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A general method for the synthesis of bridged indole alkaloids

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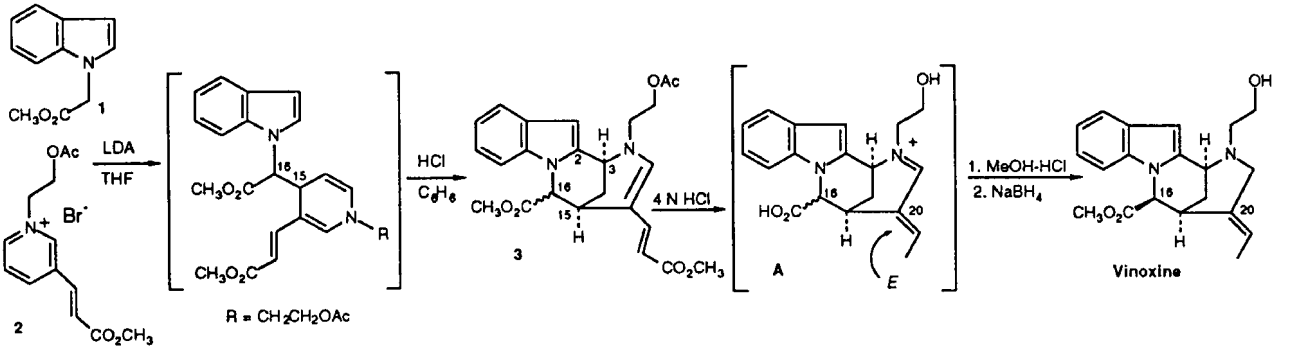
Abstract: The nucleophilic addition of indoleacetic ester enolates to pyridinium salts, followed by acid-promoted cyclization of the intermediate 1,4-dihydropyridines, leads to tetracyclic substructures of C-mavacurine, *Strychnos*, and akuammiline alkaloids. Further closure of the tryptamine chain by cyclization upon the indole nucleus has completed total syntheses of pentacyclic C-mavacurine and *Strychnos* alkaloids. The extension of the methodology to the synthesis of alkaloids having other skeletal types (akagerine, ervitsine) from 1- or 2-acetylindoles is also discussed.

Despite their evident skeletal differences, the alkaloids of the C-mavacurine, *Strychnos*, and akuammiline groups have some common structural features due to their common biogenetic origin: i) a tryptamine unit, ii) a two-carbon substituent at C-20, in most cases an ethyl or *E*-configurated ethylidene, iii) an oxidized one-carbon substituent at C-16, and iv) a (2-piperidyl)indole moiety included in a bridged polycyclic system.

These similarities suggested a common synthetic strategy for their synthesis, in which the key bonds would be: i) C-15/C-16, ii) indole/C-3, and iii) C-6/C-7. These bonds would be formed: the first, by nucleophilic addition of the enolate derived from an indoleacetic ester to the γ-position of a pyridinium salt; the second, by nucleophilic attack of the indole ring to the α-position of the resulting 1,4-dihydropyridine; and the third, by closure of the tryptamine chain by cyclization upon the indole 3-position.

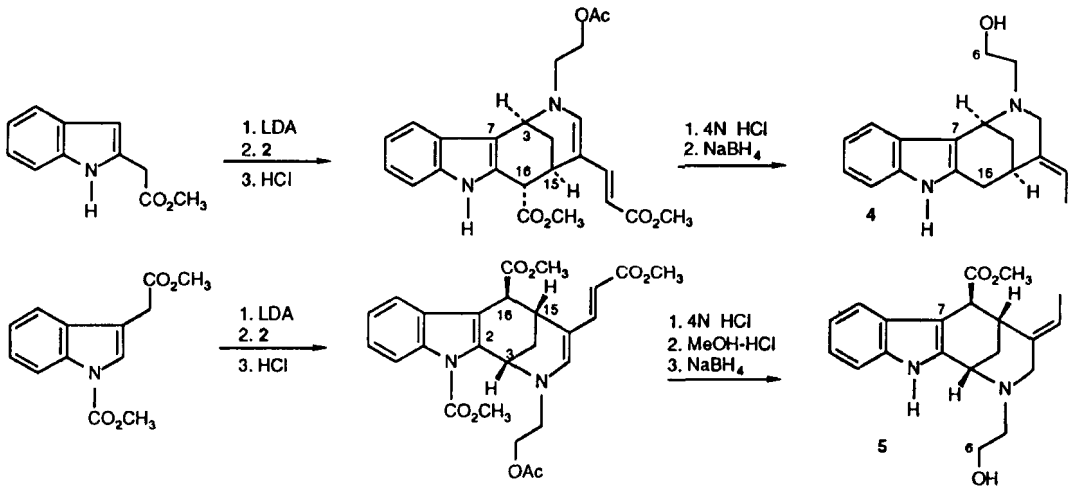
Scheme 1 shows the total synthesis of vinoxine following the above strategy, in a process that consists of only two separate synthetic steps. Thus, interaction between methyl indole-1-acetate (**1**) and pyridinium salt **2** in the presence of LDA, followed by treatment with HCl, afforded tetracycle **3** as an epimeric mixture at C-16. Further treatment of tetracycle **3** with aqueous HCl brought about both the hydrolysis of the three ester groups and the decarboxylation of the resulting acrylic acid moiety to give a conjugated iminium ion, which, after reesterification of the carboxy group at C-16, was reduced with $NaBH_4$ to give the alkaloid vinoxine.[1] The configuration of the ethylidene group is the natural one because this group is formed in a biomimetic manner, by reduction of an iminium ion conjugated to an exocyclic C-C double bond, which is more stable in the *E*-configuration.



