First Total Synthesis of the Indole Alkaloid Ervitsine. A Straightforward, Biomimetic Approach

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Ervitsine[1] is a minor 2-acylindole alkaloid isolated in 1977 from *Pandaca boiteaui*[2] with a rather unusual structure containing C_6–C_{16}[3] and C_5–C_7 bonds. Other remarkable features are the presence of a seven-membered C ring and a bridged 3(*E*)-ethylidene-5-methylenepiperidine moiety.

The biogenetic pathway to this particular structural arrangement probably involves[2] a key intermediate **C**, formed from a vobasine *N*-oxide equivalent as illustrated in Scheme I, which would be transformed either into ervitsine via a 1,2-addition or into the related alkaloid methuenine via a more favorable 1,4-addition.[4]

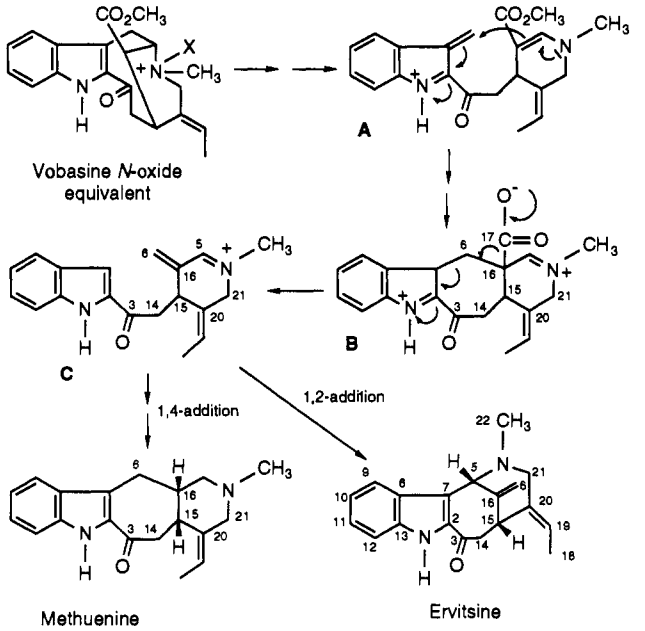
Although several synthetic approaches to simplified tetracyclic analogs of ervitsine have been described,[5] no synthesis for this alkaloid has been reported yet.

We present here the first total synthesis of ervitsine through a straightforward, biomimetic[6] sequence involving only three separate synthetic steps. The key intermediate was the iminium cation **4**, which was envisaged as a synthetic equivalent of the conjugated iminium cation **C** as it incorporates (i) a latent methylene substituent as a (dimethylamino)methyl group and (ii) a 5-aminopentadienoate moiety which could be further stereoselectively elaborated into the exocyclic (*E*)-ethylidene substituent. The iminium cation **4** would undergo regioselective cyclization to the bridged tetracyclic system of ervitsine (1,2-addition) rather than to the fused skeleton of the alkaloids of the methuenine group.

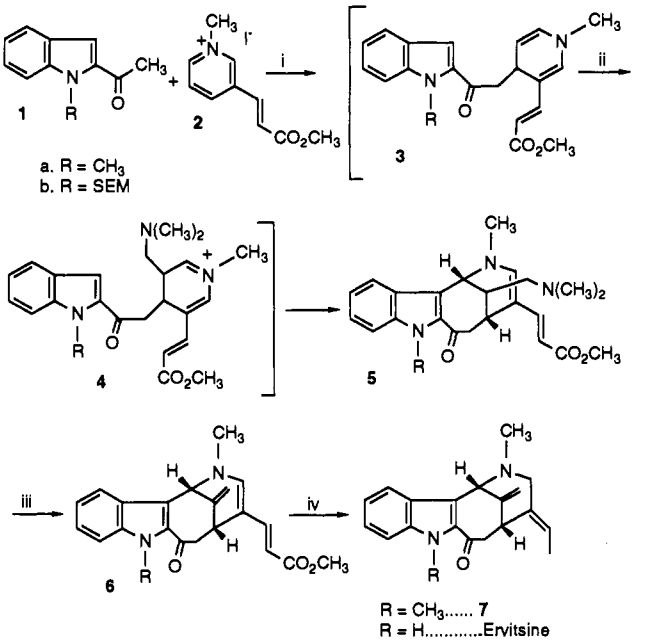
The intermediate **4** would be generated by a modification of the methodology we have successfully used for the synthesis of bridged indole alkaloids[7] based on the nucleophilic addition of an indole-containing enolate to the γ-position of a pyridinium salt[8] followed by acid treatment of the resulting 1,4-dihydropyridine. The modification would consist in trapping the initially formed dihydropyridine with an appropriate one-carbon electrophile instead of acid to give the key iminium salt required for cyclization.

