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A Straightforward Entry to the Ervitsine Skeleton. Synthesis of 16-Demethyleneervitsine

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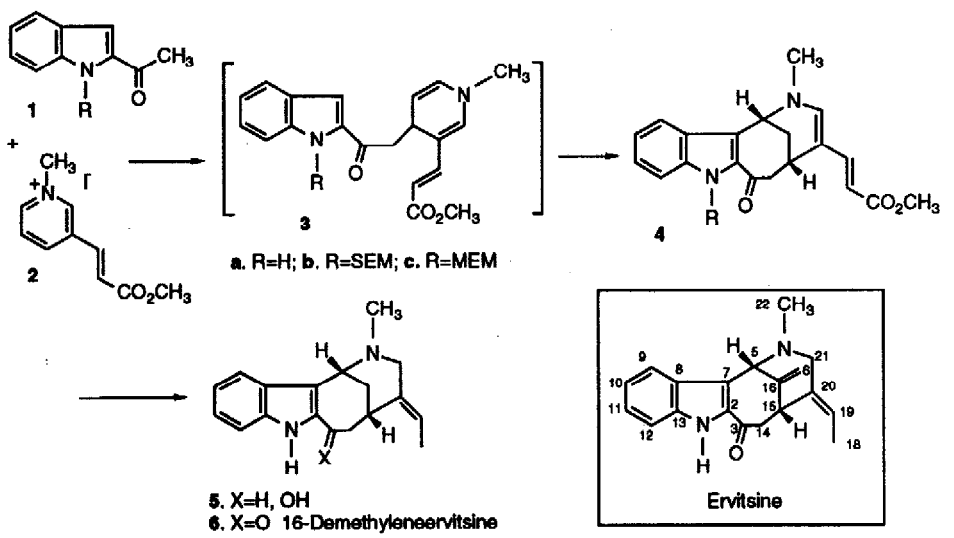
Abstract: A short synthetic route to 16-demethyleneervitsine (**6**), based on the nucleophilic addition of 2-acetylindole enolates to *N*-alkyl-β-acylpyridinium salts and further acid cyclization of the resulting 1,4-dihydropyridine intermediates, is reported.

Ervitsine[1] is a minor 2-acylindole alkaloid isolated in 1977 from *Pandaca boiteaui*[2] having a rather unusual structure, presumably related to the alkaloids of the sarpagine group, in which the tryptamine carbon atoms (C_5-C_6)[3] are in a rearranged situation with C_6-C_{16} and C_5-C_7 bonds. Other remarkable features are the presence of a seven-membered C ring included in a bridged bicyclic system and two exocyclic (16-methylene and 20-ethylidene) piperidine double bonds.

No synthesis for this alkaloid has been reported so far. Previous approaches to its tetracyclic hexahydro-1,5-methanoazonino[4,3-*b*]indole framework imply closure of C ring in the last synthetic steps by cyclization of either an iminium salt upon the indole 3-position[4] (formation of C_5-C_7 bond) or a 4-piperidineacetic acid upon

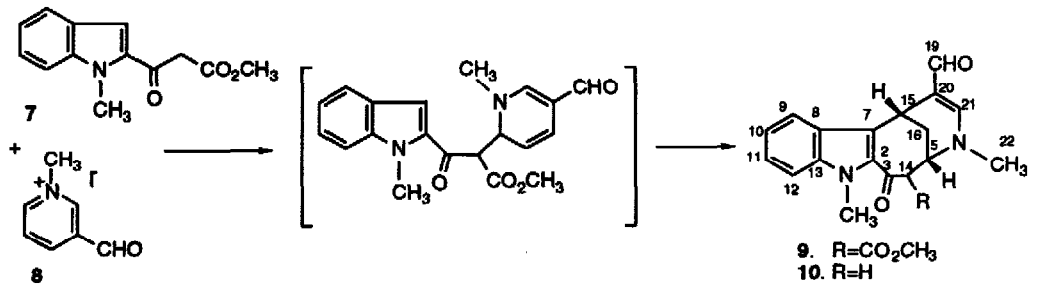


Scheme 1

the indole 2-position[5] (formation of C_2-C_3 bond). Following the latter approach a 19,20-iso-16-demethylene analog of the alkaloid has been synthesized.[5b]

We present here a new, short synthetic route to the ervitsine skeleton (Scheme 1), which allows the stereoselective incorporation of the C-20 (*E*)-ethylidene substituent present in the natural product. The synthesis is based on a nucleophilic addition-cyclization reaction sequence between a suitably substituted pyridinium salt and a 2-acetylindole enolate acting as a bis-nucleophile.[6] We have previously employed a related methodology in the synthesis of tetracyclic ring substructures of C-mavacurine, *Strychnos*, and akuammiline-type alkaloids.[7]

