Trichothecene Degradation Studies: Synthesis of 12,13-Deoxyanguidine and 12,13-Deoxyverrucarol

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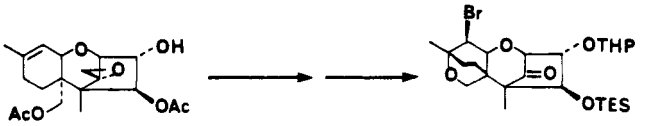
A simple procedure for synthesis of trichotheca-9,12-dienes is described. The method involves opening of the 12,13-epoxide functionality with PhSNa in EtOH at reflux followed by oxidation of the sulfide and then reductive elimination of the β-hydroxy sulfone intermediate by using 4.5% Na–Hg in MeOH. This methodology was applied to the synthesis of 12,13-deoxyanguidine (**10**) and 12,13-deoxyverrucarol (**17**), which are of interest in connection with studies of the metabolism and mechanism of action of trichothecene mycotoxins.

A characteristic structural feature of the trichothecene mycotoxins is the 12,13-epoxide unit that occurs with high regularity in this family of fungal metabolites.[2] The only known naturally occurring exceptions are verrucarin K[3] and 12,13-deoxytrichodermadiene,[4] which appear to be products of aberrant biosynthetic pathways. Very recently, however, two groups have reported the isolation of 3α,7α,15-trihydroxytrichotheca-9,12-dien-8-one (12,13-deoxyvomitoxin) from in vivo metabolism studies of vomitoxin (deoxynivalenol) in rats[5] and from in vitro studies using bovine rumen fluid.[6] Since the 12,13-epoxide unit is associated with the adverse biological properties of these mycotoxins,[7] it is likely that the microbial 12,13-deoxygenation reaction serves as a detoxification process.[6] In view of the current level of interest in the metabolism and mechanism of action of the epoxytrichothecenes, we report herein a simple method for synthesis of trichotheca-9,12-dienes that should prove generally useful for preparing reasonable quantities of these compounds for biological characterization.[8,9]

During the course of recent studies directed toward the synthesis of [^{14}C]anguidine we had occasion to explore methods for effecting a degradation of anguidine **1** to norketone **2**.[10] Our plan at the outset was to open the



1 **2**

oxirane system of **1** to give a 12,13-diol that would be degraded to a suitable 12-norketone intermediate by an oxidative cleavage reaction. Although the reactivity and chemical degradations of the trichothecene skeleton have been extensively studied,[2,11] a review of the literature revealed that bimolecular substitution reactions of the 12,13-epoxide unit are extremely rare.[12,13] The one general exception is the reaction with $LiAlH_4$ that affords tertiary alcohol derivatives in good yield.[8,11a]

The low reactivity of the trichothecene 12,13-epoxide unit toward external nucleophiles is probably the consequence of steric shielding of C(13) by the C(8)-methylene and/or the C(16)-methyl group, depending on the conformation of the cyclohexenyl system. Neighboring group assisted reactions readily occur, however, as illustrated by the interesting hydration reaction of **3** to **4**.[7b,11a,b] As would be expected the trichothecene 12,13-epoxide unit shows appreciable reactivity under acidic conditions but is ac-

(1) Fellow of the Alfred P. Sloan Foundation, 1982–1986.

(2) (a) "Developments in Food Science: Trichothecenes: Chemical, Biological, and Toxicological Aspects"; Ueno, Y., Ed.; Elsevier; New York, 1983; Vol. 4. (b) Doyle, T. W.; Bradner, W. T. in "Anticancer Agents Based on Natural Product Models"; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; Chapter 2. (c) Ueno, Y. *Adv. Nutr. Res.* **1980**, *3*, 301. (d) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63. (e) Bamburg, J. R.; Strong, F. M. in "Microbial Toxins"; Kadis, S., Ciegler, A., Ajl, S. J., Eds.; Academic Press: New York, 1971; Vol. 7, p 207.

(3) Breitenstein, W.; Tamm, C. *Helv. Chim. Acta* **1977**, *60*, 1522.

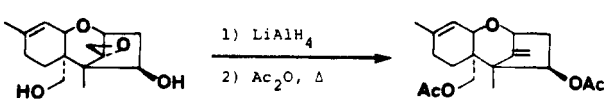
(4) Jarvis, B. B.; Vrudhula, V. M.; Midiwo, J. O.; Mazzola, E. P. *J. Org. Chem.* **1983**, *48*, 2576.

(5) Yoshizawa, T.; Takeda, H.; Ohi, T. *Agric. Biol. Chem.* **1983**, *47*, 2133.

(6) King, R. R.; McQueen, R. E.; Levesque, D.; Greenhalgh, R. *J. Agric. Food Chem.* **1984**, *32*, 1181.

(7) (a) Grove, J. F.; Mortimer, P. H. *Biochem. Pharmacol.* **1969**, 1473. (b) Grove, M. D.; Burmeister, H. R.; Taylor, S. L.; Weisleder, D.; Plattner, R. D. *J. Agric. Food Chem.* 1984, *32*, 541.

