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AN ALTERNATIVE SYNTHESIS OF (±)-DIHYDROSETOCLAVINE

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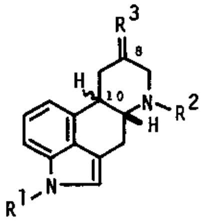
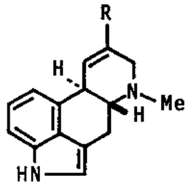
Abstract: Synthetic route was developed for 8-oxoergoline derivatives 1d and 1e starting from 4f and 4g by way of 9a and 9b. (±)-Dihydrosetoclavine (3a) was synthesized from 1d.

It was our urgent task to find an efficient way leading to functionalized ergoline derivatives 1a-1g,[1] which were expected to be suitable intermediates for the synthesis of tetracyclic ergot alkaloids, such as agroclavine (2a), elymoclavine (2b), and paspalic acid (2c). In view of our failure[2] in the preparation of 1b and 1c by dehydration of (±)-dihydrosetoclavine[3] (3a) and its congeners[4] 3e and 3f, we examined bromination reactions against the terminal methyl group of 4, in order to execute the subsequent ring closure between C-7 and the nitrogen function. In this communication, we wish to report a successful production of the key compounds 1d and 1e as well as an alternative total synthesis of 3a from 1d.

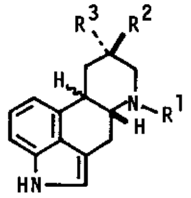
Our common intermediate 5[5] was converted into all-nitrogen protected derivatives[6] 6a,[7] mp 119-120.5°, and 6b,[7] mp 146.5-147° [(i) $LiAlH_4$, THF, reflux; (ii) NaH, ClCOOMe, DMF-THF] in 24% and 36% yields, respectively.[8] Ethylene ketal group of 6a and 6b was cleaved [p-TsOH, DME-H_2O] to give 4c,[7] mp 126.5-128°, and 4d,[7] mp 155-157°, in 100% and 96% yields. 4c was subjected to bromination reaction using $CuBr_2$ (2 equiv.) in THF in the presence of HMPA (*ca.* 1-3 equiv.),[9] giving 7a,[7] mp 148.5-150.5° [pmr[10] ($CDCl_3$) δ: 3.60 (s, NHCOOMe), 3.84 (s, $COCH_2Br$), 4.03 (s, indole-COOMe), 4.23 (dddd, J=8, 4, 4, 4 Hz, H-5), 4.73 (br. d, J=8 Hz, NHCOOMe), 7.08 (d, J=7.5 Hz, H-12), 7.30 (dd, J=7.5, 7.5 Hz, H-13), 7.39 (s, H-2), 7.91 (d, J=7.5 Hz, H-14)] in 43% yield as a single compound, whereas in the case of the cis derivative 4d, the brominated product (69% yield) consisted of 7b and 8b [ms *m/z*: 424, 422 (M^+); no C-Me in pmr]. Such transannular interaction between -NHCOOMe and ketone groups[11] was also encountered in the case of the trans derivative 7a,



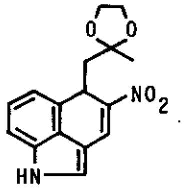
	R^1	R^2	R^3	10-H†
1a	H	Me	O	α
1b	H	Me	CH_2	α
1c	H	COOMe	CH_2	α
1d	COOMe	Me	$(OEt)_2$	α
1e	COOMe	Me	$(OEt)_2$	β
1f	COOMe	Me	O	α
1g	COOMe	Me	O	β



2a R=Me
2b R=CH_2OH
2c R=COOH



	R^1	R^2	R^3	10-H†
3a	Me	Me	OH	α
3b	Me	OH	Me	α
3c	Me	Me	OH	β
3d	Me	OH	Me	β
3e	COOMe	Me	OH	α
3f	COOMe	OH	Me	α
3g	COOMe	Me	OH	β
3h	COOMe	OH	Me	β



