Total Synthesis of Indole Alkaloids of the Ervatamine Group. A Biomimetic Approach

M.-Lluïsa Bennasar,* Bernat Vidal, and Joan Bosch*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain

Received January 2, 1996

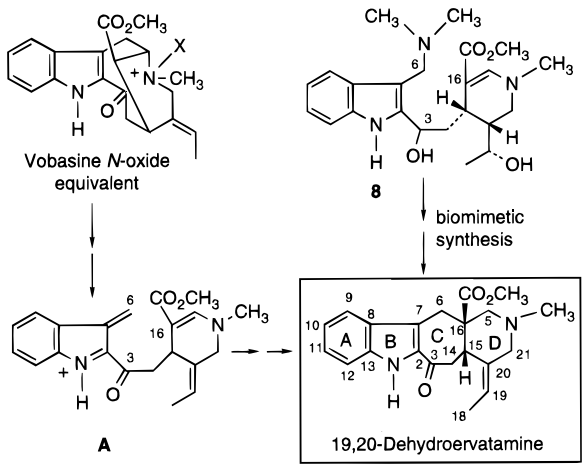
The ervatamine alkaloids[1] (19,20-dehydroervatamine,[2] ervatamine,[2] methuenine,[3] and silicine[4]) constitute a group of 2-acylindole alkaloids with an unusual structure, in which the tryptamine carbon atoms (C_5 and C_6)[5] are in a rearranged situation, forming C_5-C_{16} and C_6-C_{16} bonds. Other remarkable features are the presence of a methoxycarbonyl group at C-16, absent in the methuenine−silicine series, a seven-membered C ring included in a cis-fused[6] bicyclic system, and an ethyl or (*E*)-ethylidene group at C-20.

The biogenetic pathway to this structural arrangement probably involves a key intermediate **A**, formed from a vobasine *N*-oxide equivalent as illustrated in Scheme 1, which would be transformed into 19,20-dehydroervatamine by closure of the C ring by cyclization of the enamine moiety upon the 3-methyleneindoleninium cation (bond formed C_6-C_{16}).[7]

These alkaloids have received little attention from a synthetic standpoint: only the total synthesis of (±)-6-oxosilicine has been reported so far.[8] Additionally, the syntheses of several related tetracyclic structures,[9] including a $N_{(a)}$-methyl-16-epi-20-epi derivative of ervatamine, have been described.[8]

We present here a synthetic entry to the tetracyclic ring system of the alkaloids of the ervatamine group based on a biomimetic cyclization and the first total synthesis of the alkaloids 19,20-dehydroervatamine and 20-epiervatamine. The C_6-C_{16} seco derivative **8** was envisaged as the synthetic equivalent of the key biogenetic intermediate **A** as the 3-[(dimethylamino)methyl]-indole moiety can be considered as a latent 3-methyleneindoleninium cation. On the other hand, the functionalized two-carbon appendage on C-20 in the intermediate **8** could be further elaborated into the C-20 ethyl or ethylidene chain present in the natural products.

Scheme 1



The crucial biomimetic intermediate **8** would be prepared taking advantage of the methodology we have recently developed[10] for the synthesis of 4-substituted 1,4-dihydropyridines bearing two different electron-withdrawing groups at the β-positions, based on the nucleophilic addition of a 2-acetylindole enolate[11] to a 3-acylpyridinium salt, with trapping of the initially formed 1,4-dihydropyridine with trichloroacetic acid anhydride (TCAA).[12] The application of this methodology to the synthesis of **8** required the protection of the nitrogen atom of the starting 2-acetylindole.[13] Thus, reaction of the enolate derived from *N*-benzylated 2-acetylindole **1** with 3-acetylpyridinium salt **2** followed by *in situ* treatment with TCAA gave dihydropyridine **3** in 14% yield (minor amounts of the regioisomeric 3,5-disubstituted 1,2-dihydropyridine were also detected). A subsequent haloform-type reaction of **3** with MeONa in MeOH−THF afforded dihydropyridine **4** in 91% yield (Scheme 2). Dihydropyridines **3** and **4** were crystalline solids, stable enough to be fully characterized.[14]

Stereoselective reduction of the vinylogous amide moiety of dihydropyridine **4** was achieved by catalytic hydrogenation in THF−MeOH[15] to give the *cis*-tetrahydropyridine **5**[16] in 45% yield. Deprotection of the indole ring of **5** with $AlCl_3$[17] followed by reduction of the ketone carbonyl groups with $LiBEt_3H$ in the resulting *N*-unsub-

(1) (a) Joule, J. A. *Indoles, The Monoterpenoid Indole Alkaloids*. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1983; Vol. 25, Part 4, pp 232−239. (b) Alvarez, M.; Joule, J. Monoterpenoid Indole Alkaloids. In *The Chemistry of Heterocyclic Compounds;* Saxton, J. E., Taylor, E. C., Eds.; Wiley: Chichester, 1994; Vol. 25, Supplement to Part 4, pp 234−236.

