saturated NaCl, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography with EtOAc gave sulfide **28** (20 mg, 40%).

(b) Biacetyl Sensitized Oxidation.[17] Ester **26** (200 mg, 0.49 mmol), pyridine (1 mL), biacetyl (0.1 mL), and methanol (25 mL) were placed in a quartz tube. The tube was cooled to −20 °C and the solution irradiated (Rayonet reactor, 350 nm) under O_2 (1 atm) for 3 h. The mixture was diluted with water and extracted with CH_2Cl_2 and ether. The combined organic solution was washed with 10% HCl, saturated $NaHCO_3$, and saturated NaCl. Drying (Na_2SO_4), concentration in vacuo, and flash chromatography (EtOAc) gave sulfide **28** (96 mg, 48%): oil; MS, $C_{21}H_{30}O_6S$ calcd 410.176, found 410.178; ^1H NMR δ 0.90 (3 H, d), 1.2–2.9 (m), 3.15 (2 H, s), 3.69 (3 H, s), 3.97 (4 H, br s), 4.35 (1 H, m), 6.05 (1 H, d); ^{13}C NMR δ 10.8 (CH_3), 22.0 (CH_2), 31.4 (CH_2), 31.6 (CH_2), 31.6 (CH_2), 33.1 (CH_2), 35.1 (CH_2), 36.9 (CH_2), 39.2 (CH), 41.8 (C), 43.4 (CH), 45.6 (CH), 52.5 (OCH_3), 65.0 (OCH_2), 65.2 (OCH_2), 70.8 (CH), 110.1 (C), 128.4 (CH), 163.1 (C), 170.4 (C), 200.7 (C); IR 2.9, 3.4, 5.8, 6.0.

1β,2,3,4,4a,4bα,5,6,7,8,8a,9β,10,10aα-Tetradecahydro-9α-hydroxy-8aβ,4aβ-(1-(methoxycarbonyl)-2-thiapropano)-1α-methyl-2,7-phenanthradione 2-Oxide 2-(Ethylene Acetal) (29). Ester **26** (200 mg, 0.49 mmol) was oxidized via biacetyl sensitization as described above. The crude product (260 mg) was dissolved in CH_2Cl_2 (20 mL), and the mixture was cooled to 0 °C. *m*-CPBA (80%, 100 mg, 0.47 mmol) was added over 15 min. After 15 min, the solution was diluted with ether and washed with 10% Na_2SO_3 and saturated $NaHCO_3$. Drying (Na_2SO_4) and solvent removal in vacuo gave 150 mg of crude sulfoxide **27**. Back extraction of the aqueous washes, followed by drying and concentration in vacuo gave an additional 85 mg of crude sulfoxide **27**.

Each sample of **27** was dissolved in methanol (25 mL) and $KOCH_3$ (20 mg) added. After 15 min at room temperature, NH_4Cl (100 mg) was added to the mixtures and the solvent removed in vacuo. The residues were dissolved in CH_2Cl_2, and the solutions were washed with water. Drying (Na_2SO_4) and concentration in vacuo gave oils (102 and 70 mg, respectively). The latter oil crystallized from $CHCl_3$ to give a single sulfoxide **29** (30 mg, 14%). (The former oil gave no crystalline product): mp 250 °C dec; MS, $C_{20}H_{30}O_7S$ calcd 426, found 426; ^1H NMR δ 0.87 (3 H, d), 1.5–2.5 (m), 2.01, 3.03 (2 H, AB, J = 15 Hz), 2.50, 3.78, (2 H, AB, J = 13 Hz), 3.60 (1 H, s), 3.84 (3 H, s), 3.95 (4 H. m), 4.11 (1 H, br s).

1β,2,3,4,4a,4bα,5,6,7,8,8a,9β,10,10aα-Tetradecahydro-9α-hydroxy-8aβ,4aβ-(1-(methoxycarbonyl)-2-thiapropano)-1α-methyl-2,7-phenanthradione 2,2-Dioxide 2-(Ethylene Acetal) (30). To a solution of sulfide **28** (340 mg, 0.83 mmol) in CH_2Cl_2 (25 mL) was added 80% *m*-CPBA (200 mg, 0.93 mmol). After 5 min at room temperature, the mixture was diluted with ether and washed with saturated $NaHCO_3$ and saturated NaCl. Drying (Na_2SO_4) and solvent removal in vacuo gave crude sulfoxide **27** (130 mg). Back extraction of the aqueous washes gave more sulfoxide **27** (180 mg, 88% total).

The combined sulfoxide **27** was dissolved in methanol (40 mL) and $KOCH_3$ (50 mg) added. After 1 h at room temperature, NH_4Cl (200 mg) was added and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and the solution washed with water. Drying (Na_2SO_4) and concentration in vacuo gave crude cyclic sulfoxide **29** (320 mg, 90%).

The crude sulfoxide **29** was dissolved in CH_2Cl_2 (30 mL) and 80% *m*-CPBA (200 mg, 0.93 mmol) added. After 3 h at room temperature, the solution was washed with 10% Na_2SO_3 and dried (Na_2SO_4). Removal of the solvent in vacuo and flash chromatography (EtOAc) gave sulfone **30** (280 mg, 76%) as a mixture of diastereoisomers (4:1). Attempted recrystallization from ether/$CHCl_3$ gave a mixture of isomers: amorphous solid; ^1H NMR (major isomer) δ 0.87 (3 H, d), 1.3–2.7 (m), 2.18, 3.18 (2 H, AB, J = 15 Hz), 3.12, 3.82 (2 H, AB, J = 15 Hz), 3.86 (3 H, s), 3.95 (4 H, m), 4.17 (1 H, s), 4.85 (1 H, br s); IR 3.4, 5.7, 5.8 cm^{-1}.

1β,2,3,4,4a,4bα,5,6,7,8,8a,9β,10,10aα-Tetradecahydro-9α-hydroxy-1α-methyl-8aβ,4aβ-(2-thiapropano)-2,7-phenanthradione 2,2-Dioxide 2-(Ethylene Acetal) (31). The sulfone mixture **30** (50 mg, 0.11 mmol) was dissolved in HMPA (1 mL) and tetramethyl ammonium acetate (100 mg) added. After 2 h at 125 °C, the mixture was poured onto a plug of silica gel and eluted with EtOAc. Removal of the solvent in vacuo gave a residue (150 mg) that was purified by flash chromatography (EtOAc) to give sulfone **31** (15 mg, 35%): foam; ^1H NMR 0.88 (3 H, d), 1.2–2.8 (m), 1.89, 3.16 (2 H, AB, J = 14 Hz), 2.97, 3.18 (2 H, AB, J = 15 Hz), 2.99, 3.68 (2 H, AB, J = 15 Hz), 3.62 (1 H, br s), 3.95 (4 H, m); IR 3.4, 5.8 cm^{-1}.

