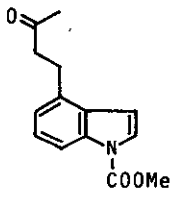
TOTAL SYNTHESES OF (±)-CHANOCLAVINE I AND (±)-DIHYDROSETOCLAVINE

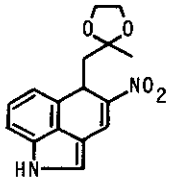
Mitsutaka Natsume* and Hideaki Muratake
Research Foundation Itsuu Laboratory
Tamagawa 2-28-10, Setagaya-ku, Tokyo 158, Japan

Abstract: Syntheses of the title ergot alkaloids 5 and 10a were achieved from the common intermediate 2, obtained by a series of reactions including our synthetic method of 4-alkylindoles.

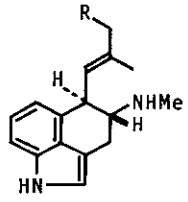
In the previous three papers,[1,2,3] we reported (i) a synthetic method of functionalized 4-alkylindoles such as 1, (ii) its transformation into a tricyclic indole derivative 2, which is expected to be a common intermediate for the synthesis of ergot alkaloids, and (iii) the first synthesis of 6,7-secoagroclavine (3) from 2 by way of a N-protected ketone derivative 4. 4 is an important compound for the synthesis of 6,7-secoergoline type of alkaloids and this time, a synthesis of (±)-chanoclavine I[4] (5) was carried out as shown in Chart 1.[5,6]



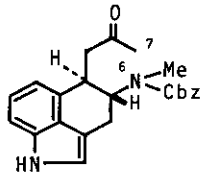
1



2

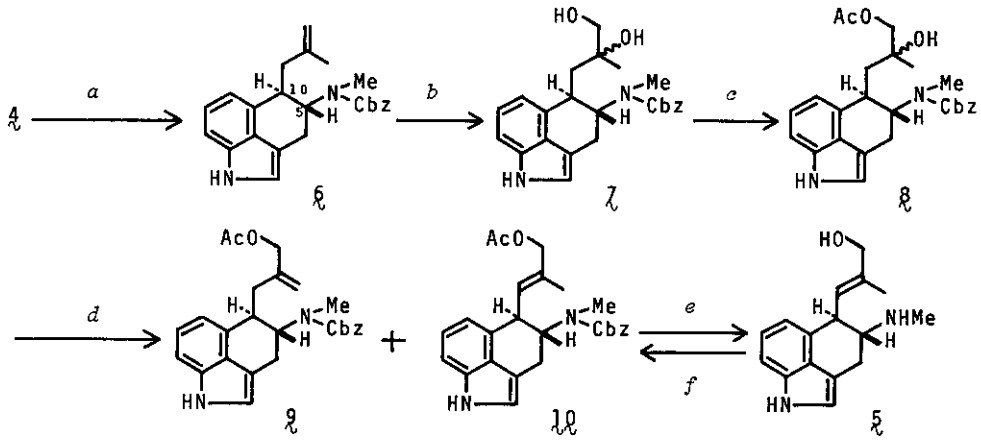


3 R=H
5 R=OH



4
Cbz=$COOCH_2Ph$

Owing to the insoluble character of chanoclavine I in most organic solvents, identification [TLC, ^1H NMR ($CDCl_3$), and IR ($CHCl_3$)] was performed at the stage of the compound 10. Natural 5 was treated with $ClCOOCH_2Ph$ in the presence of Et_3N and the resulting diacyl derivative was partially hydrolyzed[7] to an N-benzyloxycarbonyl alcohol, which was acetylated to afford 10 of the natural origin. Both natural and synthetic 10's were treated with warm diluted alkali,[7] followed by cleavage of the N-protecting group, and the recovered natural 5 was identical with chanoclavine I [mixed mp, IR (KBr)]. Synthetic 5[8] exhibited the same MS patern as natural 5, thus completing a total synthesis of (±)-5.