(2) Knox, J. R.; Slobbe, J. *Aust. J. Chem*. **1975**, *28*, 1813 and 1825.

(3) Bui, A.-M.; Debray, M.-M.; Boiteau, P.; Potier, P. *Phytochemistry* **1977**, *16*, 703.

(4) Vecchietti, V.; Ferrari, G.; Orsini, F.; Pelizzoni, F.; Zajotti, A. *Phytochemistry* **1978,** *17*, 835.

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

(6) The trans C/D ring junction is present in isomethuenine (16-epimethuenine) and 6-oxo-16-episilicine.

(7) The biogenetic relationship between the alkaloids of the vobasine and ervatamine groups through an intermediate like **A** 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.

(8) Husson, H.-P.; Bannai, K.; Freire, R.; Mompon, B.; Reis, F. A. M. *Tetrahedron* **1978,** *34*, 1363.

(9) (a) Langlois, Y.; Potier, P. *Tetrahedron* **1975**, *31*, 423. (b) Grierson, D. S.; Bettiol, J.-L.; Buck, I.; Husson, H.-P.; Rubiralta, M.; Díez, A. *J. Org. Chem*. **1992**, *57*, 6414.

(10) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem*. **1995**, *60*, 4280.

(11) For a recent review on the nucleophilic addition of indole-containing enolates to pyridinium salts and its application to the synthesis of bridged indole alkaloids, see: Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587.

(12) The addition of stabilized carbon nucleophiles to *N*-alkyl-β-acylpyridinium salts for alkaloid synthesis was 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. See also: (c) Spitzner, D.; Arnold, K.; Stezowski, J. J.; Hildenbrand, T.; Henkel, S. *Chem. Ber*. **1989**, *122*, 2027. (d) Amann, R.; Spitzner, D. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1320.

(13) Reaction of the dianion derived from 2-acetylindole with pyridinium salt **2** followed by TCAA treatment gave the corresponding 3,5-diacylated 1,4-dihydropyridine in very low yield. The use of other *N*-protected (BOC, $C_6H_5SO_2$) 2-acetylindoles was also unsuccessful.

(14) All yields are from material purified by column chromatography. Satisfactory analytical and spectral data were obtained from all new compounds.

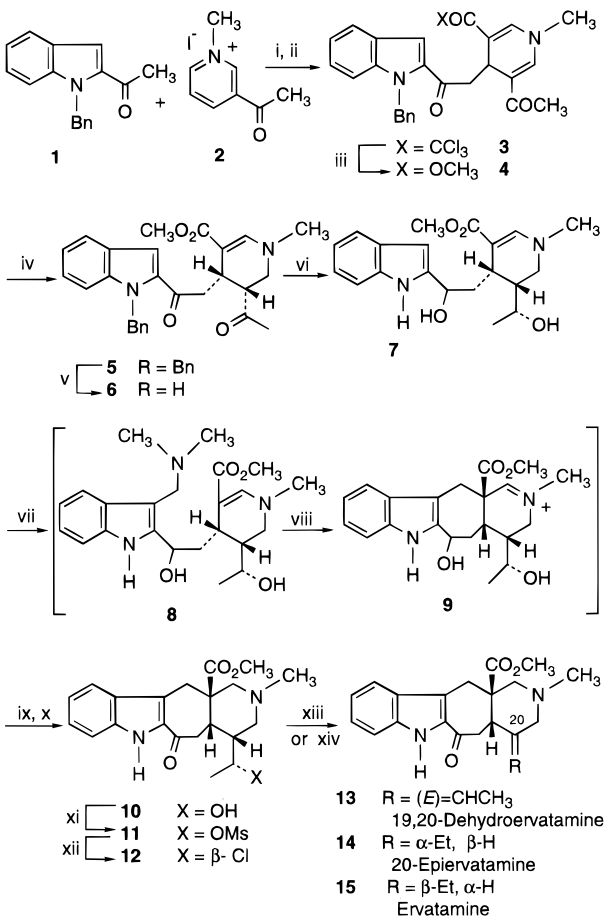
(15) Concomitant reduction of the acetyl group was observed when pure MeOH was used as the solvent for the hydrogenation.

