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INTRAMOLECULAR AZIDE CYCLOADDITION (IAC) REACTIONS IN THE INDOLE SERIES - AN APPROACH TO CLAVICIPITIC ACID

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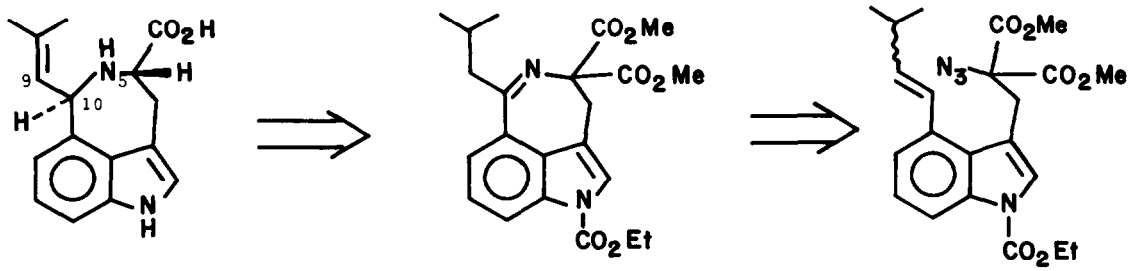
Summary: The intramolecular [3+2] cycloaddition of azide to olefin has been explored as a possible route to the structurally unique alkaloid clavicipitic acid

Clavicipitic acid (1, major isomer), a metabolite of Claviceps strain SD 58 which is isolated as a mixture of isomers, appears to represent a derailment product of ergoline biosynthesis after the first pathway-specific step, the isoprenylation of tryptophan.[1] During the course of our efforts to synthesize this structurally unique 3,4-disubstituted indole with the primary objective of making sufficient quantities available for biological testing, we decided that it would be an interesting exercise to probe the construction of such a system by intramolecular dipolar cycloaddition of azide to olefin.[2] Assuming, of course, that the cycloaddition proceeds with the proper regio-orientation, loss of nitrogen from the triazoline intermediate would lead to the 7-membered ring imine 2, a highly desirable product for this synthetic undertaking.



1 2 3

The 3,4-disubstituted indole 3 required to test this strategy was assembled readily from indole-4-carboxaldehyde[3] by a sequence of steps commencing with a Wittig reaction employing isobutylidenetriphenylphosphorane. This condensation process yielded a mixture of the Z- and E-olefins 5 (ratio ≃ 3:1, 76%). A conventional Mannich reaction served to convert the 4-(3-methyl-1-butenyl)indole

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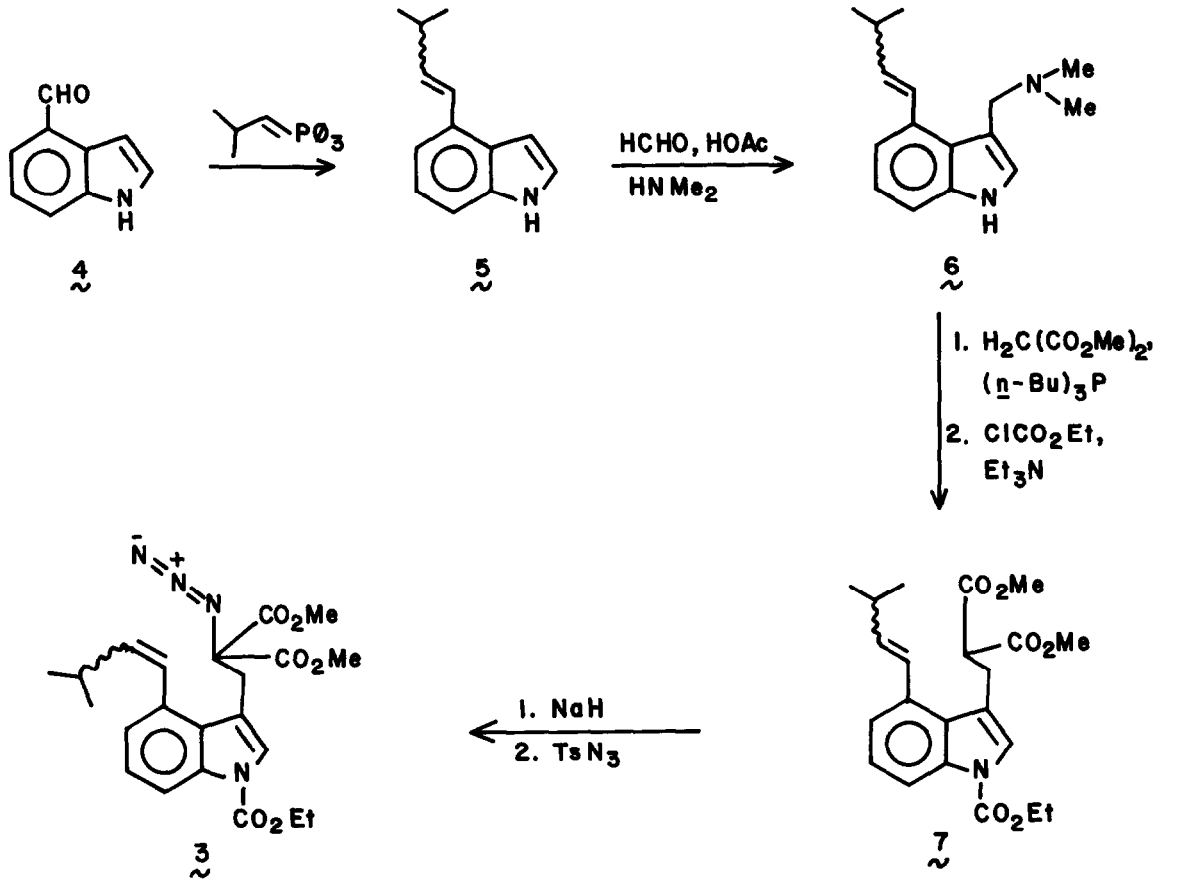
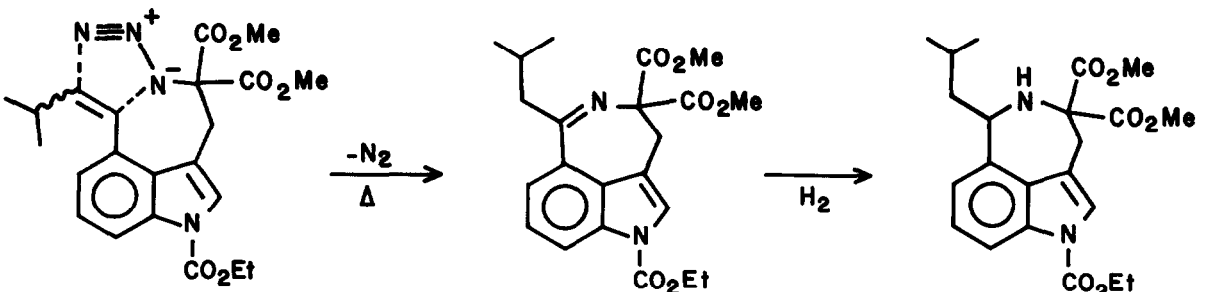
(5) to its gramine derivative 6 (81%). Tri-n-butylphosphine catalyzed reaction of 6 with dimethyl malonate[4] (74%) followed by N-carboethoxylation with ethyl chloroformate/Et_3N (80%) yielded 7.