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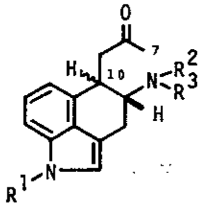
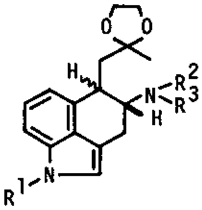
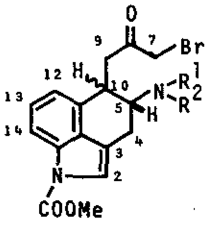


	R^1	R^2	R^3	10-H†
4a	H	H	COOCH$_2$Ph	α
4b	H	H	COOCH$_2$Ph	β
4c	COOMe	H	COOMe	α
4d	COOMe	H	COOMe	β
4e	H	Me	COOCH$_2$Ph	α
4f	COOMe	Me	COOCH$_2$Ph	α
4g	COOMe	Me	COOCH$_2$Ph	β

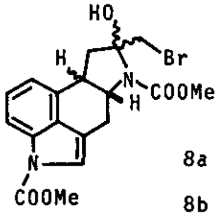


	R^1	R^2	R^3	10-H†
6a	COOMe	H	COOMe	α
6b	COOMe	H	COOMe	β
6c	H	H	COOMe	β
6d	H	Me	COOCH$_2$Ph	α
6e	H	Me	COOCH$_2$Ph	β
6f	COOMe	Me	COOCH$_2$Ph	α
6g	COOMe	Me	COOCH$_2$Ph	β

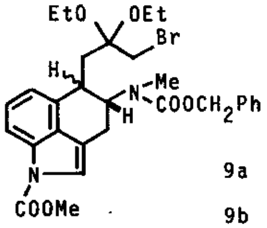
† Stereochemistry is depicted in accord with the absolute configuration of the natural products.



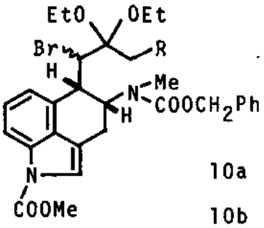
	R^1	R^2	10-H†
7a	H	COOMe	α
7b	H	COOMe	β
7c	Me	$COOCH_2Ph$	β



8a 10α-H†
8b 10β-H



9a 10α-H†
9b 10β-H



10a R=H
10b R=Br

when treated in a variety of reaction conditions (for example, ketalization, p-tosylhydrazone formation, and NaH in DMF).

The above result suggested that (i) the nitrogen function should be tertiary with easily removable protecting group and (ii) ketalization of α-bromo ketone group was essential for the prevention of the above transannular participation. For the first requirement, we selected 4f and 4g as the starting compounds, which were prepared by methoxycarbonylation of 6d[11] and 6e[11] [NaH (2 equiv.), ClCOOMe, DME-THF, -40°→ice cooling;[12] 6f: 72% and 6g: 68% yields], followed by removal of ethylene ketal group [p-TsOH, Me_2CO, r.t.; 4f: 100% and 4g: 100% yields]. 4g was brominated with $CuBr_2$ in THF-HMPA, but the reaction was very slow and required refluxing for *ca.* 30 hours. 7c [ms *m/z*: 514, 512 (M^+); pmr ($CDCl_3$, 60°) δ: 2.73 (s, N-Me), 2.99 (d, J=6.5 Hz, 2×H-9), 3.69 (s, $COC\underline{H}_2Br$), 4.00 (s, COOMe), 5.14 (s, $COOC\underline{H}_2Ph$), 6.92 (d, J=7.5 Hz, H-12), 7.33 (s, Ph), 7.82 (d, J=7.5 Hz, H-14)] was isolated in 26% yield, accompanied by the recovery of 4g in 27% yield.

