Synthesis of a Highly Functionalized Carbon Ring Skeleton for the Trichothecene Anguidine†

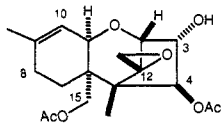
Frederick E. Ziegler* and Susan B. Sobolov[1]

Contribution from the Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06511-8118. *Received August 9, 1989*

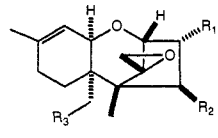
Abstract: A strategy directed toward the synthesis of the highly functionalized trichothecene anguidine (**1**) is detailed. The route entails several challenges. The first of these is the synthesis of the congested, achiral cyclopentadienyl malondialdehyde **8**, which is induced to undergo a highly diastereoselective, but modestly enantioselective, carbonyl ene reaction to give hydroxy aldehyde **7** under the influence of europium catalysts. The cyclopentadiene ring of **22d** is transformed into the bis(allyloxy) epoxide functionality of **33c**, which cyclizes regioselectively with $ZnBr_2$ to the tetracycle **35**. A new method using $(Ph_3P)_4RhH$ for the deprotection of the allyl ethers is described. Selective functionalization of the C_3, C_4, and C_{12} hydroxyl groups of triol **40a** can be accomplished, but isomerization of the exocyclic olefin of tetraacetate **48b** gives the $\Delta^{8,9}$ olefin **49** and not the desired $\Delta^{9,10}$ olefin **50**.

The trichothecenes are an ubiquitous class of mycotoxins produced by a number of genera of fungi.[2] The simplest members of this class are tetracyclic sesquiterpene epoxy olefins; more complex members of the class bear macrocylic rings tethered by ester linkages at oxygenated C_4 and C_{15} positions of the sesquiterpene nucleus. The trichothecenes have been designated as the source of varied toxicoses derived from infected grain and have also displayed antitumor, antibacterial, and antiviral activity.[3] The epoxide and olefin functionalities of the trichothecenes are critical to their mode of action,[4] which involves interaction with the 60S subunit of an intact 80S ribosome/mRNA complex that interferes with peptidyl transferase.[5] The epi-epoxide stereoisomer of anguidine has been prepared[6] and has been found to have reduced activity.[6a]

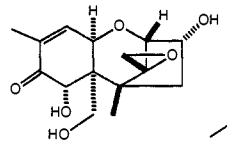
Anguidine (diacetoxyscirpenol **1**), a highly oxygenated trichothecene, was first isolated by Brian from *Fusarium equiseti*.[7] Subsequently, Sigg[8] and Dawkins[9] independently assigned the structure of anguidine by a combination of chemical and spectroscopic techniques. Anguidine has served as an important intermediate in the synthesis of the less oxygenated trichothecenes calonectrin (**2b**),[10,11] trichodermol (**2c**),[12] and verrucarol (**2d**)[12] and the more highly oxygenated trichothecenes deoxynivalenol (vomitoxin,[10] **3**) and T-2 toxin **4** among others.[13]



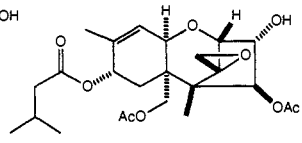
1



2a, $R_1 = R_3 = H$, $R_2 = OAc$
b, $R_1 = R_3 = OAc$, $R_2 = H$
c, $R_1 = R_3 = H$, $R_2 = OH$
d, $R_1 = H$, $R_2 = R_3 = OH$
e, $R_1 = R_2 = R_3 = H$



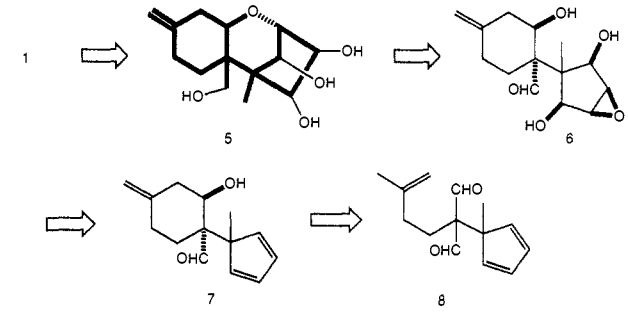
3



4

Approaches to the synthesis of the oxygenated sesquiterpene nucleus of the trichothecenes have been numerous.[2] Trichodermin (**2a**),[14] calonectrin (**2b**),[15] trichodermol (**2c**),[16] verrucarol (**2d**),[17] and 12,13-epoxytrichothec-9-ene (**2e**)[18] have all yielded to total synthesis. To date, the only successful synthesis of anguidine reported has been that of Brooks who prepared the natural antipode.[19] The plan we envisaged for the synthesis of anguidine is outlined in Scheme I. Because four of the contiguous carbons

Scheme I



of the 5-membered ring of anguidine bear oxygen functionality, the formation of the dotted O_1–C_2 bond of **5** by opening the epoxide ring of aldehyde **6** or a close congener appeared to be a viable strategy. Although each of the carbon atoms of the epoxide ring is locally enantiotopic, the asymmetry of the 6-membered

† No reprints available.

(1) Taken in part from the PhD. thesis of S.B.S., Yale University, 1989. Recipient of a Dox Fellowship, Yale University, 1987–88.

(2) McDougal, P. G.; Schmuff, N. R. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer-Verlag: New York, 1985; Vol. 47, p 153.

(3) (a) Ueno, Y. *Trichothecenes—Chemical, Biological and Toxocological Aspects, Developments in Food Science—4*; Elsevier: New York, 1983. (b) Joffe, A. Z. *Fusarium Species: Their Biology and Toxicology*; Wiley-Interscience: New York, 1986.

(4) Grove, J. F.; Mortimer, P. H. *Biochem. Pharmacol.* **1969**, *18*, 1473.

(5) Doyle, T. W.; Bradner, W. T. In *Anticancer Agents Based on Natural Products*; Cassady, J. M.; Douros, J. D., eds.; Academic: New York: 1980; Vol. 6, p 43.

(6) (a) Colvin, E. W.; Cameron, S. *J. Chem. Soc., Chem. Commun.* **1986**, 1642. (b) Roush, W. R.; Russo-Rodriquez, S. *J. Org. Chem.* **1987**, *52*, 603.

(7) Brian, P. W.; Dawkins, A. W.; Grove, J. F.; Hemming, A. G.; Lowe, D. *J. Exp. Bot.* **1961**, *12*, 1.

(8) Sigg, H. P.; Mauli, R.; Flury, E.; Hauser, D. *J. Chem. Soc., Chem. Commun.* **1965**, 26.

(9) Dawkins, A. W. *J. Chem. Soc., Chem. Commun.* **1965**, 27.

(10) Colvin, E. W.; Cameron, S. *Tetrahedron Lett.* **1988**, *29*, 493.

(11) Jeker, N.; Mohr, P.; Tamm, C. *Tetrahedron Lett.* **1984**, *25*, 5637.

(12) Fraser-Reid, B.; Tulshian, B. D. *Tetrahedron Lett.* **1980**, *21*, 4549.

(13) Wani, M. C.; Rector, D. H.; Cook, C. E. *J. Org. Chem.* **1987**, *52*, 3468.

(14) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989.

(15) Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *J. Am. Chem. Soc.* **1982**, *104*, 1114.

(16) Still, W. C.; Tsai, M. Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654.

(17) (a) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116. (b) Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6110. (c) Roush, W. R.; D'Ambra, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 1058. (d) O'Brien, M. K.; Pearson, A. J.; Pinkerton, A. A.; Schmidt, W.; Willman, K. *J. Am. Chem. Soc.* **1989**, *111*, 1499.

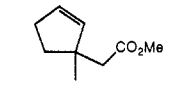
(18) (a) Fujimoto, Y.; Yokura, S.; Nakamura, T.; Morikawa, T.; Tatsuno, T. *Tetrahedron Lett.* **1974**, 2523. (b) Masuoka, N.; Kamikawa, T. *Ibid.* **1976**, 1691. (c) Hua, D. H.; Venkataraman, S.; Chan-Yu-King, R.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1988**, *110*, 4741.

(19) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472.

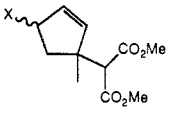
0002-7863/90/1512-2749$02.50/0

ring renders the epoxide carbons diastereotopic. Thus, the issue of diastereoselective opening of the epoxide ring would have to be addressed. The oxygenation pattern of the 5-membered ring of **6** is traditionally achieved by oxidative functionalization of the 1,3-cyclopentadiene present in aldehyde **7**. This substance can be viewed as arising via an intramolecular Lewis acid catalyzed carbonyl ene reaction (Prins) from the achiral malondialdehyde **8**. The attainment of the stereochemistry of aldehyde **7** would be a precondition to establishing the stereochemistry in anguidine. Moreover, the preparation of the malondialdehyde **8** bearing vicinal quaternary carbons loomed as a challenge in itself.

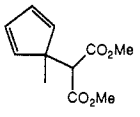
Ester **9**, prepared by the Ireland silylketene acetal Claisen rearrangement as described by Pearson,[20] was carbomethoxylated in 98% yield with LDA and methyl cyanoformate[21] to provide malonate **10a**. Free-radical bromination with *N*-bromosuccinimide provided a 1:1 mixture of allylic bromides **10b**; the stereoisomeric and/or regioisomeric nature of the mixture was not determined. After the screening of a number of conditions for dehydrohalogenation, most of which gave mixtures of cyclopentadiene **11** and lactone **12**, the product of nucleophilic displacement, $CaCO_3$/DMF at 80 °C, proved highly selective for dehydrohalogenation, providing **11** in two steps in 80% yield on multigram scale.



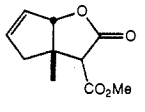
9



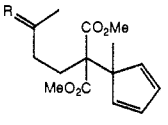
10a, X=H
b, X=Br



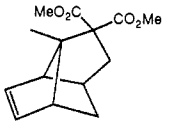
11



12



13a, R=CH2
b, R=O

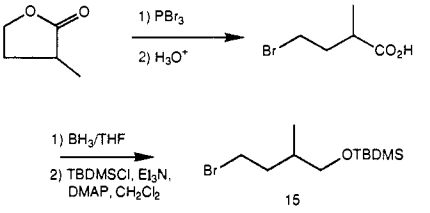


14

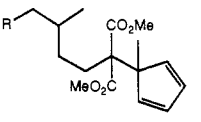
The alkylation of malonate **11** did prove to be a problem owing to the difficulty of effecting S_N2 displacement in a process that creates vicinal quaternary carbon atoms. To assure that anion formation was occurring, the malonate was treated with NaH in either THF or DMSO followed by quenching with AcOD to give the monodeuteration product. Likewise, deuteration occurred in MeOD/MeONa. The direct alkylation of the sodio malonate with 4-bromo-2-methyl-1-pentene in nonhydroxylic solvent gave recovered malonate and none of the desired olefin **13a**. Alternatively, the sodium methoxide catalyzed addition of the malonate to methyl vinyl ketone (MVK) gave principally 4-methoxy-2-butanone and only 8% of the desired ketone **13b**. The use of 3-(trimethylsilyl)-3-buten-2-one under aprotic conditions offered no improvement.[22] Although the low yield of **13b** precluded this route, the ketone was converted into olefin **13a** via Wittig methylenation. The success of this transformation prompted the examination of other MVK equivalents. When 2-(β-bromoethyl)-3,5,5-trimethyl-1,3-dioxane was employed as the electrophile under nonhydroxylic conditions, only the product of elimination, 3,5,5-trimethyl-2-vinyl-1,3-dioxane, and malonate **11** were recovered. This observation indicated that isoprene was probably being formed in the first alkylation study.

Because of the negative results of the alkylation experiment conducted thus far, the alkylation of malonate **11** with the more reactive electrophile, allyl bromide, which cannot undergo elimination, was examined. When the alkylation was conducted in THF at room temperature, the Diels–Alder adduct **14**, ostensibly arising from the undetected alkylation product, was formed. The ease of this intramolecular cycloaddition with an unactivated olefin can be attributed to the "*gem*-dimethyl effect".[23] This unrewarding result refocused our attention on the examples that had undergone elimination. Was the presence of a double bond or an oxygen atom vicinal to the hydrogen that participated in the dehydrohalogenation a contributing factor? To test this query, the sodio malonate was subjected to alkylation with *n*-butyl iodide. Alkylation occurred! This positive result required the design of an electrophile that would emulate *n*-butyl iodide and at the same time incorporate remote functionality that would permit the installation of the double bond at a later stage. Accordingly, the transformations of Scheme II led to bromide **15** in 48% overall yield. Alkylation of sodio malonate **11** with bromide **15** in THF at reflux provided the dialkylated product **16a** in 71% yield. Removal of the silyl protecting group was readily accomplished in the presence of HF/acetonitrile to afford the alcohol **16b**. Formation of the previously observed olefin **13a** was achieved by using the *o*-nitrophenyl selenide procedure of Grieco.[24] Sequential reduction of malonate **13a** to diol **17** and reoxidation under Swern conditions[25] gave rise to the key malondialdehyde **8**.