Acknowledgment. We thank the National Institutes of Health for support of this research (CA-21840). We also wish to thank the Purdue University Biological Magnetic Resonance Laboratory (NIH RR 01077) for access to the 470-MHz ^1H NMR Spectrometer and Phil Hamann and Tamin Braish for providing those spectra.

Registry No. 1, 41451-75-6; 6, 105619-37-2; (±)-7, 105619-38-3; (±)-8 (isomer 1), 105619-39-4; (±)-8 (isomer 2), 105619-34-9; (±)-8 (isomer 3), 105662-66-6; (±)-8 (isomer 4), 105619-35-0; (±)-9, 105619-41-8; (±)-10, 105619-41-8; (±)-11, 105619-42-9; (±)-12, 105619-43-0; (±)-13, 105619-44-1; (±)-14, 105639-31-4; (±)-15, 105619-45-2; (±)-16, 105619-46-3; (±)-17, 105619-47-4; (±)-18, 105619-48-5; (±)-19a, 105619-49-6; (±)-19a (dihydro deriv.), 105619-36-1; (±)-19a (enone), 105619-60-1; (±)-19b, 105619-61-2; (±)-19b (diene), 105619-62-3; (±)-19b (enone), 105619-63-4; (±)-20a, 105619-50-9; (±)-20b, 105619-64-5; (±)-21, 105619-51-0; (±)-22c, 105662-67-7; (±)-22t, 105619-52-1; (±)-23, 105619-53-2; (±)-24c, 105662-68-8; (±)-24t, 105619-54-3; (±)-25, 105619-55-4; (±)-26, 105619-56-5; (±)-27 (isomer 1), 105760-35-8; (±)-27 (isomer 2), 105619-65-6; (±)-28, 105619-57-6; 29, 105639-32-5; (±)-30 (isomer 1), 105619-58-7; (±)-30 (isomer 2), 105662-69-9; (±)-31, 105619-59-8; 1-chloro-3-pentanone, 32830-97-0.

Supplementary Material Available: Stereochemical assignment of **22c**, **22t**, **24c**, and **24t** by ^{13}C NMR chemical shifts, a tabular ^{13}C NMR comparison of **6**, **7**, **8**, **9**, **10**, **12**, **13**, **18**, **20a**, **20b**, **22c**, **22t**, **24c**, **24t**, **26**, and **28**, and X-ray crystallographic data for **24c** and **24t** (10 pages). Ordering information is given on any current masthead page.

Trichothecene Degradation Studies. 2. Synthesis of [13-^{14}C]Anguidine

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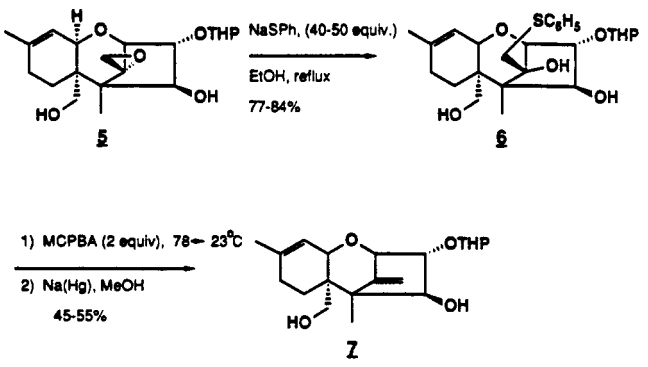
An efficient degradation and resynthesis of anguidine that pivots around norketone **4** is described. The sequence from anguidine to anguidine via **4** proceeds in 12 steps with an overall yield of 30%. This work has permitted for the first time the preparation of an enantiomerically pure, high specific activity ^{14}C-labeled epoxytrichothecene mycotoxin required for biological investigations. The radiolabel was introduced by the reaction of **4** with [^{14}C]CH_2PPh_3.

The epoxytrichothecene mycotoxins are a group of fungal metabolites that exhibit a range of significant biological properties including cyto- and phytotoxicity.[2] These mycotoxins are potent inhibitors of protein synthesis

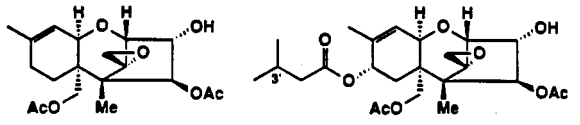
0022-3263/87/1952-0598$01.50/0

Scheme I



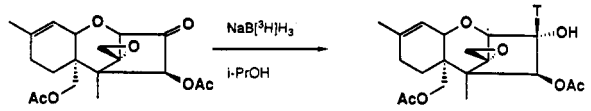
5 6 7

in eukaryotes and have been implicated in a number of diseases of plants, humans, and animals.[2a] One member of this group, anguidine (1), was the subject of phase II clinical trials as an anticancer agent[3] and others, including T-2 toxin (2), have been implicated in the "yellow rain" chemical warfare controversy.[4]



1 2

In spite of the toxicological significance of the epoxytrichothecenes, relatively little is known about their metabolic fate in mammalian systems.[2,5,6] Tritium-labeled materials have been used almost exclusively in work performed thus far, since ^3H is easily introduced by $NaB[^3H]H_3$ reduction of epoxytrichothecen-3-ones such as **3**.[7] One potential problem with use of ^3H-labeled



3 [^3H]-1

substrates in in vivo studies, however, is that the ^3H label can be lost via oxidative processes, and consequently some metabolic events may go undetected. Although this concern would be minimized if ^{14}C-labeled compounds were employed, until now such studies were not possible since skeletally labeled ^{14}C-trichothecenes were available only by biosynthesis[8] or total synthesis.[9-11] The biosynthetic procedure provides material with specific activity (ca. 1 μCi/mmol) too low to be useful for in vivo studies, whereas the total synthesis approach necessitates a labor intensive, multistep effort to gain access to racemic material.[10b]

We describe here the first practical synthesis of high specific activity [^{14}C]anguidine using natural **1** as starting material.[12] Our strategy was to degrade anguidine to norketone **4** which would be used to resynthesize [^{14}C]-**1** with incorporation of the radiolabel in a Wittig step.

1 4

In a previous publication we described the synthesis of diene **7** as summarized in Scheme I.[13,14] In an effort to improve the efficiency of this sequence, we returned to an examination of one-step methods for deoxygenation of **5** or its precursor, diacetate **8**.[15] Treatment of **8** with dia-

8 9, R = THP
10, R = H

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(2) (a) *Developments in Food Science, Vol. 4: Trichothecenes: Chemical, Biological, and Toxicological Aspects*; Ueno, Y., Ed.; Elsevier: New York, 1983. (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.

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(5) (a) Roush, W. R.; Marletta, M. A.; Russo-Rodriguez, S.; Recchia, J. *J. Am. Chem. Soc.* **1985**, *107*, 3354. (b) Roush, W. R.; Marletta, M. A.; Russo-Rodriguez, S.; Recchia, J. *Tetrahedron Lett.* **1985**, *26*, 5231.