The bromination condition [$CuBr_2$, $CH(OEt)_3$, EtOH] described by Nagata *et al*[13] was quite suitable to our objective. Simultaneous ketalization took place during bromination, thus meeting the second requirement in a single operation. A mixture of 4g and $CuBr_2$ (2.2 equiv.) in EtOH was warmed at 40-45° in the presence of $CH(OEt)_3$, yielding two products, 9b (53%) [ms *m/z*: 461 (M^+-EtOH-·Br); pmr ($CDCl_3$, 60°) δ: 0.91 (t, J=7 Hz) and 1.11 (t, J=7 Hz)($2\times OCH_2C\underline{H}_3$), 2.04 (dd, J=15, 7.5 Hz, H-9), 2.23 (dd, J=15, 4.5 Hz, H'-9), 2.90 (s, N-Me), 3.44 (s, $COC\underline{H}_2Br$), 3.95 (s, COOMe), 4.53 (ddd, J=9.5, 5, 5 Hz, H-5), 5.14 (s, $COOC\underline{H}_2Ph$), 7.26 (s, Ph), 7.76

(dd, J=6.5, 2.5 Hz, H-14)] and 10a[14] (38%) [ms *m/z*: 461 (M^+-EtOH--Br); pmr ($CDCl_3$, 60°) δ: 1.15 (6H, t, J=7 Hz, 2×$OCH_2C\underline{H}_3$), 1.53 (s, C-Me), 2.87 (dd, J=15, 4 Hz, H-4), 3.11 (s, N-Me), 3.44 (dif. q, J=7 Hz, 2×$OC\underline{H}_2CH_3$), 3.61 (dd, J=15, 12 Hz, H'-4), 3.96 (s, COOMe), 4.16 (br. d, J=4 Hz, H-10), 4.38 (ddd, J=12, 4, 4 Hz, H-5), 4.60 (br. s, $C\underline{H}Br$), 5.05 (d, J=12 Hz) and 5.22 (d, J=12 Hz)($COOC\underline{H}_2Ph$), 7.28 (s, Ph), 7.84 (dd, J=7.5, 1.5 Hz, H-14)]. Further bromination of 10a with the same reagent took place under prolonged heating at 50-83° to afford 10b in 74% yield. In the case of the trans derivative 4f, regioselective bromination [$CuBr_2$ (2.2 equiv.),$CH(OEt)_3$,EtOH, 40-43°] proceeded smoothly to give in 91% yield 9a [ms *m/z*: 542, 540 (M^+-EtOH); pmr ($CDCl_3$, 60°) δ: 1.09 (t, J=7.5 Hz) and 1.13 (t, J=7.5 Hz)(2×$OCH_2C\underline{H}_3$), 1.94 (dd, J=15.5, 5 Hz, H-9), 2.13 (dd, J=15.5, 7 Hz, H'-9), 2.39 (s, N-Me). 2.90 (1H, dd, J=17, 3.5 Hz, H-4), 3.63 (s, $COC\underline{H}_2Br$), 3.99 (s, COOMe), 5.01 (ddd, J=5.5, 3.5, 3.5 Hz, H-5), 5.13 (s, $COOC\underline{H}_2Ph$), 7.28 (s, Ph), 7.80 (br. d, J=7.5, H-14)].

With the desired compounds 9a and 9b in our hand, D ring formation of the ergoline system was carried out without difficulty. The N-protecting group was removed by catalytic hydrogenation [H_2, 10% Pd-C, EtOH] and the resulting secondary amines were directly heated in Et_3N to give 1d,[7] mp 114-115.5°, and 1e in 58% and 73% yields, respectively.[15] For the purpose of structural confirmation, both cyclized products were hydrolyzed [*ca.* 1.5% HCl in DME-H_2O (1:3), *ca.* 100°] to the unstable ketone derivatives 1f and 1g, which were reacted with MeLi in THF-Et_2O under ice-NaCl cooling, followed by treatment with *ca.* 3% KOH in MeOH-H_2O (7:1) at room temperature to give 3a, mp 255-258°, 3b, mp 231-234° (43% and 22% yields from 1d), 3c, mp 89-92°, and 3d, mp 197-199° (28% and 57% yields from 1e), identical with the corresponding compounds reported previously.[3] The formation of 3a from 4f implies an alternative total synthesis of (±)-dihydrosetoclavine. Further investigation directed toward other tetracyclic ergot alkaloids is now in progress.