Scheme 1

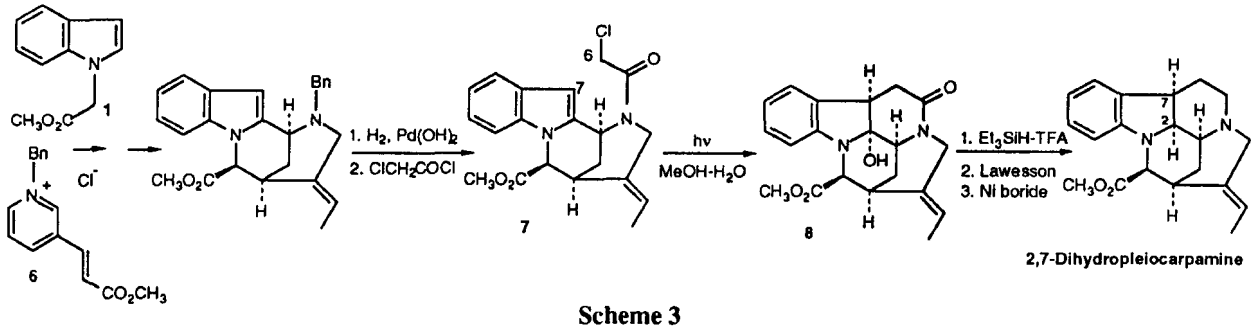
As expected, the above nucleophilic addition-cyclization sequence, with final stereoselective elaboration of the *E*-ethylidene substituent, could be extended to the synthesis of tetracyclic substructures of *Strychnos* and akuammiline alkaloids starting from indole-2- and -3-acetic esters, respectively (Scheme 2).[1,2] In the *Strychnos*

series an additional decarboxylation at C-16 occurs, to give the ethylidene derivative **4**. However, this did not constitute a serious problem, not only because there are some *Strychnos* alkaloids without substituent at C-16 but also because the methoxycarbonyl group could be efficiently reintroduced in a subsequent synthetic step.



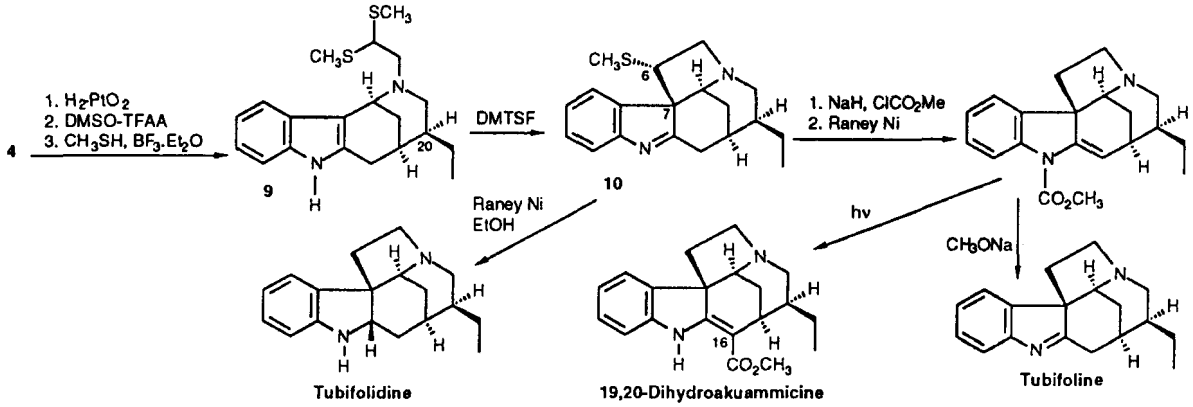
Scheme 2

Although the closure of the fifth ring of mavacurine alkaloids seemed to be *a priori* an easy task, both direct cyclization of vinoxine and other electrophilic cyclizations, either from the corresponding aldehyde or dithioacetal, resulted in failure. However, this ring closure was finally accomplished by photocyclization of chloroacetamide **7**, which was prepared following our general methodology, from ester **1** and benzylpyridinium salt **6**, with subsequent exchange of the substituent on the piperidine nitrogen. Further functional group interconversions from the resulting pentacyclic indoline **8** led to (±)-2,7-dihydropleiocarpamine[3] (Scheme 3).



