THE JOURNAL OF Organic Chemistry

VOLUME 51, NUMBER 11

MAY 30, 1986

Organoiron Approach to 3,14-Dihydroxytrichothecenes

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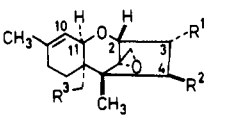
Received November 12, 1985

Total synthesis of 3α,14-dihydroxy-12,13-epoxytrichothec-9-ene, an analogue of natural products related to, e.g., calonectrin, but differing in the placement of the primary hydroxy group, is described. The synthesis commences with tricarbonyl(4-methoxy-1-methylcyclohexadienyl)iron hexafluorophosphate as an A ring synthon and illustrates the use of the $Fe(CO)_3$ group as dienol ether protection during epoxidation, osmylation, and other functional group interconversions. The selectivity during intramolecular Michael reaction of the intermediate diol from compound **11** and the triol **23**, to give tricyclic compounds **12** and **24**, was investigated. The structure of the intermediate **12**, and by inference all subsequent compounds, was confirmed by two-dimensional proton *J*-correlated (COSY) NMR spectroscopy.

The trichothecenes form a group of naturally occurring sesquiterpenes, exemplified by trichodermol (**1a**), verrucarol (**1b**), calonectrin (**1c**), and anguidine (**1d**), among others.[1] Most of these compounds show potent cytotoxic activity, and a number have been the subject of total syntheses.[2] Unfortunately, the extreme toxicity associated with the natural products has so far precluded their use as chemotherapeutic agents, and, indeed, these compounds were recently the subject of intense scrutiny[3] as possible constituents of the chemical warfare combination known as "yellow rain". One of the natural products, vomitoxin (**2**), is now known to present a serious agricultural problem, since it is produced by various species of Fusarium molds, resulting in extensive contamination of grain. Vomitoxin causes vomiting and lowers feed consumption, particularly in pigs. Concentrations greater than 5 ppm are required to cause vomiting and higher concentrations lead to feed refusal, which has been a serious economic problem in the pig industry for at least ten years but only recently attributed to vomitoxin.[4] The high toxicity of the natural products has so far prevented their use in developing antibodies,[5] since they inhibit lymphocite proliferation, which is in turn a necessary step in antibody response.



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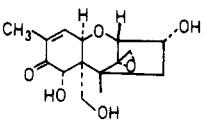


2

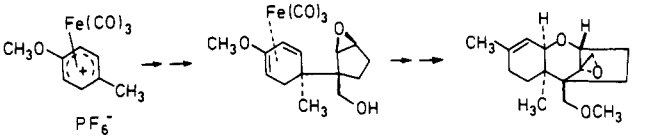
(a) $R^1 = R^3 = H$, $R^2 = OH$

(b) $R^1 = H$, $R^2 = R^3 = OH$

(c) $R^1 = R^3 = OAc$, $R^2 = H$

(d) $R^1 = OH$, $R^2 = R^3 = OAc$

Clearly, if these compounds are to be used in either chemotherapy or in antiserum development, the natural products are of little or no value. Analogues, produced either by modification of the natural products or by de novo total synthesis, might show sufficiently modified biological activity to allow their actual usage. Guided by this philosophy, we recently completed[6] the total synthesis of the simple analogue **5**, which proceeded from the cyclohexadienyl-$Fe(CO)_3$ cation **3** and via the epoxy alcohol **4**. This compound was since shown to be nontoxic.[7] Of



3 **4** **5**

(1) Reviews: Tamm, Ch. *Forstchr. Chem. Org. Naturst.* **1974**, *31*, 63. Bamburg, J. R.; Strong, F. M. *Microbial Toxins*; Kadis, S., Ciegler, A., Ajl, S. J., Eds.; Academic: New York, 1971; Vol. 7, pp 207–292. Doyle, T. W.; Bradner, W. T. *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic: New York, 1980; pp 43–72. McDougal, P. G.; Schmuff, N. R.; *Fortschr. Chem. Org. Naturst.* **1985**, *47*, 153.

(2) (a) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2069; 1978, 658. (b) Still, W. C.; Tsai, M. Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654. (c) Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *J. Am. Chem. Soc.* **1982**, *104*, 1114. (d) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116. (e) Roush, W. R.; D'Ambra, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 1058. (f) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472. (g) Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6110. Trost, B. M.; McDougal, P. G.; Haller, K. J. *Ibid.* **1984**, *106*, 383.

(3) Marshall, E. *Science* (Washington, D.C.) **1983**, *221*, 526. Ember, L. R. *Chem. and Eng. News* **1984**, (Jan 9), 7–34.

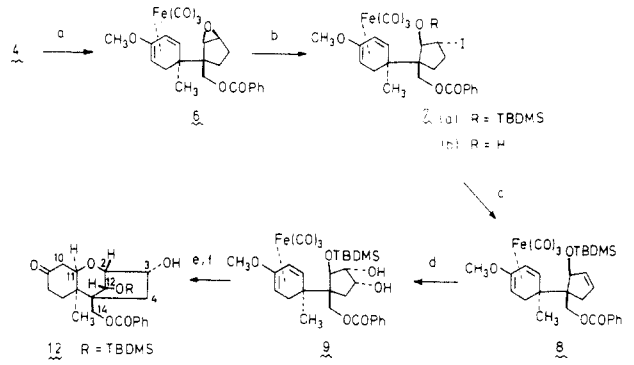
(4) See: ref 1 and *Chem. and Eng. News* **1982**, (Oct. 4), 28.

(5) Personal communication from Dr. Alan A. Brimfield, Department of Pediatrics, Uniformed Services University of The Health Sciences, Bethesda, MD 20814.

(6) Pearson, A. J.; Ong, C. W. *J. Am. Chem. Soc.* **1981**, *103*, 6686.

0022-3263/86/1951-1939$01.50/0

Scheme I[a]



[a] Reagents (yield): (a) PhCOCl, py, 20 °C, 18 h (98%); (b) *t*-$BuMe_2SiI$, 4 equiv, CH_3CN, 0 °C, 20 min; (c) DBU, 2 equiv, THF, reflux, 48 h (80–84% overall yield from **5**); (d) (i) OsO_4, 1.1 equiv, py, 20 °C, 24 h; (ii) $Na_2S_2O_5$, H_2O, 20 °C, 24 h (89%); (e) Me_3NO, 10 equiv, *N,N*-dimethylacetamide, 25 °C, 16 h; (f) $(CO_2H)_2$, H_2O, MeOH, dioxane, then basify with K_2CO_3 (29% overall from **8**).

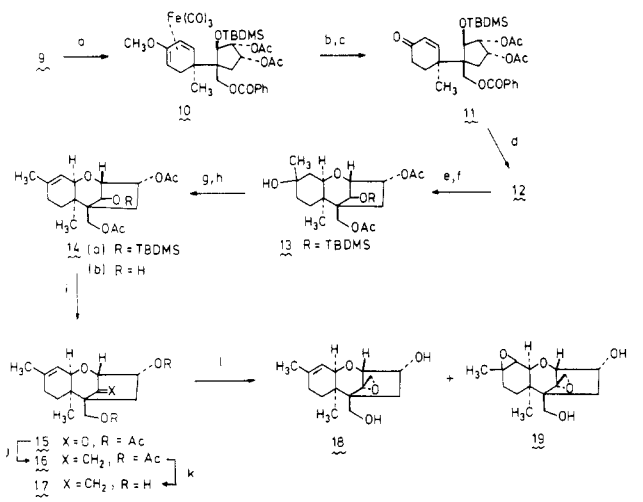
the requirements for biological activity, two of the most important structural features appear to be the 12,13-epoxide, together with hydroxyl or related functionality at C(3) or C(4). Consequently, we have placed a major emphasis on manipulating the readily accessible epoxide **4** (prepared in 5 steps from complex **3**) to give trichothecenes having the basic structure **5** but with oxygen functionality in the C ring. This paper describes the various stereocontrolled routes leading from **4** to compounds having a 3α-hydroxyl substituent.

Results and Discussion

A suitable strategy for the manipulation of epoxy alcohol **4** would involve conversion of the epoxide to an allylic alcohol, followed by functionalization of the double bond in the latter. It was recognized that a fairly robust protecting group for the primary alcohol would be required to survive some of the later steps. Accordingly, **4** was benzoylated in the usual manner to give the benzoate **6** (see Scheme I). A number of attempts to convert **6** to an allylic alcohol by using standard techniques[8] completely failed. However, treatment of **6** with *tert*-butyldimethylsilyl iodide[9] gave high yield of the protected iodohydrin **7a** which was readily converted to the allylic silyl ether **8** by base (DBU) treatment. Some loss of silyl protecting group occurred during the epoxide opening to give unprotected iodohydrin **7b**. This compound was converted back to epoxide **6** on treatment with DBU in the subsequent step and was thus recycled.

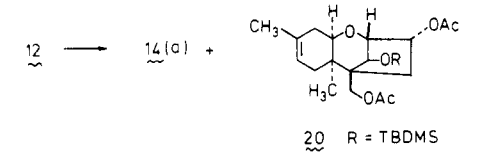
The key intermediate required in this strategy is the tricyclic compound **12** (Scheme I). In fact, there are several ways in which **8** can be converted to **12**, depending on whether or not functionalization of the allylic ether double bond precedes removal of the $Fe(CO)_3$ moiety.

Scheme II[a]



[a] Reagents (yield): (a) Ac_2O, py, 20 °C, 24 h; (b) Me_3NO, 10 equiv, benzene, 35 °C; (c) $(CO_2H)_2$, H_2O, MeOH, dioxane (54% overall from **7**); (d) K_2CO_3, 5 equiv, MeOH, H_2O, 20 °C, 2 h (88%); (e) MeMgBr, 10 equiv, THF, −78 to 0 °C, 4 h, (99%); (f) Ac_2O, py, 0 °C, 18 h, (85%); (g) $POCl_3$, py, 0 °C, 2 h, 20 °C, 22 h (61%); (h) $(n\text{-}Bu)_4NF$, THF, 20 °C, 2 h (quantitative); (i) CrO_3, 2 py, CH_2Cl_2, 20 °C, 1 h (67% overall from **12**); (j) $(CH_3PPh_3)^+I^-$, KO-*t*-Bu, ether, *t*-BuOH, reflux, 2 h; then Ac_2O, py (20–30%); (k) K_2CO_3, MeOH, H_2O, 20 °C, 2 h; (l) MCPBA (1.2 equiv) Na_2HPO_4, CH_2Cl_2, −28 °C, 22 h.

(a) Osmylation Preceding Decomplexation. Osmylation of intermediate **8** proceeded cleanly in the presence of the diene-$Fe(CO)_3$ group[10] to give a single diol **9** in high yield. This reaction illustrates the effect of a sterically demanding substituent immediately adjacent to the double bond in controlling the stereochemical outcome of reactions on that double bond,[11] since the more remote but sterically more demanding diene-$Fe(CO)_3$ substituent is evidently much less important during this reaction. Decomplexation of **9**, followed by hydrolysis of the resultant dienol ether afforded the key tricyclic intermediate **12**. However, this gave a product which was rather impure, so the more easily controlled, but longer sequence of reactions shown in Scheme II was examined. Accordingly, diol **9** was converted to the diacetate **10**, which was decomplexed and hydrolyzed to give the enone **11**. This route provided material which was easily purified prior to the cyclization step which was to follow, allowing us to properly assess the selectivity during that reaction. Selective hydrolysis of the acetates was accompanied by intramolecular Michael reaction of the resultant diol to afford a *single* tricyclic intermediate **12**, the structure of which was established un-



(7) In vitro toxicity studies were performed by Dr. Alan A. Brimfield (see ref 5) by using a continuously growing culture of transformed cells that has been designated USU-9-113-IIA7. This was isolated in April 1981 from the spleen of a nine year old girl who was suffering from idiopathic thrombocytopenic purpura. The line has a 24-h doubling time, secretes IgG, and is of B cell origin. These characteristics made it a natural candidate for use in testing B lymphocyte directed toxicity. The level of toxicity of several trichothecenes was determined by measuring inhibition of ^{3}H-leucine incorporation into protein. Compared to naturally occurring compounds, such as T2 toxin, the analogue **5** showed very low level of toxicity.