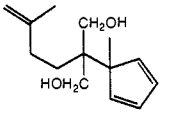
Scheme II



15



16a, R = OTDMBS
b, R = OH

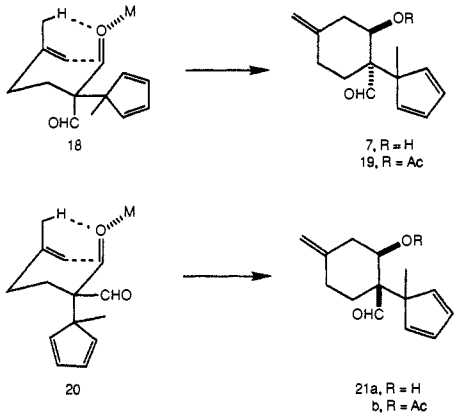


17

The Lewis acid catalyzed carbonyl ene reaction has been shown to occur by a stepwise mechanism wherein the coordinated carbonyl forms a rate-limiting complex with the olefin followed by allylic hydrogen transfer to the oxygen.[26] Operationally, the process amounts to a concerted reaction when olefins are formed and the intermediate is not trapped by nucleophiles. Accordingly, type II ene reactions[27] of 5-hexenals should proceed to give 3-methylenecyclohexenols wherein the hydroxyl group is generated in the axial orientation through a chairlike transition state. This pathway has been borne out in a number of cases.[28] Because of the steric bulk of the methylcyclopentadienyl group relative to the formyl group, the former entity should occupy an equatorial position in the transition state for cyclization. Thus, transition state **18** leading to **7** should prevail over **20** → **21a**.

The earliest observation of the intramolecular cyclization was detected upon exposure of the malondialdehyde to silica gel. These

(20) Pearson, A. J.; Chen, Y.-S.; Hsu, S.-Y.; Ray, T. *Tetrahedron Lett.* **1984**, *25*, 1235.
(21) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(22) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152.
(23) For cases of the "*gem*-dimethyl effect" in the intramolecular Diels–Alder reaction, see: (a) Boeckman, R. K.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033. (b) Sternbach, D. D.; Russona, K. D.; Onan, K. D. *Tetrahedron Lett.* **1985**, *26*, 591. (c) Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429.
(24) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(25) Swern, D.; Omura, K. *Tetrahedron* **1978**, *34*, 1651.
(26) Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160.
(27) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476.
(28) (a) Ziegler, F. E.; Wang, T.-F. *Tetrahedron Lett.* **1981**, *22*, 1179. (b) Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1983**, *105*, 7358. (c) Ziegler, F. E.; Wang, T.-F. *J. Am. Chem. Soc.* **1984**, *106*, 718. (d) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T. F. *J. Am. Chem. Soc.* **1985**, *107*, 2730. (e) Anderson, N. H.; Hadley, S. W.; Kelly, J. D.; Bacon, E. R. *J. Org. Chem.* **1985**, *50*, 4144. (f) Johnston, M. J.; Kwass, J. A.; Beal, R. B.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 5419.

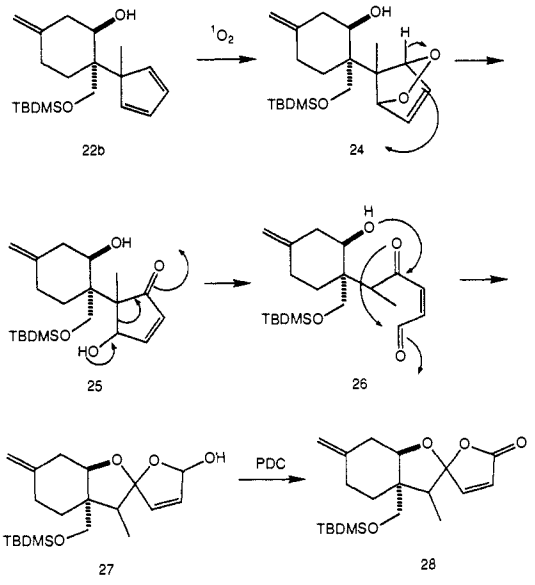


conditions gave an equal mixture of aldehydes **7** and **21a**; dimethylaluminum chloride[29] improved the ratio to 2:1. In light of Danishefsky's[30] application of lanthanide catalysts to promote the hetero Diels–Alder reaction, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium [Eu(fod)$_3$] was found to improve the diastereoselectivity to 5:1. With the added expedient of drying the reagent in situ with molecular sieves prior to the addition of the substrate, the ratio of **7**/**21a** was increased to 8:1. The mixture of β-hydroxy aldehydes was not readily separated by silica gel chromatography, but prior acetylation provided a separable mixture. The ^{1}H NMR spectra of acetates **19** and **21b** permitted the assignment of the respective stereochemistries based upon a preferred chair conformation for each of the diastereomers having the methylcyclopentadienyl group in the equatorial position. The equatorial acetoxy methine proton in the major isomer **19** appeared as a broad singlet at δ 5.57; the same proton in isomer **21b** occupied an axial position and appeared at δ 4.96 as a doublet of doublets (J = 8.0 and 5.0 Hz).

The intramolecular carbonyl ene reaction of malondialdehyde **8** was conducted in the presence of chiral catalysts[31] to ascertain both the diastereoselectivity of the reactions and the enantiomeric excess of the major component. The enantiomeric excess of the major diastereomer was measured by ^{1}H NMR integration of the methyl group of the derived acetates in the presence of (+)-Eu(hfc)$_3$.[32a] The three most promising catalysts gave the following results; the absolute configurations were not determined (% de **19**/**21b**, % ee **19**): (+)-Eu(hfc)$_3$ (5:1, 20); (+)-Eu(dppm)$_3$[32b] (4.5:1, 31); and [(*S*)-(−)-1,1′-bi-2-naphthol]TiCl$_2$ (4.5:1, 38).[31c] These catalysts provided the same enantiomer in excess; (−)-Eu(hfc)$_3$ afforded the opposite enantiomer in excess. While these results indicated that asymmetric induction is feasible in the case of the malondialdehyde, a more extensive study, in the context of the synthesis, would be warranted only if subsequent operations proved successful. To this end, the oxygenation of the cyclopentadiene ring was explored.

The first substrate to be subjected to sensitized oxygenation was silyloxy alcohol **22b**, readily prepared by selective silylation of diol **22a**, itself prepared from acetoxy aldehyde **19** by reduction with lithium aluminum hydride. The presence of the exomethylene group was not considered to be a potential complication because the rate of 1,4-addition of singlet oxygen to cyclopentadienes is faster than processes involving exocyclic methylene groups.[33] Several sets of oxygenation conditions gave rise to three compounds (A, B, and C) whose ^{1}H NMR spectra were very

Scheme III

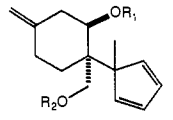


similar. A typical set of conditions was the use of tetraphenylporphine (TPP) as sensitizer in benzene or CH_2Cl_2 followed by subsequent treatment of the reaction mixture with $LiAlH_4$ or Zn/HOAc, respectively. When the reducing agents were omitted, the same three products could be isolated. This result indicated that this trio was arising prior to reduction. The ^{1}H NMR spectrum of a typical isomer revealed one exchangeable proton, a pair of cis vicinal vinyl protons (δ 6.12 (d, J = 7.3 Hz) and δ 5.96 (d, J = 7.3 Hz)), a one-proton quartet (δ 2.46 (J = 7.2 Hz)) and a three-proton doublet (δ 0.81 (J = 7.2 Hz)). The methylenecyclohexene ring remained intact. Each isomer formed a monoacetate, and oxidation of the photooxidation product with pyridinium dichromate (PDC) gave a product with infrared absorption at 1777 cm^{-1} [34] and a ^{1}H NMR with an AB vinyl pattern (δ 7.00 and 6.15 (J_{AB} = 6.5 Hz)). The data are consistent with the assignment of structure **27** to A, B, and C and for butenolide **28** as the product of oxidation. The formation of the isomers of **27** (Scheme III) requires the 1,4-addition of $^1O_2$ to **22b** to form the endo peroxide **24** which undergoes a known fragmentation[35] to the γ-hydroxycyclopentenone **25**. Subsequent retro-aldolization of **25** affords the cis ene dione that suffers double intramolecular hydration leading to the observed products. These results not only confirmed that 1,4-addition of singlet oxygen was occurring but that the diene was more reactive than the isolated double bond. Low-temperature oxygenation (−78 °C) offered itself as a means of slowing the rate of fragmentation of the endo peroxide and heavy atom solvents provided a mechanism for increasing the lifetime of singlet oxygen and thereby the rate of the reaction.[36] While CH_2Cl, $CHCl_3$, and $CFCl_3$ (Freon 11) proved ineffective because starting material was recovered, *the use of TPP in CS_2 at −78 °C proved to be an ideal combination of sensitizer and solvent*. The only drawback of the reaction conditions was that the CS_2 had to be removed at low temperature and replaced with ether at −78 °C prior to reduction of the endoperoxide with $LiAlH_4$.

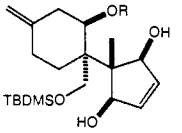
The acetate **22c**, formed by LiAl(t-BuO)$_3$H reduction of aldehyde **19** and subsequent silylation, was examined in the singlet oxygen reaction as a protected intermediate for the synthetic scheme. While the choice of the acetate eventually proved unwise, its transformation products shed light upon the regiochemistry of the singlet oxygen addition. Two products, acetoxy diol **23a** and its overreduction product triol **23b**, were obtained after oxidation and reduction. The 1,4-mode of addition of oxygen was

(29) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426 and references cited therein.
(30) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.
(31) For recent examples of chiral catalysts in the carbonyl ene reaction, see: (a) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1985**, *26*, 5535. (b) Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamomoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940.
(32) (a) Tris[3-[(heptafluoropropyl)hydroxymethylene]-(−)-camphorato]europium. (b) (+)-Tris[bis(perfluoro-2-propoxypropionyl)methano]europium: Kawa, H.; Yamaguchi, F.; Ishikawa, N. *Chem. Lett.* **1982**, 153.
(33) Foote, C. S. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; p 139.
(34) Foote, C. S.; Westhoff, M. T.; Wexler, S.; Burstain, I. G.; Schenck, G. O.; Schulte-Elte, K. H. *Tetrahedron* **1967**, *32*, 2583.
(35) Kayama, Y.; Oda, M.; Kitahara *Chem. Lett.* **1974**, 345.
(36) Kearns, D. R. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; p 115.

supported by the ^1H NMR and the 2-D ^1H–^{13}C heteronuclear shift-correlated spectra of **23b**. The cyclopentene vinyl protons appeared as an AB pattern centered at δ 5.76 and 5.73, and one of the methylene protons resonated at δ 4.92 while its counterpart was part of a three-proton signal at δ 4.82. In the 2-D spectrum, the protons of the AB pattern were associated with the cyclopentene olefinic carbons at 131 and 132 ppm. The two methylene protons were coupled to the olefinic carbon at 112 ppm. The remaining two protons of the three-proton signal at δ 4.82 were assigned to the hydroxy methine protons of the cyclopentene ring because they were coupled to carbons absorbing at 76 and 77 ppm. The similar chemical shifts of the pairs of cyclopentene carbons indicated a high degree of local symmetry in the cyclopentene ring.



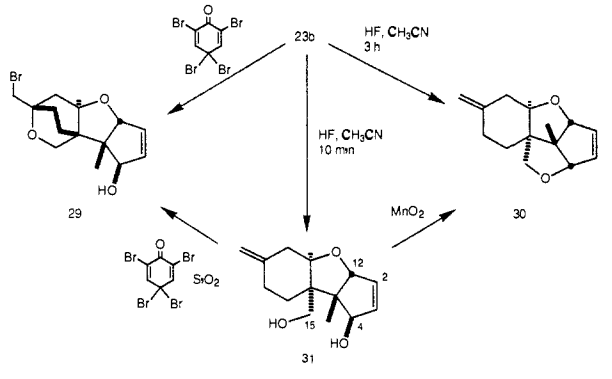
22a, $R_1 = R_2 = H$
b, $R_1 = H$, $R_2 = TBDMS$
c, $R_1 = Ac$, $R_2 = TBDMS$
d, $R_1 = CH_2OCH_3$, $R_2 = TBDMS$



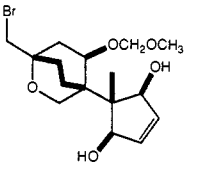
23a, R = Ac
b, R = H
c, $R = CH_2OCH_3$

The stereochemistry of the singlet oxygen reaction was inferred at this stage of the work on the basis of ease of cyclic ether formation of triol **23b**. In an effort to desilylate silyl ether **23b** upon short-term exposure to HF, tetrahydrofuran **31** was formed. Prolonged exposure to the reaction conditions afforded the bis-tetrahydrofuran **30**. Moreover, an ill-fated attempt to oxidize allylic alcohol **31** with MnO_2 gave the same product. The tetrahydrofuran **31** proved to be inert to 2,4,4,6-tetrabromocyclohexadienone;[37] however, chromatography of the reaction mixture on silica gel afforded bromo ether **29**, the same product that was derived from treatment of silyl ether **23b** with 2,4,4,6-tetrabromocyclohexadienone. This series of reactions suggests that bromoetherification of **23b** precedes tetrahydrofuran formation in the direct conversion of **23b** → **29** (Scheme IV). The syn relationship between the angular methyl group (δ 1.15) and the C_{12} proton (δ 4.55) in **31** and the angular methyl group (δ 1.03) and the C_{12} proton (δ 4.68) in **29** was established through NOE difference experiments by irradiation of the angular methyl groups. Moreover, irradiation of the C_{15} protons at δ 4.00 in diol **31** caused enhancement of the C_4 methine proton at δ 5.20. This result clearly established the relative stereochemistry at C_4, C_5, C_6, and C_{12}. A similar set of experiments confirmed the relative stereochemistry in bromo ether **29**.

