TOTAL SYNTHESIS of 19-HYDROXYTUBOTAIWINE. ASSIGNMENT OF ABSOLUTE CONFIGURATION TO A NATURAL ISOMER.

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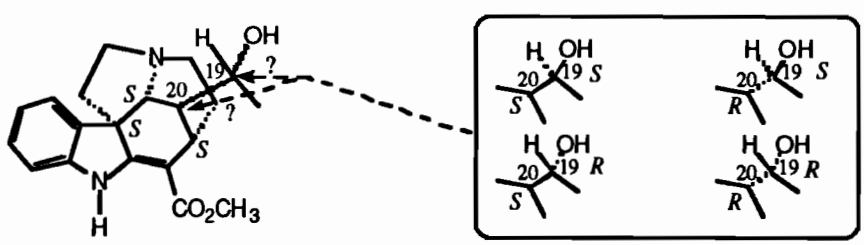
Résumé : *nous présentons la synthèse totale de deux isomères de la 19-hydroxytubotaïwine 2 racémique, en dix étapes à partir de la tryptamine. Une description détaillée par RMN à haut champ de tous les intermédiaires de cette synthèse ainsi que la structure aux rayons X de l'un d'entre eux, nous permettent de décrire la configuration absolue de l'un des deux isomères naturels.*

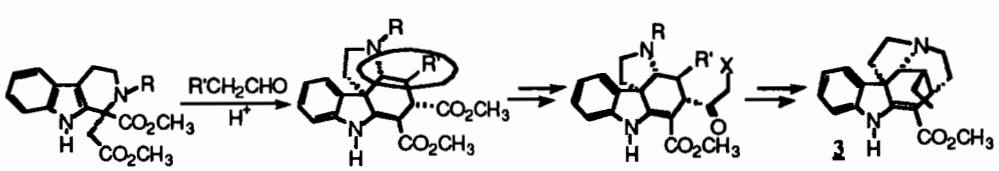
Abstract : *the total synthesis of two isomers of racemic 19-hydroxytubotaiwine 2 in ten steps from tryptamine is presented. Full high field NMR studies of all compounds generated on the way along with an X-ray structure of one intermediate allow us to describe the absolute configuration of one of the two naturally occuring isomers.*

Two isomers of 19-hydroxytubotaiwine 1a and 1b (3) have been isolated for the first time from *Alstonia angustiloba* but their structures and especially the configurations of their C-19 and C-20 could not be fully assigned. More recently a novel isolation of a 19-hydroxytubotaiwine isomer 2, named "lagunamine", from *Alstonia scholaris*, has been made by Yamauchi and al. (4).

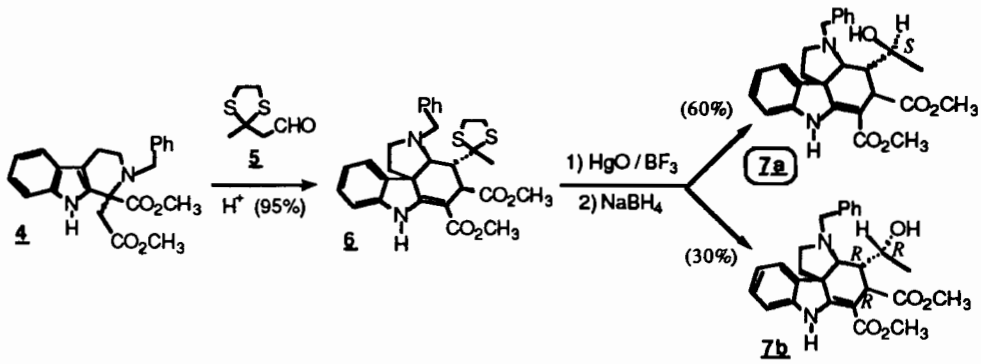


19-hydroxytubotaiwines 1a and 1b
lagunamine = 1a, 1b or 2 ?

