A Short Synthesis of $N_{(a)}$-Methylervitsine. Reactivity of the Intermediate 1,4-Dihydropyridine towards Electrophiles

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A four-step synthesis of $N_{(a)}$-methylervitsine involving the nucleophilic addition of the enolate derived from acetylindole **2** to pyridinium salt **3**, with subsequent C_6H_5SeBr-promoted cyclization of the resulting 1,4-dihydropyridine and further elaboration of the exocyclic 20*E*-ethylidene and 16-methylene substituents, is reported.

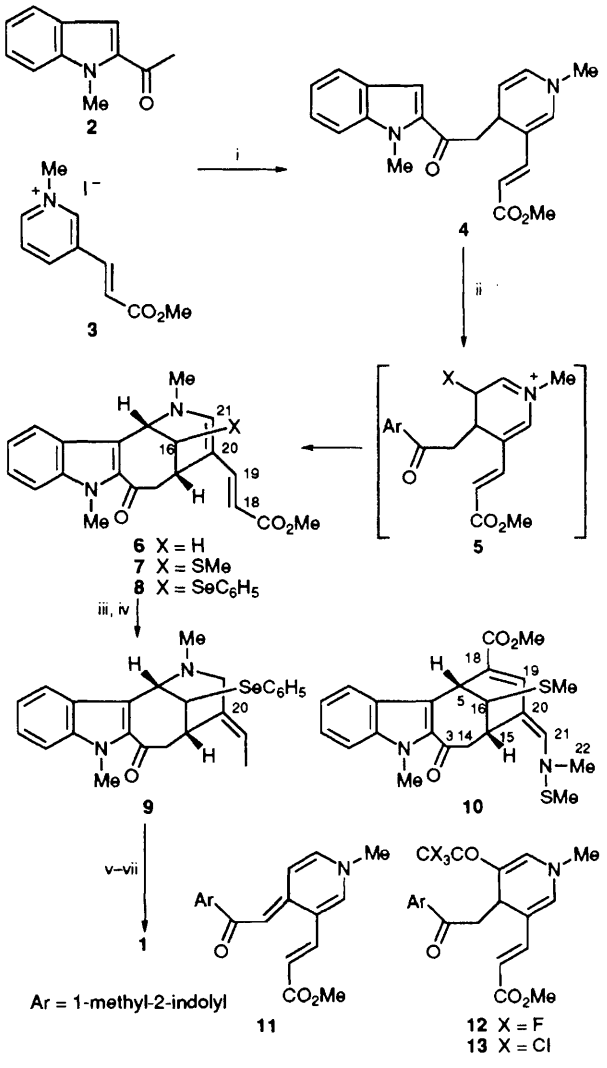
The nucleophilic addition of indole-containing enolates to pyridinium salts bearing an electron-withdrawing substituent at the β-position, followed by acid-promoted cyclization of the intermediate 1,4-dihydropyridines upon the indole nucleus has proved to be a general method for the synthesis of bridged indole alkaloids.[1] A simple modification of the above methodology, consisting of the trapping of the initially formed 1,4-dihydropyridine (*e.g.* **4**) with an electrophile other than a proton to induce cyclization,[2] could allow for the construction of highly substituted bridged piperidine systems, thus expanding the potential of the methodology. In this respect, there are very few reports[3] about further functionalization of 1,4-dihydropyridines resulting from the addition of carbon nucleophiles to pyridinium salts.