(8) Rickborn, B.; Thummel, R. P. *J. Org. Chem.* **1969**, *34*, 3583. Sharpless, K. B.; Lauver, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *Ibid.* **1980**, *102*, 1433. Murata, S.; Suzuki, M.; Noyori, R. *Ibid.* **1979**, *101*, 2738.

(9) Detty, M. R. *J. Org. Chem.* **1980**, *45*, 924.

(10) This adds to the growing number of reported examples illustrating the use of the $Fe(CO)_3$ group as a diene protection during manipulation of olefinic groups. See also: Franck-Neumann, M.; Martina, D. *Tetrahedron Lett.* **1975**, 1759. Banthorpe, D. V.; Fitton, H.; Lewis, J. *J. Chem. Soc., Perkin Trans 1* **1973**, 2051. Evans, J.; Johnson, B. F. G.; Lewis, J. *J. Organomet. Chem.* **1974**, *102*, 507. Barton, D. H. R.; Gunatilaka, A. A. L.; Nakanishi, T.; Patin, H.; Widdowson, D. A.; Worth, B. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 821. Birch, A. J.; Pearson, A. J. *J. Chem. Soc., Chem. Commun.* **1976**, 601.

(11) It should be noted here that allylic alcohols and ethers show a pronounced directing effect of the OR group, osmylation occurring trans to the oxygen substituent. See: Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. Christ, W. J.; Cha, J. K.; Kishi, Y. *Ibid.* **1983**, *24*, 3947. Stork, G.; Kahn, M. *Ibid.* **1983**, *24*, 3951.

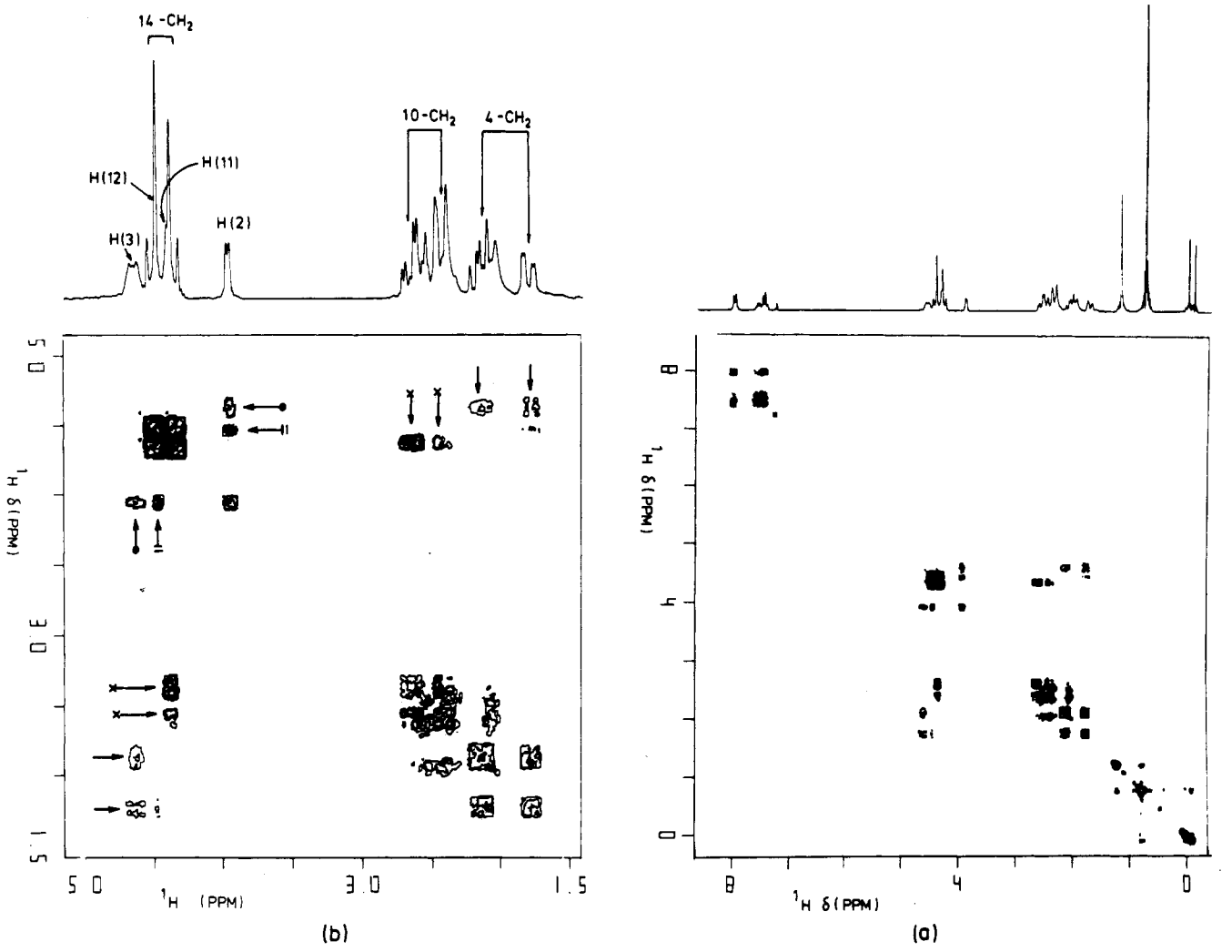


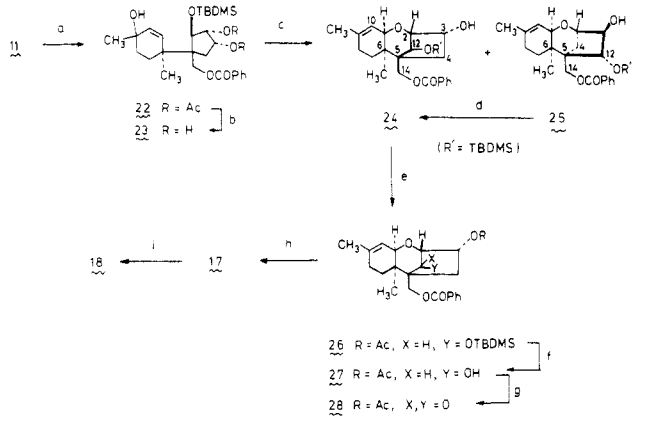
Figure 1. 2D ^1H *J*-correlated NMR spectrum of tricyclic intermediate **12**. (a) Contour plot with 1D NMR spectrum aligned (see Experimental Section for technical details). (b) Expanded region δ 2–5 with assignments. Off-diagonal peaks marked (→) indicate coupling of H(3) (δ 4.64) to 4-CH_2 (δ 1.8 and 2.1). Off-diagnoal peaks marked (⊢→) indicate coupling of H(2) (δ 3.98) to H(12) (δ 4.49). Off-diagonal peaks marked (•→) indicate coupling of H(3) (δ 4.64) to H(2) (δ 3.98). Off-diagonal peaks marked (×→) indicate coupling of H(11) (δ 4.39) to 10-CH_2 (ca. δ 2.7 and 3). (Trichothecene numbering used for assignments).

equivocally by 2D ^1H *J*-correlated NMR spectroscopy (Figure 1, also see later discussion). The overall yield from this sequence was in fact better than that from the apparently more direct approach of Scheme I. With the compound **12** in hand the stage was set for elaboration of the target analogues by using a sequence almost identical with that used in construction of the earlier analogue **5**. Treatment of **12** with excess methylmagnesium bromide resulted in conversion of the ketone to the tertiary alcohol along with concomitant loss of the benzoyl protection. Therefore, the product was acetylated to give **13**, which subsequently was dehydrated and then desilylated to give **14b** as the major product. The dehydration of **13** was found to be less regioselective than that of our earlier intermediates[6] and than that of similar intermediates used by Still and Tsai,[2b] giving substantial amounts (ca. 25% of mixture) of the isomer **20**, which could not be separated. The mixture was, therefore, carried through the remaining steps in anticipation that a separation could be accomplished at a later stage.

The reason for the regioselectivity during the aforementioned dehydration remains unclear, and neither we nor others have investigated this reaction in detail. The major product may be the thermodynamically preferred one, or the presence of the oxygen substituent at C(11) (trichothecene numbering) may result in enhanced acidity of the protons at C(10) by inductive electron withdrawal.

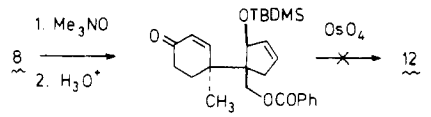
Oxidation of intermediate **14b** furnished compound **15**, which now required conversion to the methylene derivative **17** in order to secure the penultimate compound in this sequence. Subjection of **15** to a number of standard Wittig methylenation techniques which have previously been reported to give high yields in the trichothecene series[2] resulted in extremely low recovery of product or starting material. A modification of Raphael's procedure[2] which we also employed earlier[6] gave the best results, but the reaction in this particular instance was still troublesome. Partial deacetylation of the 3-OH and 14-OH groups during the Wittig reaction led to a mixture which was extremely difficult to purify. Consequently, the crude product was reacetylated and subjected to partial purification to give diacetate **16** which was then converted to **17** upon alkaline hydrolysis. It was only after this rather tedious manipulation that **17** could be obtained in a state which allowed proper purification. The product arising from the double bond isomer **20** could be easily separated at this stage by using preparative HPLC. Even so, the methylenation was extremely inefficient, giving variable yields, at most 25–30%, and this sequence allowed access to only small amounts of pure **17** (trial Wittig reactions were all conducted on ca. 5-mg scale). Consequently, selective epoxidation of **17** to give **18** was deferred until a better sequence was established for the construction of this key intermediate.

Scheme III[a]



[a] Reagents (yield): (a) 8 equiv CH_3MgBr, THF, −78 °C, 2.5 h (quantitative); (b) 5 equiv K_2CO_3, CH_3OH–H_2O (3:1), 25 °C, 2 h (83%); (c) *p*-TsOH, CH_2Cl_2 see text and Experimental Section; (d) *p*-TsOH, CH_2Cl_2, room temperature, 2 h (60% overall from **11**); (e) 10 equiv Ac_2O, pyridine, 25 °C, 18 h (84%); (f) *n*-Bu_4NF (1.5 equiv), THF, 25 °C, 2 h (87%); (g) 15 equiv CrO_3, 2 py, CH_2Cl_2, 25 °C, 1 h (85%); (h) $Ph_3P{=}CH_2$, ether, see Experimental Section; (i) MCPBA (1.2 equiv), Na_2HPO_4, CH_2Cl_2, −16 °C, 17 h.

(b) Decomplexation Preceding Osmylation. Although the osmylation step (**8** → **9**) could be performed in the presence of the $Fe(CO)_3$ group, the poor yield and impure material resulting from *direct* conversion of diol **9** to tricycle **12** prompted us to examine a minor alteration



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of the sequence, in order to try to improve the efficiency. Accordingly, complex **8** was demetalated to give the enone **21** which was treated with osmium tetraoxide in the usual way. However, a number of products resulted from this procedure, and none of the desired tricycle **12** could be detected in the NMR spectrum of the crude products. Presumably, there is a lack of selectivity for osmylation of the cyclopentene double bond vs. enone, and this clearly demonstrates the benefit of using the $Fe(CO)_3$ group as a method of protecting the masked enone functionality.