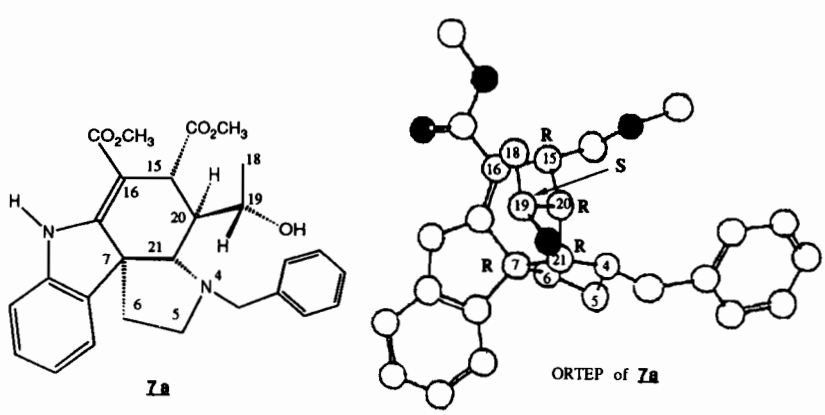
Neither spectroscopic data nor physical properties were not allowing us to answer the questions : "Which one of the four possible isomers, shown above, is 1a and 1b ?" and "Is lagunamine identical to one of them or a third isomer 2 ?" This is the reason why we decided to proceed to their total synthesis. Our strategy follows a general route, devised to synthesize alkaloids of the *Strychnos* type (5), which already led to the total synthesis of tubotaiwine 3 (6) as shown below :



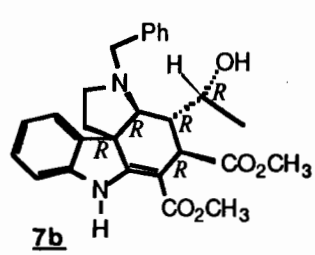
In the case of the 19-hydroxy derivative, the synthesis starts from the same special tetrahydro-ß-carboline diester 4 (7), reacted under acid catalyzed conditions, with a masked keto-aldehyde 5, to give the rearranged b-anilinoacrylate skeleton dithiane derivative 6 (8). In order to build up the good functionality at the C19 carbon atom, one must first unmask the carbonyle then transform it into the alcohol. This is done sequentially by the means of mercuric oxide over the dithiane 6 and reduction by sodium borohydride to the mixture of diastereoisomers 7a and 7b, as depicted below :



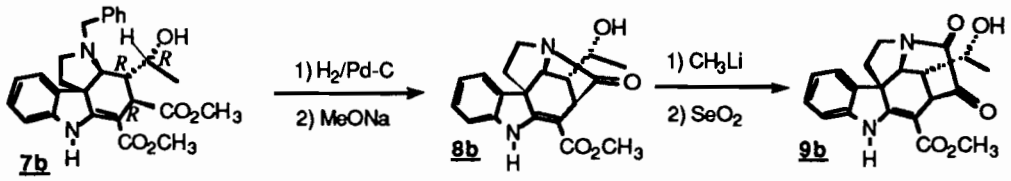
At this stage, none of the values obtained from the NMR spectra of these two isomers could afford any "diagnostic" argument to differenciate between the two configurations produced at the C19 atom. Luckyly enough, the isomer 7a crystallized; thus, it was very helpful to get an X-ray structure of it (9). From the ORTEP display of the crystal structure, it is possible to deduce the relative configurations for all the chiral centers. They are those depicted on formula 7a shown below : 7-*R*, 20-*R*, 21-*R* and 19-*S* if considering the 15-*R* (15-α-H) antipodal series.



Because of their chemical relationship, we may assign the same configuration to all the asymmetric centers but C-19 in 7b : it must, be the opposite one, *R*.

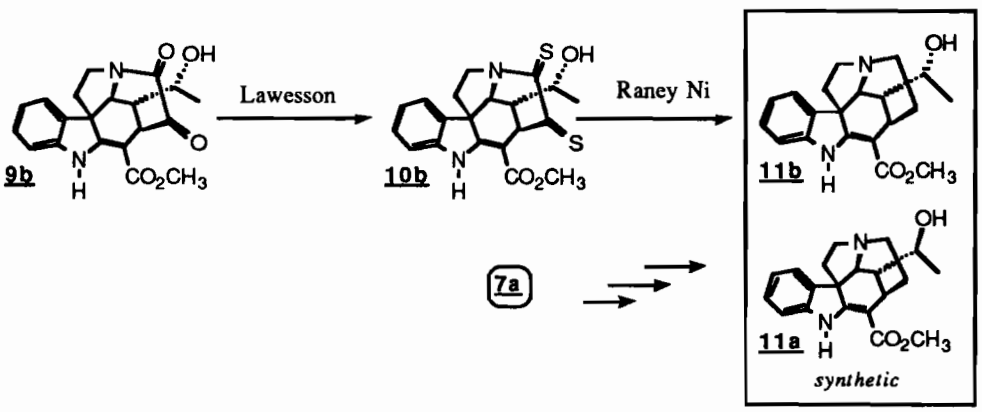


The two alcohols 7a and 7b. were separately subjected to the remaining steps needed to achieve the synthesis. The sequence is quite identical to that one used to prepare tubotaiwine (5), as described below for the b series.



