(CA40250, and GM 07183 for a training grant to C.L.M.), the Alfred P. Sloan Foundation, American Cyanamid, Merck, Sharp and Dohme, and Glaxo. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA 14599). P.J.S. would like to acknowlege financial support from the Robert A. Welch Foundation.

Supplementary Material Available: Experimental procedures and spectral data for ii, iii (footnote 11), and 2–10 (8 pages). Ordering information is given on any current masthead page.

Solvolytic Cyclization of 4,15-Anhydroverrucarol. A Facile Trichothecene–10,13-Cyclotrichothecene Rearrangement

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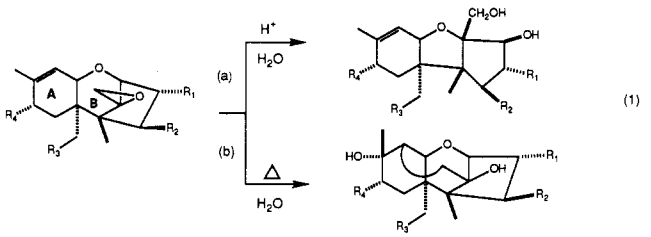
Summary: The conformation of the trichothecene ring system has been altered appreciably by introduction of an oxygen bridge between C4 and C15, which results in the C9,C10 double bond participating in the spontaneous solvolysis of the spiro epoxide group.

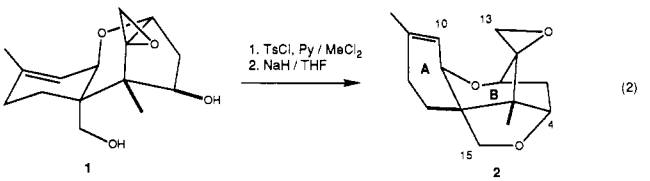
Sir: The trichothecene complex of antibiotics has attracted attention in recent years, principally due to their role as mycotoxins.[1] These sesquiterpenes exhibit a broad range of biological activity,[2] in addition to undergoing a variety of interesting chemical transformations.[3] Although the 12,13-epoxide group is very unreactive toward external nucleophiles,[4] this spiro epoxide is subject to two types of intramolecular nucleophilic ring-opening reactions, involving (1) participation by O_1 of the B-ring and (2) participation of the 9,10-double bond in the A-ring (eq 1a and 1b, respectively).[5] The former rearrangement leads to the



(1)

biologically inactive apotrichothecenes and occurs under acid conditions.[6] Rearrangement to the 10,13-cyclotrichothecenes (eq 1b), which occurs under neutral conditions, is far less commonly observed.[6,7] Herein, we report kinetic data for a 10,13-cyclotrichothecene rearrangement (eq 1b) that reveal that this reaction takes place via a solvolytic (or S_CN)[8] pathway, which to our knowledge is unprecedented for a methylene epoxide, though it does occur with suitably activated epoxides (e.g., *p*-methoxystyrene epoxide).[9]

Because the 10,13-cyclotrichothecene rearrangement requires that the 9,10 double bond become proximate to C-13, the course of events for the rearrangement should be highly dependent on the conformational bias of the tetrahydropyran ring (ring B), i.e., C-10 must come within bonding distance of C-13, which occurs only when ring B goes into a boat form. We have synthesized a bridged ether (**2**), whose conformational mobility differs markedly from normal trichothecenes, with the idea that this compound will differ significantly in its chemical behavior from normal trichothecenes. The 4,15-cyclic ether **2** was prepared in overall 40% yield (eq 2) from verrucarol (**1**), a trichothecene available from the hydrolysis of macrocyclic trichothecenes.[10] Ether **2** can readily assume the B-ring boat conformation and thus should readily undergo the 10,13-cyclotrichothecene rearrangement.



(2)

Molecular mechanics calculations MM2 (Macro Model System 1.5, W. C. Still, Columbia University) indicate that for verrucarol (**1**), the chair form of the B-ring is more stable by ca. 6 kcal/mol over that of the boat form. Somewhat surprisingly, these same calculations show that the boat form of the 4,15-cyclic ether **2** is more stable than the chair form by ca. 2 kcal/mol. This dramatic change in equilibrium appears to be due, in part, to the loss of nonbonding interactions between the C-15 group and the underside of the B/C-rings when C-15 is locked to C-4 by the oxygen bridge. This shift in equilibrium to favor the boat form of the B-ring is demonstrated by the reactivity of **2**. For example, care must be taken in the isolation of **2** since it reacts readily with water *under neutral or basic* conditions to give the 10,13-cyclotrichothecene **3a**, whose

