolide **16** as a white crystalline solid: mp 29–30.5 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.11 (s, 1 H), 7.40 (br s, 1 H), 7.05 (br s, 1 H), 4.52–4.46 (m, 2 H), 1.20–1.13 (m, 2 H), 0.08 (s, 9 H); IR (CH_2Cl_2) 2966, 1760, 1472, 1400, 1322, 1294, 1242, 1172, 1004, 862, 842 cm^{-1}; mass spectrum, *m/e* 212 (M^+). Anal. Calcd for $C_9H_{16}N_2O_2Si$: C, 50.91; H, 7.50. Found: C, 50.62; H, 7.46.

4-*O*-[[2-(Trimethylsilyl)ethoxy]carbonyl]verrucarol (17). Verrucarol (50 mg, 0.188 mmol) and DBU (0.0056 mL, 0.0375 mmol) were added sequentially to a solution of 39.9 mg (0.188 mmol) of imidazolide **16** in 1 mL in benzene. The mixture was stirred for 22 h at 25 °C and then cooled in an ice bath as 1 mL of 0.1 N HCl was added. The aqueous phase was then extracted with ethyl acetate (7 × 3 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated. The crude product was chromatographed on a 0.5-mm silica gel plate (2:1 ether–hexane, R_f 0.45) to afford 41.6 mg (54%) of **17** as a white crystalline solid. The rest of the silica gel plate was extracted to afford 29.4 mg of a colorless syrup which was dissolved in 20 mL of saturated methanolic K_2CO_3 and was stirred for 24 h at 25 °C. The solvent was then evaporated and the residue partitioned between 10 mL of water and 20 mL of ether. The mixture was neutralized by careful addition of 3 N HCl. The aqueous phase was then extracted with ethyl acetate (2 × 15 mL) and CH_2Cl_2 (6 × 15 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated. The crude verrucarol so obtained was chromatographed on a 0.25-mm silica gel plate (ethyl acetate, R_f 0.26) to afford 16.5 mg (33%) of recovered **2**. The yield of **17** corrected for recovered verrucarol was therefore 81%.

In a second experiment, conducted on the same scale but with a reaction time of 18 h, all of the products were isolated separately. This procedure afforded 34 mg (44%) of **17**, along with 11 mg (10%) of the diacylated product (R_f 0.55), 4 mg (5%) of the C-15 monoacylated trichothecene (R_f 0.19) and 9 mg (18%) of recovered verrucarol.

17: mp 128.5–129 °C (recrystallized from hexane–CH_2Cl_2); $[\alpha]^{20}_D$ +10° (*c* 3.3, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.90 (dd, *J* = 4, 8 Hz, 1 H, H_4), 5.48 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.25–4.18 (m, 2 H, $-CO_2CH_2-$), 3.87 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.82 (d, *J* = 5 Hz, 1 H, H_2), 3.81 (d, *J* = 12 Hz, 1 H, H_{15a}), 3.66 (d, *J* = 12 Hz, 1 H, H_{15b}), 3.12 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.81 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.51 (dd, *J* = 8, 15 Hz, 1 H, $H_{3\alpha}$), 2.15–1.95 (m, 5 H, $H_{3\beta}$, H_7, and H_8), 1.71 (br s, 3 H, H_{16}), 1.57 (br s, 1 H, OH), 1.09–1.02 (m, 2 H, CH_2Si), 0.88 (s, 3 H, H_{14}), 0.04 (s, 9 H, $SiMe_3$); IR ($CHCl_3$) 3630, 3500, 3016, 2960, 2910, 1728, 1275, 1086, 962, 862, 840 cm^{-1}; mass spectrum, *m/e* 392 ($M^+ - H_2O$). Anal. Calcd for $C_{21}H_{34}O_6Si$: C, 61.43; H, 8.35. Found: C, 61.22; H, 8.62.

