Tetrahedron Letters, Vol.32, No.15, pp 1787-1790, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

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

Jean Nkiliza and Joseph Vercauteren*

Laboratoire de Pharmacognosie

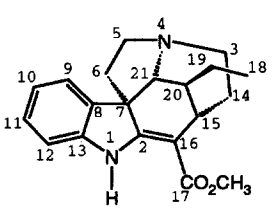
Jean-Michel Léger

Laboratoire de Chimie Analytique, associé au C.N.R.S.,
Faculté de Pharmacie, Université de BORDEAUX II,
3ter, Place de la Victoire 33076 BORDEAUX - FRANCE

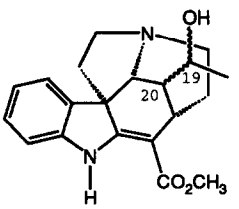
Key Words : 19-hydroxytubotaiwine; *Strychnos* alkaloid; total synthesis; indole alkaloid; lagunamine.

Summary : A total synthesis of two isomers of racemic19-hydroxytubotaiwine from tryptamine is described[1]. The absolute configuration of one of the two natural ones is defined by a NMR and X-ray study of an intermediate.

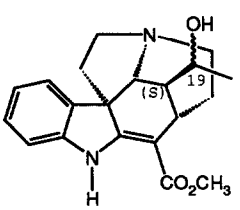
The relative and absolute configurations of the asymmetric centers of tubotaiwine **1**[2] (in particular C-20[3]) were recently established by high field NMR spectroscopy[4] and by total synthesis[5]. Two isomers of 19-hydroxytubotaiwine **2a** and **2b**[6] were isolated from *Alstonia angustiloba* but their structures and especially the configurations of C-19 and C-20 could not be fully assigned due to paucity of material. The recent novel isolation of a 19-hydroxytubotaiwine isomer **3**, named "lagunamine", from *Alstonia scholaris*[7], along with the powerful approaches to the skeleton published by Husson[8] and Bosch[9], prompt us to report our synthetic results and efforts at clarifying the configuration of the asymmetric centers of these alkaloids.



tubotaiwine **1**



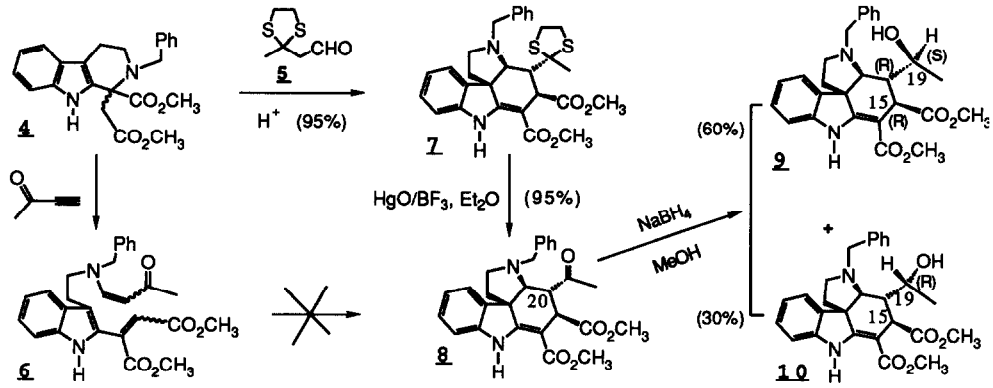
19-hydroxytubotaiwine **2a,b**



lagunamine **3**

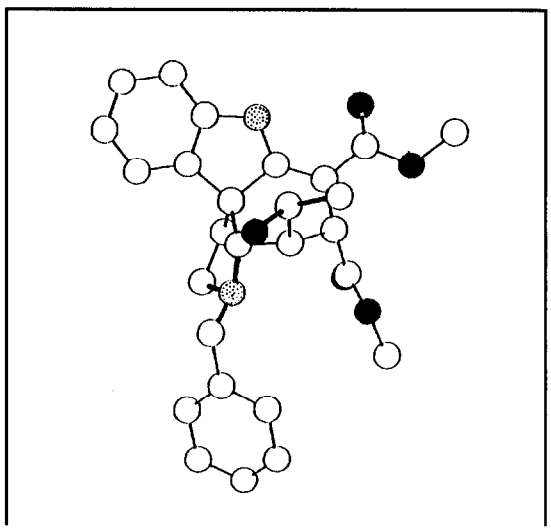
The strategy used follows the general route devised to synthesize alkaloids of the *Strychnos* type[10], which culminated in the total synthesis of tubotaiwine **1**[5]. It starts from tetrahydro-β-carboline diester **4**[11], that is allowed to react, in refluxing toluene, with a suitably designed aldehyde