(16) The isomeric *cis*-tetrahydropyridine resulting from reduction of the vinylogous urethane double bond was isolated as a minor byproduct (13% yield).

(17) Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. *Synthesis* **1984**, 738.

0022-3263/96/1961-1916$12.00/0 © 1996 American Chemical Society

Scheme 2[a]



[a] Key: (i) LDA, THF, −30 °C, 1.5 h; (ii) TCAA, 0 °C, 3 h; (iii) MeONa, MeOH−THF, rt, 3 min; (iv) H_2, PtO_2, MeOH−THF, rt, 10 h; (v) $AlCl_3$, C_6H_6, rt, 3 h; (vi) $LiBEt_3H$, −70 °C, 45 min; (vii) $Me_2N^+{=}CH_2\ I^-$, CH_2Cl_2, rt, 1 h; (viii) ICH_3, DMSO, rt, 30 min, then 70 °C, 4 h; (ix) $NaCNBH_3$, MeOH, rt, 45 min; (x) from **11**; MnO_2, $CHCl_3$, rt, 1.5 h; (xi) MsCl, Et_3N, 0 °C, 1 h; (xii) LiCl, acetone, reflux, 1 h; (xiii) DBU, DMSO−toluene, 80−100 °C, 4 h; (xiv) from **12**; *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 1 h.

stituted indole **6** gave a single diol **7** (undetermined stereochemistry at the benzylic-type carbon) in 54% overall yield.

The above reduction of the 2-acylindole moiety was necessary for the success of the subsequent aminomethylation of the indole ring. Thus, treatment of diol **7** with *N*,*N*-dimethylmethyleneimmonium iodide (Eschenmoser' salt) gave the key intermediate **8**, which underwent a biomimetic cyclization after activation of the dimethylamino group as a methiodide. Further $NaCNBH_3$ reduction of the resulting iminium salt **9** followed by MnO_2 reoxidation of the benzylic-type hydroxy group gave (±)-19-hydroxy-20-epiervatamine (**10**) in 25% overall yield from **7**.

The synthesis of (±)-19,20-didehydroervatamine (**13**) was completed in 70% yield by DBU treatment of the mesylate **11** derived from alcohol **10**. The stereoselective formation of an (*E*)-ethylidene double bond in this *anti* elimination allowed the relative stereochemistry at C-19 in **7**−**10** to be established. On the other hand, a radical reduction of chloride **12**, obtained in 71% yield from alcohol **10** via mesylate **11**, gave (±)-20-epiervatamine (**14**) in 73% yield. Given that 19,20-didehydroervatamine had been previously converted into ervatamine (**15**) by catalytic hydrogenation,[2] the above synthesis also constitutes a formal synthesis of the latter alkaloid. The ^1H and ^{13}C NMR spectra of our synthetic ervatamines were identical to those reported[18] for the natural products.

The above results not only provide the first synthetic entry to the C-16 methoxycarbonyl-substituted ervatamine alkaloids and present chemical evidence of the viability of the biogenetic proposal outlined in Scheme 1 but also significantly expand the scope and the potential of the methodology for indole alkaloid synthesis based on the reactivity of *N*-alkyl-3-acylpyridinium salts with indole-containing enolates.[19] After the initial nucleophilic attack on the γ-position, the intermediate 1,4-dihydropyridine is further functionalized to give a 3,5-diacyl-1,4-dihydropyridine and then reduced to a tetrahydropyridine,[20] ultimately leading to a cis-fused pentasubstituted piperidine with generation of the C-16 quaternary center.

Acknowledgment. Financial support from the DGICYT, Spain (Project PB94-0214) is gratefully acknowledged. Thanks are also due to the "Comissionat per a Universitats i Recerca", Generalitat de Catalunya, for Grant GRQ93-1059 and for a fellowship to B.V.

Supporting Information Available: Experimental details for the preparation of all new compounds and copies of their ^1H and ^{13}C NMR spectra (22 pages).

JO9600058

(18) Clivio, P.; Richard, B.; Zeches, M.; Le Men-Olivier, M.; Goh, S. H.; David, B.; Sevenet, T. *Phytochemistry* **1990**, *29*, 2693.

(19) For the use of this methodology in a biomimetic synthesis of ervitsine, see: Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 5340.

(20) There are very few examples of the reduction of 1,4-dihydropyridines generated by nucleophilic addition to *N*-alkylpyridinium salts: (a) Lounasmaa, M.; Koskinen, A. *Tetrahedron Lett.* **1982**, *23*, 349. (b) Lavilla, R.; Gotsens, T.; Gullón, F.; Bosch, J. *Tetrahedron* **1994**, *50*, 5233.