(c) Manipulation of 11 To Give Regiocontrolled Formation of 9,10-Double Bond. The preparation of intermediate **11** illustrates the value of being able to conduct reactions such as osmylation in the presence of the diene-$Fe(CO)_3$ group, since it is extremely difficult to accomplish such a transformation selectively on an equivalent organic intermediate, such as enone **21**.

Treatment of **11** with methylmagnesium bromide (8 equiv) in tetrahydrofuran at −78 °C for 2.5 h afforded the teritary alcohol **22** in essentially quantitative yield, without loss of acetate or benzoate groups. Selective acetate hydrolysis gave the triol **23** (Scheme III) which could now be converted to the tricyclic intermediate **24**. Based on our earlier observation of complete selectivity during conversion of **11** to **12** (Scheme II), we fully anticipated a clean conversion of **23**. Brooks et al.[2f] have reported analogous selectivity during cyclization of a closely related triol. In the event, exposure of **23** to a catalytic amount of *p*-toluenesulfonic acid in dichloromethane (room temperature, 15 min, lit. procedure used 10 min reaction time) gave a 3:1 mixture of the desired product **24** and the compound **25** resulting from cyclization of the 3-OH group (trichothecene numbering) onto the intermediate allyl cation. A similar mixture (2:1) was obtained under milder conditions (0 °C, 30 min), and these two products were separated and individually characterized. Prolonged exposure of **23** or of the mixture of **24** and **25** to acid (0.1 equiv TsOH, CH_2Cl_2, room temperature, 2 h) resulted in clean conversion to **24**, obtained in 90–95% yield. These results are discussed in more detail later.

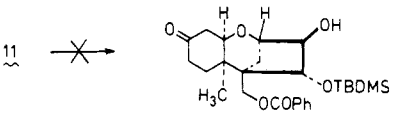
The tricyclic intermediate **24** was reacetylated to give **26**, which was desilylated to give **27**. Oxidation of the latter compound afforded the tricyclic ketone **28** in good overall yield (ca. 37% from enone **11**).

In this way **28** is accessible in appreciable quantities (100 + mg batches were typically produced, and we anticipate no problems in further scaling up of these reactions). Wittig methylenation on **28**, followed by hydrolysis of the protecting groups, proceeded satisfactorily to give the desired intermediate **17**. Although no loss of acetate was reported to occur during the methylenation of a similar compound (**29** to **30**, see ref 2f), our experiments with

29 **30**

compound **28** indicated considerable deacetylation of the 3-OH group, similar to the results with **15**. Typically, the crude product had to be reacetylated to facilitate purification. The final epoxidation step, conversion of **17** to **18**, was performed successfully by using *m*-chloroperoxybenzoic acid at low temperature. Under these conditions, little or no epoxidation of the 9,10-double bond, which would give diepoxide **19**, was observed. If the reaction is carried out with larger excesses of peracid, **19** becomes the major product, indicating that the 12,13-double bond is epoxidized somewhat faster than the 9,10 double bond.

On the Selectivity Observed during Cyclization of Compounds 11 and 23. As noted above, alkaline hydrolysis of intermediate **11** results in a single product **12** which arises from cyclization of the *pro*-C(2) hydroxyl group by intramolecular Michael addition to the enone moiety. The other possible product from this reaction, **31**,



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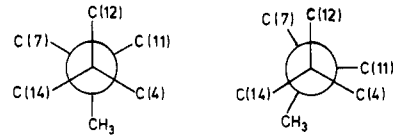
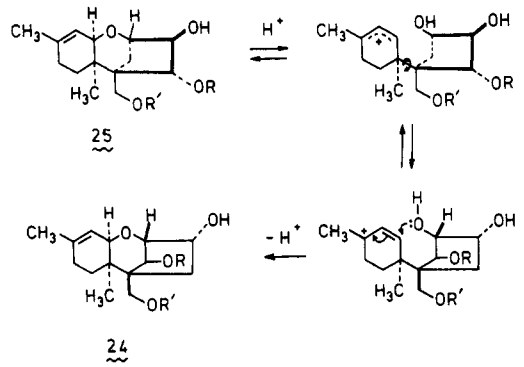
was not observed. The structure **12**, as opposed to **31**, for this product was confirmed by the two-dimensional proton *J*-correlated (COSY) NMR experiment shown in Figure 1. This clearly shows the coupling between H(3) and the 4-methylene group and with H(2). That the signal at δ 4.64 was indeed assignable to H(3) was confirmed by acetylation, when this resonance was shifted to lower field, as expected. The 2D NMR spectrum also shows a small coupling between H(2) and H(12), which would not be expected for the analogous protons (bridgehead C*H*O and C*H*OSiR_3) in a compound of structure **31**. Similarly, the preferred product during cyclization of **23** is **24**. That this is the thermodynamically more stable compound is demonstrated by the high yield conversion of a 2:1 mixture of **24** and **25** to a single product **24**, and we have included the mechanism of this interconversion in Scheme IV. The greater stability of compounds **12** vs. **31** and **24** vs. **25**, is readily explained by examining Newman projections made along the C(5)–C(6) bond, shown for **24** and **25** in Figure 2. In structure **25**, drawn for the C-ring conformation



24 25

Figure 2. Newman projections along the C(5)–C(6) bond of cyclization products **24** and **25**, illustrating the increased torsional strain of **25** compared to **24**.

Scheme IV. Mechanism of Acid-Catalyzed Conversion of 25 to 24



25 24

which places the groups attached to C(5) and C(6) at the maximum possible distance apart, there is an approximately 30° dihedral angle between, e.g., C(14) and CH_3(15), which is preserved for the other substituents on these carbon atoms. On the other hand, structure **24** has a dihedral angle of 60° between these substituents, i.e., the molecule can adopt a completely staggered arrangement. On the basis of examination of Dreiding molecular models, the nonbonded interactions between substituents attached to C(5) and C(6) appear to be the dominant features which distinguish **24** and **25**. On this basis **24** is expected to be the more stable compound, as is indeed observed.

Conclusions

We have developed a de novo synthesis of trichothecenes having structural features in common with a number of the natural products. The distinguishing feature is the presence of hydroxyl functionality at C(14) instead of at C(15), which is not attainable by manipulation of the naturally occurring compounds. We anticipate that this route will provide access to sufficient quantities of **18** to allow biological evaluation, and this will be reported elsewhere.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Solvents were freshly distilled under nitrogen as follows: tetrahydrofuran (THF) from sodium and benzophenone; diethyl ether from lithium aluminum hydride; dichloromethane and acetonitrile from calcium hydride. All reactions were carried out under an atmosphere of dry nitrogen.

Two-dimensional proton J-correlated (COSY) NMR experiments[12] were performed in $CDCl_3$ solution on a Varian XL-200 spectrometer operating with quadrature detection at a proton frequency of 200 MHz by using the program supplied in the manufacturer's software package. A sweep width of 1800 Hz, acquisition time of 0.285 s, 6.3 μs 90° proton pulse, and 1.0-s repetition rate, was used to collect four signal-averaged transients for each of the 512 spectra. The evolution time of these spectra was systematically varied to generate a 1800-Hz spectral width in the second dimension after transposition and Fourier transformation. Pseudo echo weighting was applied to the FIDs in both dimensions before Fourier transformation, and the contour plots are displayed in the absolute value mode.

Tricarbonyl[1β-((benzoyloxy)methyl]-1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)cyclopentene 2,3-β-oxide]iron (6). To a stirred solution of epoxy alcohol **4** (625 mg, 1.66 mmol)[6] in pyridine (12 mL) at room temperature under argon atmosphere was added benzoyl chloride dropwise (0.20 mL, 1.72 mmol). The resulting mixture was stirred for 18 h and diluted with 300 mL of ether. The mixture was washed with 10% HCl (3 × 30 mL) and saturated aqueous NaCl (30 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated. Flash chromatography of the resulting residue on silica gel with 30% ethyl acetate in hexane afforded the pure pale yellow crystalline epoxybenzoate **6**. Recrystallization from ether/pentane provided 780 mg (1.62 mmol, 98%): mp 131–132 °C; IR ν_{max} (CCl_4) 2045 and 1975 [$Fe(CO)_3$], 1720, 1485, 1270, 1230, 1180, 1110, 850, 710, 620 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 7.99 (2 H, d, J = 7 Hz, ortho-H), 7.57 (1 H, t, J = 7 Hz, para-H), 7.45 (2 H, t, J = 7 Hz meta-H), 5.02 (1 H, dd, J = 6.5, 2.3 Hz, 3-H), 4.38 and 4.31 (1 H each, ABq, J_{AB} = 11.7 Hz, CH_2OBz), 3.63 (1 H, m, 3′-H), 3.58 (3 H, s, OCH_3), 3.33 (1 H, m, 5-H), 3.17 (1 H, d, J = 2.4 Hz, 2′-H), 2.49 (1 H, dd, J = 15.5, 2.8 Hz, endo-6-H), 2.37 (1 H, d, J = 6.5 Hz, 2-H), 2.17–1.67 (3 H, m, 4′-H, 5′-H), 1.60 (1 H, dd, J = 15.5, 3.2 Hz, exo 6-H), 1.25 (1 H, m, 5′-H), 1.09 (3 H, s, CH_3); MS, m/e (relative intensity) 480 (M^+, 1.97), 452 (16.67), 396 (100.03), 274 (12.53), 272 (79.89); mol wt 480.0876 (calcd for $C_{24}H_{24}O_7Fe$ 480.0871). Anal. Calcd for $C_{24}H_{24}O_7Fe$: C, 60.02; H, 5.04. Found: C, 60.05; H, 4.98.

Tricarbonyl[1β-((benzoyloxy)methyl)-3α-iodo-1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-2β-((*tert*-butyldimethylsilyl)oxy)cyclopentane]iron (7a) and Tricarbonyl[1β-((benzoyloxy)methyl)-3α-iodo-1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-2β-hydroxycyclopentane]iron (7b). *tert*-Butyldimethylsilyl iodide, generated in situ by treatment of TBDMS-SePh (0.50 mL, 2.24 mmol) with iodine (284 mg, 1.12 mmol) in acetonitrile (2.7 mL) under argon atmosphere for 5 min, was added dropwise to a cooled (0 °C) solution of the epoxide **6** (269 mg, 0.56 mmol) in acetonitrile (2.7 mL) and benzene (1.6 mL) under argon atmosphere. The resulting mixture was stirred at 0 °C for 20 min and was diluted with 20 mL of saturated aqueous $NaHCO_3$ solution. The products were extracted with ether (3 × 50 mL), and the extract was washed with 30 mL of brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the resulting residue on silica gel with 5% → 30% ethyl acetate in hexane afforded the pure iodo silyl ether **7a** (brown yellow gum, 234 mg, 0.32 mmol, 58%): IR ν_{max} (CCl_4) 2045 and 1975 [$Fe(CO)_3$], 1725, 1485, 1425, 1270, 1235, 1115, 1100, 1075, 625 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 7.98 (2 H, d, J = 6.9 Hz, ortho-H), 7.58 (1 H, t, J = 6.9 Hz, para-H), 7.46 (2 H, t, J = 6.9 Hz, meta-H), 5.08 (1 H, d, J = 6.6 Hz, 3-H), 4.53 (1 H, d, J = 4.5 Hz, C*H*OTBDMS), 4.49 and 4.34 (1 H each, ABq, J_{AB} = 12.4 Hz, CH_2OBz), 4.13 (1 H, m, C*H*I), 3.67 (3 H, s, OCH_3), 3.34 (1 H, m, 5-H), 2.51 (1 H, d, J = 6.6 Hz, 2-H), 2.46–1.67 (5 H, m, 4′-H, 5′-H and endo-6-H), 1.59 (1 H, dd, J = 15.5, 3.4 Hz, exo-6-H), 1.19 (3 H, s, CH_3), 0.84 (9 H, s, *t*-BuSi), 0.23 (3 H, s, CH_3Si), 0.15 (3 H, s, CH_3Si); MS, m/e (rel intensity) 722 (M^+, 0.58), 694 (5.78), 638 (98.18), 538 (6.56), 525 (16.82), 510 (25.58), 399 (100.00); mol wt 722.0849 (calcd for $C_{30}H_{39}O_7IFeSi$ 722.0859). Also isolated was the pure iodohydrin **7b** (yellowish brown gum, 130 mg, 0.20 mmol, 35%): IR ν_{max} (CCl_4) 3600, 3500 (br), 2045, 1975, 1725, 1485, 1270, 1235, 1115, 1100, 1070, 715, 625 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 7.95 (2 H, d, $J_{o,m}$ = 7.5 Hz, ortho-H), 7.58 (1 H, t, $J_{p,m}$ = 7.5 Hz, para-H), 7.47 (2 H, t, $J_{m,o,\text{and}\,p}$ = 7.5 Hz, meta-H), 5.12 (1 H, br d, $J_{3,2}$ = 6.3 Hz, 3-H), 4.52 and 4.42 (1 H each, ABq, J_{AB} = 11.2 Hz, CH_2OBz), 4.18 (2 H, 2′- and 3′-H, obscured), 3.69 (3 H, s, OCH_3), 3.31 (1 H, m, 5-H), 2.44 (1 H, d, $J_{2,3}$ = 6.3 Hz, 2-H), 2.37–1.52 (6 H, 3 × CH_2), 1.20 (3 H, s, CH_3); MS, m/e (rel intensity) 608 (1.03), 580 (11.18), 524 (100.00), 522 (6.38), 396 (34.81), 300 (9.85); mol wt 607.9979 (calcd for $C_{24}H_{25}O_7FeI$ 607.9994).