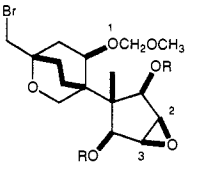
Scheme IV



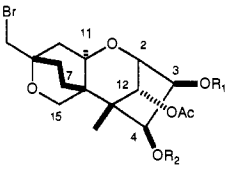
For the purpose of the synthetic plan, the methoxymethyl ether **22d**, prepared from diol **22a** by successive silylation and methoxymethylation, proved to be a properly protected intermediate. Oxygenation of **22d** by the protocol developed earlier provided the 1,4-diol **23c** in 76% yield. The demonstrated susceptibility of the 1,4-cyclopentadienol ring system to intramolecular etherification under acidic conditions required functional group manipulation under near neutral conditions. Accordingly, diol **23c** was desilylated with n-Bu_4NF followed by bromoetherification with 2,4,4,6-tetrabromocyclohexadienone to afford bromo ether **32** in 79% yield. The goal of oxygenation of all the nonquaternary carbons of the cyclopentene ring was achieved by hydroxyl-directed epoxidation of **32** with 99% m-chloroperbenzoic acid in hexane using solid $NaHCO_3$ as a buffer (85% yield). The product of this reaction, epoxide **33a**, was transformed into its diacetate **33b** in preparation for the critical cyclization reaction.



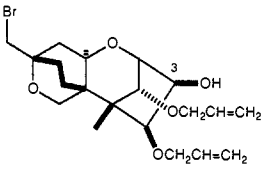
32



33a, R = H
b, R = Ac
c, $R = CH_2CH{=}CH_2$



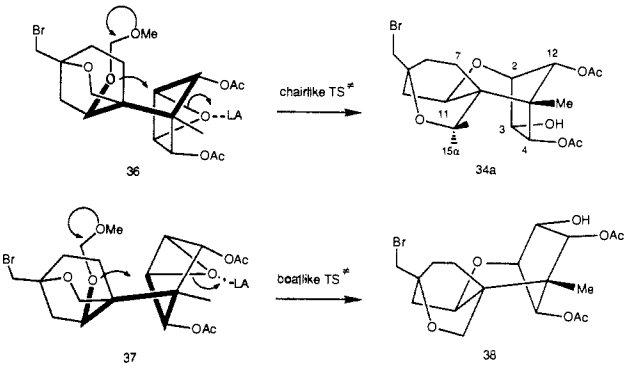
34a, $R_1 = H$, $R_2 = Ac$
b, $R_1 = Ac$, $R_2 = H$
c, $R_1 = R_2 = Ac$



35

Engendered within epoxide **33b** was the desired functionality to test a crucial aspect of the synthetic scheme. Owing to the diastereotopicity of C_2 and C_3 of the oxirane ring, Lewis acid promoted cyclization via a six-membered transition state with O_1 of the MOM ether would lead to two possible diastereomers. Thus, cyclization (Scheme V) via chairlike transition state **36**, involving O_1 and C_2, leads to the desired carbon stereochemistry present in **34a**. Alternatively, if bond formation were to occur between O_1 and C_3 via a boatlike transition state (**37** → **38**), a net inversion of the one-carbon bridge would occur. In addition, concomitant with cyclization, dealkylation was expected. The first experiment conducted met with our expectations although a price was paid. Exposure of epoxide **33b** to BF_3·Et_2O in CH_2Cl_2 at room temperature led to a 1:1 mixture of two products, the ^1H NMR of which displayed four acetate resonances and was devoid of the characteristic epoxide and methoxymethyl ether signals. The prospect that the two transition states were isoenergetic seemed improbable. This possibility was readily disproved by peracetylation of the mixture, which gave rise to a single triacetate **34c**. Thus, a single transition state was operative, ostensibly chairlike, and the mixture of acetates arose from facile ester interchange subsequent to cyclization. That the diacetates were those represented by structures **34a,b** was demonstrated by ^1H NMR (500 MHz) chemical shifts, coupling patterns, and NOE experiments on triacetate **34c**. The C_3-H (δ 5.30 (J = 7.4 Hz)) was coupled to the C_4-H (δ 5.57 (J = 7.4 Hz)) and the C_2-H (δ 4.96) and C_{12}–H (δ 4.30) appeared as singlets (cf. the structure of **34a**, Scheme V). In addition, the C_{11}-H (δ 3.82) was revealed

Scheme V



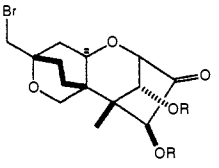
(37) Calo, V.; Ciminate, F.; Lopez, L.; Todeso, P. E. *J. Chem. Soc. C* **1971**, 3655.

as a multiplet (δ 3.80) from which arose the $C_{15\beta}$-H (δ 3.80 (J = 9.2 Hz)). This latter resonance was geminally coupled to the $C_{15\alpha}$-H (δ 3.97 (J = 9.2, 2.0 Hz) (W-coupling to C_{7a}-H)). While these data could satisfy either triacetate **34c** or the triacetate derived from **38**, the NOE difference spectra clearly distinguished between the two alternatives. Irradiation of the C_{12}-H gave enhancement of the C_2-H (7%) and no enhancement of the C_{11}-H that would be expected from the bow-stern proximity in the boatlike product. Irradiation of the C_3-H provided enhancement of the C_2-H (4%) and the C_{11}-H (9%). Finally, irradiation of the C_4-H caused an increase in the C_3-H (7%) and the $C_{15\alpha}$-H (8%).[38]

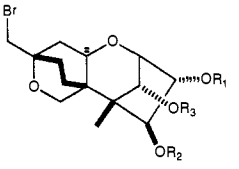
In an effort to mitigate the acyl transfer process, silica gel, $Eu(fod)_3$, $ZnBr_2$, and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) were examined as catalysts. Unfortunately, they afforded the same mixture of acetates although $ZnBr_2$ proved to be the catalyst of choice. The acyl migration problem was not solved; it was circumvented by employing the allyl residue as a protecting group. Bis(allyloxy) epoxide **33c** was readily prepared from the diol epoxide **33a** by Williamson ether synthesis using sodium hydride, allyl bromide, and tetra-*n*-butylammonium iodide in THF. Cyclization was effected at room temperature in 8 h in the presence of $ZnBr_2$ to provide the tetracycle **35** in 85% yield.

With the carbon skeleton intact save C_{13}, functional group manipulation remained as the principle task at hand. Efforts to invert the C_3 hydroxyl group of **35** by S_N2 displacement were thwarted by the reluctance of the hydroxyl group to undergo derivatization with sulfonating reagents (TsCl, MsCl, Ms_2O, or Tf_2O); similarly, the Mitsunobu[39] procedure was unsuccessful. Consequently, oxidation/reduction techniques were explored. Alcohol **35** was oxidized with Collins reagent[40] to the cyclopentanone **39a**, which was characterized by a carbonyl group at 1748 cm^{-1} in its infrared spectrum and the appearance of the C_4-H as a singlet at δ 3.87 in the ^1H NMR spectrum. Reduction of the carbonyl group with hydride reagents ($LiAlH_4$ and $NaBH_4$) consistently regenerated alcohol **35**. Attack of the carbonyl in the oxabicyclo[3.2.1]octanone ring system of **39a** was more favorable from the endo face than the exo face that bears the two allyloxy substituents. Removal of the allyl groups prior to carbonyl reduction not only offered the opportunity to remove the steric factor but also to provide for hydroxyl-directed reduction of the carbonyl group.

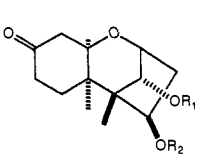
To this end, bis(allyloxy) ketone **39a** was isomerized to a mixture of propenyl ethers **39b** as described by Corey[41] [$(Ph_3P)_3RhCl$, DABCO, EtOH, reflux]. Acidic conditions proved ineffective for hydrolysis of the vinyl ethers. Ozonolysis gave rise to a complex mixture of formates that included the expected product **39c** because sequential deformylation ($KHCO_3$, MeOH), BH_3 reduction, and acetylation of the mixture gave in low yield a triacetate different from triacetate **34c**. The two-step deprotection, i.e., isomerization/hydrolysis, required of the Corey procedure is necessary to avoid premature decarbonylation of liberated propionaldehyde and thereby rendering the coordinatively unsaturated Wilkinson's catalyst inactive toward isomerization. We were intrigued by a report of Sundberg[42] that allylic amines can be deprotected in one operation with the coordinatively saturated hydridotetrakis(triphenylphosphine)rhodium [$(Ph_3P)_4RhH$] in the presence of trifluoroacetic acid in refluxing ethanol.[43] Rewardingly, application of this technique to the problem at hand transformed the bis(allyloxy) ketone **39a** into the keto diol **39d** in 72% yield.[44] Subsequent borane reduction provided the C_3 inverted triol **40a**, which was characterized as its triacetate **40b**.



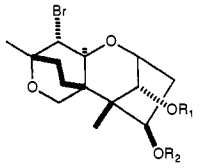
39a, R = $CH_2CH{=}CH_2$
b, R = $CH{=}CHCH_3$
c, R = CHO
d, R = H



40a, $R_1 = R_2 = R_3$ = H
b, $R_1 = R_2 = R_3$ = Ac
c, $R_1 = R_2$ = Ac, R_3 = H

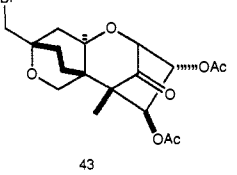


41a, $R_1 = R_2$ = H
b, R_1 = H, R_2 = PhCO

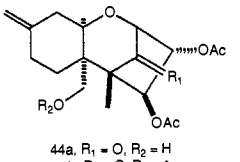


42a, $R_1 = R_2$ = H
b, R_1 = H, R_2 = Ac

Selective protection of the C_3- and C_4-hydroxyl groups was required to allow manipulation of the C_{12} functionality. Related studies with C_3-deoxy analogues demonstrated that selective acylation of the C_4-hydroxyl over the C_{12}-hydroxyl was possible. Thus, Still,[16] in his synthesis of trichodermol, was able to achieve the selective benzoylation of diol **41a**, which provided monobenzoate **41b**. In addition, Roush's synthesis of verrucarol incorporated an acetylation of diol **42a** that afforded recovered diol, diacetate, and **42b** as the only monoacetate. When triol **40a** was treated with acetic anhydride in pyridine, a ~3:1 ratio of the desired diacetate **40c** and triacetate **40b** were obtained, respectively. Molecular mechanics calculations reveal that the C_2–C_3–C_4 and C_3–C_4–C_5 bond angles of triol **40a** are 105° and 106°, respectively, the same as is computed for the C_2–C_1–C_5 bond angle of cyclopentanol (106°).[45] However, the C_2–C_{12}–C_5 bond angle is 101°. This reduced bond angle can manifest itself by increasing the s character in the C–O bond, thereby reducing the nucleophilicity of the hydroxyl group.[46] Oxidation of alcohol **40c** proceeded smoothly with the Dess–Martin periodane[47] to afford ketone **43**. The high ketone frequency (1761 cm^{-1}) of **43** relative to **39a** (1748 cm^{-1}) located the ketone function at C_{12} while the ^1H NMR spectrum and a 2-D homonuclear COSY experiment located the contiguous C_2, C_3, and C_4 protons. Subsequent reductive cleavage of the bromo ether residue of **43** with zinc dust in refluxing ethanol[48] generated the hydroxyl and olefin functionality present in ketone **44a**. The hydroxyl group of this substance was acetylated without event, leading to triacetoxy ketone **44b**. Preliminary experiments, based upon literature precedent,[2] indicated that Wittig methylenation of this ketone with methylenetriphenylphosphorane in DMSO afforded the bis-olefin **44c**.



43

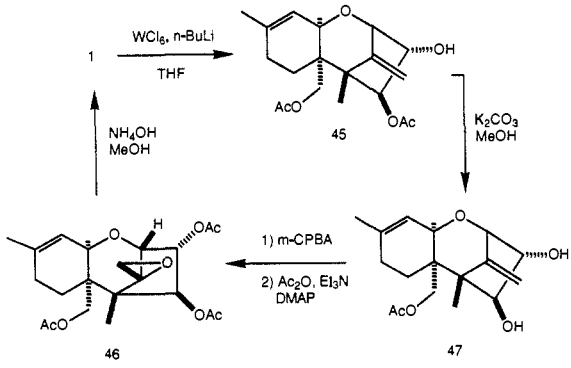


44a, R_1 = O, R_2 = H
b, R_1 = O, R_2 = Ac
c, $R_1 = CH_2$, R_2 = Ac

With limited material available, we chose to address two issues: can manipulation of the C_3, C_4, and C_{12} functionality of anguidine serve as a model for bis-olefin **44c**, and, more critical, can the exo-methylene olefin be isomerized into the correct endocyclic position? First, the issue of functional group manipulation was

(38) The $C_{15\alpha}$-H/C_4-H NOE is also seen in neosporol. Ziegler, F. E.; Nangia, A.; Tempesta, M. S. *Tetrahedron Lett.* **1988**, *29*, 1665.
(39) Mitsunobu, O. *Synthesis* **1981**, 1.
(40) Ratcliffe, R.; Rodehurst, R. *J. Org. Chem.* **1970**, *35*, 4000.
(41) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.
(42) Sundberg, R. J.; Hamilton, G. S.; Laurino, J. P. *J. Org. Chem.* **1988**, *53*, 976.
(43) (a) For the isomerization of *N*-acylallylamines with $(Ph_3P)_4RhH$, see: Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139. (b) For the preparation of the catalyst, see: Ahmad, N.; Robinson, S. D.; Uttley, M. F. *J. Chem. Soc. Dalton Trans.* **1972**, 843.
(44) The generality of this procedure will appear elsewhere.
(45) Calculations were conducted using MacroModel (W. C. Still, Columbia University) that employs Allinger's MM2 program.
(46) Bent, H. A. *Chem. Rev.* **1961**, *61*, 275.
(47) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
(48) Tsuda, K.; Ohki, E.; Nozoe, S. *J. Org. Chem.* **1963**, *28*, 783.

