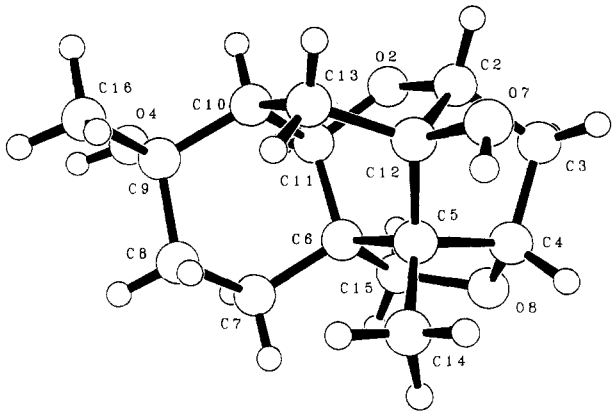
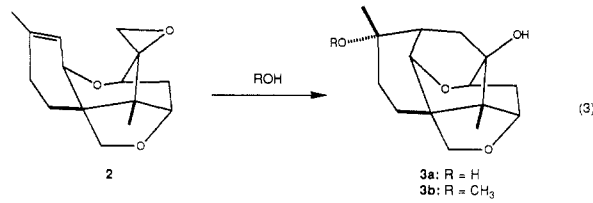


Figure 1. Ball-and-stick drawing of structure **3a** as determined by X-ray analysis. The C and O atoms are illustrated as isotropic spheres: $B = 3$ Å^2 for C and O, $B = 1.5$ Å^2 for H. Atom labels were inserted, and a laser printer plot was prepared with the PLOTMD program.[11]

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

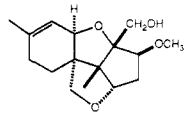
Although the solvolytic reactivity of **2** can be accounted for by the "spatiotemporal" postulate of Menger,[18] it also is entirely consistent with the thermodynamic arguments presented by Dorigo and Houk.[19] When the B-ring of the trichothecene is in the boat form, the 9,10 double bond is in an excellent 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.

Acknowledgment. Support of this work by the NIH (Grant No. CA-25967 and RR-03354) and the NSF (CHE-84-02155), which provided funds for the purchase of instrumentation, is gratefully acknowledged.

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.

(11) Luo, J.; Ammon, H. L.; Gilliland, G. PLOTMD—an Interactive Program to Modify Molecular Plots on a Graphics Terminal. *J. Appl. Crystallogr.*, in press.

(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.



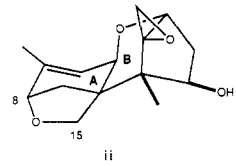
i

(13) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 237-239.

(14) Cundliffe, E.; Cannon, M.; Davies, J. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 30.

(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.



ii

(17) Feinberg, B.; McLaughlin, C. S. In ref 2c, Vol. I, p 27.

(18) Menger, F. M. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; ACS Symposium Series No. 215, Washington, D.C., 1987; p 209.

(19) Dorigo, A. E.; Houk, K. N. In *Advances in Molecular Modeling*; Liotta, D., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1, p 135.

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

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Received June 26, 1989

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)

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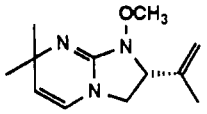
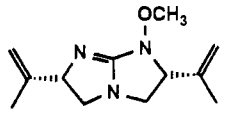
containing a tetrahydroimidazo[1,2-*a*]imidazole ring is elaborated by *A. hirtella* Benth.[1] An X-ray analysis of alchorneine methobromide revealed the relative stereostructure of alchorneine,[2] and the absolute configuration was established by correlation with L(+)-valine.[1b] The structure of isoalchorneine (**2**) was elucidated by chemical degradation to a transformation product of alchorneine (**1**).[1b] Hydroxy- and alkoxyguanidines appear only rarely



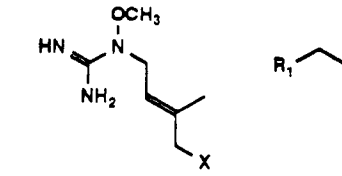
1



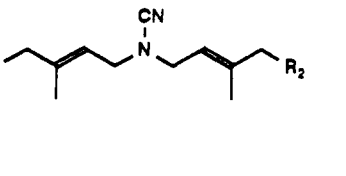
2

in nature, and since there is no in vitro method for the direct oxidation of guanidines to hydroxyguanidines we assumed that the biosynthesis of these alkaloids involves alkylation followed by cyclization of preformed hydroxy- or methoxyguanidine. *In practice we found that alkylations of methoxyguanidine with either 1,4-dichloro- or 1,4-dibromo-2-methyl-2-butene occurred exclusively on the methoxyamino nitrogen* leading to monosubstitution products **3** and **4** of no use in the preparation of alchorneines. These reactions represent new examples of the α-effect.[3]