In the context of our studies[1c,3] on biomimetic-type synthesis of the indole alkaloid ervitsine,[4] we planned to explore the reactivity of 1,4-dihydropyridines **4** towards a variety of one-carbon or heteroatom-centred electrophiles in order to develop alternative procedures for the elaboration of synthetic equivalents of the iminium cation **A**, which constitutes a key intermediate in the biogenetic pathway from vobasine to ervitsine.[5] However, reaction of 1,4-dihydropyridine **4**, derived from the enolate of 2-acetyl-1-methylindole **2**[6] and pyridinium salt **3**, either with formaldehyde or with several alkyl halides ($ClCH_2SC_6H_5$, $ClCH_2SO_2C_6H_5$ and $BrCH_2SeC_6H_5$) under a variety of experimental conditions resulted in failure. No reaction was observed with $ClP(OEt)_2$, $ClPO(OEt)_2$, or Me_3SiCl either. In all cases, the only identifiable products were the anhydro base **11**† and, in some runs, tetracycle **6** produced by a simple acid cyclization of 1,4-dihydropyridine **4**.‡ On the other hand, **4** did react with both trifluoro- and trichloro-acetic acid anhydrides to give dihydropyridines **12** and **13**, respectively, by way of the iminium intermediate **5** (X = $COCF_3$, $COCCl_3$), which undergoes rapid deprotonation instead of cyclization. In contrast, upon treatment with $[Me_2SSMe]^+$ BF_4^- (DMTSF)[7] 1,4-dihydropyridine **4** led to the C-16 (biogenetic numbering)[8] functionalized tetracycle **7**, although in low yield (< 10%) due to the fact that a further methylthiolation on the piperidine nitrogen promotes the opening of the piperidine ring and subsequent recyclization to give **10** (13% yield).

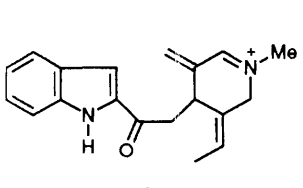
The most successful result from the synthetic standpoint was achieved when 1,4-dihydropyridine **4** was allowed to react with C_6H_5SeBr: tetracycle **8** was obtained in 20% yield as the only isolable product. Tetracycle **8** was then stereoselectively converted in 60% yield into the *E*-configured C-20 ethylidene derivative **9** by treatment with refluxing hydrochloric acid (hydrolysis and decarboxylation of the acrylate moiety) followed by chemoselective $NaBH_4$ reduction of the resulting conjugated iminium ion.[9]

Finally, the phenylseleno group of tetracycle **9** was converted into the exocyclic 16-methylene substituent of $N_{(a)}$-methylervitsine **1**. Thus, oxidation of **9** followed by methylation of the α-position of the resulting selenoxide and further elimination gave the target compound **1** in a reasonable overall yield (30%).

In summary, we have reported a short synthesis of $N_{(a)}$-methylervitsine consisting of only four separate synthetic steps, in a process involving the successive formation of two new C–C



Scheme 1 *Reagents and conditions*: i, LDA–THF, −30 °C, 1.5 h; ii, DMTSF or C_6H_5SeBr, −30 to 0 °C, 3 h; iii, 4 mol dm^{-3} HCl, 100 °C, 2 h; iv, $NaBH_4$, MeOH, 0 °C, 1 h; v, MCPBA, CH_2Cl_2, −70 °C, 20 min; vi, LDA, ICH_3, THF, −70 °C, 1 h; vii, diisopropylamine, THF, reflux, 1 h



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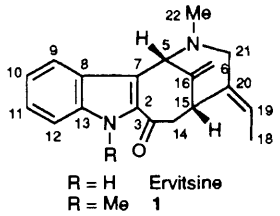

bonds with the pyridine ring in the first step, the elaboration of the *pyridine* β-substituent into an exocyclic *E*-ethylidene substituent, and finally the introduction of the exocyclic methylene group taking advantage of the reactivity of the initially formed 1,4-dihydropyridine towards C_6H_5SeBr. In this manner, the starting β-substituted *N*-methylpyridinium salt **3** has been ultimately elaborated into a bridged pentasubstituted piperidine having two different exocyclic double bonds.

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Footnotes

† All new compounds gave satisfactory analytical and spectral data. All yields are from material purified by column chromatography.

‡ In fact, tetracycle **6** was isolated in 20% yield when the initially formed 1,4-dihydropyridine **4** was treated with HCl in benzene solution.

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