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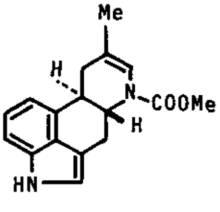
REFERENCES AND NOTES

1. The ketone derivative 1a was synthesized by Stoll *et al* from 4-aminonaphtho-

styril. A. Stoll, Th. Petrzilka, and J. Rutschmann, *Helv. Chim. Acta*, 35, 1249 (1952).

2. Application of the reaction condition, p-TsOH in refluxing $PhH-CHCl_3$ or $SOCl_2$ in pyridine to 3a and 3e afforded either the recovery of starting materials or an intractable mixture. Dehydration of 3f with $SOCl_2$ in pyridine resulted in the formation of i [ms *m/z*: 282 (M^+); pmr ($CDCl_3$) δ: 1.83 (br. s, -CH=C-<u>Me</u>), 2.17 (1H, br. dd, J=15, 12 Hz, H-9), 3.27 (ddd, J=12, 12, 4 Hz, H-10), 3.81 (s, COOMe), 4.23 (1H, dd, J=15, 4.5 Hz, H-4), 8.04 (br, s, NH)] in 53% yield.



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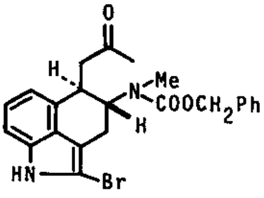
3. M. Natsume and H. Muratake, *Heterocycles*, 16, 375 (1981).
4. Compounds 3e,[7] mp 243-245°, and 3f,[7] mp 222.5-223.5°, were prepared from 4a in 25% and 19% yields, respectively, by the procedure reported in ref. 3 [(i) p-$TsCH_2NC$, TlOEt; (ii) p-TsOH, $DME-H_2O$; (iii) H_2, 10% Pd-C, DME-95% EtOH; (iv) KOH, $MeOH-H_2O$; (v) $NaBH_4$, MeOH; (vi) ClCOOMe, Et_3N, CH_2Cl_2]. The same series of treatments on 4b except the step (iii) [Na in liq. NH_3 instead of catalytic hydrogenation] yielded 3g,[16] mp 115-117° (35% yield) and 3h,[16] mp 208-211° (27% yield). Reduction of 3e and 3g with $LiAlH_4$ in boiling THF afforded 3a and 3c in 100% and 75% yields, respectively.
5. M. Natsume and H. Muratake, *Heterocycles*, 14, 445 (1980).
6. Bromination at 2 position was predominant in the absence of the COOMe group at the indole nitrogen. ii was the sole product (56% yield) by treatment of 4e with $CuBr_2$ in THF-HMPA.



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7. Satisfactory results of elementary analysis (C, H, and N) were obtained for these compounds.
8. Conversion of 6b into 6c[5] [KOH in $DME-MeOH-H_2O$, r.t., 71% yield] confirmed the structure of 6a and 6b.
9. E. Yoshii, T. Koizumi, and T. Kawazoe, The 96th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, 1976, p. II-143. Bromination of 4d proceeded at room temperature, whereas for 4c, prolonged heating under reflux in THF was required, and yet, the recovery of the starting material was observed in 11% yield.
10. All pmr spectra were taken at 90 MHz.

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

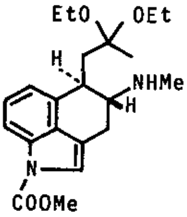
12. Recovery of 6d and 6e was observed in 11% and 26% yields. Forced condition provided unidentified by-products.

13. M. Yoshioka, I. Kikkawa, T. Tsuji, Y. Nishitani, S. Mori, K. Okada, M. Murakami, F. Matsubara, M. Yamaguchi, and W. Nagata, *Tetrahedron Lett.*, 4287 (1979).

14. 10a was a single compound having Br substituent of the unknown stereochemistry.

15. Debrominated compound **iii** was isolated as a by-product (11% yield). **iii** was converted back to 4f by treatment with ClCOOMe-Et_3N in CH_2Cl_2, followed by deketalization [p-TsOH, Me_2CO].

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



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