under acid catalyzed conditions. Use of butynone as a "masked aldehyde" leads to a vinylogous amide **6**, which in our hands, never cyclized to **8**[12]. To circumvent this difficulty, use was made of aldehyde **5**[13], in which the keto group is masked as a dithioketal, which gave **7**[14]. Ketone **8**[14] was obtained upon deprotection of **7** by red mercury(II) oxide and boron trifluoride[15].



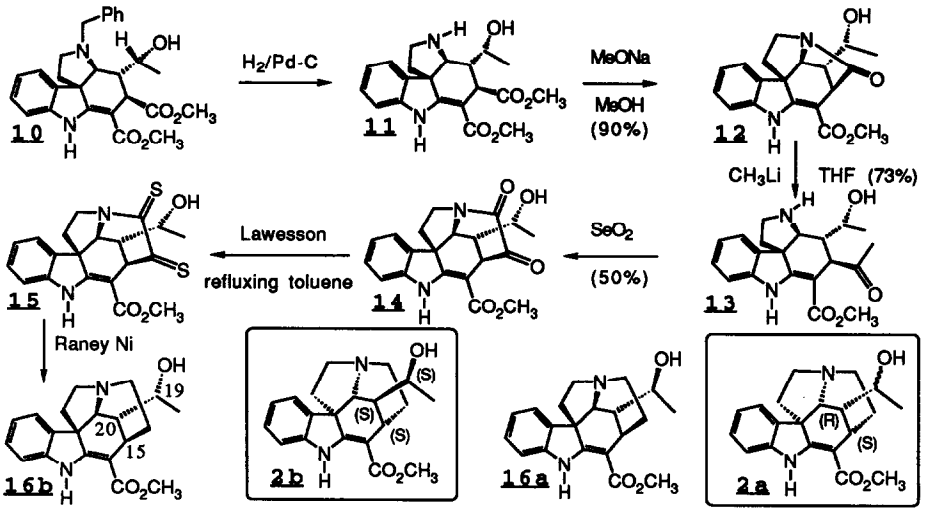
Scheme 1

In order to prevent epimerisation of C-20 in **8**, $NaBH_4$ reduction was carried out to yield a mixture of diastereoisomeric alcohols **9**[16] and **10**[17]. The major compound **9**, the faster running on tlc, crystallizes well from EtOH (mp = 228-229°C). As at this stage, it was impossible to differentiate one from the other by their spectral properties, even from high-field ^1H and ^{13}C NMR spectra[18], we decided to record cristallographic X-ray data[19] on a crystal of **9** whose ORTEP structure is shown below.



X-Ray structure of **9**

The relative configurations of all chiral centers are deduced from crystal structure and are those depicted on formula **9** (scheme 1) : 20-*R* and 19-*S* if considering the 15-*R* (15-α-H) antipodal series and, due to their chemical relationship, we assign the opposite configuration (*R*) to C-19 in **10**. All remaining steps required to achieve the total synthesis were then applied separately to both isomers **9** and **10**. The sequences are identical to those used to prepare tubotaiwine[5], but reduction of ketolactame **14**[14] to amine **16b** is achieved in two steps: transformation into thionethiolactam **15**[14] by Lawesson's reagent[20] and reduction by Raney nickel.



Direct comparisons on tlc and by NMR, IR and MS of **16a** (from **9**) and **16b** (from **10**) with natural samples **2a**, **2b** and lagunamine **3**[21] allow us to assign the relative configurations 15-*S*, 19-*S* and 20-*S* to **2b** and **3**. The slowest running spots on tlc, **2b** and **3**, are superimposable with synthetic compound **16b**. However, **16a** or **16b** are much slower running on tlc than **2a**, that must possess the inverse configuration (*R*) on C-20 at least. That **2a**, **2b** and **3** belong to the tubotaiwine series (15-β-H), and thus possess the 15-*S* configuration, is deduced from their high positive specific rotations[6,7]. Therefore, the above assigned configurations of **2b** and **3** must also be considered as the absolute ones.

