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A BIOMIMETIC ROUTE TO THE ERGOT DERAILMENT PRODUCTS, THE CLAVICIPITIC ACIDS - DETECTION OF A REACTIVE INTERMEDIATE BY ^{31}P NMR - SOME CHEMICAL UNDERPINNINGS FOR A PROPOSED INTERMEDIATE IN ERGOT ALKALOID BIOSYNTHESIS.

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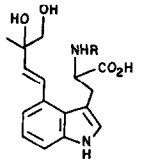
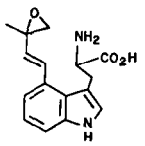
Summary: A biomimetic route to the clavicipitic acids has been developed which is based on the Mitsunobu reaction of the diol **4a**.

It has been suggested by Floss that the bis-hydroxylated 4-(γ,γ-dimethylallyl)tryptophan I (or, perhaps, more likely, its N-methyl derivative **II**) may be an intermediate along the biosynthetic pathway to the ergot alkaloids.[1] In order to further probe Nature's mechanism for generating these alkaloids, we have now prepared such materials in labeled form in order to carry out feeding studies.[2] Additionally, we have examined some chemical transformations of these materials in the laboratory in the **absence of the ergot fungus**, and we are now pleased to report that one can in a sense mimic chemically the biosynthesis of the clavicipitic acids, important ergot alkaloid derailment products.[3]



I, R=H
II, R=CH_3

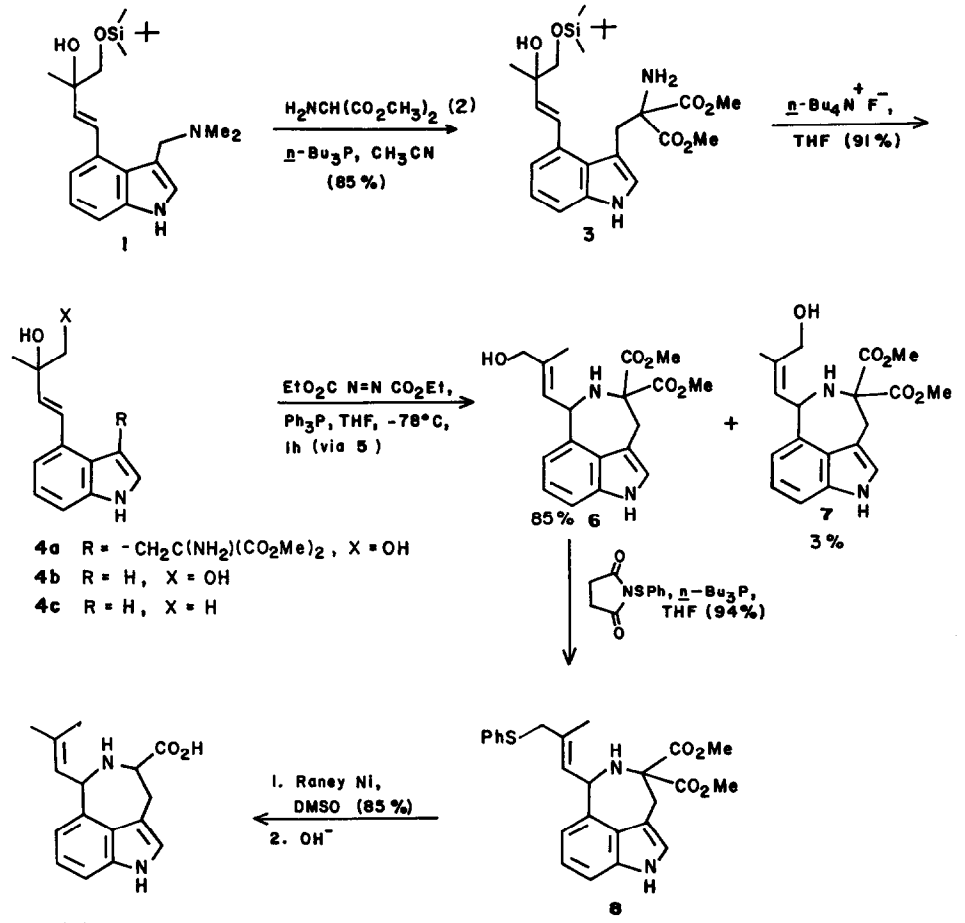


III

Starting from the relatively sensitive gramine derivative **1**,[2] a condensation reaction was carried out with dimethyl aminomalonate **2** as the partner employing tri-n-butylphosphine as catalyst[4] in acetonitrile as solvent. Isolation of only the product of carbon-carbon bond formation under these reaction conditions is noteworthy. After desilylation with n-$Bu_4N^+F^-$, the free diol **4** was simply exposed to the oxidation-reduction condensation conditions of the Mitsunobu reaction.[5] These conditions served well to provide a 7-membered ring-closed product as nearly a single geometrical isomer (85% isolated yield of the E-isomer **6** in addition to 3% of the Z-compound **7**).[6] Since in our studies with the related N-methylamino analogue of **4**,[7] ring closure failed to take place with the primary alcohol group protected as its t-butyldimethylsilyl ether, we believed **initially** that an oxyphosphonium salt had formed at the primary alcohol site, and that this

underwent ring closure to a transient vinyl oxirane which was then trapped by the neighboring amino group.[8] However, on exposing the C_3-unsubstituted diol **4b** to the Mitsunobu conditions, we were unable to isolate the putative epoxide. Furthermore, a simple carbonium ion mechanism was also ruled out, for subjection of the very sensitive tertiary alcohol **4c** to the Mitsunobu conditions at -78 °C followed by warming to room temperature led only to the complete recovery of starting material.