Our first experiments were not encouraging since exposure (-30 °C, 2 h) of pyridinium salt **2** to the dianion derived from 2-acetylindole (**1a**)[8] and then to acid (HCl-C_6H_6, rt, 2 h) led to the expected tetracycle **4a**[9,10] in a yield lower than 5%. On the other hand, the enolate (NaH, THF, rt, 30 min) derived from β-keto ester **7**[4b] did not react with salt **2** and, somewhat unexpectedly, led to the *wrong* tetracycle **9**[11] (Scheme 2) by reaction with the formyl substituted pyridinium salt **8** followed by acid cyclization of the resulting dihydropyridine, thus evidencing the occurrence of an α-attack to the pyridinium ring. Acid dealcoxycarbonylation of **9** afforded tetracycle **10**[12] in 81% yield.



Scheme 2

However, the use of the N_a-protected 2-acetylindoles **1b** and **1c**[13] was more satisfactory and the anticipated tetracycles **4b**[14] and **4c**[15] were obtained in 15% and 10% yields, respectively.

Azonino[4,3-*b*]indoles **4a-c** were easily distinguished from azonino[5,6-*b*]indoles **9**, **10** by the chemical shift values of the bridgehead carbons (see Table 1). The signal corresponding to the proton at the indole 4-position (9-H) was also of diagnostic value.

The stereoselective elaboration of the (*E*)-ethylidene substituent[16] was effected by taking advantage of the β-(tetrahydro-3-pyridyl)acrylate moiety of tetracycles **4**. Thus, treatment of **4b** with refluxing 4N hydrochloric acid brought about the hydrolysis of the ester group, with simultaneous deprotection of the indole ring, and the decarboxylation of the resulting acrylic acid to give a conjugated iminium ion. Further reduction with sodium borohydride gave alcohol **5**,[17] which was reoxidized to 16-demethyleneervitsine (**6**)[18] with manganese dioxide (overall yield from **4b**: 38%). A similar sequence either from the N_a-unsubstituted tetracycle **4a**, which was alternatively prepared in 50% yield by deprotection of **4b** (BF_3-Et_2O, Triton B), or from **4c** led to 16-demethyleneervitsine in 50% and 20% yields, respectively.

The extension of the above methodology to the total synthesis of ervitsine by taking advantage of the dihydropyridine intermediate **3** is currently being studied in our laboratory.

Table 1. Significant ^{13}C-NMR Data of 1,5-Methanoazoninoindoles 4-6, 9, and 10[a]

Compd	C-3	C-5	C-14	C-15	C-16	C-18	C-19	C-20	C-21	C-22
4a	194.6	50.4	44.8	25.3	30.5	102.0	144.4	106.3	147.5	41.5
4b	196.5	50.4	47.7	26.6	31.4	103.2	143.7	106.3	146.6	41.6
4c	196.5	50.4	47.6	26.5	31.3	103.2	143.7	106.3	146.6	41.6
5	67.6	53.4	42.3	29.3	36.3	12.1	121.6	133.6	57.2	43.0
6	195.5	53.5	49.0	28.8	34.4	12.0	122.0	134.7	54.2	43.7
9	189.6	56.5	60.3	23.5	28.1	----	185.8	125.4	152.5	41.7
10	193.6	54.4	48.0	23.9	30.7	----	184.9	125.6	153.1	41.5
19,20-iso-**6**[b,c]	196.8	54.8	52.9	38.6	35.3	12.7	121.5	----	47.3	43.7

[a] In ppm relative to TMS. Measured in $CDCl_3$ solution at 50.3 MHz. [b] Reference 5b. [c] In CD_3OD solution.

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9. All synthetic compounds are racemic. The schemes depict only the enantiomer bearing the natural configuration . Yields are from material purified by column chromatography. All new compounds gave satisfactory elemental analyses.