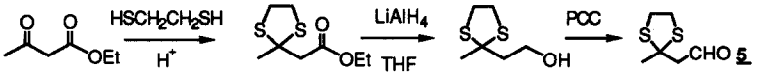
Acknowledgement : Financial support provided by *Etablissement Public Régional d'Aquitaine*, a grant from C.I.E.S. to J. N. and fruitful advice from Drs G. Massiot and K. Koerber for the preparation of the manuscript are gratefully acknowledged. Authors would like also to thank Prs. M. Zèches, L. LeMen-Olivier and Yamauchi for providing us with samples and copies of original spectra.

REFERENCES AND NOTES

1. This work is a part of PhD thesis : Nkiliza, J. *Synthèse totale de la 19-hydroxytubotaiwine et préparation d'indoloazépines de type* Iboga, University of Bordeaux II 1990.
2. More than 40 publications mention its isolation. For excellent reviews, see : a)Husson, H.-P.; Indoles in "Monoterpenoid Indole Alkaloids", Saxton, J. E., Ed., John Wiley and Sons, J., New York, **1983**, pp. 293-330. b)Lounasmaa, M.; Somersalo, P., *Fortschr. Chem. Org. Naturst.*, **1986**, *50*, pp. 27. c)Schripsema, J., van Beek, T.A., Verpoorte, R., Erkelens, C., Perera, P., Tibell, C., *J. Nat. Prod.*, **1987**, *50*, 89.
3. Biogenetic numbering according to : Le Men, J. and Taylor, W.I., *Experientia*, **1965**, *21*, 508.
4. Ref. 2c and a)Atta-ur-Rahman, Alvi, K.A., Muzaffar, A., *Planta Med.*, **1986**, 325. b)Lounasmaa, M., Koskinen, A., O'Connell, J., *Helv. Chim. Acta*, **1986**, *69*, 1343.
5. a)Total syntheses of (±) and (-)-tubotaïwines, Legseir,B., Henin, J., Massiot, G. and Vercauteren, J., to be published. b)Legseir, B. *Alcaloïdes d'*Alstonia lenormandii *var.* lenormandii *et* minutifolia. *Synthèse totale de la (±)-tubotaïwine. Utilisation de l'α-phényléthylamine comme inducteur chiral: application à la*

synthèse de la (-)-tubotaïwine, University of Reims 1987. c)Massiot, G. and Delaude, C., in "The Alkaloids", Brossi, A., Ed., Academic Press, New-York, vol. 34, 1988, chapt. 5, pp 313-315.

6. Both isomers have been isolated for the first time, from *Alstonia angustiloba*, by L. LeMen-Olivier : a)Zèches, M., Ravao, T., Richard, B., Massiot, G., LeMen-Olivier, L., Guilhem, J. et Pascard, C., *Tetrahedron Lett.*, **1984**, *25*, 659. b)Ravao, T., *Alcaloïdes de deux* Alstonia *indonésiens :* A. angustiloba *et* A. pneumatophora *(Apocynacées)*, University of Reims 1985.
7. a)Yamauchi, T., Abe, F., Padolina, W.G. and Dayrit, F.M., *Phytochemistry*, **1990**, *29*, 3321. b)Yamauchi, T., Abe, F., Chen, R.-F., Nonaka, G.-I., Santisuk, T. and Padolina, W.G., *Phytochemistry*, **1990**, *29*, 3547.
8. Rubiralta, M., Torrens, A., Reig, I., Grierson, D.S. and Husson H.-P., *Heterocycles*, **1989**, *29*, 2121.
9. a)Bosch, J., Amat, M., *Tetrahedron Lett.*, **1985**, *26*, 4951. b)Alvarez, M., Lavilla, R., Bosch, J., *Tetrahedron Lett.*, **1987**, *28*, 4457. c)Amat, M., Linares, A., Luisa Salas, M., Alvarez, M., Bosch, J., *J. Chem. Soc., Chem. Commun.*, **1988**, 420. d)Amat, M., Linares, A., Munoz, J., Bosch, J., *Tetrahedron Lett.*, **1988**, *29*, 6373.
10. a)Vercauteren, J., Bideau, A., Massiot, G., *Tetrahedron Lett.*, **1987**, *28*, 1267. b)Henin, J., Massiot, G., Vercauteren, J., *Tetrahedron Lett.*, **1987**, *28*, 1271. c)Legseir, B., Henin, J., Massiot, G., Vercauteren, J., *Tetrahedron Lett.*, **1987**, *28*, 3573.
11. Vercauteren, J., Lavaud, C., Lévy, J., Massiot, G., *J. Org. Chem.*, **1984**, *49*, 2278.
12. All new compounds were fully characterized by IR, UV, ^{1}H and ^{13}C high field NMR, MS and gave satifactorily microanalyses.
13. Prepared from ethylacetoacetate as follows :