(8) The first synthesis of a trichotheca-9,12-diene was reported by Gutzwiller and co-workers[11a] who converted verrucarol into 12,13-deoxyverrucarol diacetate (**i**) by $LiAlH_4$ reduction and acylation of the tertiary alcohol intermediate under forcing conditions. The elimination reaction, however, proceeds in very poor yield and so this method is not generally useful for synthesis of dienes such as **i**.



15 **i**

(9) Several trichotheca-9,12-dienes have been prepared by total synthesis: (a) Trost, B. M.; McDougal, P. G.; Haller, K. J. *J. Am. Chem. Soc.* **1984**, *106*, 383. (b) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *Ibid.* **1983**, *105*, 4472. (c) Roush, W. R.; D'Ambra, T. E. *Ibid.* **1983**, *105*, 1058. (d) Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *Ibid.* **1982**, *104*, 1114. (e) Schlessinger, R. H.; Nugent, R. A. *Ibid.* **1982**, *104*, 1116. (f) Still, W. C.; Tsai, M. Y. *Ibid.* **1980**, *102*, 3654. (g) Pearson, A. J.; Ong, C. W. *Ibid.* **1981**, *103*, 6686. (h) Nakahara, Y.; Tatsuno, T. *Chem. Pharm. Bull. Jpn.* **1980**, *28*, 1981. (i) Masuoka, N.; Kamikawa, T. *Tetrahedron Lett.* **1976**, 1691. (j) Fujimoto, Y.; Yokura, S.; Nakamura, T.; Morikawa, T.; Tatsuno, T. *Ibid.* **1974**, 2523. (k) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989.

(10) Roush, W. R.; Russo-Rodriguez, S., unpublished research.

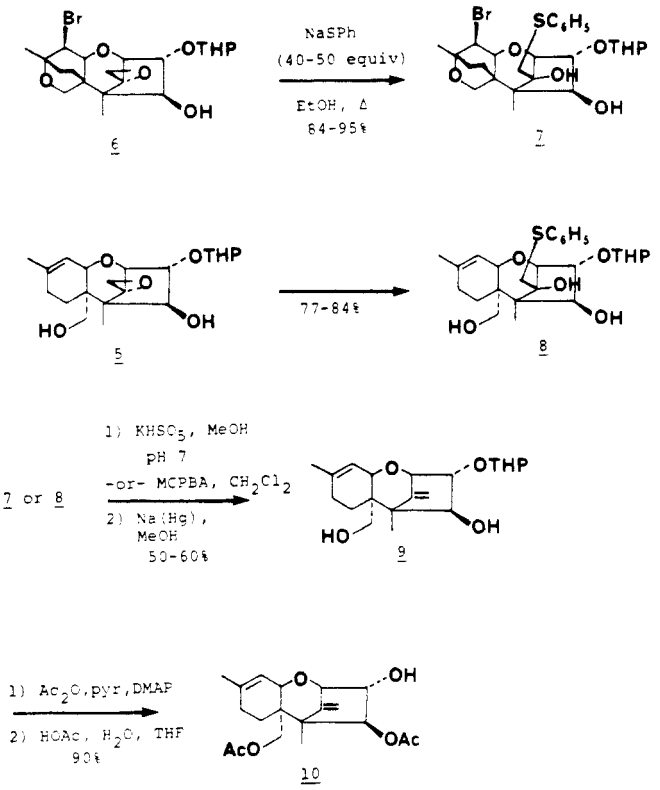
(11) (a) Gutzwiller, J.; Mauli, R.; Sigg, H. P.; Tamm, C. *Helv. Chim. Acta* **1964**, *47*, 2234. (b) Sigg, H. P.; Mauli, R.; Flury, E.; Hauser, D. *Ibid.* **1965**, *48*, 962. (c) Dawkins, A. W.; Grove, J. F. *J. Chem. Soc. C* **1970**, 369. (d) Müller, B.; Tamm, C. *Helv. Chim. Acta* **1975**, *58*, 541.

(12) Czechoslovakian workers have reported that hydrolysis of trichothecolone with 50% aqueous H_2SO_4 afforded the corresponding 12,13-diol: Pribela, A.; Lačok, P. *Polnohospodarstvo* (S10) **1976**, *22*, 278; *Chem. Abstr.* **1976**, *85*, 187470g. We have found, however, that treatment of anguidine under analogous conditions afforded only products containing apotrichothecene skeletons.

