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AN APPROACH TO THE SYNTHESIS OF LYCORINE

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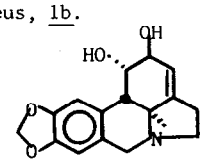
Lycorine 1, the major alkaloid constituent of the Amaryllidaceae, has long been a challenging goal for stereospecific total synthesis. Heretofore, published efforts have focussed on the elaboration of a phenanthridine moiety containing rings A,B, and C into the pentacyclic system[1]. We wish to report a new, presumably general approach to the lycorine skeleton, wherein a readily available tricyclic precursor may be converted directly into the pyrrolo[d,e]phenanthridine nucleus, 1b.



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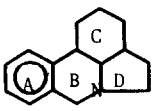

1b

Reaction of 3-pyrrolidinone ethylene ketal[2] with one equivalent of 4,5-methylenedioxyphthalic anhydride[3] in tetrahydrofuran, followed by in situ lithium aluminum hydride reduction afforded the oily aminoalcohol 2 [97%; δ6.91, 6.79 (s, each 1H); 5.99 (s, 2H); 4.55 (s, 2H); 3.93 (s, 4H); 3.62 (s, 2H); 2.65 (s, 2H)]. Subsequent Jones oxidation yielded the corresponding aminoaldehyde 3 as a sweet-smelling liquid. Low temperature addition of the aldehyde to a tetrahydrofuran suspension of propargylaluminum complex[4] prepared from propargyl bromide, mercuric chloride, and aluminum turnings generated the acetylenic ketal 4 in high yield [δ4.99 (t, 1H, J=12cps); 4.05, 3.48 (AB quartet, 2H, J=12cps); 3.8 (s, 4H); 2.58, (s, 2H); 2.85, 2.70 (AB quartet J=3cps); λ max 3.05μ, 4.7μ]. Deketalization proceeded smoothly in refluxing 10% hydrochloric acid, and the resulting acetylenic ketone 5, upon overnight stirring with mercuric sulfate in dilute sulfuric acid, rearranged to the desired aminodiketone 6[5].

The diketone 6 has structural features which should allow easy conversion of this tricyclic compound into the pentacyclic lycorine ring system. An intramolecular Michael addition should produce tetracyclic system 7a with the thermodynamically more stable trans stereochemistry about the newly-formed bond. Subsequent Aldol condensation would complete the carbocyclic network.

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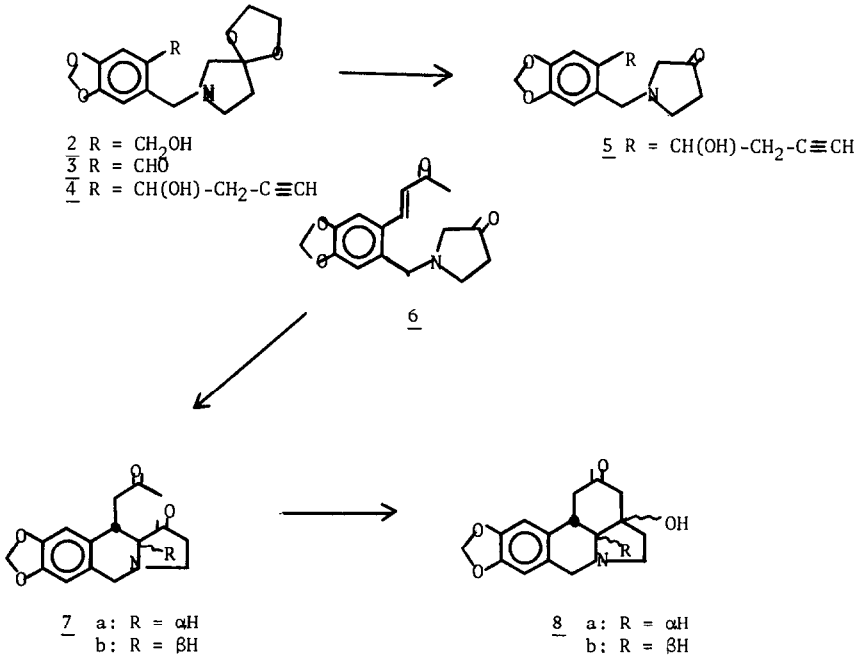
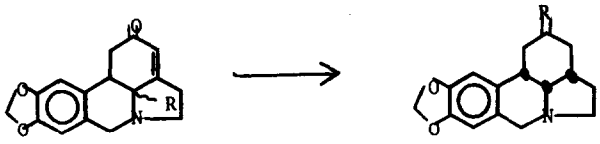