5

14. 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).
15. Vedejs, E., Fuchs, P.L., *J. Org. Chem.*, **1971**, *36*, 366.
16. Data for **2** : HRMS m/z : 462.2152, $C_{27}H_{30}N_2O_5$ requires : 462.21546, m/z (%) : 444 (3), 332 (12), 190 (100), 91 (98), 82 (19). U.V. : $\lambda_{max,\ nm}$ (MeOH) : 226, 296, 325. ^{1}H NMR δ(ppm)/TMS : 9.00 s (br) N-H; 7.26 d(7) 2H; 7.22 t(7); 7.16 t(7) H4'; 7.05 t(7) H11; 6.97 d(7) H9; 6.77 t(7) H10; 6.73 d(7) H12; 4.07 d(13) H3; 3.82 s(br) H15; 3.68 s OCH_3; 3.59 s OCH_3; 3.46 s(br) H21; 3.17 dq (8;6) H19; 2.70 m H5; 2.55 d(br) (8) H20; 2.37 m H5' and H6; 1.47 m H6'; 1.01 d(6) H18.
17. Data for **10** : U.V. : $\lambda_{max,\ nm}$ (MeOH) : 228, 298, 323. MS m/z (%): 462 ($M^{+\cdot}$ 14), 444 (3), 332(13), 190 (80), 91 (100), 82 (18). ^{1}H NMR δ(ppm)/TMS : 9.1 s (br) N-H; 7.30 d(7) 2H; 7.26 t(7) ar; 7.19 t(7) H4'; 7.08 t(7) H11; 7.02 d(7) H9; 6.81 t(7) H10; 6.77 d(7) H12; 4.23 s (br) H15; 4.11 d(13) H3; 3.71 s OCH_3; 3.63 s OCH_3; 3.41 d(13) H3'; 3.20 dq(8;6) H19; 3.06 s (br) H21; 2.72 m H5; 2.65 d (br) (8) H20; 2.38 m H5' and H6; 1.51 m H6'; 1.05 d(6) H18.
18. All 1D and homo/heteronuclear measurements are recorded on a BRUKER® AM-X instrument, at 500 MHz for proton.
19. From a single crystal of **2** whose dimensions were 0.12 x 0.12 x 0.30 mm, 3764 independent reflections were measured with an automatic Enraf Nonius CAD-4 diffractometer (graphite monochromator, Cu-Kα radiation, λ = 1.54178 Å). Among these 2470 are significative ($I \geq 3\sigma(I)$). Cell unit is monoclinic with $P2_{1/n}$ as space group and a = 7.867 (2) Å, b = 16.224 (3) Å, c = 18.832 (5) Å, β = 92.12°. The structure was solved by direct methods with MULTAN 80® and refined by the least square-means method. Thermal anisotropic factors are used for C, N and O atoms while Hydrogen atoms are added in theoretical positions, or localized by Fourier-difference, with thermal isotropic factors. The final reliability factor is R = 0.061 (Rw = 0.085). The crystallographic data and all measurements are sent to the data bank of Cambridge.
20. a)Scheiby, E.S., Pedersen, B.S., Lawesson, S.O., *Bull. Soc. Chim. Belg.*, **1978**, *87*, 299. b)Raucher, S., Klein, P., *Tetrahedron Lett.*, **1980**, 4061.
21. During the course of publication work, Pr. Yamauchi kindly provided us with sample and NMR spectrum of lagunamine, allowing us to compare it with synthetic compounds.

(Received in France 6 November 1990)