SYNTHESIS AND ABSOLUTE CONFIGURATION OF THE ALANGIUM VITIENSE ALKALOID (−)-9-DEMETHYLTUBULOSINE

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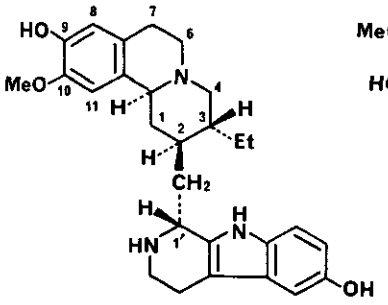
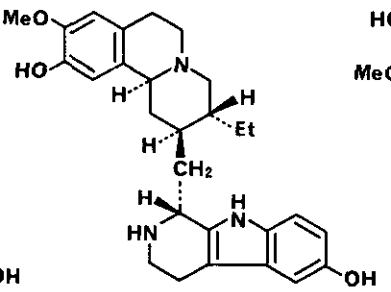
Abstract —— (−)-9-Demethyltubulosine [(−)-I] has been synthesized from the tricyclic amino acid (−)-IV through the intermediates (−)-V, (+)-VI, and (+)-VII. The identity of the synthetic (−)-I with a $C_{28}H_{35}N_3O_3$ base, isolated from Alangium vitiense, unequivocally established the structure and absolute stereochemistry of this alkaloid.

Alkaloid extracts of Alangium vitiense (Alangiaceae) have been reported to possess oncostatic activity[1] and a $C_{28}H_{35}N_3O_3$ alkaloid [mp 200°C; $[\alpha]_D^{20}$ −40° (c 1, pyridine)] from the trunk bark to increase the survival time of mice infected with leukemia L1210 or P388.[2] Our recent work[3] revealed that this A. vitiense alkaloid has the 9-demethyltubulosine structure [(−)-I] (absolute configuration shown[4]), and this was confirmed by a direct comparison with synthetic (±)-9-demethyltubulosine [(±)-I].[3,5] Tentative assignment of absolute configuration to the alkaloid was made on the basis of its cd curve[3] which is similar to that of the known A. lamarckii alkaloid (−)-10-demethyltubulosine [(−)-II].[6] We now wish to report the results of our efforts toward a chiral synthesis of the stereoformula (−)-I, which confirms the correctness of the absolute stereochemistry assignment described above.

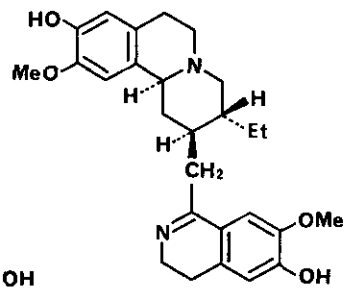
The starting material selected for the synthesis of (−)-I was the known tricyclic amino acid (−)-IV,[7] a key intermediate utilized for our recent syntheses of (+)-9-demethylpsychotrine [(+)-III][7] and (−)-9-demethylcephaeline,[8] and the synthetic scheme parallels that previously followed[5] for the racemic synthesis of I from