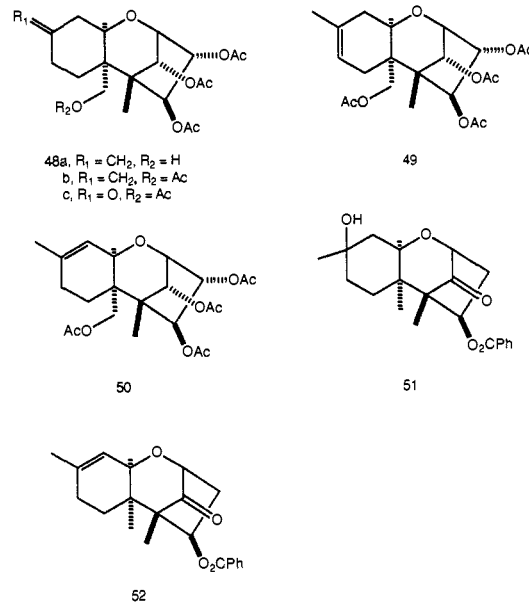
Scheme VI



considered. Bis-olefin **45** was prepared from anguidine as described by Colvin[49] (Scheme VI). Saponification of diacetate **45** gave monoacetate **47** that, in turn, underwent selective, hydroxyl-directed epoxidation.[2] Peracetylation afforded triacetate **46**, the penultimate substrate in Brooks' synthesis of anguidine.[19] Finally, ammonolysis of the C_3 acetoxy group regenerated anguidine.[50] This successful cycle augured well for the eventual transformation of any one of the several exomethylene intermediates into anguidine. The second of the two issues, olefin isomerization, proved to be problematic. Several likely transition metal catalysts for olefin isomerization were tested on the prototype olefin **22d**. The catalysts $(Ph_3P)_3RhCl$,[41] $(Et_3P)_2IrH_5$,[51] $RhH(CO)(Ph_3P)_3$,[52] and $(Ph_3P)_4RhH$[43] uniformly gave recovered starting material and $[Rh(NBD)(Ph_3P)_2^+]ClO_4^-$[53] caused reduction of the olefin. In addition, keto triacetate **44b** was inert to $RhH(CO)(Ph_3P)_3$ in refluxing ethanol over a period of 24 h.

Still had observed that dehydration of alcohol **51** with $POCl_3$ in pyridine provided a 7:1 ratio of products wherein the major component was the desired allylic ether **52**.[16] The transformation of the exomethylene group of tetraacetate **48b** into a tertiary alcohol appeared as an ideal solution to the problem. Efforts to effect hydroxymercuration with either $Hg(OAc)_2$ or $Hg(OCOCF_3)_2$ resulted in recovery of the starting material. As an alternative, the addition of HOBr to **48b** was achieved (NBS, aqueous THF), but radical debromination (Ph_3SnH, AIBN, toluene, 110 °C) gave a product whose ^1H NMR spectrum displayed no new methyl signal and revealed a methylene group attached to a hydroxyl. Less desirable was the transformation of the exo methylene to a ketone followed by the addition of a methyl anion equivalent. Although ozonolysis of **48b** gave rise to cyclohexanone **48c** without incident, the addition of Me_2CeLi[54] to the ketone group, a reaction that had proved successful in an earlier study,[55] failed to give any addition product after several attempts.

Evidence for the isomerization of the exo-methylene double bond in **48b** was achieved under two sets of conditions: trifluoroacetic acid in refluxing acetonitrile and $RhCl_3 \cdot 3H_2O$ in refluxing ethanol.[56] However, the structure of the product was in agreement with the endocyclic olefin **49** rather than the desired isomer **50**. Shorter reaction times produced no sign of **50**, even when unreacted exo-methylene olefin **48b** was still present. The position



of the olefin was revealed in a 2-D homonuclear COSY spectrum that showed the vinyl signal at δ 5.32 coupled to a high-field multiplet at δ 1.82 that was assigned to a C_7-H. The C_{11}-H (δ 4.18) displayed coupling to a C_{10}-H at δ 2.62. If isomerization had occurred in the desired sense to provide **50**, the vinyl proton would have been coupled to the single proton at C_{11}, which in the case of anguidine absorbs at δ 4.12. Anguidine itself did not undergo isomerization under both sets of conditions.

To the extent that the dehydration of alcohol **51** and the isomerization of exo-methylene olefin **48b** can be compared, the assumption can be made that the two reactions do not proceed through the same intermediate, i.e., a tertiary carbocation. That one of the reactions is kinetically controlled while the other is under thermodynamic control remains a possibility. Thus far, no determination has been made as to the more stable position of the endocyclic olefin.

Studies are being conducted to elucidate the mechanism of the isomerization and efforts are being made to apply this strategy to other members of the trichothecene family.

Experimental Section

General Methods. All reactions were performed in flame-dried glassware under nitrogen unless otherwise noted. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from benzophenone ketyl under nitrogen. Hexanes, diisopropylamine, triethylamine, pyridine, benzene, and CH_2Cl_2 were distilled from CaH_2. Dimethylsulfoxide (DMSO) was dried over DMSO anion (NaH) at 65 °C in the presence of Ph_3CH as indicator and was distilled in vacuo. All other reagents and solvents were purified when necessary by standard procedures.[57] Alkyllithiums were titrated by the method of Kofron[58] prior to use. Workup means drying (anhydrous $MgSO_4$), filtration, and concentration. Chromatography was conducted by the method of Still.[59] Infrared spectra were recorded in CCl_4 (Nicolet 5-SX FT) unless specified otherwise. NMR spectra were recorded on a Bruker WM-250 spectrometer (^1H ($CDCl_3$) δ 7.27, 250 MHz and ^{13}C ($CDCl_3$) 77.0 ppm, 62.89 MHz) unless noted otherwise. Mass spectra were recorded on a Hewlett-Packard 5989 (low-resolution) or Kratos MS-80 RFA (high-resolution) instrument in EI mode unless stated otherwise. Elemental analyses were within 0.4%. Title compounds were judged to be >95% pure by ^1H NMR spectroscopy.

Dimethyl 2-[3-(3-Methyl-1-cyclopentenyl)]malonate (10a). To an ice/salt-cooled solution of diisopropylamine (19.0 g, 26.0 mL, 188 mmol) in 100 mL of dry THF was added 82.0 mL of *n*-butyllithium (164 mmol, 1.52 M in hexanes) dropwise over 20 min. The solution was stirred at 0 °C for 30 min at which time the reaction flask was placed in a dry ice/acetone bath. To the LDA solution was added dropwise 9.6 g of methyl ester 9 (62.3 mmol in 10.0 mL of THF). The yellow solution was

(49) (a) Colvin, E. W.; Cameron, S. *J. Chem. Soc., Chem. Commun.* **1986**, 1084. (b) Idem. *Heterocycles* **1987**, *25*, 133. (c) See also: Roush, W. R.; Russo-Rodriguez, S. *J. Org. Chem.* **1987**, *52*, 598.

(50) Earlier workers reported that 1:1 1 N NH_4OH in MeOH for 4 h at room temperature effected C_4 deacetylation of anguidine. Sigg, H. P.; Mauli, R.; Flury, E.; Hauser, D. *Helv. Chim. Acta* **1965**, *48*, 962.

(51) Felkin, H.; Fillebeen-Khan, T.; Gault, Y.; Holmes-Smith, R.; Zakrzewski, J. *Tetrahedron Lett.* **1984**, *25*, 1279.

(52) Evans, D.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A* **1970**, 941.

(53) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2134.

(54) (a) Imamoto, T.; Sugiura, Y.; Takayama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

(55) Ziegler, F. E.; Nangia, A.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 1669.

(56) (a) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102. (b) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359.

(57) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. In *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: New York, 1980.

(58) Kofron, W. C.; Blaclawski, M. *J. Org. Chem.* **1976**, *41*, 1879.

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

stirred at −78 °C for 1.5 h at which time 10.7 g (0.13 mol) of methyl cyanoformate was added in one portion. The solution turned white and was stirred for an additional 45 min at −78 °C. The reaction mixture was poured into water and extracted three times with ether. The ether extracts were washed with 1 N HCl, water, and brine and worked up. Distillation (65 °C at 0.25 Torr) provided 12.9 g of malonate **10a** as a colorless oil (98% yield): IR 1747, 1735 cm^{-1}; ^1H NMR δ 5.71 (m, 2 H, vinyl H), 3.71 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.46 (s, 1 H, $CH(CO_2Me)_2$), 2.34 (m, 1 H), 2.20 (dd, J = 8.0, 5.0 Hz, 1 H, C_5), 1.72 (ddd, J = 8.0, 5.0, 2.0 Hz, 2 H, C_4), 1.22 (s, 3 H, Me). Anal. ($C_{11}H_{16}O_4$) C, H.

Dimethyl 2-[5-(5-Methyl-1,3-cyclopentadienyl)]malonate (11). To a solution of 10.0 g (47.0 mmol) of malonate **10a** in 25.0 mL of CCl_4 were added in one portion 8.34 g of *N*-bromosuccinimide (47.0 mmol, recrystallized from water) and 20.0 mg of AIBN as an initiator. The solution was heated at reflux for 20 min at which time all the succinimide was floating on the top of solution. The solids were filtered through a pad of Celite and concentrated to give 13.6 g of allylic bromides **10b** as a yellow oil (100% crude yield): ^1H NMR ($CDCl_3$, partial) δ 5.96 (m, vinyl H), 3.68 (s, 4 × 3 H, OCH_3), 3.34 (s, 1 H, $CH(CO_2Me)_2$), 1.7 (s, 2 × 3 H, Me). The crude allylic bromide (13.6 g, 47.0 mmol) was diluted with 100 mL of dimethylformamide (dried over barium oxide). To the solution was added 20.0 g of calcium carbonate (3.0 equiv) in one portion and the mixture was heated at 90 °C for 4 h. The reaction mixture was poured into 1 N HCl and extracted three times with ethyl acetate. The organic extracts were washed with water and brine solution and worked up. Flash chromatography (5% EtOAc/hexanes) on neutral alumina provided 7.89 g of dienyl malonate **11** (80% yield after two steps) as a colorless oil: R_f = 0.25 (5% EtOAc/hexanes); IR 1746, 1740, 1434 cm^{-1}; ^1H NMR δ 6.50–6.27 (m, 4 H, vinyl H), 3.71 (s, 2 × 3 H, OCH_3), 3.42 (s, 1 H, $RCH(CO_2Me)_2$), 1.32 (s, 3 H, CH_3). Anal. ($C_{11}H_{14}O_4$) C, H.

Dimethyl Tricyclo[4.3.0.0^{4,9}]non-2-ene-8,8-dicarboxylate (14). Sodium hydride (11.0 mg, 0.27 mmol, 60% dispersion) was washed three times with pentane in a flame-dried flask, and then 1 mL of dry THF was introduced. To the mixture was added 20.0 mg (0.095 mmol) of dienyl malonate **11**. The solution was heated at reflux for 1 h to form the malonate anion. After the mixture was cooled to room temperature, 26.0 μL of allyl bromide (36.0 mg, 0.3 mmol) was added. The reaction mixture was stirred for 2 h at room temperature, decomposed by the cautious addition of cold water, and extracted with ether (3×). The organic layer was washed with water, brine solution and worked up. Flash chromatography (5% EtOAc/hexanes) provided 21 mg of bicyclic malonate **14** (0.084 mmol) as a colorless oil (88% yield): R_f = 0.23 (5% EtOAc/hexanes); IR 2968, 1736 cm^{-1}; ^1H NMR δ 6.15 (m, 1 H, vinyl H), 5.77 (m, 1 H, vinyl H), 3.70, 3.66 (s, 2 × 3 H, CO_2CH_3), 2.92 (br s, 1 H, C_1), 2.57 (d, J = 12.0 Hz, 1 H, C_7), 2.52 (m, 1 H, C_4), 2.39 (ddd, J = 12.5, 2.9, 3.1 Hz, 1 H, C_7), 1.81 (m, 1 H, C_6), 1.56–1.03 (m, 2 H, C_5), 1.26 (s, 3 H, C_9–CH_3); HRMS calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1203.