4-[2-(Trimethylsilyl)ethoxy]carbonyl]verrucarin B Seco Acid 2-(Trimethylsilyl)ethyl Ester (18). Sodium hydride (4.7 mg of 60% oil dispersion, 0.117 mmol) and 0.0012 mL (0.0078 mmol) of DBU were added to a solution of 43 mg (0.078 mmol) of triester **12** in 1.2 mL of THF. The mixture was stirred for 6.5 h at 25 °C after which analytical TLC showed complete deprotection (**12**, R_f 0.50, **5**, R_f 0.40, 1% formic acid in 1:1 hexane–ethyl acetate). Triethylamine (0.0163 mL, 0.117 mmol) was added followed by 27.7 mg (0.109 mmol) of *N,N*-bis[2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (BOP-Cl)[14] and a solution of 32 mg (0.078 mmol) of trichothecene **17** in 1.5 mL of THF. 4-(Dimethylamino)pyridine (DMAP, 0.10 mL of a solution containing 24 mg of DMAP in 1.0 mL of THF, 0.019 mmol) was then added and the mixture stirred for 16 h at 25 °C. The mixture was cooled in an ice bath as 1 mL of 0.1 N HCl and 0.5 mL of ethyl acetate were added. The layers were separated and the aqueous phase was extracted with ethyl acetate (7 × 2 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated. The crude product was chromatographed on a 0.5-mm silica gel plate (1:1 hexane–ester, two developments, R_f 0.37) to afford 38 mg (64%) of **18** as a clear colorless syrup: $[\alpha]^{20}_D$ +8.2° (*c* 3.8, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 12, 16 Hz, 1 H, $H_{3''}$), 6.63 (dd, *J* = 12, 12 Hz, 1 H, $H_{4''}$), 6.09 (d, *J* = 16 Hz, 1 H, $H_{2''}$), 5.97 (d, *J* = 12 Hz, 1 H, $H_{5''}$), 5.51 (dd, *J* = 4, 8 Hz, 1 H, H_4), 5.43 (br d, *J* = 5 Hz, 1 H, H_{10}), 4.37–4.10 (m, 8 H, H_{15}, $H_{5'}$, and two sets of $-CO_2CH_2-$), 3.84 (d, *J* = 5 Hz, 1 H, H_2), 3.67 (br d, *J* = 5 Hz, 1 H, H_{11}), 3.47 (s, 1 H, $H_{2'}$), 3.12 (d, *J* = 4 Hz, 1 H, H_{13a}), 2.79 (d, *J* = 4 Hz, 1 H, H_{13b}), 2.55 (dd, *J* = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.14–1.90 (m, 7 H, $H_{4'}$, H_7, H_8, and $H_{3\beta}$), 1.72 (br s, 3 H, H_{16}), 1.42 (s, 3 H, $H_{6'}$), 1.09–1.00 (m, 4 H, CH_2Si), 0.82 (s, 3 H, H_{14}), 0.06 (s, 9 H, $SiMe_3$), 0.04 (s, 9 H, $SiMe_3$); IR ($CHCl_3$) 3040,

(29) The numbering system used for this compound follows that adopted for verrucarin B (see ref 9).

3018, 2964, 2910, 1724, 1604, 910, 860, 840 cm^{-1}; mass spectrum, m/e 762 (M^+); UV (EtOH) 263 (ϵ 24 100).

Verrucarin B Seco Acid (4). Method A. Water (0.0156 mL, 0.86 mmol) was added to a suspension of 25.1 mg (0.43 mmol) of potassium fluoride and 33 mg (0.043 mmol) of **18** in 2.4 mL of Me_2SO. The mixture was stirred for 36 h at 25 °C and then cooled in an ice bath as 30 mL of water and 25 mL of ethyl acetate were added. The pH was adjusted to 2 by careful addition of 3 N HCl. The layers were separated and the aqueous phase extracted with ethyl acetate (7 × 25 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed on a 0.5-mm silica gel plate (1% formic acid in 1:1 ether–CH_2Cl_2, R_f 0.31) to afford 20 mg (89%) of pure seco acid **4** as a white solid.