Our preliminary studies were directed to the synthesis of the $N_{(a)}$-methyl analog of ervitsine, **7** (Scheme II). Thus, interaction of 2-acetylindole **1a** with pyridinium iodide **2** in the presence of LICA (lithium isopropylcyclohexylamide), followed by treatment with $Me_2N^+{=}CH_2$ I^- (Eschenmoser's salt),[9] directly gave tetracycle **5a**[10] in 18% yield in a process involving a one-pot,

Scheme I



Scheme II [a]



[a] (i) LICA or LDA (1.5 equiv), THF. (ii) $Me_2N^+{=}CH_2$ I^- (3 equiv). (iii) MCPBA (1.5 equiv), CH_2Cl_2, −10 °C, 2 h; then toluene, reflux, 1 h. (iv) 4 N HCl, reflux, 2 h; then $NaBH_4$ (1.5 equiv), MeOH, 0 °C, 20 min.

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(2) Andriantsiferana, M.; Besselièvre, R.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1977**, 2587.

(3) The biogenetic numbering is used throughout this paper. Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(4) The biogenetic relationship between the alkaloids of the vobasine and ervatamine types through intermediates like **A** and **B** has been demonstrated. (a) Husson, A.; Langlois, Y.; Riche, C.; Husson, H.-P.; Potier, P. *Tetrahedron* **1973**, *29*, 3095. (b) Thal, C.; Dufour, M.; Potier, P.; Jaouen, M.; Mansuy, D. *J. Am. Chem. Soc.* **1981**, *103*, 4956.

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(6) Husson, H.-P. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 10.

(7) (a) Bennasar, M.-L.; Alvarez, M.; Lavilla, R.; Zulaica, E.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 1156. (b) Alvarez, M.; Salas, M.; de Veciana, A.; Lavilla, R.; Bosch, J. *Tetrahedron Lett.* **1990**, *31*, 5089. (c) Jiménez, J.-M.; Zulaica, E.; Bennasar, M.-L.; Bosch, J. *J. Chem. Soc., Chem. Commun.* in press.

(8) Carbanion nucleophile additions to *N*-alkyl-β-acylpyridinium salts for alkaloid synthesis were first used by Wenkert: (a) Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271. (b) Wenkert, E.; Guo, M.; Pestchanker, M. J.; Shi, Y.-J.; Vankar, Y. D. *J. Org. Chem.* **1989**, *54*, 1166 and references cited therein. (c) For a review, see: Bennasar, M.-L.; Lavilla, R.; Alvarez, M.; Bosch, J. *Heterocycles* **1988**, *27*, 789.

(9) The use of other one-carbon electrophiles such as CH_2O, $BrCH_2SeC_6H_5$/$TiCl_4$, $ClCH_2SC_6H_5/ZnCl_2$, $CH_3SCH_2SCH_3$/DMTSF, or CH_3SOCH_3/TFAA resulted in failure.

(10) All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR, HRMS and/or microanalysis.

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three-step sequence with formation of three C–C bonds by successive γ-nucleophilic, β-electrophilic, and α-nucleophilic attacks to the pyridine ring. Cope elimination of the corresponding *N*-oxide afforded the methylene derivative **6a** (50%), which was stereoselectively converted in 54% yield into $N_{(a)}$-methylervitsine (**7**) by treatment with refluxing hydrochloric acid followed by $NaBH_4$ reduction.[11]

The extension of this reaction sequence to the synthesis of ervitsine required the protection of the indole nitrogen.[12] As expected, operating as above, the $N_{(a)}$-protected 2-acetylindole **1b** was converted (15%) into the functionalized tetracycle **5b** by way of 1,4-dihydropyridine **3b** and iminium salt **4b**. Successive elaboration of the exocyclic methylene and (*E*)-ethylidene substituents from **5b**, as in the above **a** series, gave **6b** (45%) and then the target alkaloid ervitsine (65%). Deprotection of the indole ring took place under the hydrolytic conditions of the latter step. The ^1H NMR and mass spectra of our synthetic ervitsine were identical to those reported for the natural product,[2] whereas the ^{13}C NMR spectrum was in full agreement with the one expected for this structure.

The above results deserve interest because they provide an argument supporting the proposed biogenetic origin of ervitsine. Additionally, the synthetic methodology developed here provides the first example in which a 1,4-dihydropyridine generated by addition of an enolate to an *N*-alkyl-3-acylpyridinium salt is further functionalized,[8c] to ultimately give a bridged pentasubstituted piperidine having two different exocyclic double bonds.

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Supplementary Material Available: NMR spectra of the synthesized compounds (12 pages). Ordering information is given on any current masthead page.

(11) For a review on the elaboration of the ethylidene substituent in the synthesis of indole alkaloids, see: Bosch, J.; Bennasar, M.-L. *Heterocycles* **1983**, *20*, 2471.

(12) From our previous model studies, SEM was selected as the protective group.[5f]