1-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-3-methylbutane (15). A solution of 17.4 g of α-methyl-γ-butyrolactone (0.17 mol) and 13.0 mL of phosphorus tribromide (0.14 mol) was heated to 140 °C in an oil bath for 2 h.[60] The solution was distilled (40–60 °C at 0.25 Torr) to give the colorless acyl bromide (IR 1804 cm^{-1}). The distilled acyl bromide (diluted in 100 mL of $CHCl_3$) was hydrolyzed by stirring with water overnight. The layers were separated, and the aqueous layer was extracted with chloroform (3×). The chloroform extracts were combined and washed with water and brine solution. After workup, 16.5 g of 3-bromo-2-methylbutanoic acid was obtained as a colorless oil (54% yield): IR 3400 broad, 1704 cm^{-1}; ^1H NMR δ 3.51 (t, J = 12.0 Hz, 2 H, C_4), 2.76 (m, 1 H, C_2), 2.36–1.95 (m, 2 H, C_3), 1.26 (d, J = 15.0 Hz, 3 H, C_2–CH_3). The acid was used without further purification. To an ice-cooled solution of 16.5 g (0.091 mol) of the acid in 70 mL of dry THF was added dropwise 130 mL of borane–tetrahydrofuran complex (130 mmol, 1.0 M solution in THF). The solution was stirred at 0 °C for 1 h at which time 50 mL of aqueous tetrahydrofuran (1:1 mixture) was added dropwise to decompose the reaction mixture. The solution was saturated with potassium carbonate, the resulting layers were separated, and the aqueous layer was extracted with ether (4×). The ethereal extracts were combined and worked up. The residue was distilled to give 15.1 g of 3-bromo-2-methyl-1-butanol as a colorless oil (45 °C at 0.25 mm, 93% yield): ^1H NMR δ 4.57 (br s, 1 H, OH), 3.62–3.41 (m, 4 H, C_1, C_4), 2.13–1.69 (m, 3 H, C_2, C_3), 0.96 (d, J = 14.0 Hz, 3 H, C_2–CH_3). In a round-bottom flask were combined 15.1 g (0.09 mol) of the bromo alcohol, 10.1 g of Et_3N (14 mL, 100 mmol), 15.0 g (0.1 mol) of *tert*-butyldimethylsilyl chloride, 1.2 g (12.1 mmol) of *N,N*-dimethylamino)-pyridine (DMAP), and 75.0 mL of dry CH_2Cl_2. The mixture was stirred at room temperature for 2 h under a nitrogen atmosphere. The reaction mixture was partitioned between ether and water. The organic layer was separated and washed with water and brine solution. After workup and HPLC (Waters Prep500, hexane, silica gel) purification, 23 g (48% yield) of silyl ether **15** was isolated as a colorless oil: R_f = 0.67 (20% EtOAc/hexanes); ^1H NMR δ 3.46 (m, 4 H, C_1, C_4), 1.79 (m, 3 H, C_2, C_3), 0.89 (s, 9 H, *tert*-butylsilyl), 0.82 (d, J = 7.0 Hz, 3 H, CH_3), 0.098 (s, 6 H, dimethylsilyl).

Dimethyl 2-[4-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutyl]-2-[5-(5-methyl-1,3-cyclopentadienyl)]malonate (16a). In a flame-dried round-bottom flask was added 500 mg (2.4 mmol) of dienyl malonate **11** in 1 mL of THF to a suspension of NaH (114 mg, 2.8 mmol 60% dispersion, washed 3× with pentane) in 2 mL of dry THF. The heterogeneous mixture was heated at reflux for 1.5 h at which time it was cooled, and 1.38 g of bromide **15** (4.8 mmol) was added in one portion. The brown solution was heated at reflux for 16 h under a nitrogen atmosphere. The resulting solution was poured into water and extracted with ether (3×). The combined ether extracts were washed with water and brine solution and worked up. After flash chromatography (3% EtOAc/hexanes), 710 mg (71% yield) of alkylated diene **16a** was obtained as a colorless oil: R_f = 0.35 (5% EtOAc/hexanes); IR 2946, 1727 cm^{-1}; ^1H NMR δ 6.45–6.22 (m, 4 H, diene), 3.73 (s, 2 × 3 H, OCH_3), 3.32 (m, 2 H), 1.80–1.29 (m, 5 H), 1.28 (s, 3 H, CH_3), 0.88 (s, 9 H, *tert*-butylsilyl), 0.80 (d, J = 7.0 Hz, 3 H, C_{16}), 0.02 (s, 6 H, dimethylsilyl). Anal. ($C_{22}H_{38}O_5Si$) C, H.

Dimethyl 2-(4-Hydroxy-3-methylbutyl)-2-[5-(5-methyl-1,3-cyclopentadienyl)]malonate (16b). To a solution of 710 mg (1.73 mmol) of alkylated silyl ether **16a** in 1 mL of acetonitrile was added 1 mL of a solution of aqueous HF in acetonitrile (500 μL of 48% HF in 9.5 mL of acetonitrile). The solution was allowed to stir for 1 h at room temperature. Sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with chloroform (3×). Following workup and chromatography (20% EtOAc/hexanes), 503 mg (98% yield) of alcohol **16b** was obtained as a colorless oil: R_f = 0.3 (20% EtOAc/hexanes); IR 3549 br, 1724 cm^{-1}; ^1H NMR δ 6.45–6.24 (m, 4 H, diene), 3.74 (s, 2 × 3 H, OCH_3), 3.41 (d, J = 6.0 Hz, 2 H, CH_2OH), 1.87–0.87 (m, 7 H), 1.28 (s, 3 H, CH_3), 0.85 (d, J = 7.0 Hz, 3 H, CH_3).

Dimethyl 2-(3-Methyl-3-butenyl)-2-[5-(5-methyl-1,3-cyclopentadienyl)]malonate (13a). To a solution of 503 mg (1.7 mmol) of hydroxy malonate **16b** in 5 mL of dry THF was added sequentially 461 mg (2.0 mmol, recrystallized from 95% ethanol, mp 139–141 °C) of *o*-nitrophenyl selenocyanate,[24] and 616 μL (3.05 mmol) of tri-*n*-butylphosphine (distilled under aspirator). After 45 min the solution was concentrated and chromatographed (20% EtOAc/hexanes) to afford 900 mg of dark yellow solid (impure): R_f = 0.6 (50% EtOAc/hexane); ^1H NMR δ 8.08–7.05 (m, 4 H, aromatic H), 6.26–6.06 (m, 4 H, vinyl H), 3.54 (s, 2 × 3 H, OCH_3), 2.57 (ddd, J = 15.0, 7.0, 3.0 Hz, 2 H), 1.60–1.05 (m, 5 H), 1.07 (s, 3 H, CH_3), 0.81 (d, J = 7.0 Hz, 3 H, CH_3). The crude product was used in the next reaction.

Impure *o*-nitrophenyl selenide (900 mg) was dissolved in 5 mL of THF and cooled to 0 °C in an ice/salt bath. To the cooled solution was added 5 mL of 30% aqueous hydrogen peroxide. The solution stirred at 0 °C for 1 h and then at room temperature for 3 h. The red solution was diluted with ether and washed with $NaHCO_3$ solution (2×), H_2O, and brine solution. After workup and chromatography (5% EtOAc/hexanes) 300 mg (64% after two steps) of olefin **13a** was obtained as a colorless oil: R_f = 0.15 (20% EtOAc/hexanes); IR 2941, 1732 cm^{-1}; ^1H NMR δ 6.48–6.24 (m, 4 H, diene), 4.59 (1 H, br s, exo methylene), 4.65 (1 H, br s, exomethylene), 3.75 (s, 2 × 3 H, OCH_3), 1.88 (s, 3 H, CH_3), 1.66 (s, 4 H), 1.29 (s, 3 H, CH_3); HRMS calcd for $C_{16}H_{22}O_4$ 278.1519, found 278.1517.

2-(3-Methyl-3-butenyl)-2-[5-(5-methyl-1,3-cyclopentadienyl)]-1,3-propanediol (17). To an ice/salt-cooled mixture of 80 mg (2.1 mmol) of $LiAlH_4$ in 1 mL of ether was added dropwise 300 mg (1.08 mmol) of malonate **13a** in 1 mL of ether. The reaction mixture was stirred at 0 °C for 1 h and then at 25 °C for 1 h. The reaction mixture was decomposed by the slow addition of 80 μL of water, 80 μL of 1 N NaOH, and 240 μL of water. The reaction mixture was diluted with ether, dried with $MgSO_4$, filtered through Celite, concentrated, and purified by flash chromatography (20% EtOAc/hexanes) to give 212 mg (88% yield) of diol **17** as a colorless oil: R_f = 0.75 (50% EtOAc/Hexane); IR 3564 br, 1456 cm^{-1}; ^1H NMR δ 6.61–6.30 (m, 4 H, cyclopentadiene vinyl H), 4.72 (br s, 2 H, exo methylene), 3.74 (dd, 2 H, J = 7.0, 5.0 Hz), 3.59 (dd, 2 H, J = 6.5, 5.4 Hz), 2.11 (m, 2 H), 1.99 (t, J = 5.0 Hz, 2 H, 2 OH), 1.75 (s, 3 H), 1.63 (m, 2 H), 1.15 (s, 3 H); HRMS calcd for $C_{14}H_{22}O_2$ 222.1620; found 222.1614.

2-(3-Methyl-3-butenyl)-2-[5-(5-methyl-1,3-cyclopentadienyl)]malondialdehyde (8). To a flame-dried flask under nitrogen was added 187 mg (1.48 mmol) of oxalyl chloride in 3 mL of dry CH_2Cl_2. The solution was cooled to −78 °C in a dry ice/acetone bath, and 230 mg (210 μL, 3.0 mmol) of dry DMSO in 300 μL of CH_2Cl_2 was added dropwise and then

(60) Feugeas, C. *Bull. Soc. Chim. Fr.* **1963**, 2568.

stirred for 2 min. Diol **17** (150 mg, 0.67 mmol) was added slowly in 150 μL of CH_2Cl_2 and allowed to stir for 30 min at −78 °C. Triethylamine (682 μL, 4.9 mmol) was added to the cloudy solution, and the dry ice bath was removed. The reaction mixture was allowed to warm to room temperature over 30 min after which it was quenched with water. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered through a pad of Florisil, and concentrated. Purification by flash chromatography gave 115 mg (78% yield) of dialdehyde **8** as a colorless oil: R_f = 0.80 (20% EtOAc/hexanes); IR 2931, 1722, 1716, 1646 cm^{-1}; ^1H NMR δ 9.64 (s, 2 × 1 H, CHO), 6.50 (m, 2 H, diene), 6.42 (m, 2 H, diene), 4.75 (br s, 1 H, exo methylene), 4.62 (br s, 1 H, exo methylene), 2.12 (m, 2 H), 1.85 (m, 2 H), 1.71 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3); HRMS calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1298.

2(*R)-Acetoxy-1(*S**)-[5-(5-methyl-1,3-cyclopentadienyl)]-3-methylenecyclohexane-1-carboxaldehyde (19) and 2(*R**)-Acetoxy-1-(*R**)-[5-(5-methyl-1,3-cyclopentadienyl)]-4-methylenecyclohexane-1-carboxaldehyde (21b).** To a stirred solution of malondialdehyde **8** (530 mg, 2.43 mmol) in 5 mL of dry CH_2Cl_2 was added $Eu(fod)_3$ (629 mg, 0.6 mmol) in one portion. Dried and crushed molecular sieves (4 Å) were then added to the solution, and the mixture was stirred for 5 days at room temperature. The mixture was neutralized with Et_3N, filtered, concentrated, and chromatographed (5% EtOAc/hexanes). The cis and trans isomers were inseparable by chromatography and were used as a mixture in the next step. The isomeric alcohols **7** and **21a** (434 mg, 8:1 ratio, determined by NMR) were dissolved in benzene and 413 mg (4.4 mmol) of acetylimidazole was added. To the mixture was added diazobicyclo-[5.4.0]undecene (DBU) (56 mg, 55 μL, 0.36 mmol). The reaction was complete after 12 h. The reaction mixture was diluted with ether and washed with water (4×), brine solution, and worked up. Purification by chromatography (2% EtOAc/hexanes) afforded 66 mg (10%) of isomer **21b**: R_f = 0.20 (5% EtOAc/hexanes); IR 1736, 1720 cm^{-1}; ^1H NMR δ 9.59 (s, 1 H, CHO), 6.43 (m, 2 H, diene), 6.22 (m, 2 H, diene), 4.96 (dd, J = 8.0, 5.0 Hz, 1 H, C_2), 4.72 (s, 2 H, exo methylene), 2.58 (dd, J = 8.0, 5.0 Hz, 1 H, C_3), 2.37–1.90 (m, 5 H), 2.10 (s, 3 H, OAc), 1.05 (s, 3 H, CH_3); HRMS calcd for $C_{16}H_{20}O_3S$ 260.1413; found 260.1414. Aldehyde **19** was obtained in 52% yield (330 mg): R_f = 0.25 (5% EtOAc/Hexane); IR 1734, 1709 cm^{-1}; ^1H NMR δ 9.45 (s, 1 H, CHO), 6.38 (m, 1 H, diene), 6.30 (m, 3 H, diene), 5.57 (br s, 1 H, C_2), 4.75 (d, J = 2.0 Hz, 1 H, exo methylene), 4.30 (d, J = 2.0 Hz, 1 H, exo methylene), 2.48–1.90 (m, 6 H), 2.11 (s, 3 H, OAc), 1.09 (s, 3 H); HRMS calcd for $C_{16}H_{20}O_3$ 260.1413, found 260.1400.