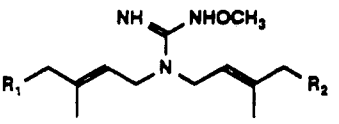
To prepare properly disubstituted methoxyguanidines, disodium cyanamide (generated in situ from cyanamide and dimsyl sodium) was alkylated with an equimolar mixture of 1-bromo-3-methyl-2-butene and (*E*)-1-(benzoyloxy)-4-bromo-2-methyl-2-butene.[4] The resulting dialkylcyanamides **5** (48%) and **6** (24% yield) were found to be readily separable by column chromatography.[5] Cyanamide **5** was converted to the corresponding methoxyguanidine **7** (90%) with methoxyamine hydrochloride (2 equiv).[6] Oxidative cyclization of **7** with $PdCl_2(CH_3CN)_2$[7] (1 equiv, 20 °C, CH_2Cl_2) gave the tetrahydropyrimidine **9** (30% yield), which on treatment with $Pd(PPh_3)_4$ (0.1 equiv) and triethylamine (5 equiv, CH_3CN, 50 °C) afforded **10**, now named alloalchorneine,[8] (95%) whose ^1H NMR spectrum differed significantly from that of alchorneine (**1**). Clearly, the α-effect[3] again caused the formation of a methoxytetrahydropyrimidine rather than a methoxyimidazolidine. To reach alchorneine (**1**) these two cyclizations had to be inverted. When a mixture of **7** and a catalytic amount of $Pd(PPh_3)_4$ in acetonitrile was heated at 50 °C for 3 h in the presence of NEt_3 the imidazolidine **11** was isolable in 81% yield. Cyclization of **11** using $PdCl_2(CH_3CN)_2$ (2 equiv, CH_2Cl_2, 40 °C, 48 h) afforded alchorneine (**1**) (46%) whose ^1H NMR, IR, UV, and MS data were identical with those described in ref 1b. Direct comparison with a sample of natural origin by chromatographic techniques confirmed its identity. Similarly, ring closure of **8**[9] prepared from **6** with NH_2OC-H_3·HCl, using $Pd(PPh_3)_4$ (0.2 equiv) and NEt_3 (10 equiv, CH_3CN, 50 °C, 24 h) gave a 1:1 mixture of isoalchorneine (**2**) and its more polar trans epimer **12** separable, although with loss of material, by chromatography. Infrared and ^1H NMR spectra of the less polar isomer were identical with those of natural isoalchorneine (**2**).

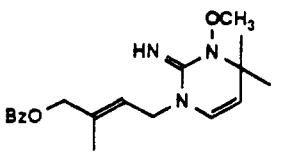


3 X=Cl
4 X=Br



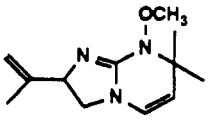
5 R_1=H; R_2=OBz
6 R_1=R_2=OBz





9

7 R_1=H; R_2=OBz
8 R_1=R_2=OBz



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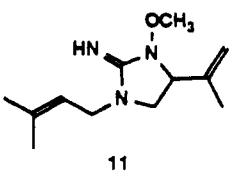
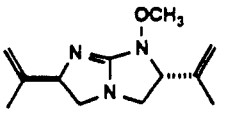
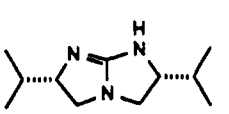


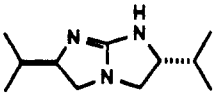
11



12



13



14

Hydrogenolysis (H_2, 10% Pd–C, AcOH, EtOH, 20 °C) of **2** and **12** afforded the tetrahydrodemethoxy derivatives **13** (colorless needles, mp 158–161 °C) and **14** (colorless needles, mp 178–181 °C), respectively. In agreement with the structures assigned both **13** (meso compound) and **14** (C_2 symmetry) exhibited only six signals in their ^{13}C spectra and only three proton signals caused by hydrogens attached to ring carbon atoms.

The greater nucleophilicity of the hydroxylamino nitrogen atom in methoxyguanidine suggests that it is not involved in the biosynthesis of the two alkaloids. There is now little doubt that the methoxy groups are introduced at a later stage with the aid of a remarkably potent oxi-

(1) (a) Khuong-Huu, F.; Leforestier, J.-P.; Maillard, G.; Goutarel, R. C. R. *Hebd. Seances Acad. Sci., Ser. C* **1970**, *270*, 2070. (b) Khuong-Huu, F.; Leforestier, J.-P.; Goutarel, R. *Tetrahedron* **1972**, *28*, 5207.