(6) For additional leading references, see: (a) Yoshizawa, T.; Sakamoto, T.; Kuwamura, K. *Appl. Environ. Microbiol.* **1985**, *50*, 676. (b) Yoshizawa, Y.; Cote, L.-M.; Swanson, S. P.; Buck, W. B. *Agric. Biol. Chem.* **1986**, *50*, 227. (c) Yoshizawa, T.; Sakamoto, T.; Okamoto, K. *Appl. Environ. Microbiol.* **1984**, *47*, 130. (d) Yoshizawa, T.; Sakamoto, T.; Anyano, Y.; Mirocha, C. J. *Agric. Biol. Chem.* **1982**, *46*, 2613. (e) Robison, T. S.; Mirocha, C. J.; Kurtz, H. J.; Behrens, J. C.; Weaver, G. A.; Chi, M. S. *J. Agric. Food Chem.* **1979**, *27*, 1411. (f) Yoshizawa, T.; Takeda, H.; Ohi, T. *Agric. Biol. Chem.* **1983**, *47*, 2133. (g) King, R. R.; McQueen, R. E.; Levesque, D.; Greenhalg, R. *J. Agric. Food Chem.* **1984**, *32*, 1181. (h) Yoshizawa, T.; Swanson, S. P.; Mirocha, C. J. *Appl. Environ. Microbiol.* **1980**, *39*, 1172. (i) Yoshizawa, T.; Swanson, S. P.; Mirocha, C. J. *Ibid.* **1980**, *40*, 901. (j) Matsumoto, H.; Ito, T.; Ueno, Y. *Jpn. J. Exp. Med.* **1978**, *48*, 393. (k) Ohta, M.; Matsumoto, H.; Ishii, K.; Ueno, Y. *J. Biochem. (Tokyo)* **1978**, *84*, 697.

(7) (a) We thank Dr. T. W. Doyle of Bristol Laboratories for providing the experimental procedure for preparation of [^3H]-**1** prior to publication. 3-[^3H]Anguidine, however, is radiochemically unstable in the crystalline state but can be stored without decomposition in frozen EtOH solution (Caggiano, T. J.; Roush, W. R., unpublished results). (b) See also: Wallace, E. M.; Pathre, S. V.; Mirocha, C. J.; Robison, T. S.; Fenton, S. W. *J. Agric. Food Chem.* **1977**, *25*, 836.

(8) Hagler, W. M.; Mirocha, C. J.; Pathre, S. V. *Appl. Environ. Microbiol.* **1981**, *41*, 1049.

(9) Fujimoto, Y.; Morooka, N.; Takahashi, K.; Tatsuno, T. *Maikotokishin (Tokyo)* **1981**, *13*, 4; *Chem. Abst.* **1982**, *97*, 39161f. These authors describe the preparation of racemic [13-^{14}C]-12,13-epoxytrichothec-9-ene by a 15-step total synthesis. The specific activity was 0.5 mCi/mmol (see Chapter II of the text cited in ref 2a).

(10) (a) For an excellent review of chemical syntheses of epoxytrichothecenes, see: McDougal, P. G.; Schmuff, N. R. *Prog. Chem. Org. Nat. Prod.* **1985**, *47*, 153. (b) Only one synthesis of an optically active epoxytrichothecene has been reported to date (Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472). Interestingly, the biological properties of racemic epoxytrichothecenes, or of the unnatural enantiomers, have not yet been described in the literature.

(11) Radiolabeled epoxytrichothecenes have also beeen prepared by acylation of suitable trichothecenols with [^3H]- or [^{14}C]acetic anhydride (Wei, R.-D.; Guan, W.-R. *K'o Hsueh Fa Chan Yueh K'an* **1976** *4*, 2374; *Chem. Abstr.* **1979**, *90*, 134963h). Such materials are not suitable for metabolism studies, however, since trichothecene esters are rapidly hydrolyzed in vivo (see ref 5, 6).

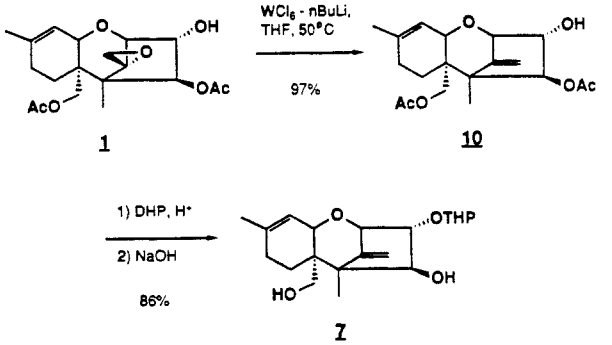
(12) Anguidine was purchased from Romer Labs of Washington, MO, and was obtained as a crude fermentation extract. This material was partitioned between CH_3CN and hexane in a continuous extractor. Crude anguidine recovered from the CH_3CN phase was purified either by direct recrystallization from ether–hexane, or by chromatography over silica gel (1:1 EtOAc–hexane) before recrystallization: mp 161–163 °C; $[\alpha]^{23}_D$ −30.3° (*c* 1.10, $CHCl_3$); lit. values: mp 162–164 °C; $[\alpha]^{24}_D$ −27° (*c* 1.28, $CHCl_3$) (see: Sigg, H. P.; Mauli, R.; Flury, E.; Hauser, D. *Helv. Chim. Acta* **1965**, *48*, 962).

(13) Roush, W. R.; Russo-Rodriguez, S. *J. Org. Chem.* **1985**, *50*, 5465.

(14) Isomerically pure THP diastereomers were used throughout this work 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 preparation and separation of **5a** and **5b**, see: Roush, W. R.; Russo-Rodriguez, S. *J. Org. Chem.* **1985**, *50*, 3224.

zomalonate and $Rh_2(OAc)_4$ in benzene at reflux (48 h) according to Ganem's procedure[16] provided only a trace of **9** (TLC analysis). Similarly, no reaction was observed when **8** was treated with the reagent prepared from $FeCl_3$ and *n*-BuLi.[17] On the other hand, a complex mixture of unidentified products was obtained upon attempted deoxygenation of **8** by using the low valent titanium preparation ($TiCl_3$–$LiAlH_4$, 4:1) described by McMurry.[18] Partial success was achieved by using the low valent tungsten reagent (WCl_6/*n*-BuLi) developed by Sharpless.[19,20] Unfortunately, however, the major product from an experiment using 2 equiv of WCl_6 and 6 equiv of *n*-BuLi was 12,13-deoxyanguidine (**10**, 47%) and not the desired THP ether **9** (20% yield).