2(*R)-(Hydroxymethyl)-2(*R**)-[5-(5-methyl-1,3-cyclopentadienyl)]-5-methylenecyclohexan-1(*R**)-ol (22a).** To a suspension of $LiAlH_4$ (175 mg, 4.6 mmol) in 10 mL of ether at 0 °C was added slowly a solution of acetoxy aldehyde **19** (600 mg, 2.3 mmol) in 3 mL of ether. The mixture was stirred for 2 h at 0 °C. Excess $LiAlH_4$ was decomposed by careful addition of 175 μL of water, 175 μL of 1 N NaOH, and 525 μL of water. $MgSO_4$ was added, and the suspension was stirred for an additional 10 min. The mixture was filtered, and 500 mg (98% yield) of trans diol **22a** was isolated as a colorless liquid after chromatography (20% EtOAc/hexanes) (in general, the material was used without further purification): IR 3552, 3459 cm^{-1}; ^1H NMR δ 6.77 (m, 2 H, diene), 6.28 (m, 2 H, diene), 4.84 (br s, 1 H, exo methylene), 4.75 (br s, 1 H, exo methylene), 4.12 (m, 1 H, C_1), 3.88 (dd, J = 11.8, 7.0 Hz, 1 H, CH_2OSi), 3.70 (dd, J = 12.0, 7.2 Hz, 1 H, CH_2OSi), 1.23 (s, 3 H), 2.62–1.21 (m, 6 H); HRMS (Cl, isobutane) calcd for $C_{14}H_{20}O_2$ $(M + H)^+$ 221.1542, found 221.1547.

2(*R)-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2(*R**)-[5-(5-methyl-1,3-cyclopentadienyl)]-5-methylenecyclohexan-1(*R**)-ol (22b).** To a solution of 880 mg (0.4 mmol) of diol **22a** in 5 mL of CH_2Cl_2 was added 1.60 mL (1.5 mmol) of Et_3N, 1.20 g (0.8 mmol) of *tert*-butyldimethylsilyl chloride, and 20 mg (0.20 mmol) of (dimethylamino)pyridine. The reaction mixture was stirred for 36 h at room temperature at which time it was diluted with ether. The organic layer was washed with water (2×) and saturated brine and worked up. The crude monosilyl ether was isolated as a colorless oil and was used in the next reaction without further purification: ^1H NMR δ 6.98 (m, 1 H, diene), 6.64 (m, 1 H, diene), 6.22 (m, 2 H, diene), 4.78 (br s, 1 H, exo methylene), 4.72 (br s, 1 H, exo methylene), 4.07 (d, J = 11.0 Hz, 1 H, CH_2OSi), 4.03 (m, 1 H, RC*H*OH), 3.79 (d, J = 11.0 Hz, 1 H, CH_2OSi), 2.19–1.45 (m, 6 H), 1.17 (s, 3 H), 0.95 (s, 9 H, *tert*-butylsilyl), 0.11, 0.10 (s, 2 × 3 H, dimethylsilyl).

3(*R)-Acetoxy-4(*R**)-[5-(5-methyl-1,3-cyclopentadienyl)]-4(*R**)-[[(*tert*-butyldimethylsilyl)oxy]methyl]methylenecyclohexane (22c).** Lithium tri-*tert*-butoxyaluminum hydride (3.46 g, 13.6 mmol) was dissolved in dry THF (10 mL) at room temperature. To the clear solution was added acetoxy aldehyde **19** (600 mg, 2.3 mmol) in dry THF (2 mL). After the solution was stirred at room temperature for 1 h, it was decomposed by the slow addition of 3 mL of water, 3 mL of NaOH, and 9 mL of water. After the mixture was stirred an additional 10 min, it was diluted with ether and worked up. Concentration gave 580 mg of a colorless liquid (97% crude yield): IR 2925, 1731, 1680 cm^{-1}; ^1H NMR δ 6.55 (m, 2 H, diene), 6.24 (m, 2 H, diene), 5.26 (t, 1 H, C_3), 4.75 (s, 1 H, exo methylene), 4.63 (s, 1 H, exo methylene), 3.75 (dd, J = 8.0, 2.0 Hz, 1 H, RC*H*OH), 3.57 (d, J = 8.0 Hz, 1 H, RC*H*OH), 2.54 (d, J = 11.0 Hz, C_2), 2.37 (d, J = 11.0 Hz, 1 H, C_2), 2.07 (s, 3 H, OAc), 2.2–1.3 (m, 4 H), 1.16 (s, 3 H, CH_3). To a magnetically stirred solution of the crude acetoxy alcohol in CH_2Cl_2 (10 mL) was added Et_3N (451 mg, 619 μL, 4.5 mmol) and *tert*-butyldimethylsilyl triflate (870 mg, 3.3 mmol). The reaction mixture was stirred for 8 h at room temperature and was then poured into ether and washed successively with 1 N HCl, water, brine, and worked up. Flash chromatography provided 780 mg (90% yield) of silyl ether **22c** as a colorless oil: R_f = 0.2 (hexanes); IR 1729, 1643 cm^{-1}; ^1H NMR δ 6.59 (m, 1 H, diene), 6.44 (m, 1 H, diene), 6.11 (m, 2 H, diene), 5.11 (br s, 1 H, C_3), 4.71 (br s, 1 H, exo methylene), 4.59 (br s, 1 H, exo methylene), 3.98 (d, J = 10.0 Hz, 1 H, CH_2OSi), 3.73 (d, J = 10.0 Hz, 1 H, CH_2OSi), 2.40 (dd, J = 3.0, 10.6 Hz, 1 H, C_2), 2.11 (dd, J = 3.2, 10.4 Hz, 1 H, C_2), 1.97 (s, 3 H, OAc), 2.10–1.98 (m, 2 H), 1.40–1.21 (m, 2 H), 1.14 (s, 3 H, CH_3), 0.94 (s, 9 H *tert*-butylsilyl), 0.10 (s, 6 H, dimethylsilyl); HRMS calcd for $C_{22}H_{36}O_3Si$ 376.2438, found 376.2434.

3(*R)-[(Methoxymethyl)oxy]-4(*R**)-[5-(5-methyl-1,3-cyclopentadienyl)]-4(*R**)-[[(*tert*-butyldimethylsilyl)oxy]methyl]methylenecyclohexane (22d).** A mixture of 64 mg (0.19 mmol) of alcohol **22b** and 240 μL (1.4 mmol) of diisopropylethylamine in 2 mL of dry CH_2Cl_2 was cooled to 0 °C with an ice salt bath. Chloromethyl methyl ether (132 mg, 1.6 mmol) was added in one portion and was stirred for 30 min at 0 °C. A catalytic amount of 4-pyrrolidinopyridine (2.0 mg, 0.015 mmol) was added and the mixture was allowed to warm to room temperature. After 4 h at room temperature, the reaction was complete. The reaction mixture was diluted with 10 mL of ether, washed with ether (4 × 10 mL) and brine, and worked up. The residue was purified by chromatography (5% ethyl acetate/hexane) to give 66 mg (92%) of methoxymethyl ether **22d** as a colorless liquid: IR 2970, 2852 cm^{-1}; ^1H NMR δ 6.71 (m, 1 H, diene), 6.52 (m, 1 H, diene), 6.14 (m, 2 H, diene), 4.79 (br s, 1 H, exo methylene), 4.68 (br s, 1 H, exo methylene), AB system 4.62, 4.59 (J_{AB} = 7.2 Hz, 2 H, OCH_2O), AB system 3.98, 3.71 (J_{AB} = 11.0 Hz, 2 H, $CH_2OTDMBS$), 3.90 (t, J = 3.0 Hz, 1 H, C_3), 3.40 (s, 3 H, OCH_3), 2.47 (dd, J = 3.2, 10.4 Hz, 1 H, C_2), 2.35 (dd, J = 3.2, 10.4 Hz, 1 H, C_2), 2.19–1.78 (m, 2 H), 1.42–1.29 (m, 2 H), 1.23 (s, 3 H, CH_3), 0.92 (s, 9 H, *tert*-butylsilyl), 0.01 (s, 6 H, dimethylsilyl); HRMS calcd for $C_{22}H_{38}O_3Si$ 378.2591, found 378.2589.

4(*R)-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4(*R**)-[4-[3(*R**),5-(*S**)-dihydroxy-4(*r*)-methyl-1-cyclopentenyl]]-3(*R**)-hydroxymethylenecyclohexane (23b).** In a long thick-walled glass tube with a ground glass joint were combined acetoxy ether **22c** (50 mg, 0.13 mmol), carbon disulfide (CS_2, 4 mL, dried over $MgSO_4$ and distilled from P_2O_5), and several crystals of tetraphenylporphine (TPP). The tube was immersed in a Cryocool bath at −78 °C; oxygen was bubbled through the solution as the solution was irradiated with a 650-W halogen lamp through a Pyrex filter. After 5 h the solution was concentrated to dryness at −78 °C under high vacuum. The residue was dissolved in ether (4 mL) at −78 °C and $LiAlH_4$ (25 mg, 0.66 mmol) was added in one portion. The mixture was stirred at −78 °C for 1.5 h and was then decomposed by the sequential addition of 25 μL of water, 25 μL of NaOH, and 75 μL of water. After 10 min the mixture was diluted with ethyl acetate and worked up. Purification by flash chromatography (30% EtOAc/hexanes) yielded 41 mg (85%) of triol **23b** as a colorless liquid: R_f = 0.5 (50% EtOAc/hexanes); IR 3588–3451 br, 2959, 2930 cm^{-1}; ^1H NMR δ 5.76 (d, J = 7.3 Hz, 1 H, vinyl H), 5.73 (d, J = 7.3 Hz, 1 H, vinyl H), 4.92 (s, 1 H, C*H*OH), 4.82 (m, 3 H, exo methylene, CHOH), 4.01 (m, 1 H, C_3), 3.90 (d, J = 11.4 Hz, 2 H, CH_2OSi), 3.73 (d, J = 10.8 Hz, 2 H, CH_2OSi), 2.60 (br s, 1 H, OH), 2.30 (d, J = 3.2 Hz, 2 H, C_2), 2.16 (m, 2 H), 2.05 (m, 2 H), 1.04 (s, 3 H, CH_3), 0.94 (s, 9 H, *tert*-butylsilyl), 0.15 (s, 6 H, dimethylsilyl); ^{13}C NMR 143, 132, 131, 112, 77, 76, 69, 63, 59, 45, 39, 30, 26 (3×), 25, 18, 10 (2×), −5 ppm; HRMS (Cl, isobutane) calcd for $C_{20}H_{36}O_4Si$ $(M + H)^+$ 369.2461, found 369.2421.

16-Bromo-4β-hydroxy-9,15-epoxyapotrichothec-3-ene (29). Triol **23b** (32 mg, 0.1 mmol) was dissolved in 3 mL of acetonitrile, and 1 mL of aqueous HF (500 μL of 0.05% HF in 9.5 mL of CH_3CN) was added. After 10 min, no starting material remained (TLC), and the reaction mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (3×). Workup gave apotrichothecenediol **31**, which was used without further purification: IR 3453 br, 2958, 2861 cm^{-1}; ^1H NMR δ 5.99 (dd, J = 1.4, 5.7 Hz, 1 H, C_3), 5.88 (m, 1 H, C_2), 5.20 (br s, 1 H, C_4), 4.80 (br s, 1 H, C_{16}), 4.76 (br s, 1 H, C_{16}), 4.55 (dd, J = 2.3, 2.1 Hz, 1 H, C_{12}), 4.00 (d, J = 13.4 Hz, 1 H, C_{15}), 3.85 (d, J = 11.0 Hz, 1 H, C_{15}), 3.74 (br s, 1 H, C_{11}), 2.53–1.94 (m, 6 H), 1.15 (s, 3 H, C_{14}). The crude diol (25 mg, 0.073 mmol) was dissolved in CH_2Cl_2 and 29 mg (0.07 mmol) of

2,4,4,6-tetrabromocyclohexadienone was added at room temperature. After 10 min, Et_3N was added to neutralize the reaction mixture. The solution was concentrated and chromatographed (EtOAc) to provide 21 mg of bromo ether **29** (77% yield after two steps) as a colorless oil: R_f = 0.2 (40% EtOAc/hexane); IR 3608, 3047, 2976, 2856 cm^{-1}; ^1H NMR δ 5.95 (dd, J = 1.7, 5.8 Hz, 1 H, C_3), 5.88 (m, 1 H, C_2), 4.99 (br s, 1 H, C_4), 4.68 (dd, J = 2.4, 1.9 Hz, 1 H, C_{12}), 4.07 (d, J = 8.9 Hz, 1 H, C_{15}), 3.98 (d, J = 9.3 Hz, 1 H, C_{15}), 3.74 (br s, 1 H, C_{11}), 3.30 (s, 2 H, C_{16}), 2.35–1.58 (m, 6 H), 1.03 (s, 3 H, C_{14}); HRMS calcd for $C_{14}H_{19}BrO_3$ (M + H^+) 314.0518, found 314.0518.