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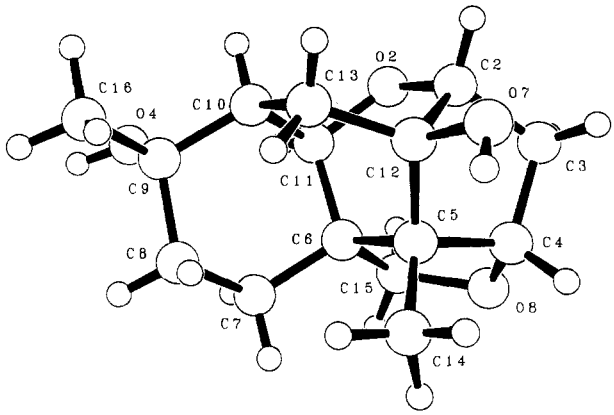
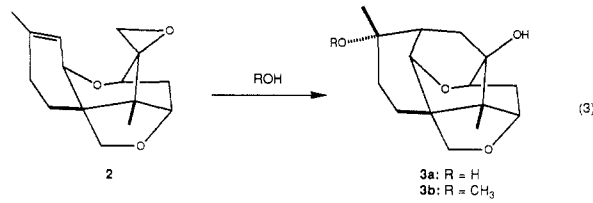


Figure 1. Ball-and-stick drawing of structure **3a** as determined by X-ray analysis. The C and O atoms are illustrated as isotropic spheres: $B = 3$ Å^2 for C and O, $B = 1.5$ Å^2 for H. Atom labels were inserted, and a laser printer plot was prepared with the PLOTMD program.[11]

structure was established by single-crystal X-ray determination and is illustrated in the drawing in Figure 1.

Compound **2** is reasonably stable (<10% reaction after 2 days) when dissolved in methanol. However, in 0.015 M NaOMe, **2** reacts to give **3b** with a $t_{1/2} \approx 22$ h at ca. 25 °C. The rate of this solvolysis is the same in 0.015 M methanolic $NaClO_4$, clearly indicating that this reaction (eq 3) is a unimolecular process.[12] When dissolved in a 5% buffered aqueous DMSO solution (50 mM Tris-HCl, 7 mM $MgCl_2$, 50 mM KCl at pH 7.6, which are conditions very similar to those employed in the protein synthesis inhibition experiments),[14] ether **2** undergoes complete rearrangement to **3a** in less than 5 min.[15,16]



(3)

2

3a: R = H
3b: R = CH_3

Although the solvolytic reactivity of **2** can be accounted for by the "spatiotemporal" postulate of Menger,[18] it also is entirely consistent with the thermodynamic arguments presented by Dorigo and Houk.[19] When the B-ring of the trichothecene is in the boat form, the 9,10 double bond is in an excellent position to attack C-13 since the distance between C-10 and C-13 is only about 3.0 Å (MM2 calculations). This is at a distance where the 9,10 double bond can exert a strong influence on the rate of opening of the 12,13-epoxide ring. This participation of the double bond in the ring opening of epoxytrichothecenes suggests that similar systems also may avail themselves of this reaction pathway if the conformation of the system can be suitably biased, e.g., by binding to an enzyme.

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Supplementary Material Available: Experimental data for compounds synthesized in this study and X-ray data for **3a** (7 pages). Ordering information is given on any current masthead page.

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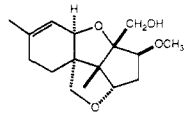
(12) Verrucarol diacetate rearranges slowly in water at reflux to the corresponding 10,13-cyclotrichothecene.[7] Both the yields and rates of this reaction are increased significantly upon addition of salts to the solution, a result consistent with this reaction occurring by an S_N1-type pathway. In methanol with added trifluoroacetic acid (0.015 M), **2** reacts rapidly to give a 9/1 mixture **3b**/i, which indicates that under suitable conditions, both types of rearrangements can be catalyzed by acid. Interestingly, the ratio of **3b**/i in this reaction corresponds to the calculated (MM2) ratio for the boat/chair forms of **2**, a correlation that on the basis of the Curtin-Hammett principle[13] may be purely fortuitous.



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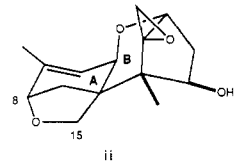
(15) The stability of **2** was assayed by ^{1}H NMR spectroscopy. A solution of 4 mg of **2** was dissolved in 20 μL of DMSO-d_6 and diluted with 500 μL of TMNa buffer (50 mM Tris, 7 mM $MgCl_2$, and 50 mM KCl adjusted with HCl to pH 7.6 at 20 °C)[14] in D_2O (pH 7.6). After 5 min, the ^{1}H NMR spectrum (200 MHz) showed only the presence of **3a** with no **2** detectable.

(16) The biological activity of trichothecenes can be traced to their ability to inhibit protein synthesis.[17] Compound **2** is inactive in the protein synthesis bioassay, whereas ii, which is incapable of assuming a B-ring boat conformation, exhibits protein synthesis inhibition activity similar to that observed for verrucarol (1). (We thank Prof. C. S. McLaughlin for furnishing these data). The inactivity of **2** may very well be likely due to its reactivity under the bioassay conditions rather than because of any inherent structural features.



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Syntheses of (±)-Alchorneine and (±)-Isoalchorneine

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Summary: The two title alkaloids have been prepared from cyanamide in four and three synthetic operations, respectively, using palladium-assisted cyclizations in the critical steps. The α-effect causes the hydroxylamino nitrogen atom in methoxyguanidine to be the most nucleophilic of the three nitrogens.

Sir: The tetrahydroimidazo[1,2-*a*]pyrimidine alkaloid alchorneine (1) was isolated from *Alchornea floribunda* Muell. (Euphorbiaceae) while its isomer isoalchorneine (2)