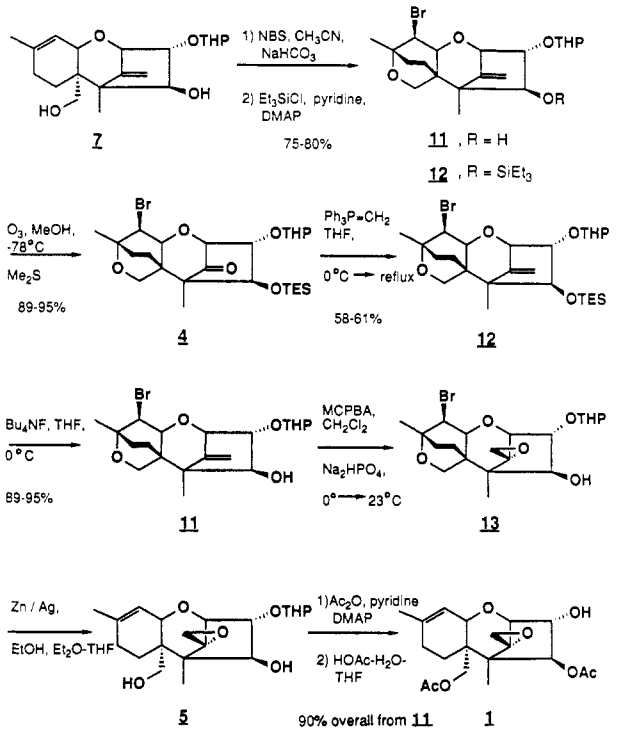
The observation that the THP ether of **10** was stable under these conditions prompted us to perform the deoxygenation directly on anguidine. Thus, treatment of **1** with 4 equiv of WCl_6 and 12 equiv of *n*-BuLi in THF at 50 °C provided 12,13-deoxyanguidine (**10**) in 97% yield.[21] Standard functional group manipulations then provided **7** in 83% yield overall for the three-step synthesis from anguidine, a considerable improvement over the lengthier sequence reported previously (Scheme I).[13]



1 **10** **7**

The synthesis of norketone **4** from diene **7** and the resynthesis of anguidine from **4** proceeded as summarized in Scheme II. The C(9)–C(10) double bond was selectively masked[22] by treatment with *N*-bromosuccinimide in CH_3CN containing excess $NaHCO_3$. The C(4)-hydroxyl group was then protected as a triethylsilyl (TES) ether giving **12** in 75–80% overall yield.[23] Ozonolysis of **12** in MeOH at −78 °C followed by Me_2S reduction of the intermediate α-methoxy hydroperoxide then completed the synthesis of the desired norketone **4** (89–95% yield after chromatography). The resynthesis of anguidine from **4** commenced with a standard Wittig methylenation that provided **12** in 58–61% yield. Deprotection of **12** by treatment with *n*-Bu_4NF in THF followed by a Na_2HPO_4-buffered MCPBA epoxidation gave **13** in high yield. The bromo ether unit was then reduced either with NaHg in MeOH or preferably with zinc–silver couple[24,25] in a Et_2O–THF–EtOH mixture to unmask the C(9)–C(10) olefin in trichothecene **5**. Finally, acylation of **5** followed by hydrolysis of the THP ether in a 1:2:1 mixture of H_2O, HOAc, and THF at 45 °C for 5–6 days completed this partial synthesis of anguidine (**1**). The overall yield of **1** from olefin **12** was 80–85%.

Scheme II



7 **11**, R = H; **12**, R = $SiEt_3$ **4** **12** **11** **13** **5** **1**

The synthesis of [13-^{14}C]anguidine was undertaken only after the sequence summarized in Scheme II had been fully optimized. [^{14}C]Methyl iodide (52 mCi/mmol) was diluted with an equal quantity of cold CH_3I and then was treated with stoichiometric Ph_3P in THF under standard conditions.[26] The resulting phosphonium salt was then deprotonated by using 1.0 equiv of phenyllithium in a THF–Et_2O–cyclohexane cosolvent mixture (13:1:2), giving a solution of $Ph_3P{=}^{14}CH_2$ that was treated with 1.0 equiv of norketone **4** in THF initially at 0 °C and then at 50 °C for 6 h. This procedure provided [^{14}C]-**12** with a specific activity of 26 mCi/mmol in 38% yield; 47% of **4** was recovered. The anomalously low yield in this case was probably the result of inadvertent contamination by moisture (incomplete ylide formation) that prevented the reaction from proceeding to completion. In no other instances were more than traces of **4** detected at the end of this step. Indeed, in a second labeling experiment differing

(15) We have previously reported that bromo ether **13** was recovered unchanged when treated with KSeCN in aqueous EtOH at reflux; $KSiMe_3$ in HMPT; $Fe(CO)_5$ in tetramethylurea; or sodium diethyl phosphorotelluroate in EtOH (see ref 13 for a discussion and pertinent literature references).

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(17) Fujisawa, T.; Sugimoto, K.; Ohta, H. *Chem. Lett.* **1974**, 883.

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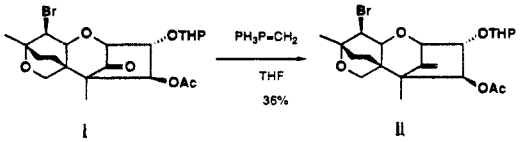
(20) While these studies were in progress, Dr. Ernest W. Colvin, University of Glasgow, informed us of his successful use of this deoxygenation method (Colvin, E. W.; Cameron, S. *J. Chem. Soc., Chem. Commun.* **1986**, 1084. Colvin E. W.; Cameron, S. *Heterocycles*, in press). We thank Dr. Colvin for providing us with these manuscripts prior to publication.

(21) The reaction proceeded only to approximately 50% conversion when 2 equiv of reagent (2 equiv of WCl_6, 6 equiv of *n*-BuLi) was used.

(22) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116.

(23) The C(4)-acetate corresponding to **12** was also prepared in early stages of this work. This blocking group was subsequently abandoned in favor of the triethylsilyl system, however, since the Wittig reaction of **i** proceeded in only 36% yield.



i **ii**

(24) Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549.

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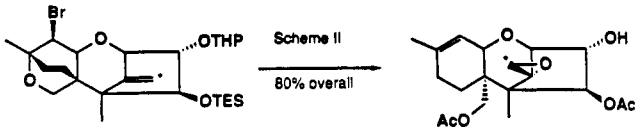
(26) (a) Pitt, C. G.; Hobbs, D. T.; Schran, H.; Twine, C. E., Jr.; Williams, D. L. *J. Label. Comp. Radiopharm.* **1975**, *11*, 551. (b) Oliver, J. E. *Ibid.* **1977**, *13*, 349.

from the first only in that the [^{14}C]methyl iodide was diluted threefold with cold CH_3I, the isolated yield of [^{14}C]-**12** was 58%, identical with that realized in experiments with unlabeled methylenetriphenylphosphorane. The specific activity of [^{14}C]-**12** from this second experiment was 9.5 ± 0.5 mCi/mmol.