4(*R)-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4(*R**)-[4-[3(*R**),5(*S**)-dihydroxy-4(*r*)-methyl-1-cyclopentenyl]]-3(*R**)-[(methoxymethyl)oxy]methylenecyclohexane (23c).** Cyclopentadiene **22d** (100 mg, 0.26 mmol) was subjected to photooxygenation (vide supra) to provide, after flash chromatography (50% EtOAc/hexanes), 81 mg (76%) of diol **23c** as a colorless liquid: R_f = 0.34 (30% EtOAc/hexanes); IR 3588–3351 br, 2925, 2861 cm^{-1}; ^1H NMR δ 5.80 (d, J = 7.3 Hz, 1 H, vinyl H), 5.67 (d, J = 7.3 Hz, 1 H, vinyl H), 5.22 (m, 1 H, OH), 4.82 (br s, 1 H, exo methylene), 4.79 (br s, 1 H, exo methylene), 4.71 (m, 2 H, 2 CHOH), 4.69 (d, J = 6.3 Hz, 1 H, OCH_2O), 4.64 (d, J = 6.3 Hz, 1 H, OCH_2O), 4.12 (br s, 1 H, C_3), 3.99 (d, J = 11.1 Hz, 1 H, $CH_2OTBDMS$), 3.73 (d, J = 10.9 Hz, 1 H, $CH_2OTBDMS$), 3.38 (s, 3 H, OCH_3), 2.71 (d, J = 9.1 Hz, 1 H, C_2), 2.48 (d, J = 9.1 Hz, 1 H, C_2), 2.23–1.91 (m, 4 H), 1.01 (s, 3 H, CH_3), 0.99 (s, 9 H, *tert*-butylsilyl), 0.098 (s, 6 H, dimethylsilyl); HRMS (Cl, isobutane) calcd for $C_{22}H_{40}O_5Si$ (M + H^+) 413.2724, found 413.2740.

1(*S)-(Bromomethyl)-4(*R**)-[4-[3(*R**),5(*S**)-dihydroxy-4(*r*)-methyl-1-cyclopentenyl]]-5(*R**)-[(methoxymethyl)oxy]-2-oxabicyclo-[2.2.2]octane (32).** Diol **23c** (100 mg, 0.24 mmol) dissolved in 1 mL of dry THF was treated with 244 μL (0.24 mmol, 1.0 M solution in THF) of tetra-*n*-butylammonium fluoride. The mixture was stirred for 8 h at room temperature, diluted with 10 mL of ether, and washed successively with water and brine solution. The ether layer was dried over $MgSO_4$, filtered through a pad of Florisil, and concentrated to give crude triol. To the crude product (61 mg, 0.23 mmol) in 1 mL of CH_2Cl_2 was added 95 mg (0.23 mmol) of 2,4,4,6-tetrabromocyclohexadienone. After 10 min at room temperature, the reaction mixture was neutralized with Et_3N and diluted with ether. The ether layer was washed with water, brine and worked up. The residual oil was chromatographed (EtOAc) to give 60 mg of bromo ether **32** (79% yield): R_f = 0.35 (EtOAc); IR 3508, 2947, 1450 cm^{-1}; ^1H NMR δ 5.56 (d, J = 5.2 Hz, 1 H, vinyl H), 5.42 (d, J = 5.0 Hz, 1 H, vinyl H), 4.61–4.44 (m, 4 H, 2× CHOH, OCH_2O), 4.06 (dd, J = 1.2, 5.4 Hz, 1 H, C_5), 3.76 (d, J = 10.5 Hz, 1 H, CH_2O), 3.65 (dd, J = 2.3, 10.5 Hz, 1 H, CH_2O), 3.25 (s, 3 H, OCH_3), 3.08 (s, 2 H, CH_2Br), 2.17 (dd, J = 1.2, 5.4 Hz, 1 H, C_6), 2.08 (dd, J = 1.2, 5.2 Hz, 1 H, C_6), 1.87–1.38 (m, 4 H), 1.05 (s, 3 H, CH_3); HRMS (Cl, isobutane) calcd for $C_{16}H_{25}BrO_3$ (M + H^+) 377.0963, found 377.0964.

1(*S)-(Bromomethyl)-4(*R**)-[5-[1(*R**),4(*S**)-dihydroxy-5(*s*)-methyl-2(*R**),3(*S**)-epoxycyclopentanyl]]-5(*R**)-[(methoxymethyl)-oxy]-2-oxabicyclo[2.2.2]octane (33a).** To a solution of diol **32** (11 mg, 0.03 mmol) in 1 mL of hexane was added 10 equiv of solid sodium bicarbonate followed by 9 mg (0.05 mmol) of *m*-chloroperbenzoic acid (>99%). The mixture was stirred for 3 h at room temperature at which time the remaining peroxide was decomposed with saturated sodium sulfite solution and partitioned between ethyl acetate and water. The layers were separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with a 15% K_2CO_3 solution (3×) and worked up. Purification by flash chromatography (EtOAc) afforded 10 mg (85%) of epoxide **33a** as a colorless oil: R_f = 0.27 (EtOAc); IR 3585, 2953, 2916, 1461, 1381; ^1H NMR δ 4.74, 4.67 (AB system, J_{AB} = 6.4 Hz, 2 H, OCH_2O), 4.30 (d, J = 1.1 Hz, 1 H, RC*H*OH), 4.20 (m, 2 H, RC*H*OH, C_5), 3.90 (d, J = 10.7 Hz, 1 H, CH_2O), 3.72 (dd, J = 2.3, 10.7 Hz, 1 H, CH_2O), 3.64 (m, 1 H, epoxide H), 3.57 (m, 1 H, epoxide H), 3.46 (s, 3 H, OCH_3), 3.27 (s, 2 H, CH_2Br), 2.05 (dd, J = 2.3, 3.2 Hz, 2 H, C_6), 1.97–1.60 (m, 4 H), 1.05 (S, 3 H, CH_3); HRMS (Cl, isobutane) calcd for $C_{16}H_{25}BrO_6$ (M + H^+) 393.0913, found 393.0941.

4(*R)-[5-[1(*R**),4(*S**)-Bis(allyloxy)-5(*s**)-methyl-2(*R**),3(*S**)-epoxycyclopentanyl]]-1(*S**)-(bromomethyl)-5(*R**)-[(methoxymethyl)-oxy]-2-oxabicyclo[2.2.2]octane (33c).** To a slurry of 100 mg (2.5 mmol, 60% dispersion in mineral oil, washed 3× with pentane) of sodium hydride in 2 mL of dry THF was added 25 mg (0.06 mmol, in 2 mL of dry THF) of diol **33a**, 61 mg (0.5 mmol) of allyl bromide (filtered through alumina), and 3 mg of tetra-*n*-butylammonium iodide. After 2 h the reaction mixture was decomposed by the slow addition of water. The mixture was then poured into ether, and the layers were separated. The ether layer was washed with saturated sodium chloride solution and worked up. Purification on silica gel (30% EtOAc/hexanes) gave 27 mg (95%) of bis-allyl epoxide **33c** as a colorless oil: R_f = 0.4 (EtOAc/hexanes); IR 2927, 1461, 1338, 1079 cm^{-1}; ^1H NMR δ 5.94 (m, 2 H, vinyl H), 5.27 (m, 4 H, vinyl H), AB system 4.84, 4.63 (OCH_2O, J_{AB} = 7.5 Hz), 4.29–4.04 (m, 5 H, =CH_2, C_{11}), 4.21 (d, J = 1.2 Hz, 1 H, CHOallyl), 4.00 (d, J = 1.2 Hz, 1 H, CHOallyl), 3.81 (d, J = 10.1 Hz, 1 H, C_{15}), 3.65–3.58 (m, 3 H, C_{15}, epoxide H), 3.39 (s, 3 H, OCH_3), 3.27 (s, 2 H, CH_2Br), 2.42 (m, 2 H), 1.96–1.70 (m, 4 H), 1.08 (s, 3 H, C_{14}); HRMS (Cl, isobutane) calcd for $C_{22}H_{33}BrO_6$ (M + H^+) 473.1539, found 473.1539.

4β,12α-Bis(allyloxy)-16-bromo-9,15-epoxy-3β-hydroxy-13-nortrichothecane (35). A stirred solution of 30 mg (0.06 mmol) of epoxide **33c** in 1 mL of CH_2Cl_2 was treated with 50 mg (0.22 mmol) of zinc bromide. After 8 h the reaction mixture was diluted with ether and poured into water. The ether layer was washed with water and brine and worked up. The residual oil was chromatographed (30% EtOAc/hexane) to afford 22 mg (85%) of tetracyclic alcohol **35** as a colorless oil: R_f = 0.42 (EtOAc/hexane); IR 3524, 2927, 2860, 1455, 1405 cm^{-1}; ^1H NMR δ 5.86 (m, 2 H, vinyl H), 5.22 (m, 6 H, vinyl H, C_4, C_{12}), 4.25, (dd, J = 4.2, 6.5 Hz, 1 H, C_3), 4.17 (s, 1 H, C_2), 4.12–3.89 (m, 4 H, CH_2Oallyl), 3.81 (d, J = 9.3 Hz, 1 H, C_{15}), 3.75 (dd, J = 2.5, 9.3 Hz, 1 H, C_{15}), 3.56 (s, 1 H, C_{11}), 3.42 (s, 2 H, C_{16}), 2.98 (d, J = 10.4 Hz, 1 H, OH), 2.26 (m, 2 H, C_{10}), 1.91–1.77 (m, 4 H, C_7, C_8), 0.98 (s, 3 H, C_{14}); HRMS (Cl, isobutane) calcd for $C_{20}H_{29}BrO_5$ (M + H^+) 429.1277, found 429.1277.

4β,12α-Bis(allyloxy)-16-bromo-9,15-epoxy-3-oxo-13-nortrichothecane (39a). Chromium trioxide (11 mg, 0.11 mmol) was added in one portion to a solution of pyridine (43 μL, 0.5 mmol) in 1 mL of CH_2Cl_2. The mixture was stirred vigorously for 15 min at room temperature. Tetracyclic alcohol **35** (10 mg, 0.02 mmol) was added rapidly to the brick red CrO_3·2pyr solution. After 1 h, the solution was filtered through Florisil and rinsed with ether. The elutant was concentrated and chromatographed (25% EtOAc/hexane) to give 10 mg (99% yield) of ketone **39a** as a colorless oil: R_f = 0.6 (30% EtOAc/hexane); IR 1748 cm^{-1}; ^1H NMR δ 5.78 (m, 2 H, vinyl H), 5.29 (m, 4 H, vinyl H), 4.38 (dd, J = 5.1, 10.1 Hz, 2 H, allyl methylene), 4.30 (dd, J = 5.9, 10.3 Hz, 2 H, allyl methylene) 4.07 (dd, J = 5.0, 10.8 Hz, 2 H, CH_2Oallyl), 3.96 (m, 3 H, CH_2Oallyl, C_{15}), 3.87 (s, 1 H, C_4), 3.80 (m, 1 H, C_2), 3.77 (d, J = 9.5 Hz, 1 H, C_{15}), 3.75 (m, 1 H, C_{11}), 3.59 (s, 1 H, C_{12}), 1.9–1.4 (m, 6 H, C_{10}, C_7, C_8), 1.08 (s, 3 H, C_{14}); HRMS (CI, isobutane) calcd for $C_{20}H_{27}BrO_5$ (M + H^+) 427.0499, found 427.0499.

16-Bromo-4β,12α-dihydroxy-9,15-epoxy-3-oxo-13-nortrichothecane (39d). To a solution of ketone **39a** (10 mg, 0.024 mmol) in 2 mL of absolute ethanol was added sequentially $(Ph_3P)_4RhH$[43b] (6.6 mg, 0.006 mmol) and 300 mg (200 μL, 2.6 mmol) of trifluoroacetic acid. The yellow solution was heated at reflux for 3 h and then was concentrated and chromatographed (80% EtOAc/hexane) to yield 6 mg (72% yield) of keto diol **39d** as a colorless oil: R_f = 0.75 (80% EtOAc/hexane); IR 1751 cm^{-1}; ^1H NMR δ 4.21 (s, 1 H, C_2), 3.92 (d, J = 6.5 Hz, 1 H, C_{15}), 3.81 (s, 1 H, C_{12}), 3.80–3.76 (m, 3 H, C_{11}, C_4, C_{15}), 3.26 (s, 2 H, C_{16}), 2.65 (br s, 1 H, OH), 2.42 (br s, 1 H, OH), 2.05–1.26 (m, 6 H), 1.15 (s, 3 H, C_{14}); HRMS calcd for $C_{14}H_{19}BrO_5$ 348.0390, found 348.0363.

16-Bromo-3α,4β,12α-trihydroxy-9,15-epoxy-13-nortrichothecane (40a). To a solution of 25 mg (0.07 mmol) of keto diol **39d** in 1 mL of dry THF was added 200 μL of borane in THF (1.0 M solution, 2.8 equiv) at room temperature. After 8 h, the excess borane was decomposed by the slow addition of 200 μL of water, followed by the addition of sufficient solid potassium bicarbonate to saturate the solution (100 mg). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3×) and worked up. Crude triol **40a** (21 mg) was isolated and used in the next reaction without further purification: ^1H NMR δ 4.82 (br s, 1 H, OH), 4.42 (br s, 1 H, C_3), 4.09 (d, J = 4.0 Hz, 1 H, C_2), 4.03 (s, 1 H, C_{12}), 4.00 (bs s 1 H, C_4), 3.84 (d, J = 10.0 Hz, 1 H, C_{15}), 3.77 (d, J = 10.2 Hz, 1 H, C_{15}), 3.42 (m, 1 H, C_{11}), 3.27 (s, 2 H, C_{16}), 2.82 (br s, 1 H, OH), 2.49 (br s, 1 H, OH), 2.27 (m, 2 H), 2.05–1.41 (m, 4 H), 0.99 (s, 3 H, C_{14}).