10. **4a:** mp 288-289 °C (acetone); ^{1}H-NMR ($CDCl_3$-CD_3OD) 2.56 (m, 16-H), 2.85 (dd, J = 15, 2.5 Hz, 1 H, 14-H), 2.96 (s, 22-H), 3.35 (m, 15-H), 3.40 (dm, J = 15 Hz, 1 H, 14-H), 3.71 (s, OCH_3), 5.00 (br s, 5-H), 5.40 (d, J = 15 Hz, 18-H), 6.40 (s, 21-H), 7.20-7.50 (m, 4 H, indole and 19-H), 7.81 (d, J = 8 Hz, 9-H), 10.47 (br s, NH).
11. **9**: mp 218-220 °C (acetone); ^{1}H-NMR ($CDCl_3$) 2.25 (m, 1 H, 16-H), 2.55 (dm, J = 13 Hz, 1 H, 16-H), 3.22 (s, 22-H), 3.70 (s, OCH_3), 3.78 (s, NCH_3), 4.15 (dd, J = 4.6, 0.9 Hz, 14-H), 4.25 (m, 5-H), 4.68 (dm, J = 4.5 Hz, 15-H), 6.80 (s, 21-H), 7.15-7.40 (m, 3 H, indole), 8.35 (d, J = 7.8 Hz, 9-H), 8.80 (s, CHO).
12. **10**: mp 171-172 °C (acetone-ether); ^{1}H-NMR ($CDCl_3$) 2.35 (m, 1 H, 16-H), 2.60 (dm, J = 12.5 Hz, 1 H, 16-H), 3.07 (dd, J = 15.4, 3 Hz, 1 H, 14-H), 3.22 (s, 22-H), 3.30 (ddd, J = 15.4, 5.4, 1.4 Hz, 1 H, 14-H), 3.75 (m, 5-H), 3.80 (s, NCH_3), 4.83 (dm, J = 5 Hz, 15-H), 6.75 (s, 21-H), 7.15-7.40 (m, 3 H, indole), 8.45 (d, J = 7.5 Hz, 9-H), 8.77 (s, CHO).
13. Compounds **1b** (93%) and **1c** (73%) were prepared by alkylation (NaH, DMF) of **1a** with SEM or MEM chloride, respectively. THF solutions of the anions derived from **1b** and **1c** were available by treatment with 1.5 equivalent of LDA at -70 °C for 30 min.
14. **4b**: mp 162 °C (methanol-ether); ^{1}H-NMR ($CDCl_3$) 0.00 (s, CH_3Si), 0.92 (t, J = 7.6 Hz, CH_2Si), 2.65 (m, 16-H), 2.90 (s, 22-H), 3.05 (m, 2 H, 14-H and 15-H), 3.42 (dd, J = 15, 6.6 Hz, 1 H, 14-H), 3.54 (t, J = 7.6 Hz, CH_2O), 3.80 (s, OCH_3), 5.01 (t, J = 2.6 Hz, 5-H), 5.50 (d, J = 15 Hz, 18-H), 5.72 and 6.00 (2 d, J = 10.6 Hz, CH_2N), 6.39 (s, 21-H), 7.30-7.50 (m, 3 H, indole and 19-H), 7.62 (d, J = 8 Hz, 12-H), 7.87 (d, J = 8 Hz, 9-H).
15. **4c**: mp 134 °C (acetone-ether); ^{1}H-NMR ($CDCl_3$) 2.56 (m, 16-H), 2.83 (s, 22-H), 2.98 (m, 2 H, 14- and 15-H), 3.32 (s, OCH_3), 3.50 (m, 5 H, 14-H and OCH_2), 3.72 (s, OCH_3), 4.91 (t, J = 2.5 Hz, 5-H), 5.44 (d, J = 15 Hz, 18-H), 5.70 and 5.93 (2d, J = 10.6 Hz, CH_2N), 6.32 (s, 21-H), 7.20-7.45 (m, 3 H, indole and 19-H), 7.59 (d, J = 8 Hz, 12-H), 7.77 (d, J = 8 Hz, 9-H).
16. For a review, see: Bosch, J.; Bennasar, M.-L. *Heterocycles* **1983**, *20*, 2471.
17. **5:** ^{1}H-NMR ($CDCl_3$) 1.71 (dd, J = 6.7, 1.7 Hz, 18-H), 1.80-3.50 (m, 8 H), 2.14 (s, 22-H), 4.37 (br s, 5-H), 5.20 (dd, J = 12, 4.8 Hz, 3-H), 5.53 (q, J = 6.7 Hz, 19-H), 7.10-7.40 (m, 3 H, indole), 7.65 (d, J = 8 Hz, 9-H).
18. **6:** mp 210 °C (acetone); ^{1}H-NMR ($CDCl_3$) 1.66 (dd, J = 6.8, 1.4 Hz, 18-H), 2.08 (s, 22-H), 2.20-3.30 (m, 8 H), 4.65 (dd, J = 5.5, 1.5 Hz, 5-H), 5.45 (q, J = 6.8 Hz, 19-H), 7.10-7.40 (m, 3 H, indole), 7.76 (d, J = 8 Hz, 9-H), 9.20 (br s, NH).

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