[^{14}C]-**12** (26 mCi / mmol) [^{14}C]-**1** (19.2 mCi /mmol)

The elaboration of [^{14}C]-**12** to [^{14}C]anguidine proceeded in 80% overall yield by using the five-step sequence summarized in Scheme II. An isotopic fractionation occurred, however, presumably during the epoxidation step, since the specific activity of [^{14}C]-**1** was decreased to a level of 19.2 mCi/mmol. Nevertheless, owing to the high counting efficiency of ^{14}C, this material meets our original objective of high specific activity and is now being used by our collaborator, Professor M. A. Marletta, in in vitro and in vivo metabolism studies. Results of those investigations will be reported in due course.

In summary, we have developed an efficient degradation and resynthesis of anguidine that pivots around norketone **4** as the key intermediate. The sequence originating with the WCl_6/*n*-BuLi deoxygenation of anguidine proceeds in 12 steps with an overall yield of approximately 30%. This work has permitted for the first time the preparation of an enantiomerically pure, high specific activity ^{14}C-labeled epoxytrichothecene mycotoxin required for biological investigations. In anticipation that other members of this family may also be needed with ^{14}C labels, we have initiated studies focusing on the development of efficient syntheses of T-2 toxin and deoxynivalenol from anguidine.[27] Finally, we conclude by noting that several of our intermediates (e.g., **4**, **11**) are ideally suited to serve as relay points in efforts in total synthesis[10] or as starting points for the synthesis of trichothecene analogues.[28] Studies along the latter lines will be reported separately.

Experimental Section

Proton (^{1}H) NMR spectra were measured at 250 and 270 MHz on Bruker WM250 and 270 instruments and at 300 and 400 MHz on Varian XL-300 and 400 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 spectrophotometer 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, NJ. 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, THF, and toluene were distilled from sodium benzophenone ketyl; methylene chloride (CH_2Cl_2) and pyridine were distilled from CaH_2. The following reagents were purified before use: MCPBA (an Et_2O solution was washed with pH 7 phosphate buffer and brine and dried in vacuo over P_2O_5); PPh_3 (recrystallized from hexane and dried in vacuo over P_2O_5); MeI (distilled from P_2O_5 and stored over $CaSO_4$ and copper wire); NBS (recrystallized from water and dried in vacuo over P_2O_5); 4-DMAP (recrystallized from cyclohexane); triethylsilylchloride (distilled from CaH_2).

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 10% MeOH in CH_2Cl_2. Flash column chromatography was performed by the method of Still[29] using Merck 230–400-mesh silica gel. All chromatography solvents were distilled before use.

Specific activities of radiolabeled compounds were determined by dilution of an aliquot of a stock solution of the radiolabeled compound in CH_2Cl_2 into MeOH (usually 5–10 μL of stock solution into 5–10 mL of MeOH). Depending on expected activity, 20 μL or 50 μL of the MeOH solution was diluted into 12 mL of Aqueous Counting Scintillant Cocktail (supplied by Amersham) and counted on a Beckman LS 1800 liquid scintillation instrument. For each determination, two solutions were prepared and were counted twice. The values reported are averages of these multiple determinations.

12,13-Deoxyanguidine (10). To a −78 °C solution of WCl_6 (535 mg, 1.35 mmol) in 3.7 mL of THF under N_2 was added *n*-BuLi (1.6 mL of a 2.5 M solution in hexane, thus 4.0 mmol).[19] The mixture was stirred at −78 °C for 15 min and then allowed to warm to 25 °C. A solution of anguidine (**1**, 120 mg, 0.33 mmol) in 1.3 mL of THF was added dropwise and the resulting black mixture was heated to 50–55 °C for 50 min. The THF was evaporated and the crude product (1.6 g) was chromatographed on a 40 mm × 15 cm flash silica gel column (gradient of 1:1 to 2:1 EtOAc–hexane) to afford 112 mg (97%) of pure deoxyanguidine. The physical and spectroscopic properties were identical with that reported previously.[13]

3α-[(Tetrahydropyranyl)oxy]-4β,15-dihydroxytrichotheca-9,12-diene (7). To a solution of deoxyanguidine **10** (112 mg, 0.32 mmol) in 1.7 mL of dry CH_2Cl_2 was added distilled dihydropyran (0.10 mL, 1.1 mmol) and pyridinium *p*-toluenesulfonate (12 mg, 0.05 mmol). The reaction mixture was stirred for 16 h at 25 °C and then was diluted with CH_2Cl_2 (40 mL) and washed with half-saturated aqueous NaCl (10 mL). The organic phase was dried (Na_2SO_4), filtered, and evaporated to afford 200 mg of a diastereomeric mixture of deoxyanguidine THP ethers (R_f 0.70, 1:1 hexane–EtOAc) as a yellow oil. This material was used in the next step without purification.

This above crude deoxyanguidine THP ether was dissolved in 4 mL of a 5:3 mixture of THF–MeOH and was treated with 4 mL of 0.3 N NaOH (1.2 mmol). The mixture was stirred at 25 °C for 2.5 h and then was partitioned between 50 mL of CH_2Cl_2 and 10 mL of H_2O. The organic extracts were dried (Na_2SO_4), filtered, and evaporated to afford 200 mg of crude **7** as a mixture of THP diastereomers.[14] The mixture was separated by careful silica gel chromatography (18 cm × 30 mm column, 2.5% MeOH in CH_2Cl_2) to give 39 mg (35%) of **7a** (R_f 0.14, 2.5% MeOH–CH_2Cl_2), 43.5 mg (39%) of **7b** (R_f 0.11), and 13 mg (12%) of mixed fractions. The overall yield of **7** was thus 86% from **10** and 83% from anguidine. Comparative physical and spectroscopic data for **7a** and **7b** are tabulated in the paper cited in ref 13.