Tricarbonyl[1β-((benzoyloxy)methyl)-1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-2β-((*tert*-butyldimethylsilyl)oxy)cyclopent-3-ene]iron (8). DBU (0.03 mL, 0.22 mmol) was added dorpwise to a stirred solution of iodo silyl ether **7a** (112 mg, 0.15 mmol) in THF (3.4 mL) under argon atmosphere. After having been refluxed for 48 h, the reaction mixture was diluted with ether (150 mL) and washed with 10% HCl (25 mL),

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distilled water (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the crude mixture on the silica gel with 20% ethyl acetate in hexane afforded the pure allylic silyl ether complex **8** (pale yellow gum like liquid) (89 mg, 0.15 mmol, 96%): IR ν_{max} (CCl_4) 2045, 1975, 1725, 1485, 1425, 1270, 1233, 1115, 1100, 1075, 915, 715, 625 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 8.0 (2 H, d, J = 7 Hz, ArH), 7.54 (1 H, t, J = 7 Hz, ArH), 7.44 (2 H, t, J = 7 Hz, ArH), 5.82 (1 H, dd, J = 5.9, 1.5 Hz, 4'-H), 5.63 (1 H, dd, J = 5.9, 1.9 Hz, 3'-H), 5.01 (1 H, br d, J = 5 Hz, 3-H), 4.73 (1 H, br m, C*H*-OTBDMS), 4.63 (1 H, br d, J = 11 Hz, CH_2OBz), 4.42 (1 H, d, J = 11 Hz, CH_2OBz), 3.62 (3 H, s, OCH_3), 3.26 (1 H, m, 5-H), 2.57 (1 H, m, endo-6-H), 2.34 (1 H, br d, J = 16 Hz, 5'-H), 2.15 (1 H, br d, J = 16 Hz, 5'-H), 1.58 (1 H, dd, J = 15, 3.2 Hz, exo-6-H), 1.20 (3 H, s, CH_3), 0.81 (9 H, s, *t*-BuSi), 0.07 (3 H, s, CH_3Si), 0.02 (3 H, s, CH_3Si); MS, m/e (rel intensity) 510 (M^+ - 3CO, 42.66), 453 (2.86), 309 (27.88), 179 (37.10), 122 (100.00), 79 (85.15); mol wt (M^+ - 3CO) 510.1887 (calcd for $C_{27}H_{38}O_4FeSi$ 510.1892). The same compound was also obtained, along with starting epoxide **6**, from which it was easily separated and the latter recycled, by treatment of the mixture of **7a** and **7b** with DBU in an identical fashion. In fact, this is the most appropriate practical means of manipulating these intermediates.

1β-((Benzoyloxy)methyl)-1-(1-methyl-4-oxocyclohex-2-enyl)-2β-((*tert*-butyldimethylsilyl)oxy)cyclopent-3-ene (21). The compound **8** (37 mg, 0.06 mmol) was converted into compound **21** by using the same procedure as in the preparation of **11** from **10**. Separation of the resulting crude mixture by preparative TLC (0.5 mm, 20 × 20 cm silica gel, 7:3 hexane/EtOAc) afforded a pure pale yellow sticky liquid, enone **21** (26 mg, 0.06 mmol, 95%): IR ν_{max} ($CHCl_3$) 1715, 1680, 1465, 1450, 1275, 1125, 1090, 1075, 930, 865, 840 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 6.86 (1 H, dd, $J_{2,3}$ = 10.4 Hz, $J_{2,6}$ = 2.1 Hz, 2-H), 5.99 (1 H, d, $J_{3,2}$ = 10.4 Hz, 3-H), 5.88 (1 H, m, 9-H), 5.68 (1 H, m, 10-H), 4.93 (1 H, br s, 8-H), 4.60 and 4.47 (1 H each, ABq, J_{AB} = 11.6 Hz, C*H*$_2$OBz), 2.68–1.94 (6 H, m, two each of 5,6, 11-H), 1.36 (3 H, s, 1-CH_3), 0.81 (9 H, s, *t*-BuSi), 0.03 (6 H, s, two CH_3Si); MS, m/e (rel intensity) 383 (M^+ - C_4H_9, 0.24), 261 (8.79), 109 (6.73), 105 (100.00), 79 (14.03), 77 (37.36), 57 (8.09); mol wt (M^+ - C_4H_9) 383.1683 (calcd for $C_{22}H_{27}O_4Si$ 383.1670).

Tricarbonyl[1β-((benzoyloxy)methyl)-3α,4α-dihydroxy-1-(2-5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-2β-((*tert*-butyldimethylsilyl)oxy)cyclopentane]iron (9). OsO_4 (0.13 g, 0.52 mmol) in pyridine (1.33 mL) was added to a solution of allylic silyl ether complex **8** (285 mg, 0.48 mmol) in pyridine (5.6 mL) at room temperature under argon atmosphere while stirring, and the mixture was allowed to stand 24 h. Water (7.7 mL) and a large excess of sodium metabisulfite (720 mg) were added, and the mixture was stirred for 24 h. Then, the product was extracted with ether (3 × 50 mL), and the combined extracts were washed with water (2 × 25 mL), 10% HCl (3 × 25 mL), water (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL), dried ($MgSO_4$), and concentrated. The crude product was flash chromatographed on silica gel with 30% ethyl acetate in hexane to give diol silyl ether complex **9** as a pale yellow foam (268 mg, 0.43 mmol, 89%): IR ν_{max} (CCl_4) 3630, 3560 (br), 2045, 1975, 1725, 1485, 1425, 1270, 1230, 1100, 1070, 910, 860, 715, 625 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 7.97 (2 H, d, J = 7 Hz, ortho-H), 7.58 (1 H, t, J = 7 Hz, para-H), 7.45 (2 H, t, J = 7 Hz, meta-H), 5.05 (1 H, dd, J = 6.5, 2.3 Hz, 3-H), 4.57 and 4.33 (1 H each, ABq, J_{AB} = 11 Hz, C*H*$_2$OCOPh), 4.21–4.05 (3 H, m, 2'-H, 3'-H, and 4'-H), 3.64 (3 H, s, OCH_3), 3.31 (1 H, m, 5-H), 2.52 (1 H, d, J = 6.5 Hz, 2-H), 2.32 (1 H, d, J = 6.1 Hz, OH), 2.23 (1 H, d, J = 15.3 Hz, endo-6-H, obscured), 2.20 (1 H, d, J = 3.5 Hz, OH), 2.06 (1 H, dd, J = 15.1, 6.5 Hz, 5'-H), 1.64 (1 H, dd, J = 15.1, 3.6 Hz, 5'-H), 1.50 (1 H, dd, J = 15.3, 3.3 Hz, exo-6-H), 1.56 (3 H, s, CH_3), 0.84 (9 H, s, *t*-BuSi), 0.12 (3 H, s, CH_3Si), 0.11 (3 H, s, CH_3Si); MS, m/e (rel intensity) 628 (M^+, 1.03), 600 (24.78), 544 (100.00), 526 (12.31); mol wt 628.1792 (calcd for $C_{30}H_{40}O_9FeSi$ 628.1791).

Tricarbonyl[3α,4α-diacetoxy-1β-((benzoyloxy)methyl)-1-(2-5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-2β-((*tert*-butyldimethylsilyl)oxy)cyclopentane]iron (10). To a stirred solution of diol silyl ether complex **9** (629 mg, 1.18 mmol) in pyridine (18 mL) was added acetic anhydride (0.67 mL, 7.08 mmol) at room temperature under argon atmosphere. Stirring was continued for 17 h, and water (5 mL) was added to the reaction mixture. After stirring for 30 min, it was diluted with ether (300 mL) and then washed with 10% HCl (3 × 40 mL), water (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (40 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the resulting residue on silica gel with 20% ethyl acetate in hexane afforded the desired diacetoxy silyl ether complex **10** (pale yellow foam). Recrystallization from ether/pentane provided pale yellow crystalline solid (791 mg, 1.18 mmol, quantitative): mp 105–106.5 °C; IR ν_{max} (CCl_4) 2045, 1975, 1750, 1725, 1490, 1370, 1270, 1240, 1115, 1070, 710, 625 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 8.04 (2 H, d, J = 7 Hz, ortho-H), 7.58 (1 H, t, J = 7 Hz, para-H), 7.47 (2 H, t, J = 7 Hz, meta-H), 5.39 (1 H, br t, J = 6 Hz, 10-H), 5.23 (1 H, dd, J = 8,6 Hz, 9-H), 5.05 (1 H, dd, J = 6.5, 2.1 Hz, 3-H), 4.63 (1 H, d, J = 11 Hz, CH_2OCOPh), 4.37 (1 H, br m, C*H*OTBDMS), 4.22 (1 H, br d, J = 11 Hz, CH_2OBz), 3.66 (3 H, s, OCH_3), 3.29 (1 H, m, 5-H), 2.46 (1 H, d, J = 6.5 Hz, 2-H), 2.24 (1 H, dd, J = 15, 7.2 Hz, 11-H), 2.06 (3 H, s, OAc), 2.05 (3 H, s, OAC), 2.06 (1 H, dd, obscured, endo-6-H), 1.72 (1 H, d, J = 15 Hz, 11-H), 1.53 (1 H, dd, obscured, exo-6-H), 1.22 (3 H, s, CH_3), 0.79 (9 H, s, *t*-BuSi), 0.12 (3 H, s, CH_3Si), –0.06 (3 H, s, CH_3Si). Anal. Calcd for $C_{34}H_{44}O_{11}FeSi$: C, 57.30; H, 6.22. Found: C, 57.61; H, 6.39.

