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A SHORT SYNTHESIS OF (±)-MESEMBRINE[1]

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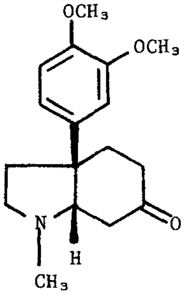
ABSTRACT An efficient synthesis of (±)-mesembrine and (±)-desdimethoxymesembrine from N-methyl-2-pyrrolidone is reported.

Alkaloids such as mesembrine (1)[2] have attracted an enormous amount of activity by synthetic organic chemists.[3] This reflects not only the presumed central nervous system activity of mesembrine and epi-mesembrine[4] but also the structural similarity of these simple *Sceletium* alkaloids to the more complex and diverse *Amaryllidaceae* alkaloids like crinine (2).[5]



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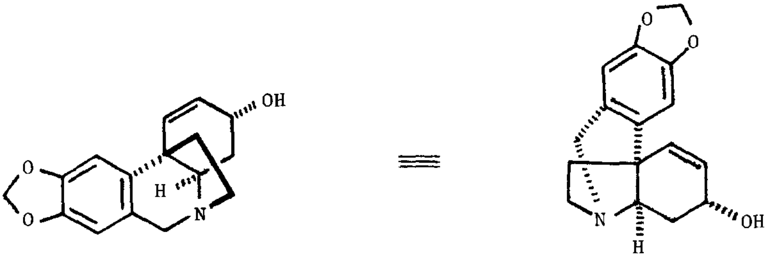

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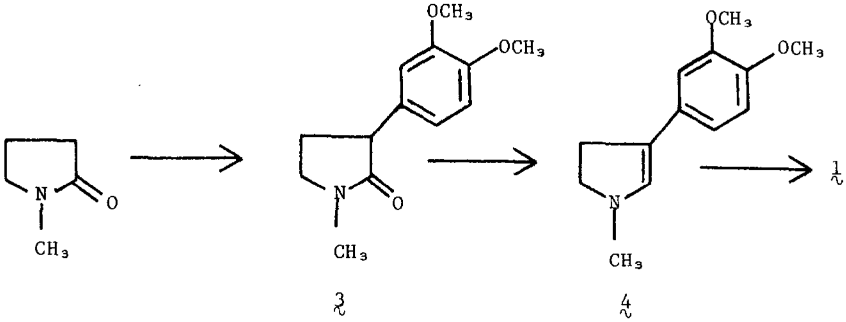
Consequently, many approaches to the synthesis of mesembrine have been extended or can be extended at least in principle to the preparation of a variety of other alkaloids. Such a general approach to mesembrine is reported here.[6]

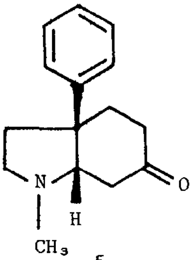
Our basic strategy is shown in equation 1.



(1)

Thus, N-methylpyrrolidone is arylated and the resulting lactam 3 is converted into the enamine 4 for annelation into mesembrine.[7]

In order to test this sequence, the phenyl analogue (desdimethoxymesembrine 5) was prepared.



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N-Methylpyrrolidone was allowed to react with 2.0 equivalents of lithium N-cyclohexyl-N-isopropylamide in tetrahydrofuran (THF) at -78°C for 1 hour and the reaction mixture was allowed to warm to 10°C over a 1 hour period followed by addition of bromobenzene (0.5 eq). The reaction mixture was stirred at RT overnight and an acidic workup gave a 43-48% yield of purified product as white crystals (mp 58-59°C, lit.[8] 59-60°C).[9] This α-phenyllactam was reduced with a slight excess of diisobutylaluminum hydride (DIBAL) in hexane/THF to give, after a workup with aqueous NaOH, the corresponding enamine, N-methyl-3-phenyl-2-pyrroline.[10] Annelation with methyl vinyl ketone according to the procedure of Stevens[7a] gave a 30-40% yield of desdimethoxymesembrine[7a,11] from the α-phenyllactam.

This strategy was then applied to the synthesis of mesembrine without difficulty. Thus, N-methylpyrrolidone was arylated with bromoveratrole (0.25 eq) to give a 30-40% yield of pure lactam 3. Reduction with 1.2 equivalents of DIBAL followed by NaOH workup and annelation with methyl vinyl ketone[7] gave 58-64% yields from the α-aryllactam 3 of mesembrine purified by column chromatography on silica gel.[12,13] To our knowledge this three-step sequence for the synthesis of mesembrine is the shortest one from readily available starting materials.[14]

ACKNOWLEDGEMENTS

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11. ^{13}C NMR ($CDCl_3$) δ35.267, 36.188, 38.734, 40.034, 40.468, 47.890, 54.824, 70.264, 126.009, 126.280, 128.664, 147.625 and 211.063. The IR and ^{1}H NMR spectra were identical to those kindly provided by Professor R. V. Stevens.
12. ^{13}C NMR ($CDCl_3$) δ35.321, 36.242, 38.897, 40.034, 40.576, 47.565, 54.824, 55.962, 56.124, 70.372, 110.299, 111.274, 118.046, 140.311, 147.679, 149.142 and 211.118. To our knowledge, this is the first published ^{13}C NMR spectrum of mesembrine! The IR and ^{1}H NMR spectra were identical to those kindly provided by Professor S. F. Martin and Professor R. V. Stevens.
13. Yields in the 60% range are possible by using the HCl-catalyzed annelation reaction. Yields of 35-40% are typical in our hands for the traditional reaction run in ethylene glycol[7a] as with the preparation of desdimethoxymesembrine. Thus, yields of mesembrine of up to 27% overall from N-methylpyrrolidone are possible without purification of the intermediate enamine.
14. Full details of this synthesis will be provided in the full paper.

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