3α-[(Tetrahydropyranyl)oxy]-10β-bromo-9α,15-epoxytrichothec-12-en-4β-ol (11a).[14] To a solution of **7a**[13] (361 mg, 1.03 mmol) in 30 mL of reagent CH_3CN was added $NaHCO_3$ (359 mg, 4.3 mmol) and *N*-bromosuccinimide (267 mg, 1.5 mmol; freshly purified). After being stirred for 2 h at 23 °C, the reaction mixture was poured into 300 mL of a 1:1:1 mixture of CH_2Cl_2, hexane, and saturated aqueous Na_2SO_3. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by flash chromatography (silica gel, 2:1 EtOAc–hexane, 40 mm × 17 cm column) to afford 340 mg (77%)

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

of bromo ether **11a**: mp 77–79 °C; $[\alpha]^{20}_D$ −13.8° (*c* 0.69, $CHCl_3$); R_f 0.21 (2:1 hexane–EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 5.17 (s, 1 H, H_{13a}), 4.78 (s, 1 H, H_{13b}), 4.66 (m, 1 H, THP), 4.43 (d, 1 H, *J* = 4.8 Hz, H_2), 4.22 (m, 2 H, H_{11} and H_4), 4.13 (dd, 1 H, *J* = 2.3, 8.7 Hz, H_{10}), 3.95 (m, 1 H, THP), 3.75 (br s, 2 H, H_{15}), 3.66 (dd, 1 H, *J* = 3.1, 4.6 Hz, H_3), 3.56 (m, 1 H, THP), 2.60 (d, 1 H, *J* = 3.2 Hz, OH), 2.2–1.5 (m, 10 H), 1.25 (s, 3 H, H_{16}), 0.88 (s, 3 H, H_{14}); IR ($CHCl_3$) 3600–3400 (br), 2940, 2778, 1450, 1380, 1340, 1120 (br), 1050, 1020, 965, 900 cm^{-1}; FAB mass spectrum (glycerol-CH_2Cl_2), 429, 431 (M + H^+). Anal. Calcd for $C_{20}H_{29}O_5Br$: C, 56.06; H, 6.83. Found: C, 55.88; H, 7.06.

Bromo ether **11b** was prepared in comparable yield by using an identical procedure: mp 62–64 °C; R_f 0.20 (2:1 hexane–EtOAc); ^1H NMR ($CDCl_3$, 250 MHz) δ 5.17 (s, 1 H, H_{13a}), 4.92 (m, 1 H, THP), 4.76 (s, 1 H, H_{13b}), 4.43 (d, 1 H, *J* = 4.8 Hz, H_2), 4.22 (m, 2 H, H_{11} and H_4), 4.14 (dd, 1 H, *J* = 2.3, 8.7 Hz, H_{10}), 4.00 (m, 1 H, THP), 3.76 (dd, 1 H, *J* = 3.0, 4.8 Hz, H_3), 3.73 (s, 2 H, H_{15}), 2.2–1.3 (m, 10 H), 1.22 (s, 3 H, H_{16}), 0.96 (s, 3 H, H_{14}); IR ($CHCl_3$) 3600, 3550–3300, 2940, 2880, 1450, 1380, 1350, 1200, 1120, 1100–1030 (br), 960, 900 cm^{-1}; mass spectrum, *m/e* 430, 428 (M^+); high resolution mass spectrum for $C_{20}H_{29}O_5{}^{79}Br$, calcd 428.1198, found 428.1197 ± 0.0006.

3α-[(Tetrahydropyranyl)oxy]-4β-[(triethylsilyl)oxy]-10β-bromo-9α,15-epoxytrichothec-12-ene (12a). To a solution of **11a** (337 mg, 0.79 mmol) in 14 mL of dry pyridine were added 4-DMAP (20 mg, 0.16 mmol) and triethylsilyl chloride (0.28 mL, 1.67 mmol, freshly distilled). After 12 h at 23 °C, the reaction was diluted with CH_2Cl_2 to a volume of 100 mL and extracted with half-saturated aqueous $NaHCO_3$ (1 × 40 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo; residual pyridine was removed by coevaporation with heptane. The crude product (560 mg) was filtered through a 6 cm × 3 cm pad of silica gel using 4:1 hexane–EtOAc as eluent to afford 420 mg (97%) of pure **12a** as an oil: $[\alpha]^{20}_D$ +12.1° (*c* 1.5, $CHCl_3$); R_f 0.50 (9:1 hexane–EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 5.11 (s, 1 H, H_{13a}), 4.90 (m, 1 H, THP), 4.72 (s, 1 H, H_{13b}), 4.49 (d, 1 H, *J* = 4.6 Hz, H_2), 4.21 (overlapping d, 1 H, *J* = 2.9 Hz, H_4, and m, 1 H, H_{10}), 4.16 (d, 1 H, *J* = 8.8 Hz, H_{11}), 3.88 (dd, 1 H, *J* = 2.8, 4.5 Hz, H_3), 3.84 (m, 1 H, THP), 3.72 (s, 2 H, H_{15}), 3.50 (m, 1 H, THP), 2.2–1.7 (m, 10 H), 1.24 (s, 3 H, H_{16}), 0.94 (t, 9 H, TES), 0.79 (s, 3 H, H_{14}), 0.60 (m, 6 H, TES); IR ($CHCl_3$) 2960, 2880, 1455, 1378, 1080 (br), 1025, 1010, 955, 900, 850 cm^{-1}; FAB mass spectrum (glycerol-CH_2Cl_2), 543, 545 (M + H^+).

Compound **11b** was prepared in comparable yield by using this procedure: R_f 0.50 (9:1 hexane–EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 5.11 (s, 1 H, H_{13}), 4.78 (m, 1 H, THP), 4.71 (s, 1 H, H_{13b}), 4.44 (d, 1 H, *J* = 4.8 Hz, H_2), 4.21 (m, 3 H, H_4, H_{10} and H_{11}), 4.17 (m, 1 H, THP), 3.73 (s, 2 H, H_{15}), 3.59 (t, 1 H, *J* = 3 Hz, H_3), 3.57 (m, 1 H, THP), 2.2–1.4 (m, 10 H), 1.24 (s, 3 H, H_{16}), 0.95 (t, 9 H, TES), 0.79 (s, 3 H, H_{14}), 0.55 (m, 6 H, TES).

