

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

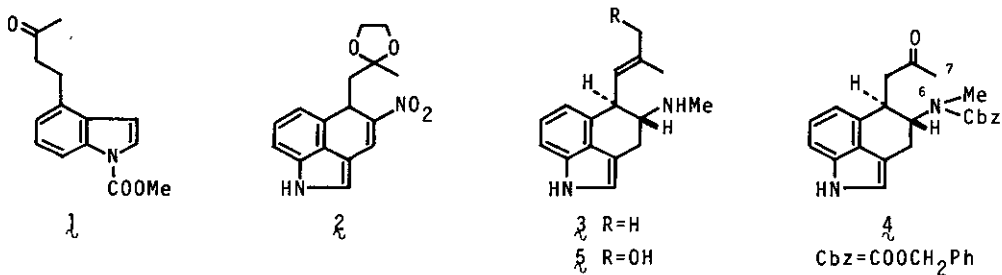
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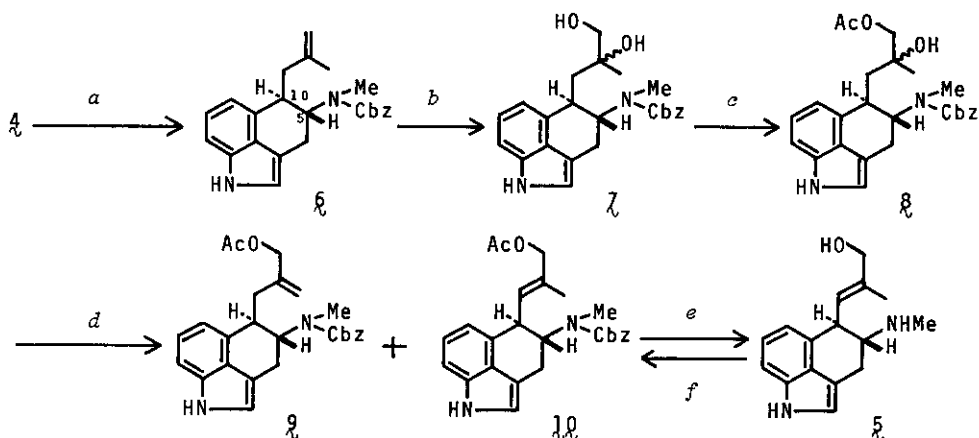
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Abstract: Syntheses of the title ergot alkaloids \mathfrak{L} and $\mathfrak{L}\mathfrak{L}\mathfrak{L}$ were achieved from the common intermediate \mathfrak{L} , obtained by a series of reactions including our synthetic method of 4-alkylindoles.

In the previous three papers,^{1,2,3} we reported (i) a synthetic method of functionalized 4-alkylindoles such as \mathfrak{L} , (ii) its transformation into a tricyclic indole derivative \mathfrak{L} , which is expected to be a common intermediate for the synthesis of ergot alkaloids, and (iii) the first synthesis of 6,7-secoagroclavine (\mathfrak{L}) from \mathfrak{L} by way of a N-protected ketone derivative \mathfrak{L} . \mathfrak{L} is an important compound for the synthesis of 6,7-secoergoline type of alkaloids and this time, a synthesis of (±)-chanoclavine I⁴ (\mathfrak{L}) was carried out as shown in Chart 1.^{5,6}



Owing to the insoluble character of chanoclavine I in most organic solvents, identification [TLC, ¹H NMR (CDCl₃), and IR (CHCl₃)] was performed at the stage of the compound $\mathfrak{L}\mathfrak{L}$. Natural \mathfrak{L} was treated with ClCOOCH₂Ph in the presence of Et₃N and the resulting diacyl derivative was partially hydrolyzed⁷ to an N-benzyloxycarbonyl alcohol, which was acetylated to afford $\mathfrak{L}\mathfrak{L}$ of the natural origin. Both natural and synthetic $\mathfrak{L}\mathfrak{L}$'s were treated with warm diluted alkali,⁷ followed by cleavage of the N-protecting group, and the recovered natural \mathfrak{L} was identical with chanoclavine I [mixed mp, IR (KBr)]. Synthetic \mathfrak{L} ⁸ exhibited the same MS pattern as natural \mathfrak{L} , thus completing a total synthesis of (±)- \mathfrak{L} .