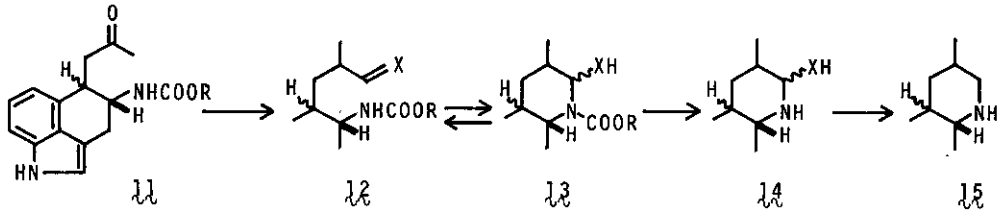
a $Ph_3P=CH_2$, THF, 0°, 46% (78%†). *b* OsO_4, Et_2O-Py, 0°→rt, 70% (80%†). *c* Ac_2O, Py, quant. *d* p-TsOH, PhH, reflux. 9: 22%, 10: 25%. *e* (i) 2% KOH in t-BuOH-H_2O (3:1), 55-60°, (ii) Na, liq. NH_3-THF. *ca.* 80% yield for both synthetic and natural compounds. *f* (i) $ClCOOCH_2Ph$, CH_2Cl_2-Py, Et_3N, (ii) 3.5% KOH in t-BuOH-H_2O (3:1), 55-60°, (iii) Ac_2O, Py.

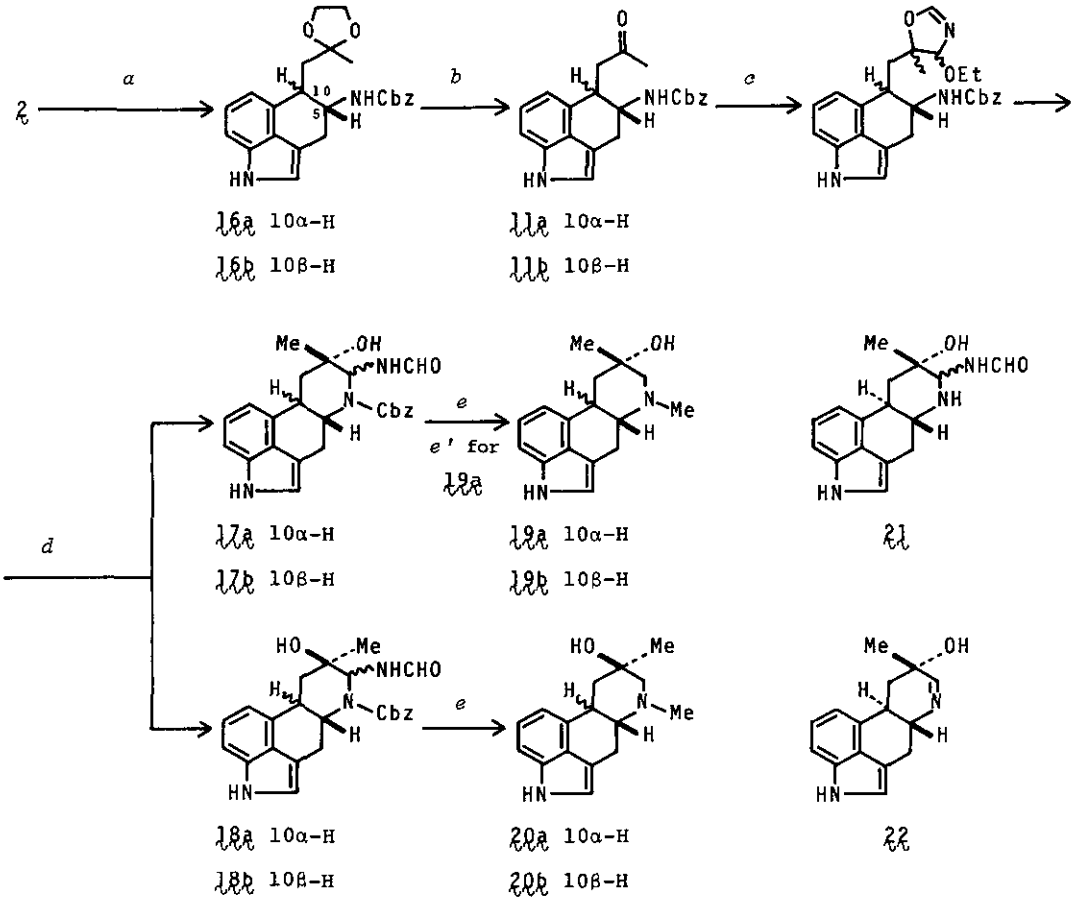
† Yield calculated on the basis of converted starting material.