3α-[(Tetrahydropyranyl)oxy]-4β-[(triethylsilyl)oxy]-10β-bromo-9α,15-epoxy-13-nortrichothecan-12-one (4a). A stream of ozone in O_2 was passed through a −78 °C solution of olefin **12a** (260 mg, 0.48 mmol) in 30 mL of dry MeOH and 2 mL of dry CH_2Cl_2 (added to keep **12a** in solution) containing 3A sieves (0.6 g). The disappearance of starting material was monitored by TLC (9:1 hexane–EtOAc eluent) and was complete in approximately 10 min at −78 °C. Excess O_3 was removed by purging the mixture with a stream of O_2, and then 10 mL of Me_2S was carefully added dropwise. The reaction mixture was allowed to warm to 23 °C and stirred for 2 h. Conversion of the α-methoxy hydroperoxide intermediate to **4a** was monitored by TLC. The sieves were removed by filtration, and the filtrate was evaporated in vacuo. The residue was dissolved in a minimum amount of ethyl acetate and chromatographed on a 25 mm × 15 cm flash silica gel column using 9:1 hexane–EtOAc as eluant, giving 232 mg (89%) of **4a**: mp 100–102 °C; $[\alpha]^{20}_D$ +89.9° (*c* 0.78, $CHCl_3$); R_f 0.55 (8:1 hexane–EtOAc); ^1H NMR (250 MHz, $CDCl_3$) δ 4.83 (br s, 1 H, THP), 4.42 (dd, 1 H, *J* = 2.3, 8.8 Hz, H_{10}), 4.38 (d, 1 H, *J* = 3.0 Hz, H_4), 4.19 (dd, 1 H, *J* = 1.2, 8.7 Hz, H_{11}), 4.12 (d, 1 H, *J* = 4.8 Hz, H_2), 4.03 (dd, 1 H, *J* = 3.0, 4.8 Hz, H_3), 3.87 (m, 1 H, THP), 3.77 (dd, 1 H, *J* = 2.4, 9.3 Hz, H_{15a}), 3.69 (d, 1 H, *J* = 9.2 Hz, H_{15b}), 3.52 (m, 1 H, THP), 2.25–1.5 (m, 10 H), 1.25 (s, 3 H, H_{16}), 0.94 (t, 9 H, TES), 0.80 (s, 3 H, H_{14}), 0.63 (m, 6 H, TES); IR ($CHCl_3$) 2950, 2880, 1765, 1710, 1455, 1355, 1100 (br), 960, 845 cm^{-1}; mass spectrum, *m/e* 462, 460 (M^+ − C_5H_8O); high resolution mass spectrum for $C_{20}H_{33}O_5{}^{79}Br^{28}Si$ (M^+ − C_5H_8O), calcd 460.128, found 460.127. Anal. Calcd for $C_{25}H_{41}O_6BrSi$: C, 55.13; H, 7.59. Found: C, 54.99; H, 7.60.

Norketone **4b** was prepared in comparable yield: R_f 0.54 (8:1 hexane–EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (br s, 1 H, THP), 4.42 (dd, 1 H, *J* = 2.6, 8.9 Hz, H_{10}), 4.38 (d, 1 H, *J* = 3.1 Hz, H_4), 4.24 (dd, 1 H, *J* = 2.1, 9.52 Hz, H_{11}), 4.08 (d, 1 H, *J* = 4.8 Hz, H_2), 4.05 (m, 1 H, THP), 3.78 (dd, 1 H, *J* = 2.3, 9.0 Hz, H_{15a}), 3.70 (m, 2 H, H_3 and H_{15b}), 3.55 (m, 1 H, THP), 2.2 (m, 1 H), 1.8–1.5 (m, 10 H), 1.27 (s, 3 H, H_{16}), 0.93 (t, 9 H, TES), 0.80 (s, 3 H, H_{14}), 0.60 (q, 6 H, TES).

Synthesis of 12a by the Wittig Olefination of 4a. A 0.4 M solution of methylenetriphenylphosphorane in THF was prepared by adding *n*-BuLi (0.49 mL of 2.4 M solution in hexane, 1.1 mmol) to methyltriphenylphosphonium iodide (401 mg, 0.99 mmol, freshly prepared from Ph_3P and CH_3I, and dried in vacuo) in THF (2.2 mL) at −78 °C for 15 min and then warmed to 0 °C. The ylide solution (0.13 mL, 0.048 mmol theoretical) was added to a 0 °C solution of **4a** (24 mg, 0.04 mmol) in 1 mL of THF. The reaction mixture was heated to reflux for 1 h and then was worked up by partitioning between Et_2O (30 mL) and H_2O (10 mL). The organic layers were dried (Na_2SO_4) and evaporated, and the crude product was chromatographed on 0.50-mm preparative TLC plate (1 elution, 8:1 hexane–EtOAc) to afford 12 mg of semisynthetic **12a** (61%) and 0.3 mg of recovered starting ketone **4a** (1%). The physical properties of **12a** were identical with those reported previously.

Semisynthetic Bromo Ether 11a. To a solution of **12a** (57 mg, 0.10 mmol) in 2 mL of THF at 0 °C was added Bu_4NF (0.12 mL of a 1 M solution, 0.12 mmol). The reaction was stirred for 1 h and then was diluted with 20 mL of Et_2O and washed with brine (1 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated. The crude product (91 mg) was purified by preparative TLC (0.50-mm silica gel plate, 2 elutions, 2:1 hexane–EtOAc) to give 43 mg of pure **11a** (96%), identical in all respects with the naturally derived material described previously.

Semisynthetic Epoxide 13a. To a solution of **11a** (23 mg, 0.055 mmol) in 0.5 mL of dry CH_2Cl_2 was added anhydrous Na_2HPO_4[30] (162 mg, 1.14 mmol) and MCPBA (96%, 41 mg, 0.23 mmol). This mixture was stirred at 23 °C for 3 h and then stored overnight at 5 °C until it was convenient to initiate the reaction workup. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with half-saturated aqueous Na_2SO_3 (10 mL) and half-saturated aqueous $NaHCO_3$ (10 mL). The organic extracts were dried (Na_2SO_4) and evaporated to give a crude product (40 mg) that was used directly in the next step without purification. Products from separate experiments were purified by preparative TLC (1:1 hexane–EtOAc as eluant; 2 elutions) to give pure samples of semisynthetic **13a**. Comparative spectroscopic data are tabulated in the paper cited in ref 14.

Semisynthetic 5a. To a suspension of Zn/Ag couple (freshly prepared from 10 mg of AgOAc and 1.72 g of Zn in 10 mL of glacial HOAc)[24] in 3 mL of dry Et_2O was added a solution of crude **13a** (sample from the preceding experiment weighed 40 mg, but contained maximally 0.055 mmol of **13a**) in 4 mL of THF followed by 0.8 mL of dry EtOH. The reaction mixture was then heated to 55–50 °C for 18 h. The solvents were evaporated and the residue suspended in acetone and filtered through a short pad of silica gel overlayered with Celite. The filtrate was concentrated and the residue dissolved in CH_2Cl_2. Residual, insoluble Zn^{2+} salts were then removed by gravity filtration. The resulting crude product (51 mg) was used in the next reaction without purification. Samples from separate experiments were purified chromatographically and were shown to be identical with authentic material previously characterized.[14]

Semisynthetic Anguidine (1). To a solution of crude **5a** (sample from the preceding experiment weighed 51 mg, but contained maximally 0.055 mmol of **5a**) in 1.7 mL of dry pyridine was added Ac_2O (0.068 mL, 0.71 mmol) and a crystal of 4-DMAP (7.2 mg, 0.06 mmol). After being stirred for 3 h at 23 °C, the solution was coevaporated with heptane (2 × 50 mL). The residue was filtered through a 1-cm pad of silica gel using 1:1 hexane–

(30) In one experiment when Na_2HPO_4 was omitted, **13** underwent an acid-catalyzed rearrangement to the apotrichothecene skeleton. Thus, use of Na_2HPO_4 as a buffer is strongly recommended.