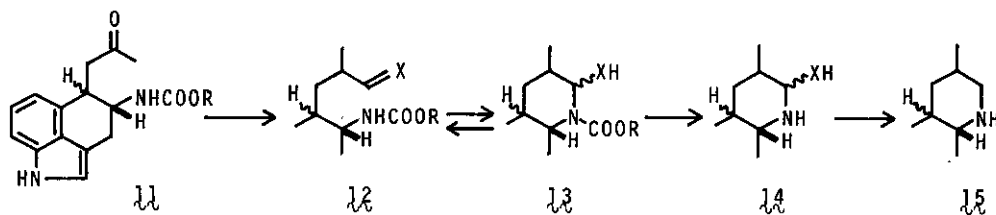
a $\text{Ph}_3\text{P}=\text{CH}_2$, THF, 0° , 46% (78%[†]). *b* OsO_4 , $\text{Et}_2\text{O}-\text{Py}$, $0^\circ \rightarrow \text{rt}$, 70% (80%[†]). *c* Ac_2O , Py, quant. *d* *p*-TsOH, PhH, reflux. 9: 22%, 10: 25%. *e* (i) 2% KOH in *t*-BuOH- H_2O (3:1), 55-60°, (ii) Na, liq. NH_3 -THF. *ca.* 80% yield for both synthetic and natural compounds. *f* (i) $\text{ClCOOCH}_2\text{Ph}$, CH_2Cl_2 -Py, Et_3N , (ii) 3.5% KOH in *t*-BuOH- H_2O (3:1), 55-60°, (iii) Ac_2O , Py.

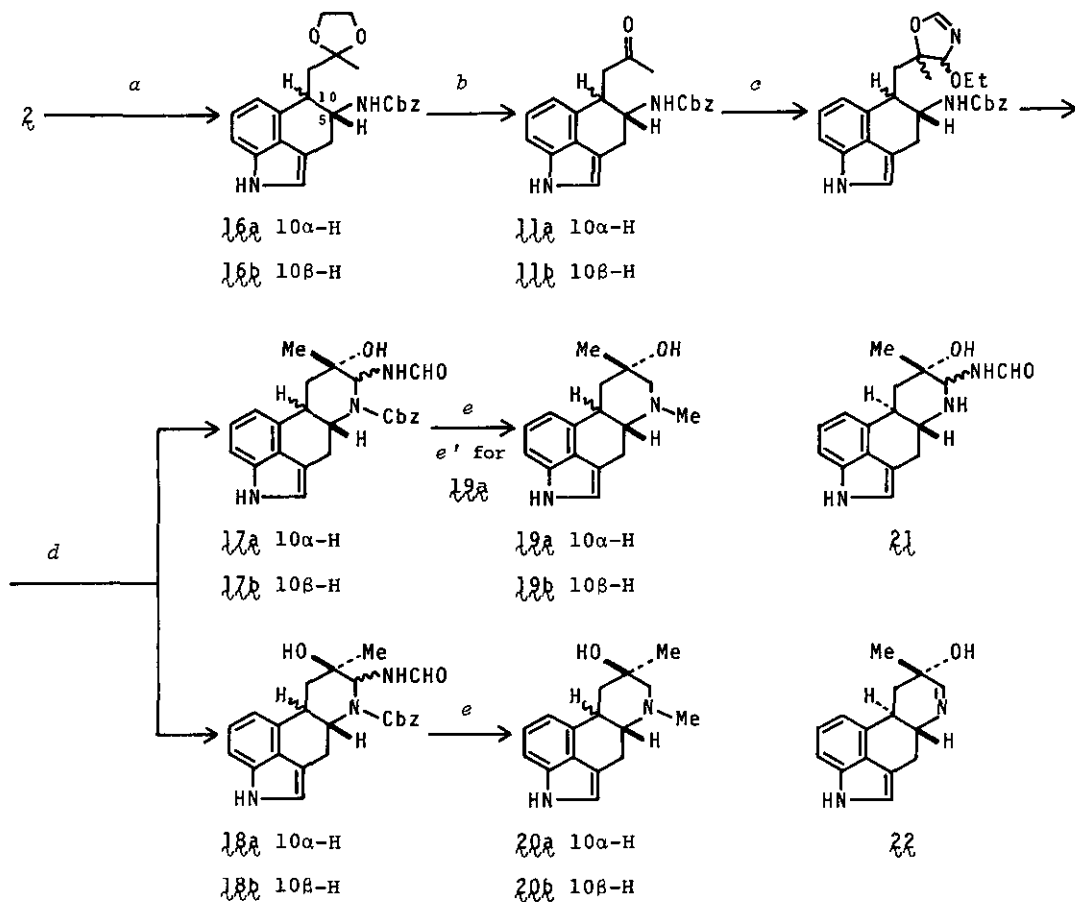
[†] Yield calculated on the basis of converted starting material.