16-Bromo-3α,4β-diacetoxy-12α-hydroxy-9,15-epoxy-13-nortrichothecane (40c). To a solution of 5 mg of crude triol (0.014 mmol) **40a** in 0.5 mL of pyridine was added 10 μL (0.1 mmol) of acetic anhydride. After having been stirred for 36 h, the reaction mixture was diluted with ether and washed with aqueous $CuSO_4$ until no color change occurred. The ether layer was washed with water and brine solution and worked up. Purification by flash chromatography (50% EtOAc/hexanes) provided 4 mg (65% yield) of diacetate **40c** as a colorless oil: R_f = 0.5 (50% EtOAc/hexanes); IR 3468, 2988, 1735, 1724 cm^{-1}; ^1H NMR δ 5.38 (d, J = 3.0 Hz, 1 H, C_4), 5.15 (dd, J = 3.2, 3.7 Hz, 1 H, C_3), 4.24 (d, J = 3.9 Hz, C_2, 1 H), 4.20–4.01 (m, 3 H, C_{11}, C_{12}, C_{15}), 3.79 (d, J = 9.8 Hz, 1 H, C_{15}), 3.22 (dd, J = 10.0, 11.2 Hz, 2 H, AB, C_{16}), 2.35 (m, 2 H), 2.17, 2.11 (s, 2 × 3 H, OAc), 1.98–1.41 (m, 4 H), 0.83 (s, 3 H, C_{14}); HRMS calcd for $C_{18}H_{25}BrO_7$ 432.0776, found 432.0783.

16-Bromo-3α,4β-diacetoxy-9,15-epoxy-12-oxo-13-nortrichothecane (43). To a stirred solution of 10 mg (0.024 mmol, 2 equiv) of the Dess–Martin periodane[47] and 5 μL of trifluoroacetic acid in 1 mL of

CH_2Cl_2 was added 5 mg (0.012 mmol) of diacetate **40c**. After 4 h the reaction mixture was diluted with ether, neutralized with saturated bicarbonate solution, and treated with NaS_2O_4. After 10 min, the layers were separated, and the organic layer was washed with $NaHCO_3$ solution, water, and brine solution and worked up. The crude residue was purified by flash chromatography (50% EtOAc/hexanes) to provide 4.6 mg (89% yield) of keto diacetate **43** as a colorless oil: R_f = 0.45 (50% EtOAc/hexanes); IR 2887, 1761, 1730 cm^{-1}; ^1H NMR δ 5.74 (d, J = 3.9 Hz, 1 H, C_4), 5.04 (dd, J = 3.1, 3.4 Hz, 1 H, C_3), 4.48 (m, 1 H, C_{11}), 4.16 (d, J = 9.7 Hz, 1 H, C_{15}), 4.14 (d, J = 3.5, 1 H, C_2), 3.79 (d, J = 10.3 Hz, 1 H, C_{15}), 3.30 (d, J = 11.0, 1 H, C_{16}), 3.30 (d, J = 11.2 Hz, 2 H, C_{16}), 2.47 (m, 2 H), 2.21, 2.10 (s, 2 × 3 H, OAc), 1.92–1.55 (m, 4 H), 0.82 (s, 3 H, C_{14}); HRMS (CI, isobutane) calcd for $C_{18}H_{23}BrO_7$ $(M + H)^+$ 430.0620, found 430.0627.

16-Bromo-9,15-epoxy-3α,4β,12α-triacetoxy-13-nortrichothecane (40b). To a solution of 21 mg (0.06 mmol) of crude triol **40a** in 1 mL of CH_2Cl_2 were added 50 μL of Et_3N (36 mg, 0.36 mmol) and 10 mg (10 μL, 0.1 mmol) of acetic anhydride and a catalytic amount of 4-pyrrolidinopyridine (1 mg). The reaction mixture was stirred at room temperature for 12 h, diluted with ether, and washed with water (2×) and brine solution. The organic layer was dried over $MgSO_4$, concentrated, and purified by flash chromatography (30% EtOAc/hexanes), providing 18 mg (63% yield over two steps) of triacetate **40b** as a colorless oil: R_f = 0.4 (40% EtOAc/hexanes); IR 2963, 2869, 1745 cm^{-1}; ^1H NMR δ 5.53 (br s, 1 H, C_4), 5.30 (t, J = 4.0 Hz, 1 H, C_3), 5.25 (s, 1 H, C_{12}), 4.30 (d, J = 4.9, 1 H, C_2), 4.18 (t, J = 3.2 Hz, 1 H, C_{11}), 4.06 (d, J = 10.1 Hz, 1 H, C_{15}), 3.82 (d, J = 9.7 Hz, 1 H, C_{15}), 3.31 (d, J = 9.0, 1 H, C_{16}), 3.29 (d, J = 9.3 Hz, 1 H, C_{16}), 2.36 (m, 2 H, C_{10}), 2.15, 2.14, 2.12 (s, 3 × 3 H, OAc), 1.96–1.54 (m, 4 H, C_7, C_8), 0.75 (s, 3 H, C_{14}); HRMS (CI, isobutane) calcd for $C_{20}H_{27}BrO_8$ $(M + H)^+$ 475.0967, found 475.0939.

15-Hydroxy-3α,4β,12α-triacetoxy-9,16-dehydro-13-nortrichothecane (48a). A solution of 18 mg (0.038 mmol) of triacetate **40b** and 25 mg (0.38 mmol) of zinc dust in 2 mL of 95% ethanol was heated at reflux for 18 h under N_2. The reaction mixture was filtered through Celite and concentrated, and the residue was chromatographed (30% EtOAc/hexanes) to provide 12 mg of exo-methylene triacetate **48a** in 80% yield: R_f = 0.35 (40% EtOAc/hexanes); IR 3517, 2963, 2939, 1746, 1728 cm^{-1}; ^1H NMR δ 6.06 (br s, 1 H, C_4), 5.45 (s, 1 H, C_{12}), 5.36 (t, J = 4.5 Hz, 1 H, C_3), 4.79 (br s, 1 H, C_{16}), 4.74 (br s, 1 H, C_{16}), 4.33 (d, J = 4.1 Hz, 1 H, C_2), 4.24 (br s, 1 H, C_{11}), 4.02 (d, J = 10.5 Hz, 1 H, C_{15}), 3.88 (d, J = 10.2 Hz, 1 H, C_{15}), 2.16, 2.13, 2.10 (s, 3 × 3 H, OAc), 2.36–1.44 (m, 6 H), 0.86 (s, 3 H, C_{14}); HRMS (CI, isobutane) calcd for $C_{20}H_{28}O_8$ $(M + H)^+$ 397.1863, found 397.1888.

3α,4β,12α,15-Tetraacetoxy-9,16-dehydro-13-nortrichothecane (48b). To a solution of 12 mg (0.03 mmol) of exomethylene triacetate **48a** in 750 μL of CH_2Cl_2 were added 20 μL of Et_3N (0.15 mmol), 10 μL of acetic anhydride (0.09 mmol), and 2 mg (0.015 mmol) of 4-pyrrolidinopyridine. The reaction mixture was stirred for 4 h at room temperature. The mixture was diluted with ether, washed with water (2×) and brine solution, and worked up. Flash chromatography (40% EtOAc/hexanes) furnished 12 mg of exo-methylene tetracetate **48b** (91% yield) as a colorless oil: R_f = 0.4 (50% EtOAc/hexanes); IR 1745, 1737 cm^{-1}; ^1H NMR δ 5.74 (d, 1 H, C_4), 5.46 (s, 1 H, C_{12}), 5.26 (dd, J = 2.1, 1.9 Hz, 1 H, C_3), 4.81 (br s, 1 H, C_{16}), 4.73 (br s, 1 H, C_{16}), 4.49 (s, 2 H, C_{15}), 4.29 (d, J = 1.9 Hz, 1 H, C_2), 3.92 (br s, 1 H, C_{11}), 2.52–1.72 (m, 6 H, C_7, C_8, C_{10}), 2.16, 2.13, 2.11, 2.10 (s, 4 × 3 H, OAc), 0.81 (s, 3 H, C_{14}); HRMS (CI, isobutane) calcd for $C_{22}H_{30}O_9$ $(M + H)^+$ 439.1959, found 439.1966.

3α,4β,12α,15-Tetraacetoxy-8,9-dehydro-13-nortrichothecane (49). Tetraacetate **48b** (4 mg, 0.01 mmol) was dissolved in 500 μL of acetonitrile, and 10 μL of trifluoroacetic acid (15.0 mg, 0.13 mmol) was added. The mixture was heated at reflux for 12 h at which time the reaction mixture was cooled, diluted with 1 mL of aqueous $NaHCO_3$, and extracted with $CHCl_3$ (3×). The organic layers were combined and worked up. The crude residue was chromatographed and 3.8 mg (95% yield) of endo olefinic tetraacetate **49** was isolated as a colorless oil: R_f = 0.4 (50% EtOAc/hexanes); IR 2908, 2865, 1743, 1732 cm^{-1}; ^1H NMR δ 5.96 (s, 1 H, C_4), 5.39 (s, 1 H, C_{12}), 5.32 (m, 2 H, C_8, C_3), 4.30 (m, 1 H, C_2), 4.18 (m, 2 H, C_{15}, C_{11}), 4.03 (d, J = 10.1 Hz 1 H, C_{15}), 2.62 (m, 1 H, C_{10}), 2.47 (m, 1 H, C_{10}), 2.16, 2.15, 2.13, 2.11 (s, 4 × 3 H, OAc), 1.82 (m, 2 H, C_7), 1.68 (s, 3 H, C_{16}), 0.94 (s, 3 H, C_{14}); HRMS (CI, isobutane) calcd for $C_{22}H_{30}O_9$ $(M + H)^+$ 439.1959, found 439.1956.

Acknowledgment. This work was supported by a grant from the National Cancer Institute, NIH (CA-39976). S.B.S. expresses her gratitude for the receipt of Dox Fellowship (Yale). We are grateful to Professor N. Ishikawa for a sample of (+)-Eu(dppm)$_3$, to Dr. J. Kadow (Bristol-Myers) for a sample of anguidine, to Dr. Edward Brown for assistance in the later stages of the work, and to Peter Demou (NMR) and Dan Pentek (mass spectra) of the Yale Chemical Instrumentation Center for technical assistance.

Registry No. 1, 2270-40-8; (±)-**7**, 125475-15-2; **8**, 125475-16-3; (±)-9, 125475-17-4; (±)-**10a**, 125475-18-5; (±)-*cis*-**10b**, 125475-45-8; (±)-*trans*-**10b**, 125475-46-9; **11**, 125475-19-6; **12**, 125475-20-9; **13a**, 125475-21-0; **13b**, 125475-49-2; (±)-**14**, 125475-22-1; (±)-**15**, 125475-23-2; (±)-**15** (alcohol), 125517-37-5; (±)-**16a**, 125475-24-3; (±)-**16b**, 125494-78-2; (±)-**16** (R = SeC_6H_4-*o*-NO_2), 125475-50-5; **17**, 125475-25-4; (±)-**19**, 125475-26-5; (±)-**21a**, 125475-27-6; (±)-**21b**, 125475-51-6; (±)-**22a**, 125475-28-7; (±)-**22b**, 125475-52-7; (±)-**22c**, 125475-54-9; (±)-**22d**, 125475-56-1; (±)-**22** (R_1 = Ac; R_2 = H), 125475-57-2; (±)-**23a**, 125475-29-8; (±)-**23b**, 125475-53-8; (±)-**23c**, 125475-55-0; (±)-**23c** (desilyl derivative), 125475-58-3; **27**, 125475-30-1; **28**, 125475-31-2; (±)-**29**, 125475-32-3; (±)-**30**, 125475-33-4; (±)-**31**, 125475-34-5; (±)-**32**, 125475-35-6; (±)-**33a**, 125475-36-7; (±)-**33b**, 125475-60-7; (±)-**33c**, 125475-62-9; (±)-**34a**, 125475-37-8; (±)-**34b**, 125475-59-4; (±)-**34c**, 125475-61-8; (±)-**35**, 125475-38-9; (±)-**39a**, 125475-39-0; (±)-**39b**, 125475-63-0; (±)-**39c**, 125475-64-1; (±)-**39d**, 125475-65-2; (±)-**40a**, 125475-40-3; (±)-**40b**, 125517-38-6; (±)-**40c**, 125475-66-3; (±)-**43**, 125475-41-4; (±)-**44a**, 125475-42-5; (±)-**44b**, 125475-68-5; (±)-**44c**, 125475-69-6; **45**, 99531-48-3; **46**, 4297-61-4; **47**, 101199-14-8; (±)-**48a**, 125475-43-6; (±)-**48b**, 125475-67-4; (±)-**48c**, 125475-70-9; (±)-**49**, 125475-44-7; (±)-Br$(CH_2)_2$CH(CH_3)COBr, 125475-47-0; (±)-Br$(CH_2)_2$CH$(CH_3)CO_2$H, 125475-48-1; MeO$(CH_2)_2$COCH$_3$, 6975-85-5; α-methyl-γ-butyrolactone, 1679-47-6; 2,4,4,6-tetrabromocyclohexadienone, 20244-61-5.