Method B. (Trimethylsilyl)ethyl ester **14** (40 mg, 0.065 mmol) was deprotected by using the procedure described in the preceding paragraph (reaction time 66 h). 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 0.31) to afford 23.5 mg (70%) of seco acid **4**: mp 75–78 °C; $[\alpha]^{20}_D$ −16° (c 1.27, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 8.43 (dd, J = 12, 16 Hz, 1 H, $H_{3''}$), 6.71 (dd, J = 12, 12 Hz, 1 H, $H_{4''}$), 6.12 (d, J = 16 Hz, 1 H, $H_{2''}$), 6.02 (d, J = 12 Hz, 1 H, $H_{5''}$), 5.42 (br d, J = 5 Hz, 1 H, H_{10}), 4.61–4.56 (m, 1 H, H_4), 4.38–4.29 (m, 2 H, $H_{5'}$), 4.32 (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), 3.62 (d, J = 5 Hz, 1 H, H_{11}), 3.52 (s, 1 H, $H_{2'}$), 3.14 (d, J = 4 Hz, 1 H, H_{13a}), 2.83 (d, J = 4 Hz, 1 H, H_{13b}), 2.62 (dd, J = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.2–1.75 (m, 7 H, $H_{4'}$, H_7, H_8, and $H_{3\beta}$), 1.72 (br s, 3 H, H_{16}), 1.45 (s, 3 H, $H_{6'}$), 0.92 (s, 3 H, H_{14}); IR ($CHCl_3$) 3400–2800 (acid OH), 3016, 2976, 1746, 1718, 1700, 1602, 1272, 1204, 1072, 962 cm^{-1}; mass spectrum, m/e 500 ($M^+ - H_2O$); UV (EtOH) 262 (ϵ 18 300).

Verrucarin B (3) and *E,E* Isomer 19. Method A. Pivaloyl chloride (0.095 mL, 0.077 mmol) was added to a solution of 0.0134 mL (0.096 mmol) of triethylamine and 10.0 mg (0.019 mmol) of seco acid **4** in 10 mL of CH_2Cl_2. The solution was stirred for 15 min at 25 °C and then 4-PP (0.50 mL of 0.39 M solution in CH_2Cl_2, 0.019 mmol) was added. This mixture was stirred for 90 min at 25 °C before being concentrated in vacuo. The residue was chromatographed on a 0.5-mm silica gel plate (1:1 ether–CH_2Cl_2) to give 5.3 mg (55%) of verrucarin B (R_f 0.61) and 3.3 mg (34%) of *E,E* isomer **19** (R_f 0.44).

Method B. A solution of mixed anhydride **21** (generated in situ from 7.0 mg (0.013 mmol) of seco acid **4** as described in the preceding paragraph) in 7 mL of CH_2Cl_2 was treated with 4-PP (0.020 mL of 0.067 M CH_2Cl_2 solution, 0.0013 mmol). The solution was stirred for 2 h at 25 °C and then additional 4-PP was added (0.010 mL of 0.067 M CH_2Cl_2 solution, 0.00065 mmol). The solution was stirred for a total of 17 h at 25 °C, but some mixed anhydride and seco acid still remained (TLC analysis). In an attempt to force the reaction to completion, additional pivaloyl chloride (0.0017 mL, 0.013 mmol) and triethylamine (0.0019 mL, 0.013 mmol) were added. The solution was stirred for 3 h at 25 °C (TLC analysis showed no change). The mixture was then concentrated to a final volume of ca. 2 mL. Ethyl acetate (2 mL) and 1 mL of 0.1 N HCl were added, and the aqueous layer extracted with ethyl acetate (7 × 2 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on a 0.25-mm silica gel plate (1% formic acid in 1:1 ether–CH_2Cl_2) to afford 3.7 mg (54%) of verrucarin B (R_f 0.74) and 0.7 mg (10%) of *E,E* isomer **19** (R_f 0.55).

