

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

Tozo Fujii,\* Masashi Ohba, and Hiroshi Hatakeyama

*Faculty of Pharmaceutical Sciences, Kanazawa University,  
Takara-machi, Kanazawa 920, Japan*

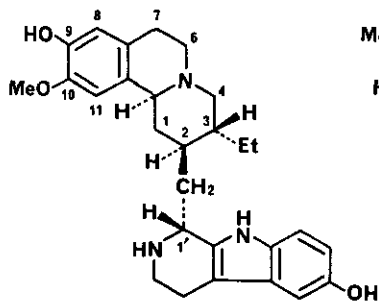
Christiane Kan-Fan and Henri-Philippe Husson

*Institut de Chimie des Substances Naturelles du C.N.R.S.,  
91190 Gif-sur-Yvette, France*

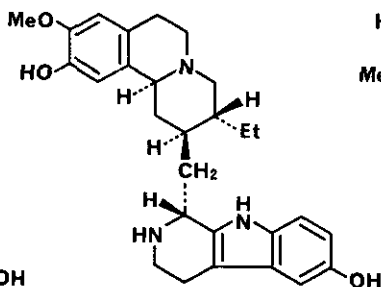
**Abstract** — (-)-9-Demethyltubulosine [(-)-I] has been synthesized from the tricyclic amino acid (-)-IV through the intermediates (-)-V, (+)-VI, and (+)-VII. The identity of the synthetic (-)-I with a  $C_{28}H_{35}N_3O_3$  base, isolated from Alangium vitiense, unequivocally established the structure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

Alkaloid extracts of Alangium vitiense (Alangiaceae) have been reported to possess oncostatic activity<sup>1</sup> 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.<sup>2</sup> Our recent work<sup>3</sup> revealed that this A. vitiense alkaloid has the 9-demethyltubulosine structure [(-)-I] (absolute configuration shown<sup>4</sup>), and this was confirmed by a direct comparison with synthetic (±)-9-demethyltubulosine [(±)-I].<sup>3,5</sup> Tentative assignment of absolute configuration to the alkaloid was made on the basis of its cd curve<sup>3</sup> which is similar to that of the known A. lamarckii alkaloid (-)-10-demethyltubulosine [(-)-II].<sup>6</sup> 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.

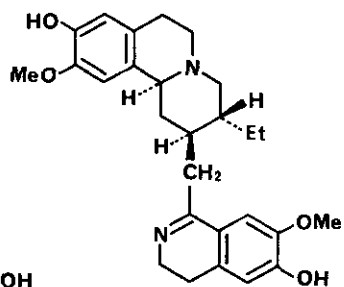
The starting material selected for the synthesis of (-)-I was the known tricyclic amino acid (-)-IV,<sup>7</sup> a key intermediate utilized for our recent syntheses of (+)-9-demethylpsychotrine [(+)-III]<sup>7</sup> and (-)-9-demethylcephaeline,<sup>8</sup> and the synthetic scheme parallels that previously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



