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A biomimetic synthesis of (−)-$N_{(a)}$-methylervitsine

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A straightforward, biomimetic synthesis of (−)-$N_{(a)}$-methylervitsine involving the nucleophilic addition of the enolate derived from 2-acetylindole 1 to chiral, non-racemic pyridinium salt 2, followed by (Me_2N^+=CH_2) I^- induced cyclization of the resultant 1,4-dihydropyridine, with subsequent elaboration of the exocyclic 16-methylene and 20*E*-ethylidene substituents, is reported.

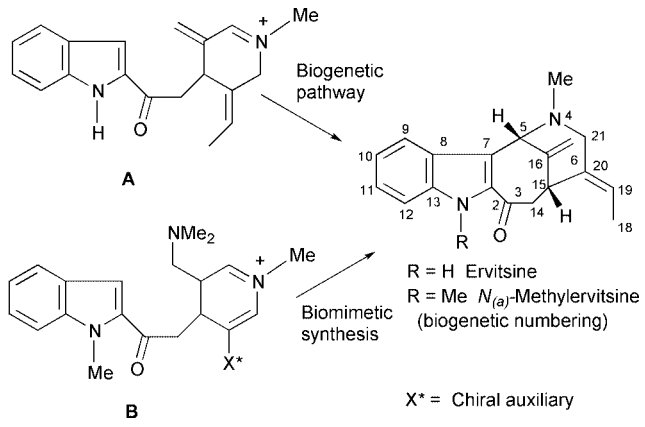
Biomimetic syntheses of natural products reproduce the key steps of their biosynthesis through processes similar to those believed to be occurring in nature.[1] The conjugate iminium cation **A** has been postulated as the key biogenetic intermediate *en route* to ervitsine, a rare 2-acylindole alkaloid isolated from *Pandaca boiteaui*,[2] with a particular skeleton in which the tryptamine carbon atoms C_5–C_6 are in a rearranged situation forming the unusual C_7–C_5–C_{16}–C_6 bond array.[3] Consequently, this bridged alkaloid incorporates a seven membered C ring and a piperidine moiety bearing two different (16-methylene and 20*E*-ethylidene) exocyclic double bonds (Scheme 1).

We report here a biomimetic synthesis of (−)-$N_{(a)}$-methylervitsine *via* the dihydropyridinium cation **B**, which can be envisaged as a synthetic equivalent of the key biogenetic intermediate **A**. This cation incorporates a latent exocyclic methylene group (the dimethylaminomethyl substituent), and *a priori* should be accessible by nucleophilic addition of a 2-acetylindole enolate to the 4-position of a 3-acyl-*N*-alkylpyridinium salt, followed by electrophile (Me_2N^+=CH_2)-induced cyclization of the resulting 1,4-dihydropyridine. The acyl substituent X* would act as a chiral auxiliary, thus allowing the stereoselective generation of the stereocentre at the pyridine 4-position (corresponding to C-15 in ervitsine), and it would then be stereoselectively converted into the exocyclic *E*-ethylidene substituent of the alkaloid. In this approach, taking into account the bridgehead character of C-5 and C-15, the configuration of the latter determines that of the former after the biomimetic cyclization.

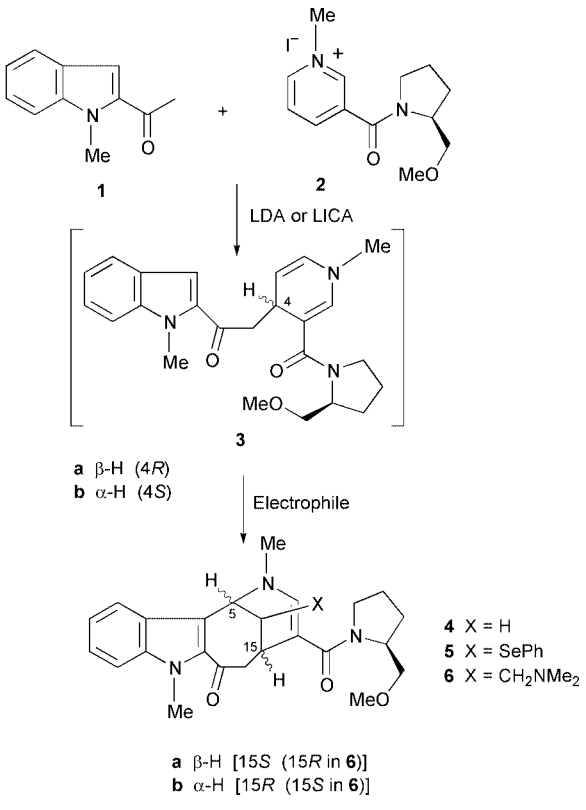
The stereoselective synthesis of chiral non-racemic 1,4-dihydropyridines[4] has been previously achieved by diastereoface-selective addition of suitable organometallic reagents to *N*-acylpyridinium salts carrying chiral auxiliaries, usually at the 3-position of the pyridine ring: oxazoline,[5] aminal,[6] [(η^5-C_5H_5)Fe(CO)(PPh_3)],[7] and amides derived from (*S*)-thiazolidine-2-thiones and (*S*)-oxazolidinones.[8]

In our case, we decided to study the addition of the enolate derived from 2-acetylindole **1** to *N*-methylpyridinium salt **2**, a nicotinic amide derived from (*S*)-*O*-methylprolinol (Scheme 2). The addition of indole-containing enolates to *N*-alkylpyridinium salts bearing an electron-withdrawing group at the 3-position has extensively been used in our laboratory as the initial step of a general scheme for the synthesis of indole alkaloids in the racemic series.[9] However, there are few examples of the use of this methodology for the enantioselective synthesis of alkaloids, and they deal with chiral enolates instead of chiral pyridinium salts.[10]

As can be observed in Table 1, acid induced cyclization of the initially formed dihydropyridine **3** gave a 3:1 diastereomeric mixture of tetracycles **4a** and **4b** (entry 1), whereas PhSeCl (entry 2) or (Me_2N^+=CH_2) I^- (entry 3) induced cyclization afforded 2:1 diastereomeric mixtures of the C-16 substituted tetracycles **5** or **6**, respectively, in which the 15-H β isomers (**a** series) predominated (see below for the determination of the absolute stereochemistry).