Method C. A solution of mixed anhydride **21** (generated in situ from 9.5 mg (0.018 mmol) of seco acid **4** as described above) in 9.5 mL of THF was cooled in an ice bath as 0.016 mL (0.11 mmol) of DBU was added. The red solution was stirred for 75 min at 25 °C (reaction appeared to be clean and complete by TLC analysis). The mixture was cooled in an ice bath as 2.5 mL of 0.1 N HCl was added (color changed immediately from red to yellow). The mixture was extracted with ethyl acetate (8 × 5 mL), and the combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on a 0.25-mm silica gel plate (1% formic acid in 1:1 ether–CH_2Cl_2) to give 2.2 mg (24%) of verrucarin B. Only a trace of *E,E* isomer **19** was present by TLC analysis. The yield of verrucarin B was 58% when this procedure was performed on 2.5 mg (0.0048 mmol) of **4**.

Synthetic verrucarin B obtained by these methods was identical with an authentic sample provided by Professor C. Tamm: mp >300 °C; lit.[5d] mp >330 °C; $[\alpha]^{20}_D$ +94° (c 1.2, $CHCl_3$); $[\alpha]^{23}_D$ +94° (c 0.99 $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.90 (dd, J = 11, 16 Hz, 1 H, $H_{3''}$), 6.64 (dd, J = 11, 11 Hz, 1 H, $H_{4''}$), 6.18 (d, J = 11 Hz, 1 H, $H_{5''}$), 6.07 (d, J = 16 Hz, 1 H, $H_{2''}$), 5.85 (dd, J = 4, 8 Hz, 1 H, H_4), 5.44 (br d, J = 5 Hz, 1 H, H_{10}), 4.51 (d, J = 12 Hz, 1 H, H_{15a}), 4.42–4.28 (m, 2 H, $H_{5'}$), 4.35 (d, J = 12 Hz, 1 H, H_{15b}), 3.87 (d, J = 5 Hz, 1 H, H_2), 3.60 (d, J = 5 Hz, 1 H, H_{11}), 3.40 (s, 1 H, $H_{2'}$), 3.15 (d, J = 4 Hz, 1 H, H_{13a}), 2.84 (d, J = 4 Hz, 1 H, H_{13b}), 2.53 (dd, J = 8, 15 Hz, 1 H, $H_{3\alpha}$), 2.32 (ddd, J = 15, 6, 3 Hz, 1 H, $H_{4'a}$), 2.21 (ddd, J = 15, 5, 5 Hz, 1 H, $H_{3\beta}$), 2.1–1.7 (m, 5 H, H_7, H_8, and $H_{4'b}$), 1.74 (br s, 3 H, H_{16}), 1.57 (s, 3 H, $H_{6'}$), 0.89 (s, 3 H, H_{14}); IR ($CHCl_3$) 3040, 2980, 1750, 1710, 1190, 1080, 1040, 965, 880 cm^{-1}; UV (EtOH) 258.5 (ϵ 22 400).