3α,4α-Diacetoxy-1β-((benzoyloxy)methyl)-1-(4-methoxy-1-methylcyclohexa-2,3-dienyl)-2β-((*tert*-butyldimethylsilyl)oxy)cyclopentane and 3α,4α-Diacetoxy-1β-((benzoyloxy)methyl)-1-(1-methyl-4-oxocyclohex-2-enyl)-2β-((*tert*-butyldimethylsilyl)oxy)cyclopentane (11). Anhydrous trimethylamine oxide (1.50 g, 20.06 mmol) was added to a stirred solution of diacetoxy silyl ether complex **10** (715 mg, 1.00 mmol) in benzene (18 mL) at room temperature under argon. The resulting mixture was stirred at 50 °C for 19 h and cooled to room temperature. The reaction mixture was filtered through Celite and washed through with ether (350 mL). The filtrate was washed with water (40 mL) and brine (40 mL), dried ($MgSO_4$), and concentrated to give the desired dienol ether (pale yellow foam) (522 mg, 0.98 mmol, 98%): IR ν_{max} (CCl_4) 1750, 1725, 1660, 1370, 1270, 1245, 1225, 910, 840, 715 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 8.07 (2 H, d, J = 7 Hz, ortho-H), 7.56 (1 H, t, J = 7 Hz, para-H), 7.47 (2 H, t, J = 7 Hz, meta-H), 5.91 (1 H, d, J = 10.4 Hz, 2-H), 5.72 (1 H, dd, J = 10.4, 2.2 Hz, 3-H), 5.43 (1 H, td, J = 6, 3 Hz, 4'-H), 5.34 (1 H, dd, J = 8, 6 Hz, 3'-H), 4.66 (1 H, d, J = 8 Hz, C*H*OTBDMS), 4.62 and 4.36 (1 H each, ABq, J_{AB} = 11 Hz, C*H*$_2$OCOPh), 4.47 (1 H, m, 5-H), 3.55 (3 H, s, OCH_3), 2.80 (1 H, dd, J = 16, 3 Hz, 6-H), 2.37 (1 H, dd, J = 15.7, 6.8 Hz, 6-H), 1.06 (1 H, dd, obscured, 5'-H), 2.09 (3 H, s, OAc), 2.06 (3 H, s, OAc), 1.94 (1 H, dd, J = 15.8, 2.6 Hz, 5'-H), 1.12 (3 H, s, CH_3), 0.80 (9 H, s, *t*-BuSi), 0.09 (3 H, s, CH_3Si), –0.02 (3 H, s, CH_3Si).

To a stirred solution of the crude dienol ether (522 mg, 0.98 mmol) in methanol (13 mL) was added a solution of oxalic acid (529 mg, 5.88 mmol) in distilled water (3 mL) at room temperature under argon. The resulting mixture was stirred for 1 h and quenched with saturated aqueous $NaHCO_3$ (100 mL). The product was extracted with ether (3 × 100 mL), and the ether extract was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was flash chromatographed on silica gel with 50% ethyl acetate in hexane to give pure enone **11** (pale yellow foam) (530 mg, 0.95 mmol, 97%): IR ν_{max} (CCl_4) 1755, 1725, 1690, 1370, 1270, 1240, 1110, 1095, 1070, 860, 840, 715 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 8.04 (2 H, d, J = 7.1 Hz, ortho-H), 7.58 (1 H, t, J = 7.1 Hz, para-H), 7.47 (2 H, t, J = 7.1 Hz, meta-H), 7.07 (1 H, dd, J = 10.6, 2.1 Hz, 2-H), 6.02 (1 H, d, J = 10.6 Hz, 3-H), 5.43 (1 H, td, J = 5.8, 3Hz, 4'-H), 4.64 and 4.38 (1 H each, ABq, J_{AB} = 11 Hz, CH_2OBz), 4.43 (1 H, d, J = 8.4 Hz, 2'-H), 2.57–1.82 (6 H, m, two each of 5-, 6-, 5'-H), 2.08 (3 H, s, OAc), 2.04 (3 H, s, OAc), 1.29 (3 H, s, CH_3), 0.78 (9 H, s, *t*-BuSi), 0.05 (3 H, s, CH_3Si), –0.05 (3 H, s, CH_3Si); MS, m/e (rel intensity) 501 (M^+ - C_4H_9, 3.98), 379 (1.99), 337 (4.08), 179 (55.16), 105 (100.00); mol wt (M^+ - C_4H_9) 501.1937 (calcd for $C_{26}H_{33}O_8Si$ 501.1956).

14-((Benzoyloxy)methyl)-12β-((*tert*-butyldimethylsilyl)oxy)-3α-hydroxy-9-oxo-13,16-bisnortrichothecene (12). To a stirred solution of diacetoxy enone **11** (530 mg, 0.95 mmol) in methanol (12 mL) was added potassium carbonate (656 mg, 4.75 mmol) in water (3 mL) at room temperature under argon atmosphere. After stirring for 2 h, the resulting mixture was diluted with 350 mL of ether and washed with distilled water (30 mL),

10% HCl (2 × 30 mL), water (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on silica gel with 50% ethyl acetate in hexane afforded the desired tricyclic hydroxy ketone **12** (pale yellow foam). Recrystallization from ether/pentane provided a pure white crystalline solid (397 mg, 0.84 mmol, 88%): mp 118–119 °C; IR ν_{max} ($CHCl_3$) 3600, 3420 (br), 1715, 1460, 1275, 1095 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 8.00 (2 H, d, $J_{o,m}$ = 7 Hz, ortho-H), 7.59 (1 H, t, $J_{p,m}$ = 7 Hz, para-H), 7.46 (2 H, t, $J_{m,o}$ = $J_{m,p}$ = 7 Hz, meta-H), 4.64 (1 H, m, 3-H), 4.52 and 4.36 (1 H each, ABq, J_{AB} = 12 Hz, CH_2OBz), 4.49 (1 H, d, $J_{12,2}$ = 1.3 Hz, 12-H, obscured), 4.39 (1 H, m, 11-H, obscured), 3.98 (1 H, dd, $J_{2,3}$ = 5.3 Hz, $J_{2,12}$ = 1.3 Hz, 2-H), 2.66 (1 H, dd, J_{gem} = 16 Hz, $J_{10,11}$ = 4.5 Hz, 10-H), 2.63–2.04 (6 H, m, one each of 10-, 4-H and two each of 8-, 7-H), 1.98 (1 H, d, $J_{OH,3}$ = 4.2 Hz, OH), 1.80 (1 H, dd, J_{gem} = 14 Hz, $J_{4,3}$ = 2.6 Hz, 4-H), 1.25 (3 H, s, CH_3), 0.81 (9 H, s, *t*-BuSi), 0.05 (3 H, s, CH_3Si), –0.05 (3 H, s, CH_3Si); MS, *m/e* (rel intensity) 417 (0.61), 399 (0.20), 295 (13.75), 277 (4.89), 265 (1.08), 235 (0.94), 187 (3.08), 179 (100.00), 169 (13.44), 105 (17.54); mol wt ($M^+ - C_4H_9$) 417.1741 (calcd for $C_{22}H_{29}O_6Si$ 417.1723). Anal. Calcd for $C_{26}H_{38}O_6Si+{}^1/_2H_2O$: C, 64.56; H, 8.13. Found: C, 64.78; H, 7.90.

12β-((*tert*-Butyldimethylsilyl)oxy)-3α,9,14-trihydroxy-13-nortrichothecane. To a stirred solution of tricyclic hydroxy ketone **12** (300 mg, 0.63 mmol) in THF (12 mL) at –78 °C under argon was added dropwise MeMgBr (3.2 M in ether) (1.98 mL, 6.32 mmol). The reaction temperature was raised to 0 °C, and stirring was continued for 4 h. Then water (3 mL) was added dropwise to the reaction mixture to destroy the excess MeMgBr while stirring. The resulting mixture was diluted with 300 mL of ether, washed with water (3 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was flash chromatographed to give a pure tertiary alcohol. Recrystallization from ether/pentane provided a pure white crystalline solid (240 mg, 0.62 mmol, 98%): mp 154–155 °C; IR ν_{max} ($CHCl_3$) 3600, 3500 (br), 1465, 1405, 1390, 1085, 1060, 1045, 843 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 4.61 (1 H, m, 3-H), 4.58 (1 H, br s, 12-H), 4.03 (1 H, br s, 11-H), 3.90 (1 H, dd, J_{gem} = 11.4 Hz, $J_{14\text{-}OH}$ = 2.6 Hz, 14-H), 3.87 (1 H, 2-H, obscured), 3.67 (1 H, dd, J_{gem} = 11.4 Hz, $J_{14\text{-}OH}$ = 8.7 Hz, 14-H, became ABq after D_2O shake), 2.54 (1 H, dd, J_{gem} = 14.5 Hz, $J_{4,3}$ = 10.8 Hz, 4-H), 2.46 (1 H, dd, $J_{OH,14}$ = 8.7 Hz, $J_{OH,14}$ = 2.6 Hz, 1°-OH, exchange D_2O), 2.33–1.18 (7 H, one of 4-H and two each of 7-, 8-, 10-H), 1.97 (1 H, d, $J_{OH,3}$ = 4.7 Hz, 2°-OH, exchange D_2O), 1.16 (3 H, s, 9-CH_3), 0.94 (3 H, s, 6-CH_3), 0.89 (9 H, s, *t*-BuSi), 0.15 (3 H, s, CH_3Si), 0.12 (3 H, s, CH_3Si); MS, *m/e* (rel intensity) 293 (7.63), 219 (14.18), 187 (11.04), 169 (15.89), 159 (17.00), 121 (14.15), 107 (31.89), 75 (100.00); mol wt ($M^+ - 2H_2O\text{-}C_4H_9$) 293.1570 (calcd for $C_{16}H_{25}O_3Si$ 293.1580). Anal. Calcd for $C_{20}H_{38}O_5Si$: C, 62.14; H, 9.91. Found: C, 62.39; H, 9.92.

3α,14-Diacetoxy-12β-((*tert*-butyldimethylsilyl)oxy)-9-hydroxy-13-nortrichothecane (13). Acetic anhydride (0.74 mL, 7.89 mmol) was added to a stirred solution of 12β-((*tert*-butyldimethylsilyl)oxy)-3α,9,14-trihydroxy-13-nortrichothecane (305 mg, 0.79 mmol from the above preparation) in pyridine (6 mL) at 0 °C under argon atmosphere. After having been stirred for 17 h, the reaction mixture was treated with water (1 mL) and stirred for another 30 min. The resulting mixture was diluted with 300 mL of ether, washed with 10% HCl (3 × 25 mL), water (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL), and dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography of the crude product on silica gel with 50% ethyl acetate in hexane afforded the desired diacetoxy alcohol **13**. Recrystallization from ether/pentane yielded a pure white crystalline solid (316 mg, 0.67 mmol, 85%): mp 126–128 °C; IR ν_{max} ($CHCl_3$) 3600, 3500 (br), 1730, 1465, 1110, 1075, 915, 858, 845 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 5.27 (1 H, m, 3-H), 4.50 (1 H, br s, 12-H), 4.32 (1 H, ABq, J_{AB} = 11.6 Hz, CH_2OAc), 4.20 (1 H, br d, $J_{2,3}$ = 4.2 Hz, 2-H), 4.07 (1 H, ABq, J_{AB} = 11.6 Hz, CH_2OAc), 3.87 (1 H, br s, 11-H), 2.36–1.25 (8 H, two each of 4-, 7-, 8-, 10-H), 2.10 (3 H, s, OAc), 2.09 (3 H, s, OAc), 1.17 (3 H, s, 9-CH_3), 0.95 (3 H, s, 6-CH_3), 0.87 (9 H, s, *t*-BuSi), 0.11 (3 H, s, CH_3Si), 0.06 (3 H, s, CH_3Si). Anal. Calcd for $C_{24}H_{42}O_7Si$: C, 61.24; H, 8.99. Found: C, 60.83; H, 8.68.