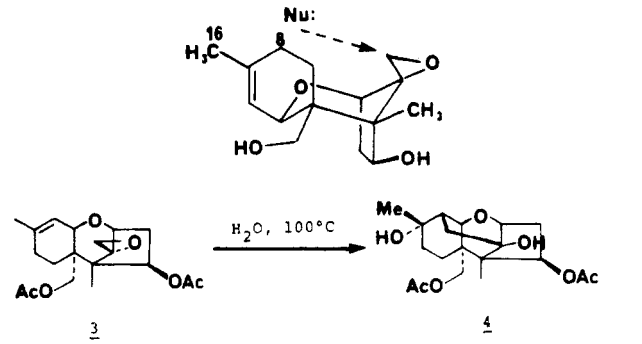
(13) Several studies have noted the lack of reactivity of trichothecenes with thiols such as glutathione, cysteine, and dithiothreitol: (a) Nakamura, K.; Ohta, M.; Ueno, Y. *Chem. Pharm. Bull.* **1977**, *25*, 3410. (b) Ueno, Y.; Matsumoto, H. *Ibid.* **1975**, *23*, 2439.

0022-3263/85/1950-5465$01.50/0

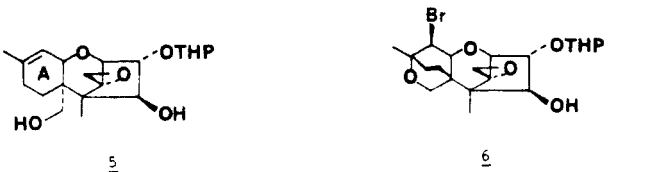
Scheme I



companied by a facile skeletal rearrangment to the apotrichothecene nucleus.[2,11,14]

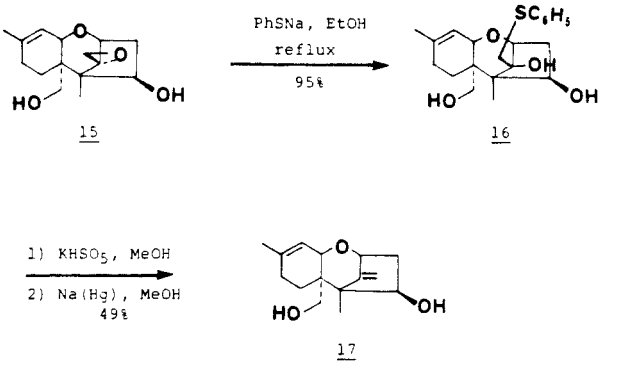


We began by screening the reactions of THP ether **5** and the derived bromo ether **6**[15] with a range of reagents known



to deoxygenate simple epoxides. Examination of molecular models suggested that the hydroxymethyl bridge helps to tie back the A ring, thereby making the epoxide unit somewhat more accessible to nucleophilic attack. Unfortunately, no reaction was observed when **6** was treated with excess KSeCN[16] in aqueous MeOH or EtOH at reflux or in Me_2SO at 100 °C. Tamm has previously reported unsuccessful attempts to deoxygenate verrucarol by using this reagent.[3] Similarly, starting material was recovered unchanged when treated with $KSiMe_3$ in HMPT,[17] $Fe(CO)_5$ in tetramethylurea,[18] and sodium diethyl phosphorotelluroate in EtOH.[19] Attempts to effect epoxide hydrolysis with either **5** or **6** by using NaOAc in aqueous EtOH (reflux) or KOH in aqueous dioxane or Me_2SO (100 °C) were also unproductive.

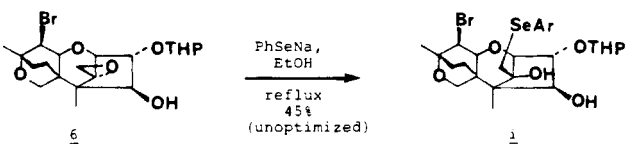
Scheme II



Success was finally achieved when **6** was treated with NaSPh in EtOH at reflux (Scheme I). This reaction is extremely slow and requires 4 days to reach completion using 10 equiv of thiophenoxide (58% yield). With a much larger excess of reagent (40–50 equiv; 1.5–2 M in EtOH) the reaction is complete within a 20–24-h period and affords adduct **7** in 84–95% yield.[20] Under analogous conditions trichothecene **5** was converted to thiophenyl adduct **8** in 77–84% yield (see Scheme I).[21] Oxidation of either **7** or **8** with $KHSO_5$ in MeOH in the presence of aqueous pH 7 phosphate buffer[22] or with 2.1 equiv of MCPBA in CH_2Cl_2 (−78 → 23 °C) afforded the corresponding sulfone that was directly reduced by using 4–5% Na–Hg amalgam in MeOH to give diene **9** in 50–60% overall yield.[23] Acylation of **9** followed by THP ether hydrolysis then completed this synthesis of 12,13-deoxyanguidine (**10**).

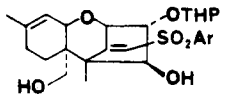
The major byproduct of the conversion of **7** or **8** to **9** is tertiary alcohol **11** (10–20%) that results from sulfone reductive cleavage without β-elimination of hydroxide.