19: mp 170–175 °C; $[\alpha]^{20}_D$ +145° (c 0.19, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.52 (dd, J = 14, 15 Hz, 1 H, $H_{3''}$ or $H_{4''}$), 7.24 (dd, J = 14, 15 Hz, 1 H, $H_{4''}$ or $H_{3''}$), 6.54 (d, J = 14 Hz, 1 H, $H_{2''}$ or $H_{5''}$), 6.22 (d, J = 15 Hz, 1 H, $H_{5''}$ or $H_{2''}$), 5.42 (br d, J = 5 Hz, 1 H, H_{10}), 5.29 (dd, J = 3, 8 Hz, 1 H, H_4), 5.14 (d, J = 13 Hz, 1 H, H_{15a}), 4.75–4.68 (ddd, J = 12, 4, 2 Hz, 1 H, $H_{5'a}$), 4.11–4.00 (m, 1 H, $H_{5'b}$), 3.90 (d, J = 13 Hz, 1 H, H_{15b}), 3.88 (d, J = 5 Hz, 1 H, H_2), 3.48 (br d, J = 5 Hz, 1 H, H_{11}), 3.34 (s, 1 H, $H_{2'}$), 3.12 (d, J = 4 Hz, 1 H, H_{13a}), 2.86 (d, J = 4 Hz, 1 H, H_{13b}), 2.68 (dd, J = 16, 8 Hz, 1 H, $H_{3\alpha}$), 2.46 (ddd, J = 16, 5, 3 Hz, 1 H, $H_{3\beta}$), 2.34–1.95 (m, 6 H, $H_{4'}$, H_7, and H_8), 1.76 (br s, 3 H, H_{16}), 1.62 (s, 3 H, $H_{6'}$), 1.02 (s, 3 H, H_{14}); IR (CH_2Cl_2) 2980, 2940, 1755, 1720, 1600, 1320, 1174, 1082, 1000, 970 cm^{-1}; mass spectrum, m/e 500 (M^+).

Isomerization of 19 to Verrucarin B and *Z,E* Isomer 20. One crystal of iodine was added to a solution of 2.0 mg (0.0040 mmol) of *E,E* isomer **19** in 1 mL of benzene. The red solution was stirred for 90 min at 25 °C. A small amount of **19** remained (TLC analysis) so an additional small crystal of iodine was added. The solution was stirred for an additional 1 h at 25 °C and then was diluted with 10 mL of benzene. Solid sodium sulfite (Na_2SO_3) was added and the mixture stirred until the red color disappeared. The solution was filtered and concentrated to a dark yellow liquid residue which consisted of a 2:1 mixture of verrucarin B and **20** (250 MHz NMR analysis). This material was chromatographed on a 0.25-mm silica gel plate (1:2 hexane–ether; two developments) to afford 1.2 mg (60%) of verrucarin B (R_f 0.44) and 0.6 mg (30%) of the *Z,E* isomer **20** (R_f 0.34): ^1H NMR (250 MHz, $CDCl_3$) δ 8.02 (dd, J = 12, 15 Hz, 1 H, $H_{4''}$), 6.72 (dd, J = 12, 12 Hz, 1 H, $H_{3''}$), 6.11 (d, J = 15 Hz, 1 H, $H_{5''}$), 5.97 (d, J = 12 Hz, 1 H, $H_{2''}$), 5.47 (br, d, J = 5 Hz, 1 H, H_{10}), 5.18 (dd, J = 4, 8 Hz, 1 H, H_4), 5.02–4.95 (m, 1 H, $H_{5'a}$), 4.30 (d, J = 13 Hz, 1 H, H_{15a}), 4.00–3.91 (m, 1 H, $H_{5'b}$), 3.93 (d, J = 13 Hz, 1 H, H_{15b}), 3.86 (d, J = 5 Hz, 1 H, H_2), 3.63 (br d, J = 5 Hz, 1 H, H_{11}), 3.45 (s, 1 H, $H_{2'}$), 3.21 (d, J = 4 Hz, 1 H, H_{13a}), 2.87 (d, J = 4 Hz, 1 H, H_{13b}), 2.76 (dd, J = 8, 16 Hz, 1 H, $H_{3\alpha}$), 2.46–2.35 (m, 1 H, $H_{3\beta}$), 2.18–1.81 (m, 6 H, H_7, H_8, and $H_{4'}$), 1.75 (br s, 3 H, H_{16}), 1.36 (s, 3 H, $H_{6'}$), 1.09 (s, 3 H, H_{14}); UV (EtOH) 260 (ϵ 18 500).

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