3α,14-Diacetoxy-12β-((*tert*-butyldimethylsilyl)oxy)-13-nortrichothec-9-ene (14a). To a stirred solution of the diacetoxy alcohol **13** (200 mg, 0.42 mmol) in pyridine (5.5 mL) at 0 °C under argon was added phosphorus oxychloride (0.79 mL, 8.50 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 16 h. The resulting mixture was diluted with 250 mL of ether, washed with 10% HCl (3 × 25 mL), water (25 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL), dried ($MgSO_4$), and concentrated. Residue was flash chromatographed to give a mixture of the desired alkene **14a** and a double bond isomer **20** (3:1 ratio) (117 mg, 0.26 mmol, 61%). Recrystallization from ether/pentane afforded a white crystalline solid: mp 80–81 °C; IR ν_{max} ($CHCl_3$) 1730, 1465, 1380, 1370, 1110, 1075, 915, 875, 845 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 5.40 (1 H, dd, $J_{10,11}$ = 5.5 Hz, $J_{10,8}$ = 1.1 Hz, 10-H), 5.26 (1 H, dt, $J_{3,4\beta}$ = 11.0 Hz, $J_{3,4\alpha}$ = $J_{3,2}$ = 4.2 Hz, 3-H), 4.37 (1 H, br s, 12-H), 4.26 (1 H, ABq, J_{AB} = 11.4 Hz, CH_2OAc), 4.15 (1 H, 2-H, obscured), 4.11 (1 H, ABq, J_{AB} = 11.4 Hz, CH_2OAc), 3.83 (1 H, br d, $J_{11,10}$ = 5.5 Hz, 11-H), 2.18–1.06 (6 H two each of 4-, 7-, and 8-H), 2.12 (3 H, s, OAc), 2.05 (3 H, s, OAc), 1.70 (3 H, br s, 9-CH_3), 0.85 (9 H, s, *t*-BuSi), 0.85 (3 H, s, 6-CH_3, obscured), 0.07 (3 H, s, CH_3Si), 0.03 (3 H, s, CH_3Si); MS, *m/e* (rel intensity) 395 (13.93), 335 (3.18), 275 (19.54), 261 (8.32), 227 (8.28), 201 (31.89), 117 (100.00), 108 (11.50), 93 (10.41), 79 (2.81), 57 (4.30); mol wt ($M^+ - C_4H_9$) 395.1866 (calcd for $C_{20}H_{31}O_6Si$ 395.1925).

3α,14-Diacetoxy-12β-hydroxy-13-nortrichothec-9-ene (14b). Tetra *n*-butylammonium fluoride (1 M solution in tetrahydrofuran) (0.29 mL, 0.29 mmol) was added dropwise to a stirred solution of diacetoxy silyl ether (a mixture of double bond isomers, **14a** and **20**) (88 mg, 0.19 mmol) in THF (2 mL) at room temperature under nitrogen atmosphere. After having been stirred for 2 h, the reaction mixture was diluted with ether (40 mL) and washed with water (2 × 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated to give a pale yellow crude product, 66 mg (0.19 mmol, quantitative). For the purpose of characterization, a small amount of the crude product was separated by HPLC with 50% ethyl acetate in hexane to yield a pure desired hydroxy alkene **14b** (pale yellow gum): IR ν_{max} ($CHCl_3$) 3450 (br), 1730, 1460, 1070, 915 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 5.41 (1 H, br d, $J_{10,11}$ = 5.2 Hz, 10-H), 5.33 (1 H, dt, $J_{3,4\beta}$ = 11.0 Hz, $J_{3,4\alpha}$ = $J_{3,2}$ = 4.0 Hz, 3-H), 4.48 (1 H, ABq, J_{AB} = 12.2 Hz, CH_2OAc), 4.28 (1 H, s, 12-H), 4.27 (1 H, d, $J_{2,3}$ = 4.0 Hz, 2-H), 4.07 (1 H, ABq, J_{AB} = 12.2 Hz, CH_2OAc), 3.84 (1 H, br d, $J_{11,10}$ = 5.2 Hz, 11-H), 3.07 (1 H, br s, 2°-OH), 2.17–1.25 (6 H, 3 × CH_2), 2.12 (3 H, s, OAc), 2.11 (3 H, s, OAc), 1.70 (3 H, br s, 9-CH_3), 0.93 (3 H, s, 6-CH_3); MS, *m/e* (rel intensity) 338 (M^+, 4.63), 323 (18.96), 295 (5.97), 124 (100.00), 108 (51.06), 95 (10.40), 93 (46.00), 84 (16.00), 79 (15.05), 67 (12.50); mol wt 338.1727 (calcd for $C_{18}H_{26}O_6$ 338.1733). The corresponding 8,9-double bond isomer hydroxy alkene was also obtained pure: ^1H NMR δ ($CDCl_3$, 200 MHz) 5.33 (1 H, m, 3-H, obscured), 5.29 (1 H, d, 8-H, obscured), 4.52 (1 H, ABq, J_{AB} = 12.3 Hz, CH_2OAc), 4.27 (1 H, br d, $J_{11,10}$ = 4.6 Hz, 11-H), 4.18 (1 H, br s, 12-H), 4.02 (1 H, ABq, J_{AB} = 12.3 Hz, CH_2OAc), 3.87 (1 H, br d, $J_{2,3}$ = 4.4 Hz, 2-H), 3.27 (1 H, d, $J_{OH,12}$ = 2.9 Hz, OH), 2.48–1.08 (6 H, 3 × CH_2), 2.11 (6 H, s, 2 × OAc), 1.65 (1 H, br s, 9-CH_3), 0.95 (3 H, s, 6-CH_3).

3α,14-Diacetoxy-13-nortrichothec-9-en-12-one (15). To a stirred solution of pyridine (0.3 mL, 3.72 mmol) in dichloromethane (4.6 mL) at room temperature under argon was added chromium trioxide (186 mg, 1.86 mmol) in small portions, and the mixture was stirred for 30 min. The hydroxy alkene, as the crude product from the previous reaction [a mixture (3:1) of **14b** and the corresponding 8,9-double bond isomer] (63 mg, 0.18 mmol), was added to the Collins reagent at room temperature. The resulting mixture was stirred for 1 h, then diluted with ether (15 mL), and filtered through a silica gel column (2 × 5 cm), and the column was washed through with ether (80 mL). The ether eluent was washed with 10% HCl (10 mL), water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on the silica gel with 40% ethyl acetate in hexane afforded diacetoxy ketone as a 3:1 mixture of desired compound **15** and undesired 8,9-double bond isomer (41.7 mg, 0.12 mmol, 67% for two steps from diacetoxysilyl ether **14a** and its double bond isomer). Recrystallization from 30% ether in pentane provided a pure white crystalline solid: mp 110–111 °C; IR ν_{max} ($CHCl_3$) 1760, 1740, 1380, 1050 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 5.43 (1 H, dd, $J_{10,11}$ = 5.4 Hz, $J_{10,8}$ = 1.5 Hz, 10-H), 5.12 (1 H, dt, $J_{3,4\beta}$

= 11 Hz, $J_{3,4\alpha} = J_{3,2}$ = 5.0 Hz, 3-H), 4.39 (1 H, ABq, J_{AB} = 11.4 Hz, CH_2OAc), 4.24 (1 H, br d, $J_{11,10}$ = 5.4 Hz, 11-H), 4.02 (1 H, ABq, J_{AB} = 11.4 Hz, CH_2OAc), 3.92 (1 H, d, $J_{2,3}$ = 5 Hz, 2 H), 2.62 (1 H, dd, J_{gem} = 15 Hz, $J_{4\beta,3}$ = 11-Hz, 4β-H), 2.22 (1 H, dd, J_{gem} = 15 Hz, $J_{4\alpha,3}$ = 5 Hz, 4α-H), 2.18 (3 H, s, OAc), 2.02 (3 H, s, OAc), 1.71 (3 H, br s, 9-CH_3), 2.20–1.54 (4 H, two each of 7-, 8-H), 0.93 (3 H, s, 6-CH_3); MS, *m/e* (rel intensity) 336 (M^+, 0.27), 277 (18.02), 234 (9.76), 217 (11.95), 216 (10.02), 173 (21.71), 124 (21.09), 108 (100.00), 93 (16.23); mol wt 336.1577 (calcd for $C_{18}H_{24}O_6$ 336.1564).

3α,14-Diacetoxytrichotheca-9,12-diene (16). A solution of freshly sublimed potassium *tert*-butoxide in *tert*-butyl alcohol (0.08 mL, 0.78 N, 0.06 mmol) was added to a stirred suspension of triphenylmethylphosphonium bromide (22 mg, 0.06 mmol) in ether (0.8 mL), and the mixture was stirred under gentle reflux in nitrogen atmosphere for 1 h and then cooled to room temperature. A solution of diacetoxy ketones (3:1 ratio of **15** and 8,9-double bond isomer) (4 mg, 0.01 mmol) in ether (0.3 mL) was added, and stirring was continued for 2 h under gentle reflux. Then, the mixture was cooled to room temperature, poured into water (10 mL), and extracted with ethyl acetate (3 × 10 mL). The extract was washed with brine, dried ($MgSO_4$), and concentrated to afford a crude product (20 mg). The crude product mixture was reacetylated (Ac_2O, pyridine, 0 °C, 16 h) to give a mixture of diacetoxy alkene and starting material. This reaction procedure was repeated 2 more times with 5 and 3 mg of ketone. The crude products for these 3 runs were combined and separated by preparative HPLC with 50% ethyl acetate in hexane to afford the starting ketone (4 mg, 0.012 mmol, 33%), the desired diacetoxy alkenes (pale yellow sticky liquid) **16** and 8,9-double bond isomer (3:1 ratio) (2.5 mg, 0.007 mmol, 31%, based on the recovered starting material): IR ν_{max} ($CHCl_3$) 1730, 1680, 1380, 1080, 1050, 920 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 5.41 (1 H, dd, $J_{10,11}$ = 5.2 Hz, $J_{10,8}$ = 1.2 Hz, 10-H), 5.15 (1 H, s, 13-H), 4.94 (1 H, dt, $J_{3,4\beta}$ = 11.2 Hz, $J_{3,4\alpha} = J_{3,2}$ = 4.7 Hz, 3-H), 4.71 (1 H, s, 13-H), 4.31 (1 H, d, $J_{2,3}$ = 4.7 Hz, 2-H), 4.26 (1 H, ABq, J_{AB} = 11.7 Hz, CH_2OAc), 4.18 (1 H, ABq, J_{AB} = 11.7 Hz, CH_2OAc), 3.98 (1 H, br d, $J_{11,10}$ = 5.2 Hz, 11-H), 2.38 (1 H, dd, J_{gem} = 14.4 Hz, $J_{4\beta,3}$ = 11.2 Hz, 4β-H), 2.14 (3 H, s, OAc), 2.05 (3 H, s, OAc), 1.70 (3 H, br s, 9-CH_3), 2.29–1.13 (5 H, 4α-H and two each of 7-, 8-H), 0.88 (3 H, s, 6-CH_3); MS, *m/e* (rel intensity) 201 (3.90), 171 (1.32), 124 (3.24), 108 (100.00), 95 (6.59), 93 (27.63), 79 (9.62); mol wt (M^+ – $CH_3$2Ac) 201.1277 (calcd for $C_{14}H_{17}O$ 201.1290).