(2) Cesario, M.; Guilhem, J. C. R. *Hebd. Seances Acad. Sci., Ser. C* **1970**, *271*, 1552. Cesario, M.; Guilhem, J. *Acta Crystallogr., Sect. B.* **1972**, *B28*, 151.

(3) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York, 1985; p 310.

(4) (a) Ohsugi, M.; Takahashi, S.; Ichimoto, I.; Ueda, H. *Nippon Nogei Kagaku Kaishi* **1973**, *47*, 807. (b) Oroshnik, W.; Mallory, R. A. *J. Am. Chem. Soc.* **1950**, *72*, 4608.

(5) This reaction also produced symmetrical cyanamide (R^1 = R^2 = H, 24% yield). See: Donetti, A.; Omodei-Sale, A.; Mantegani, A. *Tetrahedron Lett.* **1969**, 3327.

(6) After flushing with argon, the reaction flask was sealed and then introduced into an oil bath preheated to 85 °C. The temperature was then raised slowly (~1 °C/min) to 130 °C and held there for 1 h.

(7) For the synthesis of heterocycles utilizing palladium-assisted intramolecular amination of olefins, see: (a) Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. soc.* **1976**, *98*, 2674. Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800. (b) Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. (c) Godleski, S. A.; Meinhart, J. D.; Miller, D. J.; Van Wallendael, S. *Tetrahedron Lett.* **1981**, 2247.

(8) Compound **10** was also obtained in 48% yield in a one-pot procedure from **7** and $PdCl_2(CH_3CN)_2$, followed by treatment with triphenylphosphine in dichloromethane.

(9) Prepared in 93% yield from disodium cyanamide with 2 equiv of (*E*)-1-(benzoyloxy)-4-bromo-2-methyl-2-butene.

dative enzyme. The disubstituted guanidine alkaloid, pterogynine (N_1,N_1-diisopentenylguanidine),[10] may prove to be a biosynthetic intermediate.

Acknowledgment. Generous financial support by the National Institutes of Health (Grant GM 09686) and by Hoffmann-La Roche, Inc., Nutley, NJ, is gratefully acknowledged. We thank Dr. F. Khuong-Huu (Gif/s/Yvette) for a sample of natural alchorneine and spectra of natural isoalchorneine.

Supplementary Material Available: ^1H and ^{13}C NMR, IR, and MS data for **1**, **2**, and **5–14**, all racemic, where applicable (4 pages). Ordering information is given on any current masthead page.

(10) Hart, N. K.; Johns, S. R.; Lamberton, J. A.; Willing, R. I. *Aust. J. Chem.* **1970**, *23*, 1679.

Synthetic 8-Vinylbenzo[*d*]naphtho[1,2-*b*]pyran-6-one *C*-Glycoside

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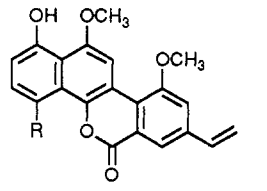
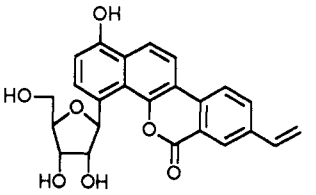
Received July 10, 1989

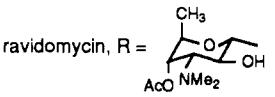
Summary: Synthesis of 8-ethenyl-1-hydroxy-4-(β-D-ribofuranosyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one, a *C*-glycoside analogue of ravidomycin and gilvocarcin V, has been achieved by a sequence of reactions involving Lewis acid catalyzed coupling of the aglycon and carbohydrate followed by introduction of the vinyl group and unmasking of the carbohydrate and phenolic hydroxyls.

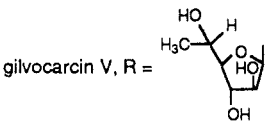
Sir: We have reported palladium-mediated[1,2] and Lewis acid catalyzed[3] aglycon–carbohydrate coupling reactions for syntheses of benzo[*d*]naphtho[1,2-*b*]pyran-6-one *C*-glycosides related to the *C*-glycoside antitumor antibiotics,[4] ravidomycin,[5] the gilvocarcins[6] (toromycin[7]), and the chrysomycins[8] (virenomycin,[9] the albacarcins[10]). We now report the synthesis of a *C*-glycoside (**1**) that possesses an underivatized C-1 phenolic hydroxyl and a vinylic substituent at C-8,[11] the functional groups considered critical for the photolytic nicking of DNA.[11a,12]





1





defucogilvocarcin, R = H

In in vitro studies,[11a,12-15] gilvocarcin V, its naturally occurring[16] aglycon defucogilvocarcin, and the synthetic aglycon analogue 8-ethenyl-1-hydroxybenzo[*d*]naphtho-[1,2-*b*]pyran-6-one[11a] (**2e**) have been shown to intercalate into DNA and to cause single-strand breaks (nicks) when irradiated. The ability of synthetic aglycon analogue **2** to nick DNA[11a] establishes the 1-hydroxy and 8-vinyl (ethenyl) substituents as sufficient for bioactivity; however, neither **2** nor defucogilvocarcin is nearly as effective as the *C*-glycoside gilvocarcin V[12] or ravidomycin.[17] The evidence that the carbohydrate moieties of these *C*-glycoside antibiotics play significant (but perhaps not structurally specific) roles in their antibiotic actions[4,11a,12-15] provides a rationale for synthesis of *C*-glycoside analogues[18] such as **1**.