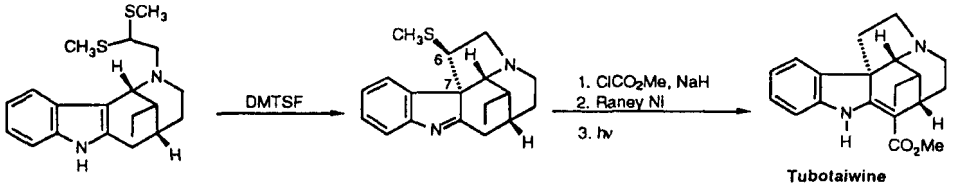
Scheme 3

In the *Strychnos* series, the closure of the fifth ring was satisfactorily effected by way of a thionium ion generated by treatment of dithioacetal **9** with dimethyl(methylthio)sulfonium fluoroborate (DMTSF). The resulting pentacyclic indolenine **10** was then converted to the *Strychnos* alkaloids tubifolidine, tubifoline, and 19,20-dihydroakuammicine (Scheme 4).[4]



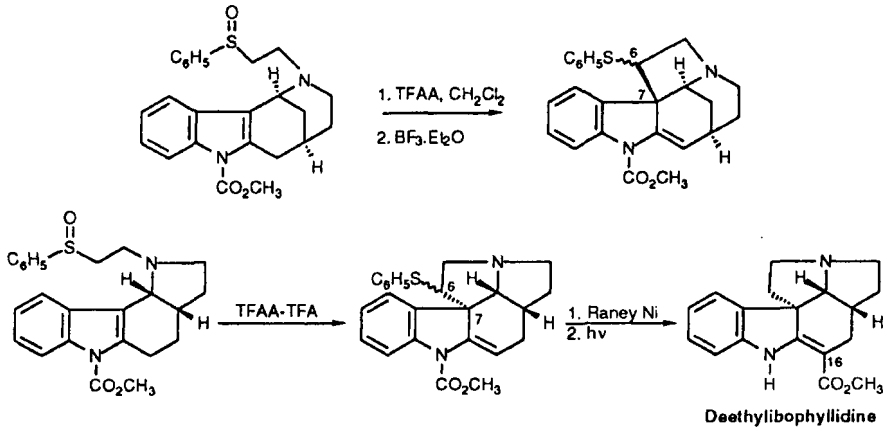
Scheme 4

The above DMTSF-induced cyclization provides a new and general synthetic entry to pentacyclic *Strychnos* alkaloids, not only with the Strychnan skeletal type but also with the Aspidospermatan skeletal type, for instance tubotaiwine[5] (Scheme 5).



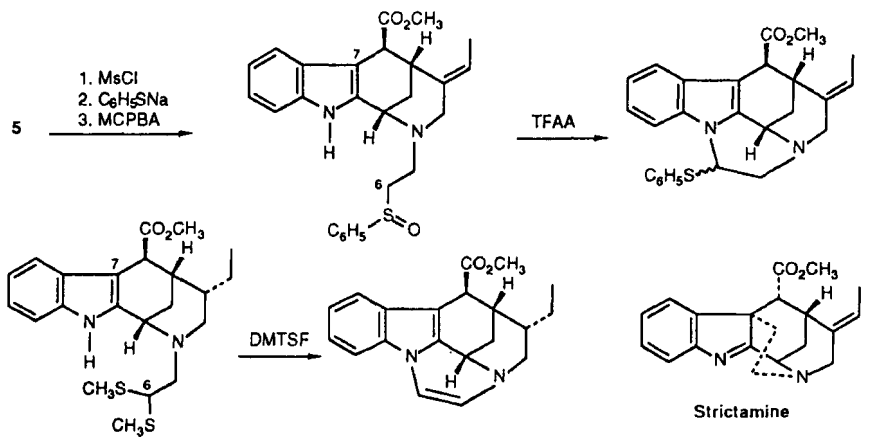
Scheme 5

An alternative way of generating the crucial thionium ion required for the construction of the quaternary center (C-7) present in several groups of indole alkaloids is by Pummerer rearrangement of a sulfoxide.[6] Scheme 6 shows the usefulness of this method in the elaboration of the pentacyclic ring system of *Strychnos* alkaloids[7] and in establishing a new synthetic entry to the alkaloids of the ibophyllidine group.[8] In this approach the methoxycarbonyl group required as the protecting group on the indole nitrogen could be further photochemically rearranged to C-16 in the same way as in the above synthesis of *Strychnos* alkaloids.



