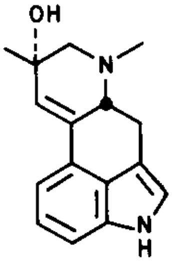
HETEROCYCLES, Vol 20, No 4, 1983

SYNTHESIS OF SETOCLAVINE

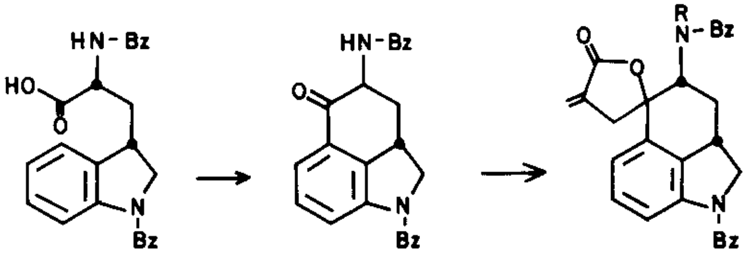
Julius Rebek, Jr. and Dar-Fu Tai
Department of Chemistry, University of Pittsburgh,
Pittsburgh, Pennsylvania 15260

Abstract - The first total synthesis of the ergot alkaloid setoclavine is described. Tryptophan is the starting material and methods used are of some generality for the synthesis of other ergot alkaloids.

Setoclavine, despite its relatively simple structure, has been prepared only through formal synthesis[1] or by isolation from natural sources.[2] Our program of synthesis of ergot alkaloids from tryptophan has now led to the preparation of (±)-setoclavine and we report here our methods.



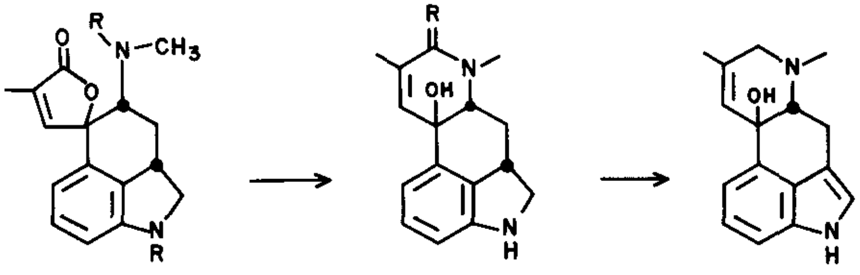
Setoclavine



1 **2** **3**

Bz = Benzoyl

Tryptophan, blocked as its dihydro, dibenzoyl derivative[3] 1, was converted to the ketone 2 from which the methylene lactone 3 was obtained as previously described.[4] Double bond isomerization ($RhCl_3$)[5] then N-alkylation (MeI, NaH) gave the butenolide 4a, m.p. >275°C, which was deblocked[6] ($Et_3O^+BF_4^-$;H_3O^+) to the amine 4b, m.p. 194°C (57% from 3). Treatment with base (NaOMe/HOMe) led to the lactam 5a which was reduced (LAH/THF) to the amine 5b. Oxidation (MnO_2) of the indoline yielded 6(45% from 4b), which rearranged quantitatively to (±)-setoclavine, m.p. 206°C. Such

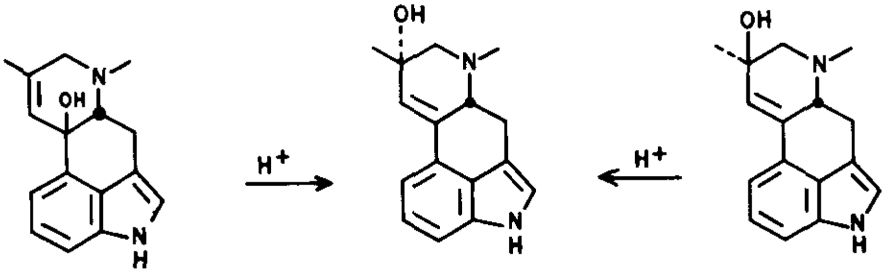


4a R = Benzoyl
4b R = H

5a R = O
5b R = H_2

6

rearrangements had been observed with quite similar structures[7a] and involve the capture of nucleophiles at C_8 on the less hindered α face. In accord with this reasoning, (±)-isosetoclavine[7b] rearranged cleanly to (±)-setoclavine when we treated a sample with 1N HCl.



6

Setoclavine

Isosetoclavine

ACKNOWLEDGEMENTS - We are grateful for the National Institutes of Health for support and to Dr. E. Kornfeld of the Eli Lilly company for a sample of (±)-isosetoclavine.

REFERENCES

1. A. Hofmann, R. Brunner, H. Kobel and A. Brack, *Helv. Chim. Acta.*, 40, 1358 (1957).
2. M. Abe, S. Yamatodani, T. Yamano, and M. Kusumoto, *Bull. Agr. Chem. Soc., Japan*, 19, 92 (1955).
3. J. W. Daly, A. N. Mauger, O. Yonemitsu, V. K. Antonov, K. Takase, and B. Witkop, *Biochemistry*, 6, 648 (1967).
4. J. Rebek, Jr. and Y. K. Shue, *J. Am. Chem. Soc.*, 102, 5426 (1980).
5. P. A. Grieco, M. Nishizawa, N. Marinovic and W. J. Ehmann, *J. Am. Chem. Soc.*, 98, 7102 (1976). All new compounds were characterized by IR, mass and 300 MHz ^{1}H NMR spectra.
6. S. Hanessian, *Tetrahedron Lett.*, 1549 (1967); S. W. King, J. M. Riordan, E. M. Holt and C. H. Stammer, *J. Org. Chem.*, 47, 3270 (1982).
7. a.) N. J. Bach and E. C. Kornfeld, *Tetrahedron Lett.*, 3225 (1974) b.) E. C. Kornfeld and N. J. Bach, *Chem. Ind.*, 1233 (1971).

Received, 9th December, 1982