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A MODEL FOR THE CONSTRUCTION OF RINGS I TO V OF STRYCHNINE.

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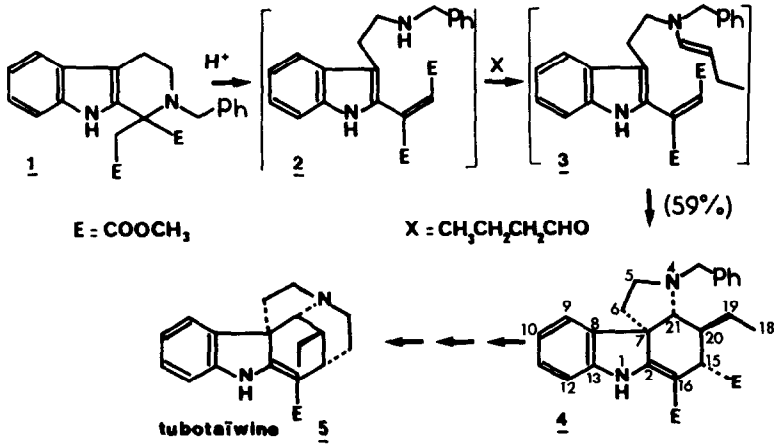
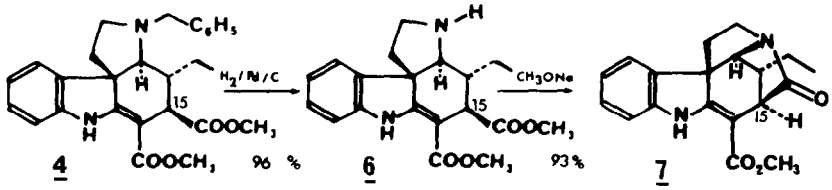
Summary : A simple and straightforward synthesis of a common intermediate towards *Aspidosperma* and *Strychnos* alkaloids is presented.

Despite numerous successes in the construction of the skeleton of *Aspidosperma* alkaloids, the "Diels-Alder" route[1] has not yet been applied to the synthesis of *Strychnos* alkaloids (such as tubotaïwine 5). In order to achieve this goal a suitable indolofumarate 2 ought to be prepared and this is easily done when using our recently published[2] tetrahydro-ß-carboline 1. The purpose of this letter is to present our results in this area.



SCHEME 1

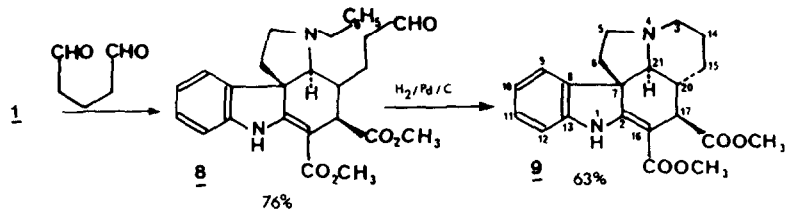
Refluxing of 1 with an excess of butyraldehyde in toluene in the presence of AcOH under a nitrogen atmosphere for 12 hours led to the formation of a major compound to which structure 4 is given[3,4]. Compound 4 is a crystalline solid (m.p. 140°C) whose U.V. spectrum (λmax nm= 226, 298, 326) and colouration upon CeIV spraying are typical of anilinoacrylic chromophores. Carbon and proton NMR are fully in agreement with the proposed structure and demonstrate its existence as a single diastereoisomer. Inspection of molecular models and interproton coupling constants allow proposition of the relative configurations depicted in formula 4. The crucial cis relationship between the nitrogen N(4) and the ester on C-15 is unambiguously proven by selective debenzylation (H_2 / Pd/C, AcOH) leading to the amino-ester 6[4] then easily converted into lactam 7 (m.p. 220°C)[4] (see scheme 2).



SCHEME 2

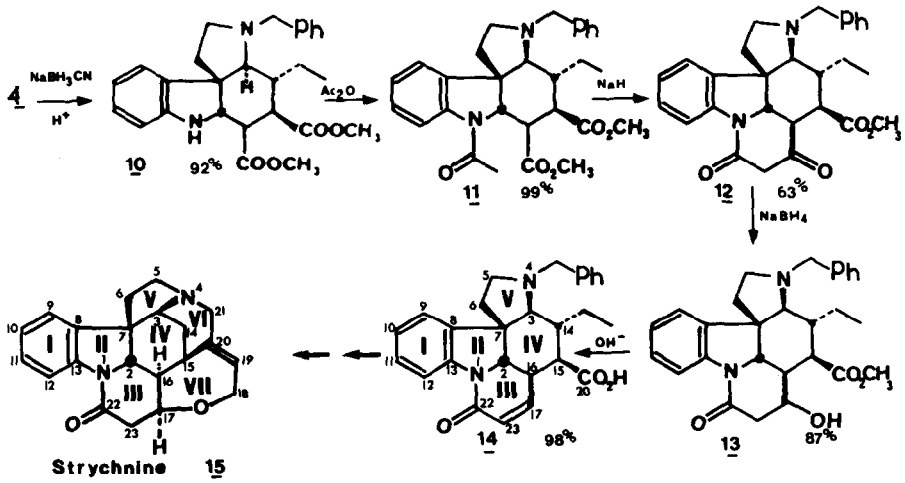
Formation of 4 may be rationalized through an intermediate such as 3 which is the enamine derived from 2. Exclusive formation of a *trans*-enamine leads to the observed relative configurations of C-20 and C-21 (and therefore C-7). At variance with Kuehne's conditions[1b-1d] the process described herein is purely acid-catalyzed and does not require any base to fragment an ammonium intermediate; the reaction proceeds in a single step from 1 to 4. The versatility of this approach is demonstated by the following two examples.

Condensation of 1 with glutaraldehyde leads to aldehyde 8[4] in 76% yield. Debenzylation of 8 is accompanied by in situ immonium formation and subsequent reduction to pentacyclic derivative 9[4] (see scheme 3). An important feature of 9 is the trans ring junction of C and D rings ($J_{H\text{-}20\text{-}21}$ = 8 Hz); this stereochemistry is not easily obtained using other routes[5].



SCHEME 3

As a further use of the sequence, a model for 5 of 7 rings of strychnine 15 (rings I,II,III,IV and V[6]) has been prepared according to scheme 4. Thus, reduction of the acrylate double bond of 4 ($NaBH_3CN/H^+$) affords dihydro derivative 10[4] which is uneventfully acetylated to amide 11[4]. Cyclization of 11 to the ketolactam 12 is achieved under basic conditions (NaH/THF). To the best of our knowledge, and although this route may be close to the biogenesis[7], this is the first example of such an approach to the construction of the lactam ring of strychnine 15. This ring was further elaborated to alcohol 13[4] and acid 14[4] which are similar to some of the Woodward synthesis intermediates[6].



SCHEME 4

High field NMR investigations of lactam 12 shows that it is a single isomer with the configurations of the five relevant asymmetric centers in agreement with those of the natural products. Work is in progress towards the preparation of more elaborated targets in the field.

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3- Partial NMR data (401 MHz; ppm; J(Hz)): 9.12 (broad s; N-1 H), 3.82 (d; J=2.5; H-15), 3.78 and 3.68 (s; 3H; esters), 2.98 (s; w1/2=2.5, H-21), 2.61 (broad t; J=7; H-20), 1.00 (m; H-19), 0.92 (m; H-19'), 0.83 (t; J=7; 3 H-18).

4- All new compounds have been fully characterized spectrally and compositions determined either by HRMS or by combustion.

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