Deprotonation of the malonate derivative with sodium hydride and reaction of the anion with tosyl azide[5] provided the key 3,4-disubstituted indole 3 (62%).

On heating 3 in o-dichlorobenzene at 190-195°C for 8 h (or one week at 85-90°C) it was converted in good yield to a single imine (62%). The intermediate triazoline could not be detected. Since the 300 MHz ^1H NMR of this new product showed relatively broad peaks, an indication of conformational interconversions, the imine was hydrogenated over palladium on carbon to give a single amine in 92% yield. Contrastingly, the NMR of this amine displayed sharp and easily interpretable signals, a fact which allowed us to firmly assign structure 8 to

the hydrogenation product. 8: IR ($CHCl_3$) 3388, 1726, 1381, 1401 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.86-8.00 (m, 1 H), 7.00-7.33 (m, 3 H), 4.46 (overlapping m, 1 H and q, 2 H, J = 7.4 Hz), 3.07, 4.33 (ABq, 2 H, J = 4.0 Hz), 3.79 (s, 3 H), 3.73 (s, 3 H), 2.89 (br s, 1 H), 1.89-2.06 (m, 1 H), 1.58-1.89 (m, 2 H), 1.44 (t, 3 H, J = 7.4 Hz), 1.01 (d, 3 H, J = 7.4 Hz), 0.93 (d, 3 H, J = 7.4 Hz); irradiation of H_{10} (δ = 4.46) partially collapsed the two multiplets between 1.58 and 1.89 δ (C_9 protons); mass spectrum (70 eV) m/e = 416 (M^+), 401, 359.



3 2 8

The directionality of the initial [3+2] dipolar cycloaddition reaction of 3 can be understood in part on the basis of the perhaps outmoded, but nonetheless predictive formalism of Huisgen[6] in which the unsubstituted nitrogen of the azide is considered to be electrophilic and the internal nitrogen nucleophilic in character. The carbon atom of the olefin nearest the indole ring might best be able to accommodate some partial positive charge character. More importantly, however, the geometric and steric constraints for cycloaddition are such that formation of the other regioisomer (especially in the case of the cis olefin) appears prohibitive (see Dreiding models). These latter factors can, of course, completely dominate the aforementioned resonance considerations (or calculated HOMO/LUMO interactions).

In summary, we believe that the work reported herein does offer a reasonable route to clavicipitic acid and its analogues. The use of a more highly functionalized Wittig reagent in the opening step of the synthesis, or the introduction of additional functionality into 2 through utilization of the activating effect of the imine functional group should make it possible to synthesize the parent structure 1.[7,8]

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References and Notes

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7. For other efforts directed toward clavicipitic acid, see S. Nakatsuka, H. Miyazaki and T. Goto, Chem. Lett., 407 (1981).
8. All new compounds displayed satisfactory IR, ^{1}H NMR and mass spectral properties. Yields have not been optimized in any of the reaction steps.

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