Initial attempts to circumvent this problem by activating the C(12)-hydroxyl group prior to the reduction step were unsuccessful, owing to extreme steric congestion that precluded direct functionalization of this position. Carbonate **12**, however, was prepared by a three-step sequence



(14) Godtfredsen, W. O.; Vangedal, S. *Acta. Chem. Scand.* **1965**, *19*, 1088.
(15) Roush, W. R.; Russo-Rodriguez, S. *J. Org. Chem.* **1985**, *50*, 3224.
(16) Behan, J. M.; Johnston, R. A. W.; Wright, M. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1216.
(17) Dervan, P. B.; Shippey, M. A. *J. Am. Chem. Soc.* **1976**, *98*, 1265.
(18) Alper, H.; Des Roches, D. *Tetrahedron Lett.* **1977**, 4155.
(19) Clive, D. L. J.; Menchen, S. M. *J. Org. Chem.* **1980**, *45*, 2347.
(20) The reaction of **6** with excess PhSeNa in EtOH similarly affords phenylselenide adduct **i**.
(21) The reaction of **5** with PhSNa in Me_2SO (10 equiv of PhSNa, 1 M in Me_2SO, 25 °C; 5 days to reach 80% completion) is considerably faster than in EtOH, but the yield of **8** is not improved owing to the difficulty of product isolation.
(22) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.
(23) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833. (b) Matsumura, Y.; Trost, B. M. *J. Org. Chem.* **1977**, *42*, 2036.

from **7** in approximately 90% overall yield [(i) carbonyl diimidazole, C_6H_6, 23 °C; (ii) DBU, C_6H_6 reflux; (iii) MCPBA, CH_2Cl_2, 23 °C]. Treatment of **12** with 5% Na–Hg in MeOH at 23 °C produced a small amount of **9** with vinyl sulfone **13** as the major product (75%). Performing



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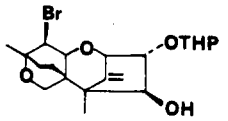

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this reaction at −20 °C in the presence of KH_2PO_4 minimized **13** (ca. 10%) and provided a mixture of **9** and **14** in 68% yield. Since the overall yield of **9** via the sequence involving sulfone carbonate **12** was only slightly better than the more direct three-step synthesis originating from **5** (Scheme I), this latter route has been used for all subsequent preparative scale experiments.

As a second illustration of this methodology we have synthesized 12,13-deoxyverrucarol (**17**; Scheme II). The spectroscopic data and physical constants of this compound were in excellent agreement with literature values.[3]

In summary, we have developed a simple method for degradation of 12,13-epoxytrichothec-9-enes to trichotheca-9,12-dienes by a three-step sequence involving opening of the 12,13-epoxide with PhSNa followed by oxidation of the sulfide to a sulfone and then reduction of this intermediate with sodium amalgam.[24] This procedure should be applicable to most epoxytrichothecene mycotoxins except, perhaps, epoxytrichothecen-8-ones, which are very base sensitive and, without masking of the A-ring enone functionality, may not survive the conditions of our PhSNa reaction. Trichothecene esters may also not be compatible with this three-step sequence, but provisions can easily be made to reintroduce these at the end of the synthesis as was done here with 12,13-deoxyanguidine (**10**; Scheme I). Use of diene **9** in a synthesis of [^{14}C]anguidine will be reported shortly.

Experimental Section

Proton (^{1}H) NMR spectra were measured at 250 and 270 MHz on Bruker WM250 and 270 instruments. Chemical shifts are reported in δ units using tetramethylsilane or the 7.24 ppm resonance of residual chloroform as internal reference. Infrared spectra were measured on a Perkin-Elmer Model 283B infrared spectrophotomer calibrated with the 1601-cm^{-1} absorption of polystyrene. IR spectra are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a Rudolph Autopol III automatic polarimeter using a 1-cm^3 capacity quartz cell (10-cm path length). Mass spectra (low and high resolution) were measured on a Finnegan MAT 8200 instrument. Elemental analyses were performed by Robertson Laboratory, Inc., Florham Park, N.J. Melting points were obtained on a Thomas Hoover melting point apparatus and are uncorrected.

All reactions were conducted in flame- or oven-dried glassware under atmospheres of dry argon or nitrogen. The following solvents were purified before use: ether and THF were distilled from sodium benzophenone ketyl; methylene chloride (CH_2Cl_2) and pyridine were distilled from CaH_2; methanol and ethanol were distilled from Mg metal.

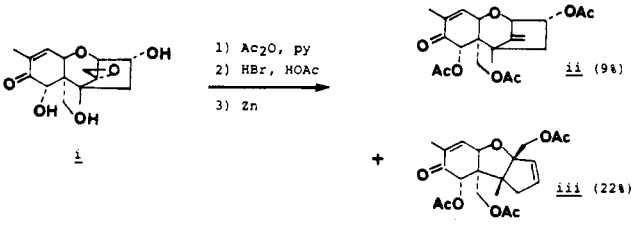
Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm × 10 cm plates coated with a 0.25-mm layer of silica gel containing PF 254 indicator (Analtech). Preparative thin-layer chromatography (PTLC) was performed by using 20 cm × 20 cm plates coated with 0.25- or 0.5-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were visualized by staining with iodine vapor or by charring with ethanolic H_2SO_4. Compounds were eluted from the absorbants by using 15% MeOH in CH_2Cl_2. Flash column chromatography was performed by the method of Still[25] using Merck 230–400-mesh silica gel. All chromatography solvents were distilled before use.