Chart 1

Construction of the tetracyclic ergoline skeleton was next attempted by assuming an intramolecular cyclization from 12 to 13, if one could achieve the introduction of an aldehyde equivalent into the ketone group of 11. When R equaled to the benzyl group, removal of the N-protecting group from 13 by the catalytic hydrogenation would produce 14 at first and then end up in the formation of a stable D ring as 15, whereas, in the case of R=Me, any reaction on 13 might involve the participation of an equilibrium form 12 to afford ring-opened derivatives as by-products. Based on this consideration, 11a[5] and 11b[5] were synthesized from 2 (Chart 2) and submitted to the one carbon elongation reaction producing an aldehyde function.[9]

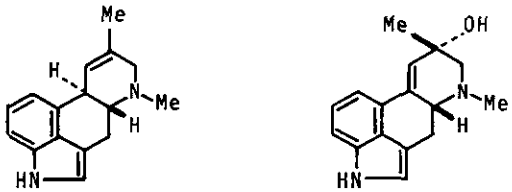
A satisfactory result was obtained by the condensation of tosylmethylisocyanide (TosMIC) with 11b using TlOEt as a base[10] and subsequent treatment with p-TsOH in





a (i) $LiAlH_4$, THF, reflux, (ii) $ClCOOCH_2Ph$, CH_2Cl_2, Et_3N; **16a**: 28%, **16b**: 33%. *b* Me_2CO, p-TsOH, rt; **11a**: 85%, **11b**: 85%. *c* p-$TsCH_2NC$, TlOEt, EtOH-DME (4:1), rt. *d* p-TsOH, DME-H_2O (6:1), rt. *e* H_2, 10% Pd-C, CH_2O-H_2O, MeOH. *e'* (i) H_2, 10% Pd-C, MeOH, (ii) 5% KOH in MeOH-H_2O (14:1), reflux, (iii) H_2, 10% Pd-C, CH_2O-H_2O, MeOH.

Chart 2



23 **24**

DME-H_2O afforded 17b [MS *m/e*: 419 (M^+), 401 (M^+-H_2O), 356 (M^+-H_2O-NH_2CHO); ^1H NMR ($CDCl_3$, 60°)[11] δ: 1.45 (≥C-Me), 7.93 (>N-CHO)] and 18b [MS *m/e*: 419 (M^+), 401 (M^+-H_2O); ^1H NMR ($CDCl_3$, 60°) δ: 1.20 (≥C-Me), 8.35 (>N-CHO)], which were hydrogenated over 10% Pd-C in the presence of CH_2O. Formation of (±)-19b[8] [mp 88-91°, MS *m/e*: 256 (M^+), ^1H NMR ($CDCl_3$) δ: 1.34 (s, Me), 2.19 (br. s, OH), 2.39 (s, N-Me), 6.88 (br. s, H-2), 7.96 (br., indole NH)] and (±)-20b[8] [mp 217-219°, MS *m/e*: 256 (M^+), ^1H NMR ($CDCl_3$-CD_3OD) δ: 1.19 (s, Me), 2.57 (s, N-Me)] was observed in 33% and 20% yields, respectively, from 11b. The structure of 19b was confirmed by comparison with a hydrogenation product of setoclavine (*vide infra*).