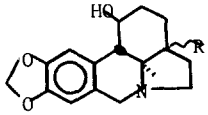
Base-catalyzed cyclization of 6 using potassium carbonate in water-methanol-chloroform (2:5:3) produced as the only reaction product a highly crystalline substance [mp 163-166°; λmax 5.80μ; m/e 287 (M+); overall 15% from 2], having IR, NMR, and mass spectral data completely consistent with the pentacyclic hydroxy-ketone 8. Furthermore, p- toluenesulfonic acid cleanly dehydrated 8 to the enone 9 [90%; mp 162-164°;λ max 5.95μ][5a]. Authentic, optically active 9a (mp 157-158° d) has previously been prepared[6] by an unambiguous degradation of lycorine. Comparison of the natural and synthetic material revealed nearly identical solution infrared spectra (chloroform) but vastly different thin-layer chromatographic behavior. Accordingly, synthetic 9 was reduced catalytically (10% Pd/C) to a single dihydro derivative 10 [90%; mp 128-130°; λmax 5.81μ; m/e 271 (M+)][5b]. Reduction of the tosylhydrazone 11 using sodium cyanoborohydride[7] afforded an 80% yield of crystalline compound having melting point, infrared spectrum (carbon disulfide), and tlc characteristics identical with racemic γ-lycorane 12[8]. This, then, confirmed the identity of the synthetic desoxy-2-lycorinone as the B/C-cis fused isomer 9b.



9 a: R = αH
b: R = βH

10 R = O
11 R = N-NHTs
12 R = H_2

The unusual specificity in the cyclization step leading only to 9b indicates a high degree of stereochemical control. This could reflect the greater stability of the cis aldol product 8b, although molecular models do not strongly support such a possibility. Two additional mechanistic proposals merit consideration. The Michael addition may proceed stereospecifically to produce only tetracyclic diketone 7b which could cyclize directly to the pentacyclic system 8b faster than it equilibrates. Alternatively, the intermediates 7 may be sufficiently long-lived to allow equilibration, but even then, the cis isomer 7b almost certainly will close ring C faster, as Dreiding models clearly indicate. Assuming, then, the likelihood of kinetic control over product formation, an attempt was made to equilibrate the B/C junction in 9b. While 9b was destroyed by the action of sodium hydride or sodium methoxide, it was recovered unchanged from neat, refluxing trifluoroacetic acid.



13 R = βH
14 R = αH

Regrettably, these results give no meaningful indication of the relative stability of 9a and 9b. However, indirect evidence supporting the near-equivalence of these two structures may be inferred from the fact that β-dihydrocaranine 13 upon Oppenauer oxidation, isomerizes to a mixture of cis and trans ketones about the B/C junction[9].

ACKNOWLEDGEMENT

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(5a) IR, NMR, and mass spectral data are completely consistent with the proposed structure.

(5b) Satisfactory combustion analysis was obtained for this compound.

(6) K. Kotera, Tetrahedron 12 240 (1961); Dr. Kotera of Shionogi LTD. kindly provided a generous sample of 9a .

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(8) K. Kotera Tetrahedron 12 248 (1961); We are grateful to Dr. Kotera for providing the infrared spectrum of γ-lycorane.

(9) α-dihydrocaranone, prepared in the same fashion from 14, isomerizes entirely to the all-cis ketone^{6,8}.