EtOAc as eluant to afford 60 mg of crude **8a**. This material was dissolved in a solvent mixture containing 0.46 mL of HOAc, 0.23 mL of THF, and 0.23 mL of H_2O and was stirred at 40 °C for 6 days. This mixture was coevaporated from heptane (2 × 50 mL) and the crude product was purified by preparative TLC (1:1 hexane–EtOAc) to afford 19 mg (0.052 mmol) of pure, semisynthetic anguidine. The overall yield for the four-step sequence from **11a** was 94%. The physical properties of semisynthetic **1** were indistinguishable from those of authentic, naturally derived material:[12] mp 160–162°; $[\alpha]^{21}_D$ -30.9° (*c* 1.11, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 5.51 (d, 1 H, J = 4.9 Hz, H_{10}), 5.10 (d, 1 H, J = 2.9 Hz, H_4), 4.15 (m, 2 H, H_{15a} and H_3), 3.93 (d, 1 H, J = 12.4 Hz, H_{15b}), 3.68 (d, 1 H, J = 4.9 Hz, H_2), 3.18 (d, 1 H, J = 2.6 Hz, OH), 3.05 (d, 1 H, J = 3.9 Hz, H_{13a}), 2.76 (d, J = 3.9 Hz, H_{13b}), 2.12 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 1.69 (s, 3 H, H_{16}), 0.80 (s, 3 H, H_{14}).

[^{14}C]Methyltriphenylphosphonium Iodide. To a -78 °C solution of PPh_3 (56.3 mg, 0.22 mmol) in 0.15 mL of dry THF was added via syringe a solution of $^{14}CH_3I$ (13.7 mg, 0.1 mmol, 5 mCi, 52 mCi/mmol, New England Nuclear) in 1.5 mL of THF that had been precooled to -78 °C. The sealed reaction mixture was stirred at ambient temperature for 2 h before addition of cold CH_3I (7.3 μL, 0.11 mmol). This mixture was then stirred for 43 h. The solvent was removed by syringe and the crystals of $Ph_3P^{14}CH_3I$ were carefully rinsed under N_2 with dry toluene (3 × 1 mL). This sample of phosphonium salt was dried in vacuo for 1.5 h (25 °C) and was used immediately in the next reaction.

Synthesis of [^{14}C]-12b. To a stirred suspension of $PPh_3{}^{14}CH_3{}^+I^-$ (from the previous experiment, theoretically 0.22 mmol) in 0.54 mL of dry THF at -78 °C was added PhLi (0.13 mL of 1.7 M solution in 7:3 cyclohexane–Et_2O, 0.22 mmol). The suspension turned bright yellow and was stirred at -78 °C for 20 min and then warmed to 0 °C and stirred at this temperature for 10 min. The clear, red-orange ylid solution was cooled to 0 °C and then a solution of ketone **4b** (117 mg, 0.22 mmol) in 1.1 mL of THF was added dropwise. The mixture was heated to 50 °C for 6 h and stored at -78 °C overnight. The solution was diluted with Et_2O (30 mL) and washed with H_2O (10 mL) and 1:1 saturated Na_2SO_3–1 M K_2CO_3 (10 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were dried (Na_2SO_4), filtered, and concentrated to afford 147 mg of an orange oil. The product mixture was separated by flash chromatography (25 mm × 15 cm column, hexane–EtOAc 20:1; mixed fractions were rechromatographed on a 15 mm × 12 cm column), giving 44.9 mg (38%) of [^{14}C]-**12b** and 56 mg (47%) of recovered **4b**. The yield of **12b** based on unrecovered **4b** was 72%. Compound **12b** was identical with authentic samples by TLC and 300-MHz ^{1}H NMR analysis and had a specific activity of 26 mCi/mmol.

In a second experiment, $[^{14}C]CH_3PPh_3{}^+I^-$ was prepared from Ph_3P (0.36 mmol), $[^{14}C]CH_3I$ (0.09 mmol, 5 mCi, 58 mCi/mmol), and unlabeled CH_3I (0.27 mmol). The salt was dried in vacuo for 6 h before use and then was converted to the ylide by using the procedure described above. The ylide was treated with **4b** (195 mg, 0.36 mmol) in THF at reflux for 1 h. The reaction was worked up and the product purified as described above, giving 113 mg (58% yield) of **12b** (specific activity 9.5 ± 0.5 mCi/mmol).

Synthesis of [^{14}C]Anguidine. [^{14}C]-**12b** (44.9 mg, 0.08 mmol, 26 mCi/mmol) was converted into 25 mg of [^{14}C]-**1** (19.2 mCi/mmol) by using the procedures described previously for unlabeled materials. The overall yield was 80%. Only two purifications were performed—the first at the stage of [^{14}C]-**11** and the second at the end of the sequence. The [^{14}C]anguidine so obtained was identical with authentic samples by TLC, HPLC (radiochemical detection used in both cases), and 300-MHz ^{1}H NMR.

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Trichothecene Degradation Studies. 3. Synthesis of 12,13-Deoxy-12,13-methanoanguidine and 12-Epianguidine, Two Optically Active Analogues of the Epoxytrichothecene Mycotoxin Anguidine

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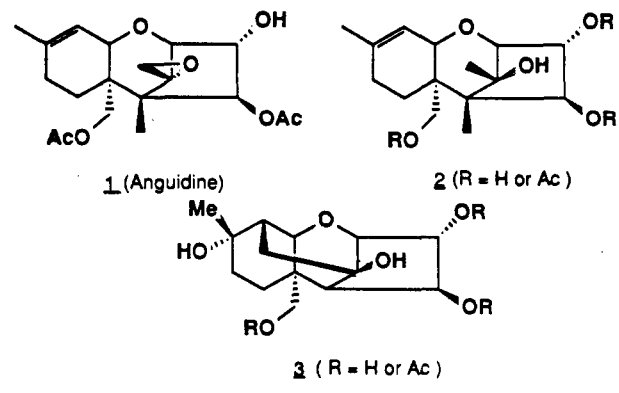
The title compounds were synthesized in order to further explore the apparent requirement of the trichothecene 12,13-epoxide unit for biological activity. Cyclopropane analogue **4** was prepared via a sequence involving a Simmons–Smith cyclopropanation of the anguidine degradation intermediate **6**, whereas the key step in the synthesis of 12-epianguidine (**5**) was the dimethylsulfonium methylide mediated cyclopropanation of norketone **9**. These compounds are among the first skeletally modified, semisynthetic trichothecene analogues to be prepared for biological evaluation.

A characteristic structural feature of the trichothecene mycotoxins is the 12,13-epoxide that occurs with high frequency in the naturally occurring members of this family.[2] This unit appears to be essential for the manifestation of cytotoxicity and other deleterious biological effects (e.g., feed refusal by animals) since chemically modified trichothecenes such as **2** (prepared via $LiAlH_4$ reduction of **1**) and **3** (product of epoxide substitution via



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