3α-(Tetrahydropyranyloxy)-10β-bromo-4β,12-dihydroxy-13-thiophenoxy-9α,15-epoxytrichothecene (7). A freshly prepared solution of NaSPh in EtOH (20 mL of a 1.44 M solution) was added to bromo ether **6a**[15,26] (192 mg, 0.43 mmol). The reaction was heated to reflux for 21 h, then diluted with CH_2Cl_2 (70 mL), and washed with 30 mL of 10% aqueous KOH. The organic layer was dried (Na_2SO_4), filtered, and evaporated to afford 700 mg of an orange solid that was purified on a 30 mm × 15 cm flash silica gel column using 2.5% MeOH in CH_2Cl_2. This gave 235 mg (95%) of pure **7a**:[26] mp 72–75 °C; R_f 0.21 (2.5% MeOH in CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.47 (d, 2 H, aromatic), 7.32–7.19 (m, 3 H, aromatic), 4.66 (m, 1 H, THP), 4.35 (dd, 1 H, J = 2.3, 4.7 Hz, H_3), 4.28 (br dd, 1 H, J = 2.0, 8.4 Hz, H_{10}), 4.22 (d, 1 H, J = 7.3 Hz, H_{11}), 4.15 (m, 1 H; after D_2O wash becomes d, J = 2.5 Hz, H_4), 4.09 (d, 1 H, J = 14.1 Hz, H_{13a}), 3.90 (d overlapping with m, 2 H, J = 4.8 Hz, H_2 and THP), 3.80 (dd, 1 H, J = 2.7, 9.0 Hz, H_{15a}), 3.71 (d, 1 H, J = 9.7 Hz, H_{15b}), 3.54 (s, 1 H, OH), 3.50 (m, 1 H, THP), 2.90 (m, 1 H, OH), 2.40–2.19 (m, 2 H), 1.3 (s, 3 H, H_{16}), 0.95 (s, 1 H, H_{14}); IR (CH_2Cl_2) 3540, 3460 (br), 2940, 2870, 1580, 1480, 1450, 1435, 1380, 1350, 1195, 1150, 1100, 1070, 1050, 1030, 980, 960, 900, 860, 840 cm^{-1}; mass spectrum, m/e 556 (M^+ (^{81}Br)), 554 (M^+ (^{79}Br)); high-resolution mass spectrum for $C_{26}H_{35}O_6{}^{79}BrS$, calcd 554.1138, found 554.1334 ± 0.0008.

3α-(Tetrahydropyranyloxy)-4β,12α,15-trihydroxy-13-thiophenoxytrichothec-9-ene (8). A freshly prepared solution of NaSPh in EtOH (45 mL of a 1.5 M solution) was added to THP ether **5b**[26] (518 mg, 1.41 mmol). The mixture was heated to reflux for 20 h, then diluted with CH_2Cl_2 (100 mL), and washed with 10% aqueous KOH (2 × 30 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated to afford 1.48 g of an orange oil. This material was purified by chromatography on a 50 mm × 14 cm flash silica gel column using 2:1 EtOAc–hexane as eluant to give 567 mg (84%) of pure **8b**:[26] mp 159–160 °C; $[\alpha]^{21}_D$ −78.4° (c 1.45, $CHCl_3$); R_f 0.33 (2:1 EtOAc–hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41–7.16 (m, 5 H, aromatic), 5.40 (br d, 1 H, J = 4.5 Hz, H_{10}), 4.91 (m, 1 H, THP), 4.31 (dd, 1 H, J = 2.3, 4.9 Hz, H_3), 4.14 (br d, 1 H, J = 6.6 Hz, H_4; after D_2O wash becomes d, J = 2.0 Hz), 4.06 (d, 1 H, J = 13.8 Hz, H_{13a}), 4.00 (m, 1 H, THP), 3.89–3.84 (m, 2 H, H_2 and H_{11}), 3.81 (d, 1 H, J = 12.3 Hz, H_{15a}), 3.52–3.45 (m, 2 H, THP and OH), 3.43 (d, 1 H, J = 12.1 Hz, H_{15b}), 3.11 (d, 1 H, J = 13.7 Hz, H_{13b}), 2.93 (br m, 1 H, OH), 2.1–1.8 (m, 3 H), 1.71 (s, 3 H, H_{16}), 1.17 (s, 3 H, H_{14}); IR ($CHCl_3$) 3660, 3600–3400 (br), 2980, 1590, 1460, 1430, 1380, 1335 cm^{-1}; mass spectrum, m/e 476 (M^+), 391 ($M^+ - C_5H_9O$); high-resolution mass spectrum, for $C_{21}H_{27}O_5S$ ($M^+ - C_5H_9O$), calcd 391.1579, found 391.157 ± 0.001. Anal. Calcd for $C_{26}H_{36}O_6S$: C, 65.52; H, 7.62. Found: C, 65.62; H, 7.67.

