

A NEW SYNTHESIS OF (+)-CHILENAMINE, AN ISOINDOLOBENZAZEPINE
ALKALOID[†]

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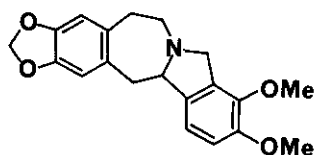
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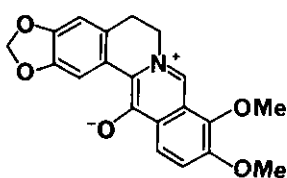
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Abstract—(+)-Chilenamine (1), an isoindolobenzazepine alkaloid, was efficiently synthesized starting from 6-bromo-2,3-dimethoxybenzaldehyde (5) and 3,4-methylenedioxyphenethylamine (6) via the N-substituted benzazepine (10) by radical cyclization.

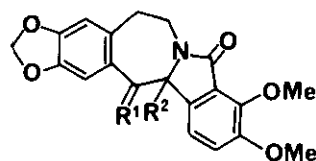
(+)-Chilenamine (1), a representative isoindolobenzazepine alkaloid, was first synthesized¹ from berberinephenolbetaine (2) and referred to as "Schöpf's base VI." Several syntheses² of 1 were reported before its isolation from *Berberis darwinii*.³ Some oxygenated isoindolobenzazepine alkaloids³ such as chilenine (3)⁴ and lennoxamine (4)⁵ have also been isolated. Recently we developed a new method for a synthesis of protoberberine⁶ and dibenzopyrrocoline⁷ alkaloids by cyclization using a sulfur stabilized-carbocation.⁸ Our attention is now focused on application of this procedure for an efficient synthesis of an



1



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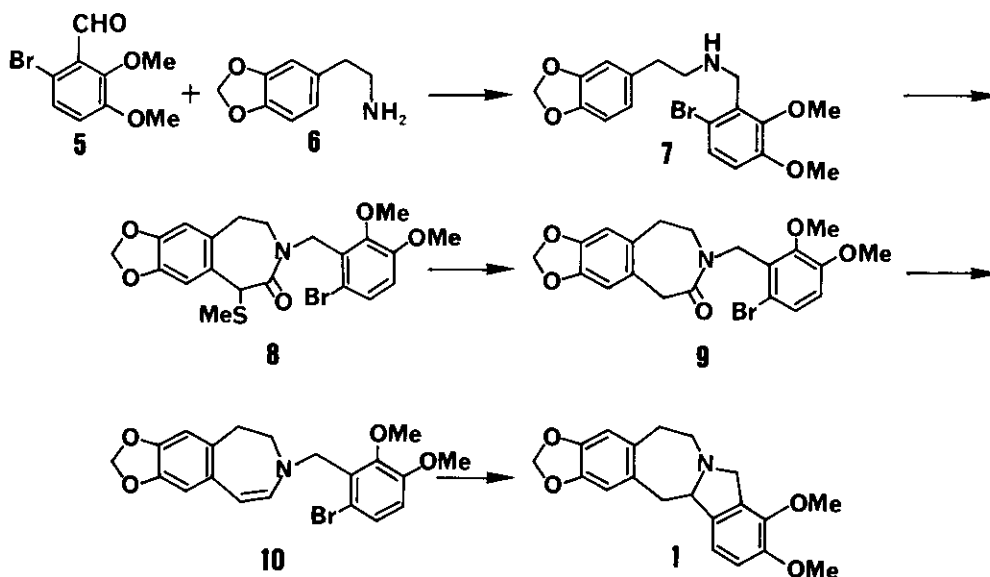
3 R¹=O, R²=OH

4 R¹=H₂, R²=H

[†]Dedicated to the memory of Professor Tetsuji Kametani.

isoindolobenzazepine alkaloid, (+)-chilenamine (1) from readily available starting materials.

Condensation of 6-bromo-2,3-dimethoxybenzaldehyde (5)⁹ with 3,4-methylenedioxyphenethylamine (6) in methylene chloride in the presence of molecular sieves, followed by reduction with sodium borohydride in methanol gave the secondary amine (7; 70%). The bromine on the aromatic ring plays an important role as a blocking group as well as a radical initiator in the later stage. The amine (7) was successively treated with α -chloro- α -methylthioacetyl chloride and stannic chloride⁸ in methylene chloride to yield the seven-membered lactam [8; 49%; δ 4.69 ppm (1H, s)]. Desulfurization of 8 was realized by zinc dust in refluxing acetic acid to afford the lactam [9; 98%; δ 3.81 ppm (2H, s)], which was subsequently exposed to diisobutylaluminum hydride in dry tetrahydrofuran at -78°C to yield the enamine [10; 80%; 6.17 ppm (1H, d, $J=10.3$ Hz) and 4.97 ppm (1H, d, $J=10.3$ Hz)]. Finally, treatment of 10 with tributyltin hydride in the presence of azobisisobutyronitrile in benzene under reflux effected radical cyclization to afford (+)-chilenamine [1; 95%; m/z 339 (M^+ ; 100%)]. The synthetic chilenamine was identical with an authentic sample.¹



Thus we could provide a new and convenient synthesis of (+)-chilenamine, a basic isoindolobenzazepine alkaloid. Further application of this procedure for a synthesis of chilenine (3) and lennoxamine (4) is now in progress.

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