7b 8b 9b

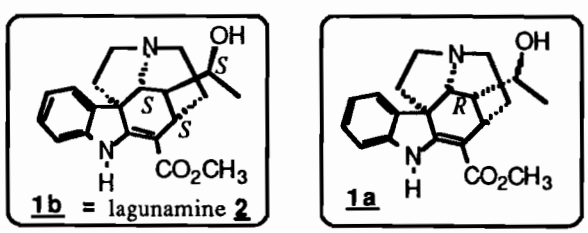
It proceeds through the chemodifferenciation of the two carbomethoxyle groups *via* the lactam 8b that allows us to introduce the missing carbon by reaction with methyllithium. Oxidation of the intermediary methylketone to the ketolactame 9b is carried out by means of selenium dioxide. However, the reduction of ketolactam 9b to the amine 11b is achieved in only two steps : transformation into thionethiolactam 10b by the Lawesson's reagent (10) and reduction by Raney nickel :



9b 10b 11b 11a 7a

The same sequence, applied in the a series, yields the other C19-isomer 11a.

Then, the natural isomers of 19-hydroxytubotaiwine 1a and 1b isolated from *Alstonia angustiloba* and another one, named "lagunamine" 2, from *Alstonia scholaris* were compared on tlc and also their spectroscopic data to the two synthetic compounds 11a and 11b. allows us to assign the relative configurations as follows : 15-*R*, 19-*R* and 20-*R* to 1b and 2. Indeed, the slowest running spot on tlc, 1b and lagunamine 2, are identical to each other and superimposable (in all their properties but specific rotation) with the synthetic compound 11b. However, neither 11a nor 11b could match with 1a that is faster running on tlc and whose ^1H NMR spectra show main discrepencies. Hence, 1a must, at least, possess the inverse relative configuration *S* at C20.



1b = lagunamine 2 1a

At last, that 1a, 1b and 2 belong to the tubotaiwine series (15-β-H), and thus possess the 15-*S* absolute configuration, is deduced from their high positive specific rotations (3,4). Therefore, the configurations 7-*S*, 15-*S*, 19-*S*, 20-*S* and 21-*S* of 1b and 2 must be considered as the absolute ones and 1a must have, at least, a 7-*S*, 15-*S*, 20-*R* and 21-*S* configuration but its configuration at C19 cannot be deduced from this work.

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8. All compounds are prepared in their racemic form, but for easier reading in the schemes, we have depicted only one enantiomeric series (the relative configuration for all carbons in this series is the one depicted on the formulae).
9. This part of the work was done by Dr. J.M. Léger who is deeply acknowledged. From a single crystal of 7b, 3764 independent reflections were measured with an automatic Enraf Nonius CAD-4 diffractometer (graphite monochromator, Cu-Ka radiation, l = 1.54178 Å). Among these, 2470 were significative (I≥ 3s(I)). The cell unit was monoclinic with $P2_{1/n}$ as space group and a = 7.867 (2) Å, b = 16.224 (3) Å, c = 18.832 (5) Å, b = 92.12°. The structure was solved by direct methods with MULTAN 80® and refined by the least square-means method.
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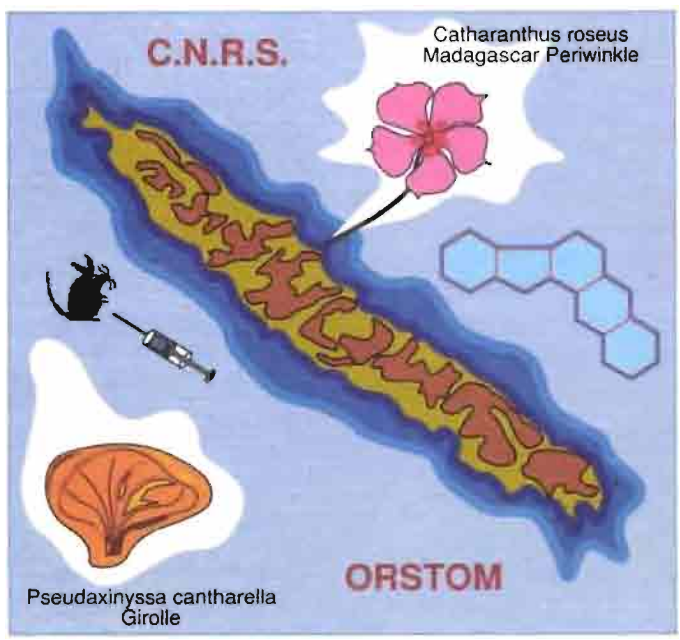

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