3α-(Tetrahydropyranyloxy)-4β,15-dihydroxytrichotheca-9,12-diene (9). Method A. To a −78 °C solution of sulfide **8b**[26]

(24) After our studies were completed, King and Greenhalgh (King, R. R.; Greenhalgh, R. *Can. J. Chem.* **1985**, *63*, 1089) reported a method for 12,13-deoxygenation of deoxynivalenol (**i**) involving epoxide opening with HBr in HOAc followed by Zn reduction. This procedure, however, suffers from the low overall yield of the desired compound (**ii**) as well as production of an apotrichothecene (**iii**) as the major product. We were curious whether this sequence could be successfully applied to anguidine (**1**) but found that treatment of 3α,4β,15-scirpentriacetate with HBr in HOAc afforded *exclusively* products of skeletal rearrangement.



i

(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *34*, 2923.

(26) Isomerically pure THP diastereomers were used in order to facilitate analysis of reaction mixtures. Isomers in the "a" series derive from the faster moving THP diastereomer of **5** whereas the "b" series derives from the slower moving isomer of **5**. For separation of **5a** and **5b**, see ref 15.

(772 mg, 1.62 mmol) in 13 mL of CH_2Cl_2 was added MCPBA (574 mg, 3.29 mmol) in one portion. The reaction was stirred at −78 °C for 30 min, then allowed to warm slowly to ambient temperature, and stirred for an additional 5 h. The reaction was diluted with 80 mL of CH_2Cl_2 and washed successively with half-saturated Na_2SO_3 (1 × 20 mL) and half-saturated $NaHCO_3$ (2 × 30 mL). The organic layer was dried (Na_2SO_4), filtered through absorbent cotton, and evaporated. The crude product (845 mg) was purified on a 50 mm × 17 cm flash silica gel column using 2.5:1 EtOAc–hexane to give 613 mg (74%) of pure sulfone: mp 95–100 °C; R_f 0.34 (2.5:1 EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.93 (d, 2 H, aromatic), 7.62 (m, 3 H, aromatic), 5.34 (br d, 1 H, J = 4.8 Hz, H_{10}), 4.90 (m, 1 H, THP), 4.72 (s, 1 H, OH), 4.32 (dd, 1 H, J = 2.4, 4.9 Hz, H_3), 4.11 (m, 3 H, H_2, H_4 and H_{13a}), 3.93 (m, 1 H, THP), 3.85 (br d, 1 H, J = 4.9 Hz, H_{11}), 3.75 (dd, 1 H, J = 4.5, 12.0 Hz, H_{15a}), 3.50–3.35 (m, 2 H, THP and OH), 3.37 (d, 1 H, J = 13.7 Hz, H_{13b}), 2.83 (d, 1 H, J = 12.2 Hz, H_{15b}), 1.58 (s, 3 H, H_{16}), 1.19 (s, 3 H, H_{14}); IR ($CHCl_3$) 3460 (br), 3000, 2950 (br), 2865, 1450, 1385, 1310, 1250 (br), 1125, 1078, 1035, 970, 915, 870 cm^{-1}; mass spectrum, m/e 423 (M^+ − C_5H_9O); high-resolution mass spectrum for $C_{21}H_{27}O_7S$ (M^+ − C_5H_9O), calcd 423.1478, found 423.1473 ± 0.0006.

To a solution of the above sulfone (598 mg, 1.18 mmol) in 15 mL of MeOH was added Na_2HPO_4 (989 mg, 7.0 mmol) and 5% Na–Hg (2.56 g, 5.6 mmol of Na^0). After being stirred for 1.5 h at 23 °C, the reaction was evaporated under reduced pressure and partitioned between half-saturated NaCl (20 mL) and Et_2O (50 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL) and CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product (460 mg) was purified on a 25 mm × 18 cm flash silica gel column using 2:1 EtOAc–hexane as eluant to afford 267 mg (64%) of pure **9b**[26] and 105 mg (24%) of **11**. Data for **9b**: R_f 0.17 (1:1 hexane–EtOAc); mp 170–173 °C; $[\alpha]^{21}_D$ − 104° (c 1.07, $CHCl_3$); H NMR (250 MHz, $CDCl_3$) δ 5.46 (d, 1 H, J = 5.3 Hz, H_{10}), 5.12 (s, 1 H, H_{13a}), 4.91 (br s, 1 H, THP), 4.75 (s, 1 H, H_{13b}), 4.53 (br s, 1 H, H_4), 4.27 (d, 1 H, J = 4.7 Hz, H_2), 4.08 (m, 1 H, THP), 3.98 (d, 1 H, J = 5.5 Hz, H_{11}), 3.79 (br d, 1 H, J = 12 Hz, H_{15a}), 3.69 (dd, 1 H, J = 3.5, 4.3 Hz, H_3), 3.54 (m, 2 H, THP and H_{15b}), 2.04–1.8 (m, 4 H), 1.67 (s, 3 H, H_{16}), 1.11 (s, 3 H, H_{14}); IR ($CHCl_3$) 3620, 3550–3350 (br), 2980, 2925, 1450, 1380, 1110, 1055, 1010, 960, 890 cm^{-1}; mass spectrum, m/e 265 (M^+ − C_5H_9O); high-resolution mass spectrum for $C_{15}H_{21}O_4$ (M^+ − C_5H_9O), calcd 265.1441, found 265.1439 ± 0.0004.

