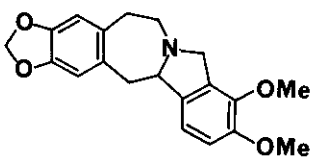
A NEW SYNTHESIS OF (±)-CHILENAMINE, AN ISOINDOLOBENZAZEPINE ALKALOID†

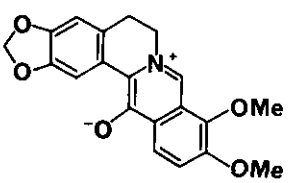
Shingo Yasuda, Yu-ichi Sugimoto, Chisato Mukai, and
Miyoji Hanaoka*
Faculty of Pharmaceutical Sciences, Kanazawa University
Takara-machi, Kanazawa 920, Japan

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.

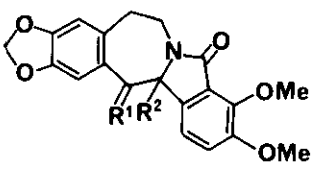
(±)-Chilenamine (1), a representative isoindolobenzazepine alkaloid, was first synthesized[1] from berberinephenolbetaine (2) and referred to as "Schöpf's base VI." Several syntheses[2] of 1 were reported before its isolation from Berberis darwinii.[3] Some oxygenated isoindolobenzazepine alkaloids[3] such as chilenine (3)[4] and lennoxamine (4)[5] have also been isolated. Recently we developed a new method for a synthesis of protoberberine[6] and dibenzopyrrocoline[7] 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



2

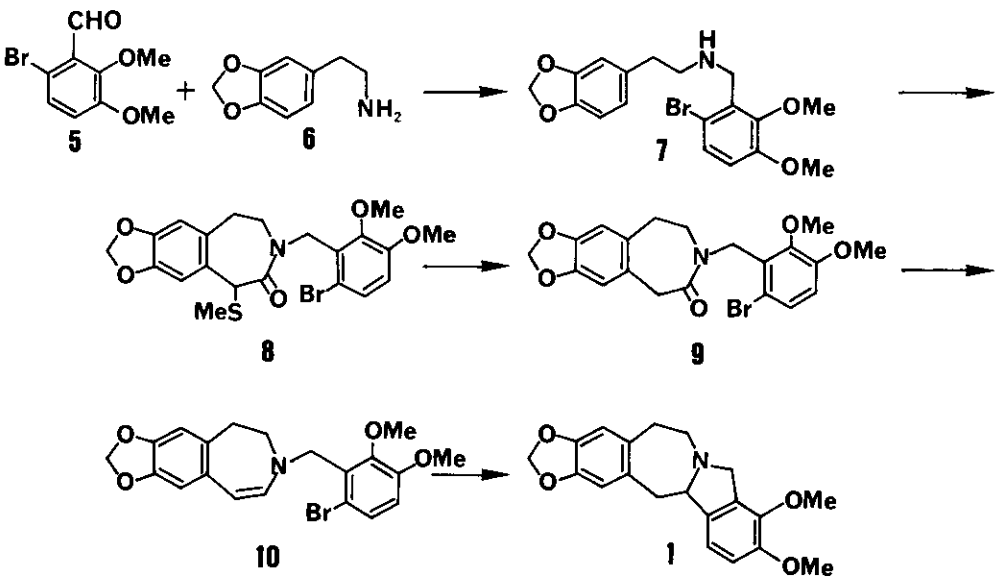


3 R^1=O , R^2=OH
4 R^1=H_2, R^2=H

†Dedicated to the memory of Professor Tetsuji Kametani.

isoindolobenzazepine akaloid, (±)-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 chloride[8] 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=10.3Hz) and 4.97 ppm (1H, d, J=10.3Hz)]. 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.

REFERENCES

1. C. Schöpf and M. Schweickert, Chem. Ber., 1965, **98**, 2566.
2. (a) S. Teitel, W. Klötzer, J. Borgese, and A. Brossi, Can. J. Chem., 1972, **50**, 2022; (b) H.O. Bernhard and V. Snieckus, Tetrahedron Lett., **1971**, 4867; (c) M. Shamma, J. L. Moniot, and D. M. Hindenlang, Tetrahedron Lett., **1977**, 4273.
3. E. Valencia, I. Weiss, S. Firdous, A. J. Freyer, M. Shamma, A. Urzúa, and V. Fajardo, Tetrahedron, 1984, **40**, 3957.
4. V. Fajardo, V. Elango, B.K. Cassels, and M. Shamma, Tetrahedron Lett., 1982, **23**, 39.
5. E. Valenica, A.J. Freyer, M. Shamma, and V. Fajardo, Tetrahedron Lett., 1984, **25**, 599.
6. S. Yasuda, T. Hirasawa, and M. Hanaoka, Tetrahedron Lett., 1987, **28**, 2399.
7. S. Yasuda, T. Hirasawa, S. Yoshida, and M. Hanaoka, Chem. Pharm. Bull., 1989, **37**, 1682.
8. Y. Tamura, J. Uenishi, H. Maeda, H. D. Choi, and H. Ishibashi, Synthesis, **1981**, 534.
9. T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, J. Chem. Soc., Perkin Trans. 1, **1976**, 1221.

Received, 30th August, 1989