USEFUL INTERMEDIATES FOR THE SYNTHESIS OF ERGOT ALKALOIDS

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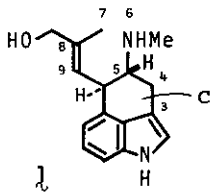
Abstract: 6-Substituted 8-oxo-6,7-secoergoline and 8-oxo-10β-6,7-secoergoline derivatives, 17 and 18, were synthesized as useful intermediates for the ergot alkaloid synthesis, starting from the readily available compound, 1-methoxycarbonyl-4-(3-oxo-1-butyl)indole (7).

As reported previously,[1] we found a novel procedure for preparation of 4-alkylindoles in five steps from 1-methoxycarbonylpyrrole. This knowledge was applied to the synthesis of the ergot alkaloids,[2] and in this communication, we wish to describe a synthetic route to obtain key intermediates for 6,7-secoergolines, such as chanoclavine I[3] (1), chanoclavine II[4] (2), and 6,7-secoagroclavine[5] (3).



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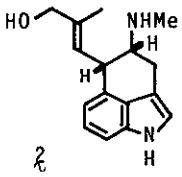

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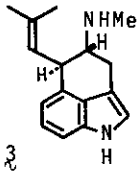

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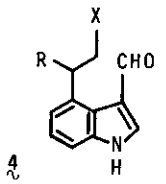

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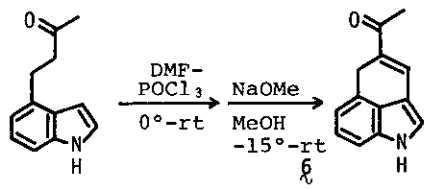
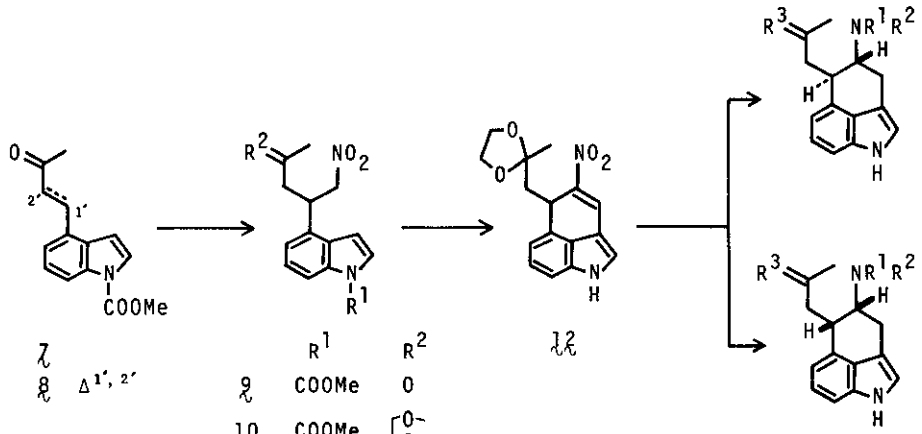


5 6

Construction of the ring C of the 6,7-secoergoline system was planned by an intramolecular aldol condensation of 3-formylindole (4) having an appropriate side chain with an activation group X. Preliminary experiment was carried out by using previously obtained compound 5[1] and Vilsmeier-Haack formylation[6] of 5, followed by treatment with NaOMe in MeOH was found to afford 6,[7,8] mp 170-172°(decomp), in

90% yield. In this reaction, isolation of an unstable 3-formylindole derivative[7] 4 (R=H, X=MeCO), mp 138-140°, was possible in 36% yield, and it was converted to 6 (94% yield) with NaOMe in MeOH, but the direct cyclization as above resulted in the formation of the desired product in high yield. In order to perform the ergot alkaloid synthesis, we selected the nitro function for the activation group X in the formula 4 and the suitable compound 11 for the C ring construction was synthesized in the following manner.