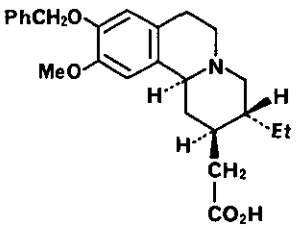
(−)-I



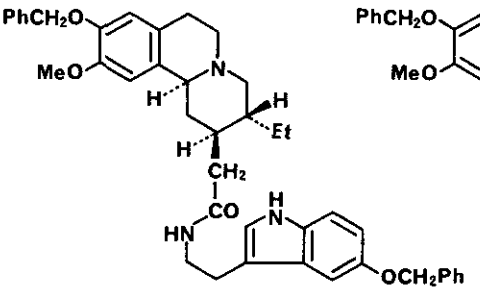
(−)-II



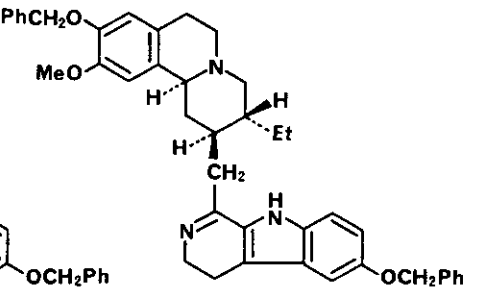
(+)-III



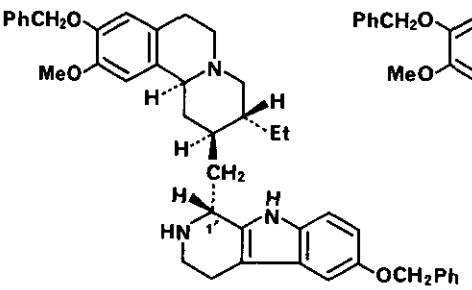
(−)-IV



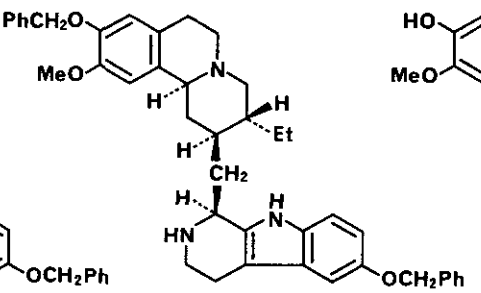
(−)-V



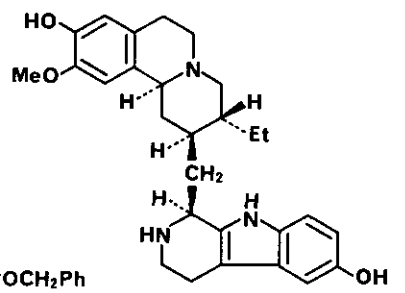
(+)-VI



(+)-VII



(+)-VIII



(−)-IX

(±)-IV. Condensation of (−)-IV with 5-benzyloxytryptamine[9] by the diethyl phosphorocyanidate method[10] [$(EtO)_2P(O)CN/Et_3N$, $HCONMe_2$, room temp., 6 h] afforded the amide (−)-V [mp 168–168.5°C; $[\alpha]_D^{19}$ −8.0° (c 0.50, EtOH)][11] in 86% yield. Bischler–Napieralski cyclization of (−)-V ($POCl_3$, boiling toluene, 2.5 h) gave the dihydro-β-carboline (+)-VI [63% yield; $[\alpha]_D^{27}$ +34.6° (c 1.00, EtOH)], which was then reduced with H_2 over Adams catalyst (dioxane, 1 atm, 29°C, 1.5 h). Chromatographic separation [silica gel, $CHCl_3$–EtOH (10 : 1, v/v)] of the hydrogenation products furnished (+)-O,O-dibenzyl-9-demethyltubulosine [(+)-VII] [31% yield; $[\alpha]_D^{24}$ +7.6° (c 1.00, EtOH)] and its 1'-epimer [(+)-VIII] [57% yield; $[\alpha]_D^{24}$ +6.8° (c 1.00, EtOH)] as glassy materials. On debenzylation [Pd–C/H_2, MeOH–AcOH (1 : 1, v/v), 1 atm, 24°C, 3 h], (+)-VII gave the target molecule (−)-I [mp 203–205°C; $[\alpha]_D^{25}$ −81.0° (c 1.00, pyridine)] in 90% yield. A similar debenzylation of the epimeric base (+)-VIII produced the corresponding phenolic base (−)-IX [mp 200–202°C; $[\alpha]_D^{25}$ −98.8° (c 1.00, pyridine)] in 86% yield. The stereochemistry at C-1' of (−)-I, (+)-VII, (−)-IX, and (+)-VIII was confirmed by the identity of their solution ir ($CHCl_3$) [available only for (+)-VII and (+)-VIII][12] and ^1H and ^{13}C nmr spectra and tlc mobility with those of the corresponding racemic modifications[5] of established stereochemistry.

Finally, the synthetic (−)-I was found to be identical with a natural sample of the $C_{28}H_{35}N_3O_3$ alkaloid by a direct comparison of the tlc mobility and uv (MeOH, 0.1 N aqueous NaOH, or 0.1 N aqueous HCl), ir (Nujol), ^1H nmr (Me_2SO-d_6), ^{13}C nmr (Me_2SO-d_6), and cd (EtOH) spectra. Thus, the stereoformula (−)-I is a complete expression for this A. vitiense alkaloid. It is of interest to note that the 10-demethyl isomer (−)-II[6] as well as the 9-demethylated congeners such as (+)-9-demethylpsychotrine [(+)-III][6b,7] and 9-demethylprotoemetinol[13] occur in another species of the same genus, Alangium lamarckii Thw.

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