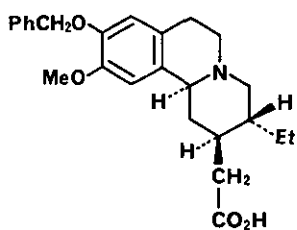
(-)-I



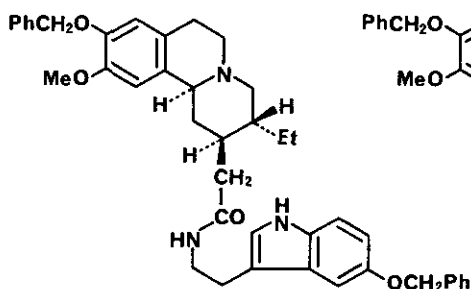
(-)-II



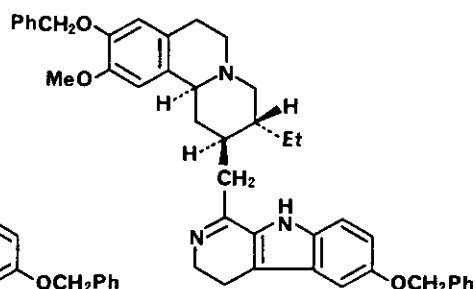
(+)-III



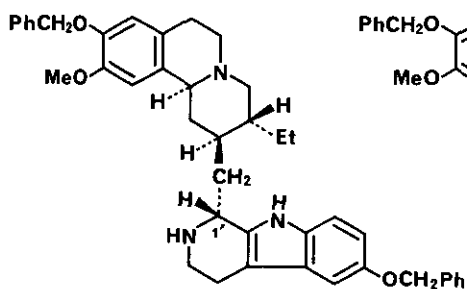
(-)-IV



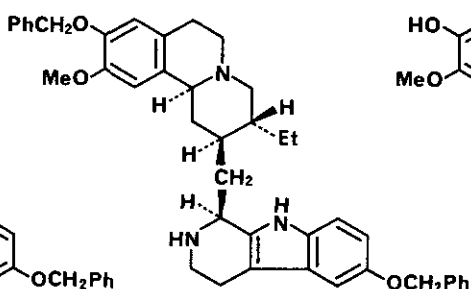
(-)-V



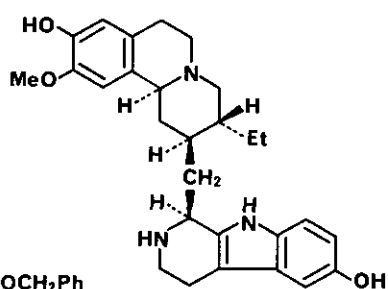
(+)-VI



(+)-VII



(+)-VIII



(-)-IX

(±)-IV. Condensation of (-)-IV with 5-benzyloxytryptamine<sup>9</sup> by the diethyl phosphorocyanidate method<sup>10</sup> [(EtO)<sub>2</sub>P(O)CN/Et<sub>3</sub>N, HCONMe<sub>2</sub>, room temp., 6 h] afforded the amide (-)-V [mp 168–168.5°C;  $[\alpha]_D^{19}$  -8.0° (c 0.50, EtOH)]<sup>11</sup> in 86% yield. Bischler-Napieralski cyclization of (-)-V (POCl<sub>3</sub>, 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<sub>2</sub> over Adams catalyst (dioxane, 1 atm, 29°C, 1.5 h). Chromatographic separation [silica gel, CHCl<sub>3</sub>-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 debenylation [Pd-C/H<sub>2</sub>, 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 debenylation 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<sub>3</sub>) [available only for (+)-VII and (+)-VIII]<sup>12</sup> and <sup>1</sup>H and <sup>13</sup>C nmr spectra and tlc mobility with those of the corresponding racemic modifications<sup>5</sup> of established stereochemistry.

Finally, the synthetic (-)-I was found to be identical with a natural sample of the C<sub>28</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub> 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), <sup>1</sup>H nmr (Me<sub>2</sub>SO-d<sub>6</sub>), <sup>13</sup>C nmr (Me<sub>2</sub>SO-d<sub>6</sub>), 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<sup>6</sup> as well as the 9-demethylated congeners such as (+)-9-demethylpsychotrine [(+)-III]<sup>6b,7</sup> and 9-demethylprotoemetinol<sup>13</sup> occur in another species of the same genus, *Alangium lamarckii* Thw.

ACKNOWLEDGMENT One (T. F.) of the authors is pleased to acknowledge the support of this work by a grant from the Japan Research Foundation for Optically Active Compounds.

## REFERENCES

1. (a) M. Hayat, G. Mathé, E. Chenu, H. P. Husson, T. Sévenet, C. Kan, and P. Potier, *C. R. Hebd. Séances Acad. Sci., Ser. D*, 1977, 285, 1191; (b) G. Mathé,

- M. Hayat, E. Chenu, H. P. Husson, T. Sévenet, C. Kan, and P. Potier, Cancer Res., 1978, 38, 1465.
2. E. Chenut, M. B. Hayat, H. P. Husson, C. Kan-San, G. Mathé, P. Potier, and T. Sévenet, Fr. Demande 2,393,004 (1978) [Chem. Abstr., 1979, 91, 181442t].
  3. C. Kan-Fan, R. Freire, H.-P. Husson, T. Fujii, and M. Ohba, Heterocycles, 1985, 23, 1089.
  4. Unless otherwise noted, the structural formulas of optically active compounds in this paper represent their absolute configurations.
  5. (a) M. Ohba, M. Hayashi, and T. Fujii, Heterocycles, 1980, 14, 299; (b) Idem, Chem. Pharm. Bull., 1985, 33, 3724.
  6. (a) A. Popelak, E. Haack, and H. Spingler, Tetrahedron Lett., 1966, 1081; (b) S. C. Pakrashi and E. Ali, ibid., 1967, 2143; (c) T. Fujii, M. Ohba, A. Popelak, S. C. Pakrashi, and E. Ali, Heterocycles, 1980, 14, 971; (d) T. Fujii and M. Ohba, Chem. Pharm. Bull., 1985, 33, 4314.
  7. (a) T. Fujii, M. Ohba, S. C. Pakrashi, and E. Ali, Tetrahedron Lett., 1979, 4955; (b) T. Fujii and M. Ohba, Chem. Pharm. Bull., 1985, 33, 583.
  8. (a) T. Fujii and M. Ohba, Heterocycles, 1982, 19, 857; (b) Idem, Chem. Pharm. Bull., in press.
  9. L. Bretherick, K. Gaimster, and W. R. Wragg, J. Chem. Soc., 1961, 2919.
  10. T. Shioiri, Y. Yokoyama, Y. Kasai, and S. Yamada, Tetrahedron, 1976, 32, 2211.
  11. The assigned structures of all new compounds were supported by elemental analyses and/or satisfactory spectral data, which matched those of the previously reported<sup>5</sup> racemic modifications.
  12. The ir spectra of (-)-I and (-)-IX in CHCl<sub>3</sub> were not measured owing to their poor solubility in this solvent.
  13. (a) E. Ali, R. R. Sinha, B. Achari, and S. C. Pakrashi, Heterocycles, 1982, 19, 2301; (b) T. Fujii, M. Ohba, H. Suzuki, S. C. Pakrashi, and E. Ali, ibid., 1982, 19, 2305.

Received, 31st October, 1985