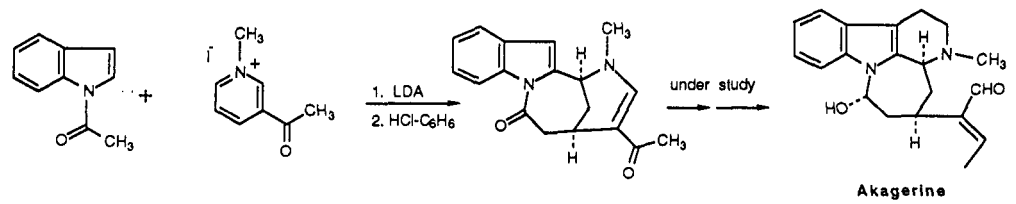
Scheme 6

Up to now we have not succeeded in the closure of the fifth ring of akuammiline alkaloids. Among the numerous experiments we have done in this series, the examples of Scheme 7 illustrate that cyclization occurs upon the indole nitrogen. Attempted cyclizations from tetracyclic N_{ind}-protected derivatives resulted in failure.[9]



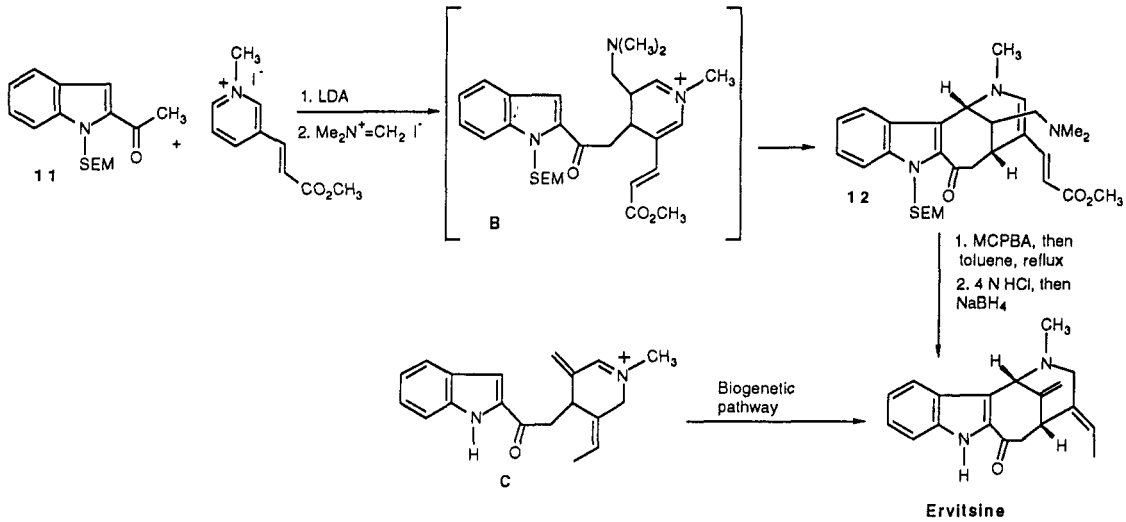
Scheme 7

The potential and general character of the strategy for the synthesis of bridged indole alkaloids based on the addition of carbon nucleophiles to pyridinium salts, with subsequent cyclization of the resulting dihydropyridines, is further illustrated by the use of 1,4-bis-nucleophiles derived from either 1- or 2-acetylindole to give tetracyclic systems with a seven-membered ring, as found in the alkaloids akagerine and ervitsine. The preliminary results obtained in the first case confirm the usefulness of this approach (Scheme 8).



Scheme 8

On the other hand, by using a slight modification of this strategy, from 2-acetylindole **11** we have accomplished the first total synthesis of ervitsine.[10] In this case, the initially formed 1,4-dihydropyridine was treated with an iminium salt instead of acid. The resulting iminium cation **B** underwent *in situ* cyclization to provide tetracycle **12** in a process involving a one-pot, three-step sequence, with formation of three new C-C bonds (Scheme 9). Two additional synthetic steps complete this straightforward synthesis of ervitsine. This synthesis is biomimetic, because the iminium intermediate **B** can be envisaged as a synthetic equivalent of the iminium cation **C**, which constitutes a key intermediate in the biogenetic pathway from vobasine to ervitsine.



Scheme 9

In conclusion, the methodology based on the nucleophilic addition of stabilized carbon nucleophiles to pyridinium salts constitutes a powerful tool for the synthesis of bridged indole alkaloids belonging to a variety of structural types, either tetracyclic (as vinoxine and ervitsine) or pentacyclic, in the latter case after closure of the tryptamine chain by cyclization upon the indole ring.

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