Scheme I. Biomimetic Synthesis of the Clavicipitic Acids



Clavicipitic Acids

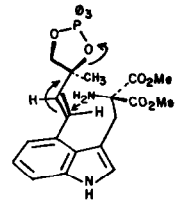
Finally, to probe the mechanism for ring closure in a more direct manner, the diol **4b** was again subjected to the Mitsunobu conditions, and after 1.5 h at -78 °C, a ^{31}P NMR spectrum was taken. A strong signal was observed at -37.4 ppm, a chemical shift which is nearly identical to chemical shifts reported by Guthrie and Jenkins for related cyclic O,O-phosphoranes (-26.6 to -41.1 ppm) generated in the Mitsunobu reaction.[5,9] Also, no phosphorous resonance corresponding to triphenylphosphine oxide (+25 ppm) was observed!

Thus we come to the reasonable conclusion that our seven-membered nitrogen

containing ring is formed by S_N2' attack on a vinyl cyclic O,O-phosphorane **5** (Scheme 2), rather than a vinyl oxirane. The overall process provides a remarkably mild procedure for activating a hindered tertiary alcohol to S_N2' attack through initial activation of a primary alcohol. Such an activation scheme based on the juxtaposition of functional groups may actually find analogies in biological systems.

The cyclic phosphorane **5** is related in a functional sense to **III**, a compound proposed previously by Pachlatko as being a key intermediate in ergot alkaloid biosynthesis.[10] Since the carbon site α to the amino group in our compound is quaternary, carbon-carbon bond formation is excluded. In the Pachlatko proposal, this carbon atom of the amino acid appendage of **III** is activated (perhaps by pyridoxal 5'-phosphate)[1,10] so as to allow carbon-carbon bond formation with C-ring closure. In the case of **5**, however, the nitrogen atom serves as the nucleophile leading to the seven-membered ring skeleton of the clavicipitic acids along a pathway rather similar to that proposed by Floss in his rationalization of the fungal production of these alkaloids.[3a] The stereochemistry of the major olefin isomer can be explained by the structure shown in Scheme 2, in which the less congested of the two possible syn S_N2' transition state modes (i.e., the

Scheme 2. Proposed Intermediate in the Ring-Closure Step



5

one that leads to the E-isomer) is displayed.[11]

To complete the total synthesis of the clavicipitic acids, the primary hydroxyl group of **6** was replaced by a phenylthio group,[13] and a Raney nickel desulfurization reaction was carried out in DMSO as solvent.[14] Lastly, as in our previous synthesis of these natural products,[13] a hydroxide promoted ester hydrolysis/decarboxylation step gave rise to the clavicipitic acids, which were best characterized as their N-acetyl methyl ester derivative prepared by acetic anhydride, methanol treatment.

In summary, the present chemistry provides access to the clavicipitic acids in a simple and direct fashion. More importantly, however, the scheme sheds further light on the manner in which Nature herself may have contrived to prepare these materials in our own larger chemosphere.

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References and Notes

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2. The gramine derivative **1** was prepared from 4-ethynylindole through a sequence of steps involving: (a) hydrostannylation, (b) metal-metal exchange, (c) condensation of the vinyl anion with the t-butyldimethylsilyl ether derivative of acetol and (d) reaction of the new 4-substituted indole with N,N-dimethyl(methylene)ammonium chloride. A full paper containing the experimental details of this process will be published after the results of the feeding studies are known.
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6. Spectral data for **6**: IR ($CHCl_3$) 3600, 3490, 3350, 2990, 2950, 1735, 1425, 1280, 1200, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.02 (br s, 1 H), 7.18 (d, 1 H, J = 8.1 Hz), 7.03 (m, 1 H), 6.96 (br s, 1 H), 6.75 (d, 1 H, J = 7.1 Hz), 5.73 (d m, 1 H, J = 8.7 Hz), 5.38 (d, 1 H, J = 8.7 Hz), 4.18 (br s, 2 H), 3.95 (dd, 1 H, J = 15.7, 1.2 Hz), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.54 (d, 1 H, J = 15.7 Hz), 1.79 (d, 3 H, J = 1.2 Hz). The assignment of E and Z stereochemistry to **6** and **7** is based on a comparison of the chemical shift data for their vinylic protons as well as on an analysis of the coupling patterns observed for the methylene protons of their hydroxymethyl groups. The ergot alkaloids chanoclavine I and isochanoclavine I show very similar differences in their respective ^1H NMR spectra, see: Stauffacher, D.; Tscherter, H. Helv. Chim. Acta **1964**, 47, 2186.
7. The free diol of this N-methyl derivative does, in fact, ring close under the Mitsunobu conditions to provide the N-methyl analogues of **6** and **7** in isolated yields of 84% and 5%, respectively.
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