3α,14-Dihydroxytrichotheca-9,12-diene (17). The same procedure in the preparation of compound **12** was used to transform diacetates (3:1 ratio of **16** and 8,9-double bond isomer; 3 mg, 0.009 mmol) to diols (3:1 ratio of **17** and 8,9-double bond isomer; 2 mg, 0.008 mmol, 90%). The mixture was easily separated by HPLC with 70% ethyl acetate in hexane to afford the desired diol **17** (white crystalline solid): mp 141–143 °C (recrystallized from 50% ether in pentane): IR ν_{max} ($CHCl_3$) 3600, 3440 (br), 1680, 1380, 1100, 1040, 920 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 5.43 (1 H, dd, $J_{10,11}$ = 5.4 Hz, $J_{10,8}$ = 1.3 Hz, 10-H), 5.23 (1 H, s, 13-H), 4.76 (1 H, s, 13-H), 4.18 (1 H, dt, $J_{3,4\beta}$ = 10.8 Hz, $J_{3,4\alpha} = J_{3,2}$ = 4.5 Hz, 3-H), 4.10 (1 H, d, $J_{2,3}$ = 4.5 Hz, 2-H), 4.04 (1 H, br d, $J_{11,10}$ = 5.4 Hz, 11-H), 3.90 (1 H, ABq, J_{AB} = 11.4 Hz, 14-H), 3.64 (1 H, ABq, J_{AB} = 11.4 Hz, 14-H), 2.52 (1 H, dd, J_{gem} = 14.2 Hz, $J_{4\beta,3}$ = 10.8 Hz, 4β-H), 1.87 (1 H, dd, J_{gem} = 14.2 Hz, $J_{4\alpha,3}$ = 4.5 Hz, 4α-H), 1.70 (3 H, s, 9-CH_3), 2.05–1.25 (4 H, two each of 7-, 8-H), 0.85 (3 H, s, 6-CH_3); MS, found 219.1387 (M – CH_2OH), calcd for $C_{14}H_{19}O_2$ 219.1377. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.32; H, 9.25.

The corresponding 8,9-double bond isomer gave the following: IR ν_{max} ($CHCl_3$) 3595, 1600, 1455, 1380, 1095, 1030, 1020, 920 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 5.33 (1 H, m, 8-H), 5.23 (1 H, s, 13-H), 4.19 (1 H, m, 3-H, obscured), 4.16 (1 H, 11-H, obscured), 4.09 (1 H, d, $J_{2,3}$ = 4.3 Hz, 2-H), 3.84 (1 H, d, J_{gem} = 11.4 Hz, CH_2OH), 3.72 (1 H, br d, J_{gem} = 11.4 Hz, CH_2OH), 2.42 (1 H, dd, J_{gem} = 14.0 Hz, $J_{4\beta,3}$ = 10.8 Hz, 4β-H), 2.29–1.26 (4 H, two each of 7-, 10-H), 1.66 (3 H, br s, 9-CH_3), 0.90 (3 H, s, 6-CH_3).

3α,4α-Diacetoxy-1β-((benzoyloxy)methyl)-1-(1-methyl-4-hydroxy-4-methylcyclohex-2-enyl)-2β-((*tert*-butyldimethylsilyl)oxy)cyclopentane (22). Methylmagnesium bromide (3.2 M in ether) (3.9 mL, 12.5 mmol) was added dropwise to a stirred solution of diacetoxy enone **11** (874 mg, 1.60 mmol) in 25 mL of THF at –78 °C under argon atmosphere. After having been stirred for 2.5 h, the excess methylmagnesium bromide was destroyed by adding 1 mL of water dropwise to the mixture at –78 °C. The resulting mixture was warmed to room temperature, diluted with ether (200 mL), washed with water (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated to afford the tertiary alcohol **22** as a pale yellow sticky liquid (919 mg). An analytical sample was obtained by purification of a small sample by HPLC with 50% ethyl acetate in hexane: IR ν_{max} ($CHCl_3$) 3600, 3500 (br), 1740, 1720, 1605, 1465, 1450, 1375, 1120, 1070, 850, 840 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 8.05 (2 H, d, $J_{o,m}$ = 7.0 Hz, ortho-H), 7.58 (1 H, t, $J_{p,m}$ = 7.0 Hz, para-H), 7.48 (1 H, t, J = 7.0 Hz, meta-H), 5.66 and 5.60 (1 H each, d, J = 11.0 Hz, 2-, 3-H), 5.38 (1 H, m, 4′-H), 5.27 (1 H, dd, J = 8.0 Hz, 6.0 Hz, 3′-H), 4.64 (1 H, d, J_{gem} = 11.0 Hz, CH_2OBz), 4.51 (1 H, d, J = 8.0 Hz, 2′-H), 4.33 (1 H, d, J_{gem} = 11.0 Hz, CH_2OBz), 2.28 (1 H, dd, J_{gem} = 16.0 Hz, $J_{4',5'}$ = 7.0 Hz, 5′-H), 2.07 (3 H, s, OAc), 2.06 (3 H, s, OAc), 1.97–1.21 (5 H, two each of 5-, 6-H, one of 5′-H), 1.31 (3 H, s, 4-CH_3), 1.15 (3 H, s, 1-CH_3), 0.80 (9 H, s, Si-*t*-Bu), 0.14 (3 H, s, SiCH_3), –0.06 (3 H, s, $SiCH_3$); MS, *m/e* (rel intensity) 377 (2.02), 317 (3.36), 201 (10.34), 107 (80.73), 105 (100.00), 77 (21.57); mol wt (M^+ – $C_4H_9H_2OHOBz$) 377.1784 (calcd for $C_{20}H_{29}O_5Si$ 377.1781).

3α,4α-Dihydroxy-1β-((benzoyloxy)methyl)-1-(1-methyl-4-hydroxy-4-methylcyclohex-2-enyl)-2β-((*tert*-butyldimethylsilyl)oxy)cyclopentane (23). To a stirred solution of tertiary alcohol **22** (919 mg, 1.60 mmol) in 25 mL of MeOH–H_2O (3:1 ratio) at room temperature was added potassium carbonate (1.10 g, 8.0 mmol). After having been stirred for 2 h, the reaction mixture was diluted with 300 mL of ethyl acetate and washed with 10% HCl (2 × 20 mL), water (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (30 mL), dried ($MgSO_4$), and concentrated to give triol **23** (728 mg, 1.48 mmol). An analytical sample was obtained by recrystallization from ether/pentane to yield white crystalline solid **23**: mp 130–132 °C; IR ν_{max} ($CHCl_3$) 3600, 3540 (br), 1715, 1605, 1465, 1450, 1275, 1120, 865, 840 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 7.96 (2 H, d, $J_{o,m}$ = 7.0 Hz, ortho-H), 7.57 (1 H, t, $J_{p,m}$ = 7.0 Hz, para-H), 7.44 (2 H, t, $J_{m,p} = J_{m,o}$ = 7.0 Hz, meta-H), 5.78 and 5.60 (1 H each, d, $J_{3,2} = J_{2,3}$ = 10.3 Hz, 2-, 3-H), 4.62 and 4.35 (1 H each, ABq, J_{AB} = 11.0 Hz, CH_2OBz), 4.18–4.13 (3 H, 8-, 9-, 10-H, obscured), 2.18–1.24 (6 H, 3 × CH_2), 1.31 (3 H, s, 4-CH_3), 1.13 (3 H, s, 1-CH_3), 0.85 (9 H, s, Si-*t*-Bu), 0.13 (3 H, s, $SiCH_3$), 0.11 (3 H, s, SiCH_3); MS, *m/e* (rel intensity) 275 (6.89), 187 (10.37), 169 (46.91), 125 (23.91), 107 (95.85), 105 (100.00), 77 (32.74); mol wt (M^+ – C_4H_9 – 2H_2O – HOBz) 275.1478 (calcd for $C_{16}H_{23}O_2Si$ 275.1438).

14-(Benzoyloxy)-12β-((*tert*-butyldimethylsilyl)oxy)-3α-hydroxy-13-nortrichothec-9-ene (24). To a stirred solution of crude triol **23** (728 mg, 1.48 mmol) in dichloromethane (18 mL) at room temperature under argon atmosphere was added *p*-toluenesulfonic acid (28 mg, 0.15 mmol); stirring was continued for 2 h, and the reaction mixture was diluted with ether (300 mL), washed with distilled water (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was flash chromatographed on silica gel with 40% ethyl acetate in hexane to give a pure tricyclic hydroxy silyl ether **24** as a pale yellow foam (454 mg, 0.96 mmol, 61% overall yield for three steps from compound **11**): IR ν_{max} ($CHCl_3$) 3600, 1715, 1605, 1465, 1450, 1390, 1280, 1120, 1100, 915, 875, 845 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 8.01 (2 H, d, $J_{o,m}$ = 7.0 Hz, ortho-H), 7.58 (1 H, t, $J_{p,m}$ = 7.0 Hz, para-H), 7.45 (2 H, t, $J_{m,o} = J_{m,p}$ = 7.0 Hz, meta-H), 5.45 (1 H, br d, $J_{10,11}$ = 5.2 Hz, 10-H), 4.62 (1 H, m, 3-H), 4.49 (1 H, s, 12-H), 4.47 and 4.39 (1 H each, ABq, J_{AB} = 10.4 Hz, CH_2OBz), 4.00 (1 H, d, $J_{11,10}$ = 5.2 Hz, 11-H), 3.97 (1 H, d, $J_{2,3}$ = 4.2 Hz, 2-H), 2.17–1.54 (6 H, 3 × CH_2), 1.71 (3 H, s, 9-CH_3), 0.93 (3 H, s, 6-CH_3), 0.81 (9 H, s, Si-*t*-Bu), 0.03 (3 H, s, $SiCH_3$), –0.06 (3 H, s, $SiCH_3$); MS, *m/e* (rel intensity) 415 (0.50), 293 (6.42), 219 (26.05), 201 (8.98), 179 (98.79), 108 (17.83), 105 (100.00), 93 (22.06); mol wt (M^+ – C_4H_9) 415.1950 (calcd for $C_{23}H_{31}O_5Si$ 415.1926).

When this reaction was done at 0 °C for 0.5 h by using 3.4 mg of triol **23**, 0.1 equiv of *p*-toluenesulfonic acid and 0.4 mL of dichloromethane, the product obtained was a mixture of **24** and **25** (2:1 ratio). HPLC separation of the mixture afforded the pure compound **24** (fully characterized above) and the isomeric compound **25**: IR ν_{max} ($CHCl_3$) 3500 (br), 1715, 1605, 1465, 1450, 1390, 1315, 1275, 1100, 1070, 865, 840 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 8.00 (2 H, d, $J_{o,m}$ = 7.0 Hz, ortho-H), 7.58 (1 H, t, $J_{p,m}$ = 7.0 Hz,

para-H), 7.46 (2 H, t, $J_{m,p} = J_{m,o} = 7.0$ Hz, meta-H), 5.37 (1 H, br d, $J_{10,11} = 4.2$ Hz, 10-H), 4.56 and 4.34 (1 H each, ABq, $J_{AB} = 11.2$ Hz, CH_2OBz), 4.28 (1 H, br s, 4-H), 4.24 (1 H, m, 3-H, obscured), 3.78 (1 H, 2-H, obscured), 3.72 (1 H, d, $J_{11,10} = 4.2$ Hz, 11-H, obscured), 2.24–1.25 (6 H, 3 × CH_2), 1.72 (3 H, s, 9-CH_3), 0.93 (3 H, s, 6-CH_3), 0.78 (9 H, s, Si-*t*-Bu), 0.14 (3 H, s, $SiCH_3$), 0.10 (3 H, s, $SiCH_3$); MS, *m/e* (rel intensity) 415 (1.29), 293 (4.29), 219 (20.35), 201 (6.29), 179 (56.89), 108 (19.25), 105 (100.00), 93 (17.75); mol wt ($M^+ - C_4H_9$) 415.1951 (calcd for $C_{23}H_{31}O_5Si$ 415.1927). The NMR data for **25** are in agreement with data for compounds of the same stereochemistry reported by Koreeda,[13] thus supporting the structural assignment. The compound **25** was completely converted to compound **24** by treating with 0.1 equiv of *p*-toluenesulfonic acid in dichloromethane at room temperature for 2 h.