(1) Outten, R. A.; Daves, G. D.; Jr. *J. Org. Chem.* **1987**, *52*, 5064–5066.
(2) Outten, R. A.; Daves, G. D. Jr. *J. Org. Chem.* **1989**, *54*, 29–35.
(3) Kwok, D.-I.; Outten, R. A.; Huhn, R.; Daves, G. D., Jr. *J. Org. Chem.* **1988**, *53*, 5359–5361.
(4) For a recent review of *C*-glycoside antibiotics see: Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1–65.
(5) Findlay, J. A.; Liu, J. S.; Radics, L.; Rakhit, S. *Can. J. Chem.* **1981**, *59*, 3018–3020.
(6) Hirayama, N.; Takahashi, K.; Shirahata, K.; Ohashi, Y. Sasada, Y. *Bull. Soc. Chem. Jpn.* **1981**, *54*, 1338–1342.
(7) Horii, S.; Fukase, H.; Mizuta, E.; Hatano, K.; Mizuno, K. *Chem. Pharm. Bull.* **1980**, *28*, 3601–3611. Jain, T. C.; Simolike, G. C.; Jackman, L. M. *Tetrahedron* **1983**, *39*, 599–605.
(8) Weiss, U.; Yoshihira, K.; Highet, R. J.; White, R. J.; Wei, T. T. *J. Antibiot.* **1982**, *35*, 1194–1201.
(9) Brazhnikova, M. G.; Kudinova, M. K.; Kulyaeva, V. V.; Potapova, N. P.; Rubasheva, L. M.; Rozynov, B. V.; Horvath, G. *Antibiotiki* **1984**, *29*, 884–892.
(10) Matson, J. A.; Myllymaki, R. W.; Doyle, T. W.; Bush, J. A. U.S. Patent 4,461,831, July 24, 1984; *Chem. Abstr.* **1985**, *102*, 4456a.
(11) Synthetic studies of the aglycon system and of the carbohydrate present in ravidomycin, (–)-methyl ravidosaminide, have been reported. See: (a) McGee, L. R.; Confalone, P. N. *J. Org. Chem.* **1988**, *53*, 3695–3701. (b) Findlay, J. A.; Daljeet, A.; Murray, P. J.; Rej, R. N. *Can. J. Chem.* **1987**, *65*, 427–431. (c) Macdonald, S. J. F.; McKenzie, T. C.; Hassen, W. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1528–1530. (d) Patten, A. D.; Nguyen, N. H.; Danishefsky, S. *J. Org. Chem.* **1988**, *53*, 1003–1007. (e) McKenzie, T. C.; Hassen, W.; Macdonald, S. J. F. *Tetrahedron Lett.* **1987**, *28*, 5435–5436. (f) McKenzie, T. C.; Hassen, W. *Tetrahedron Lett.* **1987**, *28*, 2563–2566. (g) Knapp, S.; Lal, G. S.; Sahai, D. *J. Org. Chem.* **1986**, *51*, 380–383.
(12) Tse-Dinh, Y.-C.; McGee, L. R. *Biochem. Biophys. Res. Commun.* **1987**, *143*, 808–812.
(13) Greenstein, M.; Monji, T.; Yeung, R.; Maiese, W. M.; White, R. J. *Antimicrob. Agents Chemother*, **1986**, *29*, 861–866.
(14) Elespuru, R. K.; Gonda, S. K. *Science* **1984**, *223*, 69–71.
(15) Wei, T. T.; Byrne, K. M.; Warnick-Pickle, D.; Greenstein, M. *J. Antibiot.* **1982**, *35*, 545–548.
(16) Misra, R.; Tritch, H. R., III; Pandey, R. C. *J. Antibiot.* **1985**, *38*, 1280–1283.
(17) Rakhit, S.; Eng, C.; Baker, H.; Singh, K. *J. Antibiot.* **1983**, *36*, 1490–1494.
(18) Acid- or base-catalyzed rearrangements of gilvocarcin V and ravidomycin have yielded analogues not found in nature; see ref 7 and 17.

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