Method B. To a solution of bromo ether **7a**[26] (235 mg, 0.42 mmol) in 10 mL of CH_2Cl_2 was added 304 mg (1.8 mol) of MCPBA. The reaction was stirred at ambient temperature for 20 min, then diluted with 50 mL of CH_2Cl_2, and washed with half-saturated Na_2SO_3 (1 × 40 mL) and half-saturated $NaHCO_3$ (1 × 40 mL). The organic layer was dried (Na_2SO_4), filtered through absorbent cotton, and evaporated. The crude sulfone (271 mg) was dissolved in 5.8 mL of MeOH and treated with 421 mg (2.97 mmol) of Na_2HPO_4 and 1.51 g of 4.5% Na–Hg (2.96 mmol of Na^0). After being stirred for 3 h at room temperature, the reaction was poured into H_2O (50 mL) and extracted with Et_2O (1 × 40, 2 × 10 mL) and CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The crude residue (154 mg) was purified by chromatography on 25 mm × 17 cm flash silica gel column using 1:1 hexane–EtOAc to afford 82 mg (55% from **7a**) of **9a** and 15 mg (10%) of **11**. Data for **9a**:[26] R_f 0.20 (1:1 hexane–EtOAc); ^1H NMR ($CDCl_3$, 250 MH_2) δ 5.44 (br dd, 1 H, J = 1.2, 5.4 Hz, H_{10}), 5.12 (s, 1 H, H_{13a}), 4.77 (s, 1 H, H_{13b}), 4.68 (dd, 1 H J = 2.3, 5.2 Hz, THP), 4.47 (d, 1 H, J = 2.9 Hz, H_4), 4.27 (d, 1 H, J = 4.6 Hz, H_2), 3.99 (m, 1 H, THP), 3.92 (br d, 1 H, J = 5.5 Hz, H_{11}), 3.81 (d, 1 H, J = 11.9 Hz, H_{15a}), 3.68 (dd, 1 H, J = 3.2, 4.7, Hz, H_3), 3.53 (br m, 2 H, H_{15b} and THP), 1.67 (s, 3 H, H_{16}), 1.13 (s, 3 H, H_{14}).

12,13-Deoxyanguidine (10). To a solution of **9** (18 mg, 0.05 mmol) in 0.6 mL of dry pyridine was added acetic anhydride (26 μL, 0.28 mmol) and 4-(dimethylamino)pyridine (1 mg, 0.01 mmol). The reaction was stirred for 2 days; then, the pyridine and acetic anhydride were coevaporated with heptane (2 × 50 mL). The crude material was purified on one 0.25-mm preparative TLC plate (one elution with 1:1 hexane–EtOAc) to afford 20 mg of 12,13-deoxyanguidine THP ether (R_f 0.70 (1:1 hexane–EtOAc)). This material was dissolved in 0.2 mL of THF, 0.2 mL of H_2O, and 0.4 mL of glacial HOAc and then stirred for 6 days at ambient temperature. The acetic acid was coevaporated with heptane (2 × 25 mL) and the resulting residue purified on a 0.25-mm preparative TLC plate (two elutions with 1:1 hexane-EtOAc) to afford 16 mg (90%) of pure **10**: R_f 0.40 (1:1 hexane–EtOAc); mp 134–135 °C; $[\alpha]^{21}_D$ −68.4° (c 1.27, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.48 (d, 1 H, J = 5.6 Hz, H_{10}), 5.20 (d, 1 H, J = 2.7 Hz, H_4), 5.16 (s, 1 H, H_{13a}), 4.80 (s, 1 H, H_{13b}), 4.26 (d, 1 H, J = 4.8 Hz, H_2), 4.15 (d, 1 H, J = 12.4 Hz, H_{15a}), 4.10 (d, 1 H, J = 5.7 Hz, H_{11}), 3.98 (d, 1 H, J = 12.3 Hz, H_{15b}), 3.82 (m, 1 H, H_3), 3.07 (d, 1 H, J = 3 Hz, OH), 2.08 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 1.67 (s, 3 H, H_{16}), 1.05 (s, 3 H, H_{14}); IR ($CHCl_3$) 3560 (br), 2970, 2910, 1725, 1435, 1370, 1230 (br), 1150, 1040 (br), 980, 950, 900 cm^{-1}; mass spectrum m/e 290 (M^+− HOAc), 230 (M^+ − 2 HOAc); high-resolution mass spectrum for $C_{17}H_{22}O_4$ (M^+ − HOAc), calcd 290.1518, found 290.1519 ± 0.0004. Anal. Calcd for $C_{19}H_{26}O_6$:C, 65.11; H, 7.48. Found: C, 64.86; H, 7.67.