3α-Acetoxy-14-(benzoyloxy)-12β-((*tert*-butyldimethylsilyl)oxy)-13-nortrichothec-9-ene (26). Hydroxy silyl ether **24** (453 mg, 0.96 mmol) was acetylated by using the same procedure as for the preparation of compound **10** to give acetoxy silyl ether **26** as a pale yellow foam (416 mg, 0.81 mmol, 84%) which was used for the next step without purification. An analytical sample was obtained by HPLC with 30% ethyl acetate in hexane: IR ν_{max} ($CHCl_3$) 1735, 1715, 1605, 1465, 1455, 1380, 1280, 1110, 1080, 915, 880, 845 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 8.00 (2 H, d, $J_{o,m} = 7.0$ Hz, ortho-H), 7.57 (1 H, t, $J_{p,m} = 7.0$ Hz, para-H), 7.44 (2 H, t, $J_{m,o} = J_{m,p} = 7.0$ Hz, meta-H), 5.42 (1 H, dd, $J_{10,11} = 5.6$ Hz, $J_{10,8} = 1.3$ Hz, 10-H), 5.32 (1 H, dt, $J_{3,4\beta} = 10.8$ Hz, $J_{3,4\alpha} = J_{3,2} = 4.4$ Hz, 3-H), 4.50 (1 H, ABq, $J_{AB} = 11.7$ Hz, CH_2OBz), 4.47 (1 H, d, $J_{12,2} = 1.5$ Hz, 12-H, obscured), 4.19 (1 H, dd, $J_{2,3} = 4.4$ Hz, $J_{2,12} = 1.5$ Hz, 2-H), 3.90 (1 H, d, $J_{11,10} = 5.6$ Hz, 11-H), 2.28 (1 H, dd, $J_{gem} = 14.5$ Hz, $J_{4\beta,3} = 10.8$ Hz, 4β-H), 2.13 (3 H, s, OAc), 2.11–1.77 (5 H, two each of 7-, 8-H and 4α-H), 0.93 (3 H, s, 6-CH_3), 0.82 (9 H, s, Si-*t*-Bu), 0.06 (3 H, s, $SiCH_3$), 0.04 (3 H, s, $SiCH_3$); MS, *m/e* (rel intensity) 457 (1.80), 335 (1.35), 275 (10.83), 179 (100.00), 105 (57.07), 93 (11.29), 77 (12.22); mol wt ($M^+ - C_4H_9$) 457.2054 (calcd for $C_{25}H_{33}O_6Si$ 457.2038).

3α-Acetoxy-14-(benzoyloxy)-12β-hydroxy-13-nortrichothec-9-ene (27). Acetoxy silyl ether **26** (416 mg, 0.81 mmol) was converted into acetoxy alcohol **27** by the same procedure used to obtain compound **14b**. Flash chromatography of the crude product **27** with 50% ethyl acetate in hexane followed by recrystallization from 40% ether in pentane provided a pure white crystalline solid (283 mg, 1.42 mmol, 73% overall yield for two steps from compounds **24**): mp 146–148 °C; IR ν_{max} ($CHCl_3$) 3600, 3460, (br), 1735, 1715, 1605, 1450, 1380, 1280, 1120, 1100, 1070, 965, 915 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 8.03 (2 H, d, $J_{o,m} = 7.0$ Hz, ortho-H), 7.61 (1 H, t, $J_{p,m} = 7.0$ Hz, para-H), 7.47 (2 H, t, $J_{m,p} = J_{m,o} = 7.0$ Hz, meta-H), 5.41 (1 H, d, 10-H, obscured), 5.38 (1 H, dt, $J_{3,4\beta} = 10.8$ Hz, $J_{3,2} = J_{3,4\alpha} = 4.5$ Hz, 3-H, obscured), 4.70 (1 H, ABq, $J_{AB} = 12.4$ Hz, CH_2OBz), 4.38 (1 H, 13-H, obscured), 4.35 (1 H, ABq, $J_{AB} = 12.4$ Hz, CH_2OBz), 4.29 (1 H, dd, $J_{2,3} = 4.5$ Hz, $J_{2,12} = 1.8$ Hz, 12-H), 3.88 (1 H, d, $J_{11,10} = 5.4$ Hz, 11-H), 3.13 (1 H, d, $J_{OH,12} = 2.8$ Hz, OH), 2.23 (1 H, dd, $J_{gem} = 14.5$ Hz, $J_{4\beta,3} = 10.8$ Hz, 4β-H), 2.13 (3 H, s, OAc), 2.12–1.59 (4 H, two each of 7-, 8-H), 1.84 (1 H, dd, $J_{gem} = 14.5$ Hz, $J_{4\alpha,3} = 4.5$ Hz, 4α-H), 1.69 (3 H, s, 9-CH_3), 1.00 (3 H, s, 6-CH_3); MS, *m/e* (rel intensity) 400 (M^+, 3.44), 385 (12.72), 357 (2.90), 278 (2.66), 124 (62.35), 108 (39.20), 105 (100.00), 93 (25.63), 77 (36.30); mol wt 400.1890 (calcd for $C_{23}H_{28}O_6$ 400.1878). Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.70; H, 7.12.

3α-Acetoxy-14-(benzoyloxy)-13-nortrichothec-9-en-12-one (28). The compound **27** (66 mg, 0.16 mmol) was converted into compound **28** by using the same procedure as in the preparation of **15**. HPLC separation of the crude product with 50% ethyl acetate in hexane afforded pure **28** as a white foam (56 mg, 0.14 mmol, 85%): IR ν_{max} ($CHCl_3$) 1760, 1745, 1720, 1680, 1605, 1450, 1380, 1275, 1120, 1055, 965, 915 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 7.93 (2 H, d, $J_{o,m} = 7.0$ Hz, ortho-H), 7.56 (1 H, t, $J_{p,m} = 7.0$ Hz, para-H), 7.42 (2 H, t, $J_{m,p} = J_{m,o} = 7.0$ Hz, meta-H), 5.48 (1 H, br d, $J_{10,11} = 5.7$ Hz, 10-H), 5.17 (1 H, dt, $J_{3,4\beta} = 11.2$ Hz, $J_{3,4\alpha} = J_{3,2} = 5.0$ Hz, 3-H), 4.59 and 4.36 (1 H each, ABq, $J_{AB} = 11.7$ Hz, CH_2OBz), 4.30 (1 H, br d, $J_{11,10} = 5.7$ Hz, 11-H), 3.98 (1 H, d, $J_{2,3} = 5.0$ Hz, 2-H), 2.71 (1 H, dd, $J_{gem} = 15$ Hz, $J_{4\beta,3} = 11.2$ Hz, 4β-H), 2.36 (1 H, dd, $J_{gem} = 15.0$ Hz, $J_{4\alpha,3} = 5.0$ Hz, 4α-H), 2.19 (3 H, s, OAc), 2.06–1.61 (4 H, two each of 7-, 8-H), 1.73 (3 H, s, 9-CH_3), 1.01 (3 H, s, 6-CH_3); MS, *m/e* (rel intensity) 339 (0.87), 217 (3.02), 124 (9.45), 108 (100.00), 105 (52.60), 93 (21.70), 77 (19.18); mol wt (M^+ - OAc) 339.1591 (calcd for $C_{21}H_{23}O_4$ 339.1607). Anal. Calcd for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58. Found: C, 69.11; H, 6.58.

3α,14-Dihydroxytrichotheca-9,12-diene (17). The compound **28** (50 mg, 0.12 mmol) was treated with methyltriphenylphosphonium bromide (5 equiv), KO-*t*-Bu, *t*-BuOH, and ether, (38 °C, 4 h) followed by acetic anhydride (6 equiv) and pyridine (room temperature, 20 h); the same procedure which was used to convert compound **15** into compound **16** to yield the crude product 180 mg. After the crude product was partially purified by flash chromatography on silica gel with 50% ethyl acetate in hexane to get rid of the base line and slow running impurities, it was hydrolyzed by sodium hydroxide (10 equiv) and methanol–water (9:1) (room temperature, 2 h) as the usual method to obtain a crude product (26 mg). Flash chromatography of the resulting crude product on silica gel with 80% → 100% ethyl acetate in hexane afforded the desired diol **17** (white crystalline solid) (13.5 mg, 0.05 mmol, 43% overall yield). The diol **17** was identical in all spectroscopic features with the diol produced by alkaline hydrolysis of diacetoxy alkene **16**.

12,13-Epoxy-3α,14-dihydroxytrichothec-9-ene (18). This epoxidation was performed several times on a small scale (1–2 mg). With this amount of material, there is a technical difficulty involved in the use of correct amounts of reactants. On a number of runs, complete conversion to monoepoxide **18** was observed, but if the reactant excess metachloroperbenzoic acid was used, substantial amounts of diepoxide **19** are formed. When carried out with 7.1 mg of intermediate **17**, the following procedure gave monoepoxide and recovered starting material only.

To a stirred suspension of MCPBA (6.3 mg, 0.036 mmol) and Na_2HPO_4 (43 mg, 0.304 mmol) in dichloromethane (0.8 mL) at −16 °C under argon atmosphere was added the diol **17** (7.6 mg, 0.030 mmol) in dichloromethane (0.3 mL). After having been stirred for 17 h at −16 °C, the reaction mixture was quenched with 10 mL of water and extracted with ethyl acetate (3 × 10 mL). The extract was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. NMR of the crude compound showed a mixture of desired monoepoxide and starting material ca. 1:1. The reaction was repeated by treating the resulting crude product with MCPBA (3.1 mg, 0.018 mmol) to afford a crude mixture, 6.1 mg. The resulting residue was separated by PLC (0.5 mm, 20 × 20 cm silica gel, 8:2 ethyl acetate/hexane) to give a pure recovered starting material (2.2 mg, 0.009 mmol) and the desired monoepoxide **18**. Recrystallization from ether/pentane provided white crystalline solid **18** (4.6 mg, 0.017 mmol, 80% yield, on the basis of the recovered starting material): mp 130–132 °C; IR ν_{max} ($CHCl_3$) 3600, 3520, 1380, 1050 cm^{-1}; ^1H NMR δ ($CDCl_3$, 200 MHz) 5.47 (1 H, dd, $J_{10,11} = 5.1$ Hz, $J_{10,8} = 1.4$ Hz, 10-H), 4.50 (1 H, dt, $J_{3,4\beta} = 11.0$ Hz, $J_{3,2} = J_{3,4\alpha} = 4.5$ Hz, 3-H), 4.11 (1 H, d, $J_{11,10} = 5.1$ Hz, 11-H), 3.74 (1 H, d, $J_{gem} = 11.9$ Hz, 14-H), 3.50 (1 H, d, $J_{2,3} = 4.5$ Hz, 2-H), 3.46 (1 H, br d, $J_{gem} = 11.9$ Hz, 14-H, obscured), 3.26 and 3.23 (1 H each, ABq, $J_{AB} = 3.3$ Hz, 13-H), 2.92 (1 H, dd, $J_{gem} = 14.6$ Hz, $J_{4\beta,3} = 11.0$ Hz, 4β-H), 2.04–1.25 (4 H, two each of 7- and 8-H), 1.82 (1 H, dd, $J_{gem} = 14.6$ Hz, $J_{4\alpha,3} = 4.5$ Hz, 4α-H), 1.72 (3 H, s, 9-CH_3), 0.85 (3 H, s, 6-CH_3); MS, *m/e* (rel intensity) 266 (M^+, 8.40), 251 (22.32), 124 (74.10), 108 (100.00), 93 (88.98); mol wt 266.1520 (calcd for $C_{15}H_{22}O_4$ 266.1513).

Acknowledgment. We are grateful to the U.S. Public Health Service, National Institutes of Health, for financial support of this research (Grant GM 30757), and to the National Science Foundation (CHE 80-24633) and National Institutes of Health (RR-01689) for provision of funds toward the purchase of high field NMR equipment. We also thank Dr. R. P. Lattimer and Dr. Bill Kroenke of the BF Goodrich Company and Professor H. Andrist of Cleveland State University for providing mass spectra on some of the compounds reported here. Assistance with the 2D NMR from Fredrick Swiecinski of this department is gratefully acknowledged.

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