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A New Synthesis of (±)-Mesembrine Involving the Intramolecular Nucleophilic Attack of an Allyl Anion on a Carbonyl Function of an Imide

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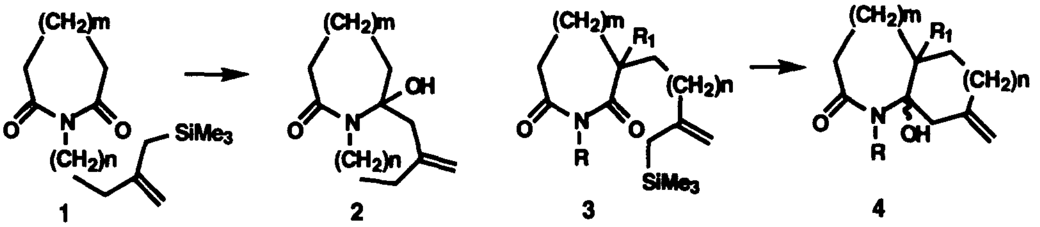
Abstract: A synthesis of (±)-mesembrine by the fluoride ion induced intramolecular cyclization of a suitably substituted allylsilane on to a neighbouring carbonyl function of an imide is described.

Imides substituted on the nitrogen with allylsilane function of the type **1** undergo intramolecular cyclization induced by fluoride ion to furnish compounds of the type **2** in excellent yields[1]. This reaction invokes the true ketonic character of one of the carbonyl groups of the imide function of **1**.

We reasoned that N-substituted imides of the type **3** bearing an allylsilane unit on the carbon adjacent to either of the carbonyl groups would also undergo similar intramolecular cyclization to yield compounds of the type **4**.

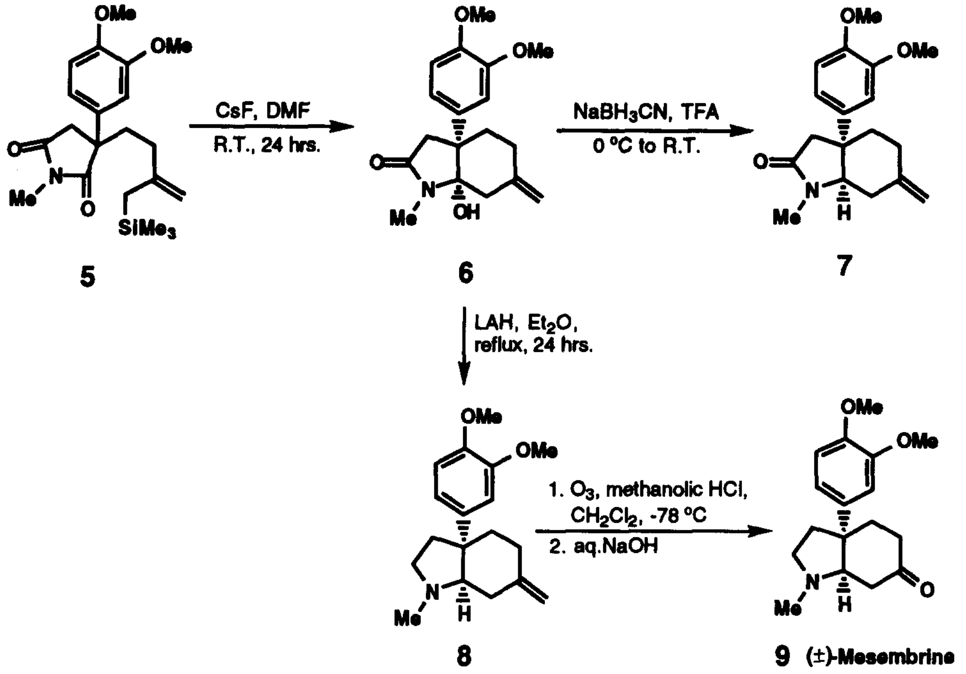


m and n = 0 to 2

In order to ascertain if this reaction would indeed follow the expected course and also to demonstrate its applicability to natural product synthesis if it did, we chose the *Sceletium* alkaloid, mesembrine (**9**)[2], as the target.

We were gratified to find that when a DMF solution of compound **5**, prepared according to the procedure outlined by Gramain and Remuson[3], was exposed to an equivalent of powdered, dry cesium fluoride at room temperature overnight, the key intermediate **6**[4] could be isolated in 60% yield. Treatment of compound **6** with sodium cyanoborohydride in trifluoroacetic acid furnished **7**[4] (70%) from which (±)-mesembrine (**9**) has been prepared earlier[3]. Therefore, the sequence **5** → **6** → **7** constitutes a formal synthesis of the alkaloid[5].

However, we decided to complete the synthesis by a two-step method different from the three-step procedure described in the literature[3]. Compound **8**[4], obtained in 95% yield by the lithium aluminum hydride reduction of **7**, was subjected to ozonolysis in methanol containing hydrogen chloride followed by basic work-up to yield (±)-mesembrine (**9**) (40%), whose IR and NMR characteristics were the same as those reported by Stevens and Wentland[7].



References and Notes.

1. Kamireddy, B.; Magolda, R.L.; Reddy, G.S. Private communication. These authors used benzyl tri-n-butylammonium fluoride in their cyclizations. Thanks are due to Dr. Kamireddy for details pertaining to this reaction.
2. Popelak, A.; Lettenbauer, G.*The Alkaloids*; Manske, R.H.F. Ed.; Academic Press; New York, NY, 1967; Vol. IX; Chap. 11. Lewis, J.R. *Nat. Prod. Rept.*. **1994**, *11*, 329.
3. Gramain, J.-C.; and Remuson, R. *Tetrahedron Lett.* **1985**, *26*, 4083. Taguchi, H.; Oh-Ishi, T.; Kugita, H. *Chem. Pharm. Bull.*. **1970**, *18*, 299.
4. The NMR and mass spectra of this compound were consistent with the structural assignment.
5. This part was presented at the 18th IUPAC Symposium on Natural Products, Strasbourg, France, September, 1992.
6. Many syntheses of racemic, (+)- and (-)-mesembrine are known. For pertinent references, *cf.* Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.*. **1995**, *60*, 6785.
7. Stevens, R.V.; Wentland, M.P. *J. Amer. Chem. Soc.*. **1968**, *90*, 5580.

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