Scheme 1



Scheme 2

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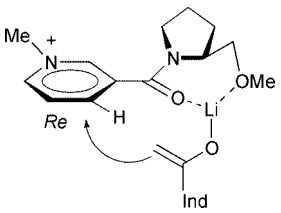
Table 1 Reactions of the enolate derived from **1** with pyridinium iodide **2**[a]

Entry	Electrophile[b]	Product (yield, %)[c]	Diastereomer ratio (a:b)
1	HCl/C_6H_6	**4** (25)	74:26[d]
2	ClSePh	**5** (40)	2:1[e]
3	$CH_2{=}NMe_2\ I^-$	**6** (40)	68:32[d]

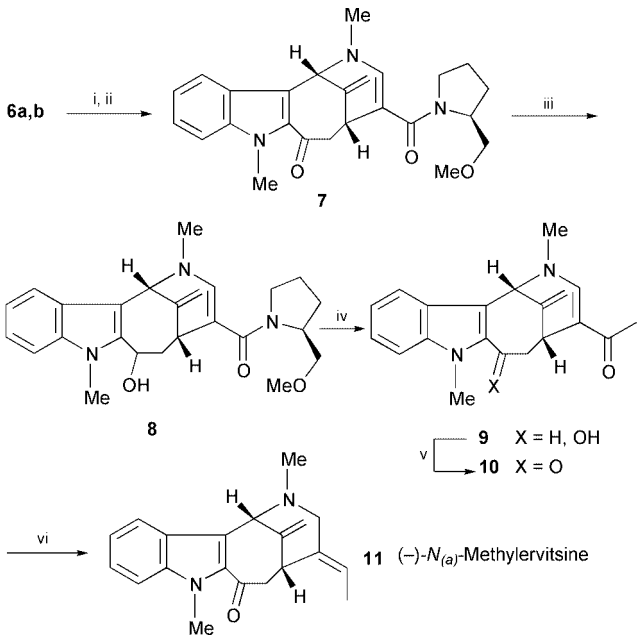
[a] Generation of the enolate with LDA (LICA in entry 3) at −78 °C for 30 min, then interaction with **2** at −30 °C for 1.5 h. [b] Addition at −30 °C to the reaction mixture, then rt for 2 h. [c] Isolated yield of chromatographically pure diastereomeric mixtures. [d] Calculated by HPLC. [e] Approximate ratio calculated by ^{1}H-NMR.

In this way, the tetracyclic ring system of ervitsine has been assembled in a straightforward manner, in a one-pot process involving the formation of three carbon–carbon bonds (C_{14}–C_{15}, C_6–C_{16} and C_5–C_7). This clearly indicates that the interaction of 1,4-dihydropyridine **3** with $(Me_2N^+{=}CH_2)\ I^-$ generates the key biomimetic intermediate **B**, which undergoes the crucial biomimetic cyclization.

The formation of tetracycles **4a**–**6a** as the major products implies that the lithium enolate of **1** preferentially approaches the *Re* face of pyridinium ring **2**, probably after the initial complexation of the lithium cation to both the carbonyl oxygen and the methoxy group of the auxiliary.



The diastereomeric mixture of tetracycles **6a**,**b** was converted into the corresponding 16-methylene derivatives by Cope elimination *via* the respective *N*-oxides in 45% overall yield (Scheme 3). At this point both diastereomers were efficiently separated by crystallization (ether–acetone–hexanes). The absolute configuration of the major diastereomer **7**,[11] coincident with that of natural (−)-ervitsine, was unambiguously determined by X-ray crystallography.[12] Removal of the chiral auxiliary from **7** required the previous chemoselective reduction of the 2-acylindole carbonyl group with lithium borohydride to give alcohol **8** (80%), which was converted into the acetyl derivative **9** by reaction with methyllithium (54%). Finally, after regeneration of the 2-acylindole carbonyl group with MnO_2 (quantitative), the stereoselective elaboration of the 20*E*-ethylidene substituent was accomplished by treatment of **10** with trimethyloxonium tetrafluoroborate followed by controlled sodium borohydride reduction (25%).[13] The ee (> 99%) of the resulting (−)-$N_{(a)}$-methylervitsine (**11**), $[\alpha]_D$ −60.5 (*c* 0.1, $CHCl_3$), was determined by chiral HPLC using racemic $N_{(a)}$-methylervitsine as reference. Finally the NMR spectra of **11** matched those of the racemic material.[9e]



Scheme 3 Synthesis of (−)-$N_{(a)}$-methylervitsine. *Reagents and conditions*: i, 70% *m*-CPBA, CH_2Cl_2, −10 °C, 2 h; ii, toluene, reflux, 1 h, 45%, then separation of diastereomers; iii, $LiBH_4$, THF, rt, overnight, 80%; iv, MeLi, THF, 0 °C, 4 h, 54%; v, MnO_2, CH_2Cl_2, rt, 2 d, quantitative; vi, $Me_3O{\cdot}BF_4$, CH_2Cl_2, rt, 2 h, then $NaBH_4$, MeOH, 0 °C, 1 h, 25%.

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