4β,12α,15-Trihydroxy-13-thiophenoxytrichothec-9-ene (16). A freshly prepared solution of NaSPh in EtOH (8.2 mL of a 1.79 M solution, 14.7 mmol) was added to verrucarol (**15**; 82 mg, 0.31 mmol). The reaction was heated to reflux for 24 h and then was diluted with CH_2Cl_2 (50 mL) and washed with 10% aqueous KOH (2 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated to afford a red-orange solid. This crude product was purified by chromatography on a 30 mm × 14 cm flash silica gel column with 2:1 EtOAc–hexane as eluant to afford 115 mg (95%) of sulfide **16**: mp 64–66 °C; $[\alpha]_D^{21}$ −43.7° (c 0.75, $CHCl_3$); R_f 0.27 (2:1 EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.42 (d, 2 H, aromatic), 7.25 (m, 3 H, aromatic), 5.36 (br d, 1 H, J = 4.0 Hz, H_{10}), 4.40 (br ddd, 1 H, J = 2.4, 7.8, 10.8 Hz, H_4; becomes dd, J = 2.4, 7.9 Hz after D_2O wash), 4.09 (d, 1 H, J = 13.1 Hz, H_{13a}), 3.94 (d, 1 H, J = 5.3 Hz, H_2), 3.75 (br d, 1 H, J = 12.4 Hz, H_{15a}), 3.65 (s, 1 H, OH), 3.45 (m, 2 H, H_{15b} and H_{11}), 3.29 (br d, 1 H, J = 11 Hz, OH), 3.17 (d, 1 H, J = 13.4 Hz, H_{13b}), 2.46 (dd, 1 H, H, J = 7.8, 15.7 Hz, $H_{3\alpha}$), 2.1–1.8 (m, 3 H), 1.75 (s, 3 H, H_{16}), 1.27 (s, 3 H, H_{14}); IR ($CHCl_3$) 3590, 3520 (br), 3440 (br), 3000, 2950, 2820, 1570, 1465, 1435, 1380, 1345, 1200 (br), 1070 cm^{-1}; mass spectrum, m/e 377, 376, (M^+); high-resolution mass spectrum for $C_{21}H_{28}O_4{}^{32}S$, calcd 376.1708, found 376.1711.

12,13-Deoxyverrucarol (17). To a solution of sulfide **16** (59 mg, 0.16 mmol) in 6.6 mL of MeOH was added 4.6 mL of 0.1 M pH 7 phosphate buffer and solid potassium hydrogen persulfate (oxone, 299 mg, 0.49 mmol).[22] The reaction was stirred for 3 h, then diluted with H_2O, and extracted with CH_2Cl_2 (1 × 20 mL, 3 × 10 mL). The organic extracts were dried (Na_2SO_4), filtered, and evaporated to give 69 mg of sulfone (R_f 0.13 in 2:1 EtOAc–hexane).

To a suspension of the above crude sulfone (69 mg) in 6.0 mL of dry MeOH was added anhydrous Na_2HPO_4 (167 mg, 0.82 mmol) and 4.5% sodium amalgam (587 mg, 0.15 mmol of Na^0). The reaction was stirred for 2.5 h, then diluted with H_2O (50 mL), and extracted with Et_2O (3 × 25 mL). The organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product (39 mg) was purified by chromatography on two 0.25-mm preparative plates (three elutions with 2:1 EtOAc–hexane) to afford 19.6 mg (49% for two steps) of pure **17**: mp 55–60 °C; $[\alpha]^{21}_D$ −108.8° (c 1.08, $CHCl_3$) [lit.[3] $[\alpha]_D$ −98 ± 2° (c 0.71, $CHCl_3$)]; R_f 0.22 (2:1 EtOAc–hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 5.38 (br d, 1 H, J = 5.3 Hz, H_{10}), 5.11 (s, 1 H, H_{13a}), 4.69 (br s, 2 H, H_4 and H_{13b}), 4.36 (d, 1 H, J = 5.3 Hz, H_2), 3.74 (d, 1 H, J = 11.8 Hz, H_{15a}), 3.68 (d, 1 H, J = 5.5 Hz, H_{11}), 3.55 (d, 1 H, J = 11.8 Hz, H_{15b}), 3.45 (s, 1 H, OH), 2.52 (dd, 1 H, J = 7.5, 15.0 Hz, $H_{3\alpha}$), 2.1–1.75 (m, 4 H), 1.66 (s, 3 H, H_{16}), 1.14 (s, 3 H, H_{14}); IR ($CHCl_3$) 3620, 3550–3300 (br), 2960, 1670, 1430, 1375, 1330, 1200 (br), 1060, 1010, 895 cm^{-1}; mass spectrum, m/e 250 (M^+); high-resolution mass spectrum for $C_{15}H_{22}O_3$, calcd 250.1569, found 250.1568 ± 0.0004.