The same series of reaction were applied to 11a. A mixture of the tetracyclic derivatives 17a and 18a was formed analogously, but the catalytic hydrogenation required the prolonged reaction time, and yet 21 [^1H NMR (DMSO-d_6) δ: 1.11 (≥C-Me), 8.12 and 8.15 (-NHCHO), 10.58 (indole NH)] was isolated in addition to (±)-dihydroisosetoclavine[8,12] (20a) [mp 232-236°, MS *m/e*: 256 (M^+), ^1H NMR ($CDCl_3$-CD_3OD) δ: 1.50 (s, Me), 2.43 (s, N-Me)] in 16% yield from 11a. 21 was once treated with 5% KOH in MeOH-H_2O (formation of 22), followed by the catalytic hydrogenation in the presence of CH_2O. (±)-Dihydrosetoclavine[8] (19a) [mp 252-256°, MS *m/e*: 256 (M^+), ^1H NMR (DMSO-d_6) δ: 1.18 (s, Me), 2.37 (s, N-Me), 10.63 (br., indole NH)] was obtained in 12% yield from 11a.

In order to confirm the structures of synthetic 19a and 19b, preparation of the authentic samples was carried out from agroclavine (23). 23 was converted to setoclavine[13] (24) according to the procedure described in the literature[4a,14] and the catalytic hydrogenation[15] of 24 yielded dihydrosetoclavine[13,16] (19a) (43%) and 19b (7%). Identification of (±)-19a with dihydrosetoclavine was performed by TLC (10% MeOH-$CHCl_3$, Rf=0.2), MS, ^1H NMR ($CDCl_3$-CD_3OD, DMSO-d_6), and ^{13}C NMR (DMSO-d_6) spectra.

Acknowledgement —— Authors' thanks are due to Dr. S. Ohmomo of the University of Tsukuba for his exceptional cooperation in providing us with precious samples of chanoclavine I and agroclavine. A part of this work was supported by Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture, which is gratefully acknowledged.

REFERENCES AND NOTES

1. M. Natsume and H. Muratake, *Tetrahedron Lett.*, 3477 (1979).

2. M. Natsume and H. Muratake, *Heterocycles*, 14, 445 (1980).

3. M. Natsume and H. Muratake, *Heterocycles*, 14, 1101 (1980).

4. (a) A. Brack, A. Hofmann, R. Brunner, and H. Kobel, *Helv. Chim. Acta*, 40, 1358 (1957). (b) Three total syntheses of chanoclavine I were reported: H. Plieninger and D. Schmalz, *Chem. Ber.*, 109, 2140 (1976); A.P. Kozikowski and H. Ishida, *J. Am. Chem. Soc.*, 102, 4265 (1980); W. Oppolzer and J.I. Grayson, *Helv. Chim. Acta*, 63, 1706 (1980).

5. Spectral data fully supported the structures.

6. Preliminary experiments using the corresponding 5,10-cis compound: Application of a modified Shapiro's olefin synthesis of tosylhydrazones [P.C. Traas, H. Boelens, and H.J. Takken, *Tetrahedron Lett.*, 2287 (1976)] was found to be fruitless; and thermolysis of α-epoxysulfoxides [V. Reutrakul and W. Kanghae, *Tetrahedron Lett.*, 1377 (1977)] afforded a low yield of an inseparable mixture of α,β-unsaturated aldehydes.

7. Usage of MeOH instead of t-BuOH has a possibility of changing in part N-COO-CH_2Ph to N-COOMe.

8. Satisfactory results of high resolution mass spectra were obtained for these compounds.

9. Addition of Ph_3P=CHOMe or $MeNO_2$ as well as the Darzen reaction gave unsuccessful results, see Ref. 3.

10. O.H. Oldenziel and A.W. van Leusen, *Tetrahedron Lett.*, 163, 167 (1974).

11. All ^1H NMR spectra were taken at 90 MHz.

12. This material is not isolated from the nature but corresponds to a dihydro derivative of isosetoclavine.

13. The material exhibited the same IR spectrum as reported in the literature.[4a]

14. S. Yamatadani and M. Abe, *Bull. Agr. Chem. Soc. Japan*, 19, 94 (1955).

15. H. Tscherter and H. Hauth, *Helv. Chim. Acta*, 57, 113 (1974).

16. This alkaloid was first isolated from *Claviceps paspali* Stevens *et* Hall.[15]

Received, 8th December, 1980