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, 11a⁵ and 11b⁵ were synthesized from 2 (Chart 2) and submitted to the one carbon elongation reaction producing an aldehyde function.⁹

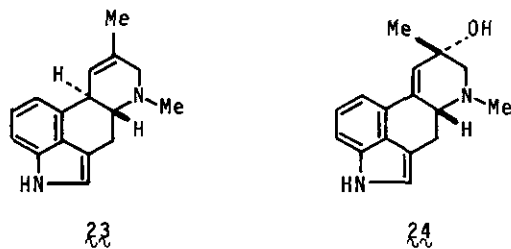
A satisfactory result was obtained by the condensation of tosylmethylisocyanide (TosMIC) with 11b using TlOEt as a base¹⁰ and subsequent treatment with *p*-TsOH in





a (i) LiAlH_4 , THF, reflux, (ii) $\text{ClCOOCH}_2\text{Ph}$, CH_2Cl_2 , Et_3N ; $16a$: 28%, $16b$: 33%. *b* Me_2CO , *p*-T SOH , rt; $11a$: 85%, $11b$: 85%. *c* *p*-T SCH_2NC , TIOEt, EtOH-DME (4:1), rt. *d* *p*-T SOH , DME- H_2O (6:1), rt. *e* H_2 , 10% Pd-C, $\text{CH}_2\text{O}-\text{H}_2\text{O}$, 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, $\text{CH}_2\text{O}-\text{H}_2\text{O}$, MeOH.

Chart 2



DME-H₂O afforded 17b [MS *m/e*: 419 (M⁺), 401 (M⁺-H₂O), 356 (M⁺-H₂O-NH₂CHO); ¹H NMR (CDCl₃, 60°) δ: 1.45 (>C-Me), 7.93 (>N-CHO)] and 18b [MS *m/e*: 419 (M⁺), 401 (M⁺-H₂O); ¹H NMR (CDCl₃, 60°) δ: 1.20 (>C-Me), 8.35 (>N-CHO)], which were hydrogenated over 10% Pd-C in the presence of CH₂O. Formation of (±)-19b⁸ [mp 88-91°, MS *m/e*: 256 (M⁺), ¹H NMR (CDCl₃) 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 (±)-20b⁸ [mp 217-219°, MS *m/e*: 256 (M⁺), ¹H NMR (CDCl₃-CD₃OD) 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-d₆) δ: 1.11 (>C-Me), 8.12 and 8.15 (-NHCHO), 10.58 (indole NH)] was isolated in addition to (±)-dihydroisotococlavine^{8,12} (20a) [mp 232-236°, MS *m/e*: 256 (M⁺), ¹H NMR (CDCl₃-CD₃OD) δ: 1.50 (s, Me), 2.43 (s, N-Me)] in 16% yield from 11a. 21 was once treated with 5% KOH in MeOH-H₂O (formation of 22), followed by the catalytic hydrogenation in the presence of CH₂O. (±)-Dihydrosetoclavine⁸ (19a) [mp 252-256°, MS *m/e*: 256 (M⁺), ¹H NMR (DMSO-d₆) 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 setoclavine¹³ (24) according to the procedure described in the literature^{4a,14} and the catalytic hydrogenation¹⁵ of 24 yielded dihydrosetoclavine^{13,16} (19a) (43%) and 19b (7%). Identification of (±)-19a with dihydrosetoclavine was performed by TLC (10% MeOH-CHCl₃, R_f=0.2), MS, ¹H NMR (CDCl₃-CD₃OD, DMSO-d₆), and ¹³C NMR (DMSO-d₆) spectra.

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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-CH₂Ph to N-COOMe.
8. Satisfactory results of high resolution mass spectra were obtained for these compounds.
9. Addition of Ph₃P=CHOMe or MeNO₂ as well as the Darzen reaction gave unsuccessful results, see Ref. 3.
10. O.H. Oldenzien 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).
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16. This alkaloid was first isolated from *Claviceps paspali* Stevens et Hall.¹⁵

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