7 $\Delta^{1',2'}$ 8

	R^1	R^2
9	COOMe	O
10	COOMe	$\begin{bmatrix}O\\O\end{bmatrix}$
11	H	$\begin{bmatrix}O\\O\end{bmatrix}$

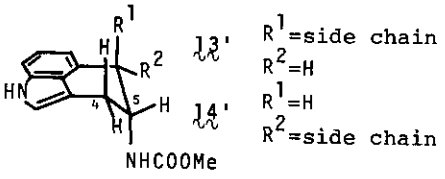
12

trans†	cis†	R^1	R^2	R^3
13	14	H	COOMe	$\begin{bmatrix}O\\O\end{bmatrix}$
15	16	Me	Me	$\begin{bmatrix}O\\O\end{bmatrix}$
17	18	H	COOMe	O
19	20	Me	Me	O

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

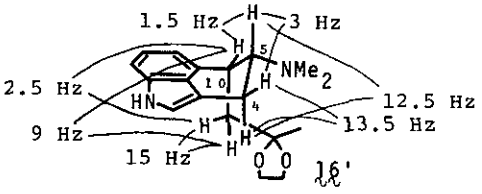
7→8: i) NBS,$(PhCOO)_2$,CCl_4,reflux. ii) Al_2O_3. 8→9: CH_3NO_2,KF,18-crown-6,CH_3CN,reflux. 9→10: $\begin{matrix}Me\\Et\end{matrix}\!\!\times\!\!\begin{matrix}O\\O\end{matrix}$, TsOH,PhH,50-55°. 10→11: 5%KOH in MeOH-H_2O(5:1),rt. 11→12: i) DMF-$POCl_3$,0°-rt. ii) KOH in MeOH-H_2O(12:1),0°. 12→13+14: i) $LiAlH_4$,THF,reflux. ii) ClCOOMe,Et_3N,CH_2Cl_2. 12→15+16: i) $LiAlH_4$,THF,reflux. ii) H_2,10% Pd-C,CH_2O,MeOH. 13→17, 14→18, 15→19, 16→20: TsOH,Me_2CO,rt.

1-Methoxycarbonyl-4-(3-oxo-1-butyl)indole[1] (7) was brominated with NBS as usual, and the CCl_4 solution was directly passed through an Al_2O_3 column. An α,β-unsaturated ketone derivative[7,9] 8, mp 106-107.5°, was obtained in 91% yield. Conjugate addition of CH_3NO_2 into 8 was carried out in the condition of Belsky[10] to produce 9 in 93% yield. The ketone group of 9 was protected as ethylene ketal in order to differentiate two active methylenes, and 10,[11] obtained in 91% yield, was hydrolyzed with mild alkali[1] to yield the aimed compound 11[12] (93% yield). Formation of the C ring was achieved as expected with the Vilsmeier-Haack reagent, followed by an alkaline treatment, and 12[7,13], mp 157-159°, was obtained



13' R^1=side chain, R^2=H

14' R^1=H, R^2=side chain



16'

in 75% yield as insoluble orange prisms.

12 was reduced with $LiAlH_4$[14] and a mixture of primary amines was transformed either to an isomeric pair of carbamates (13)[15] (31% yield) and (14)[16] (38% yield) or to a pair of dimethylamino derivatives 15[17] (25% yield) and 16[18] (36% yield). $LiAlH_4$ reduction of 14, followed by hydrogenation over Pd-C in the presence of CH_2O afforded 16 in 66% yield, and this experiment correlated isomeric pairs of carbamates and dimethylamino derivatives. In the NMR spectra of 13 and 14, small coupling constant values were observed between C-4 methylene protons and the C-5 proton adjacent to the nitrogen function (3.5 Hz and 3.5 Hz for 13, and 4 Hz and 6 Hz for 14), and this fact suggested that the carbamate group in 13 and 14 was situated in the axial configuration as illustrated by the formulae 13' and 14'. On the other hand, the coupling pattern of non-aromatic protons of 16 was assigned as shown in 16', and the dimethylamino group was oriented in the equatorial fashion. A small coupling constant between H-5 and H-10 concluded that the stereochemistry between dimethylamino group and side chain was cis relationship. 13, 14, 15, and 16 were converted to ketone derivatives 17 [MS *m/e*: 286 (M^+)], 18 [MS *m/e*: 286 (M^+)], 19[7], mp 175-176°, and 20 [MS *m/e*: 256 (M^+)] in 95%, 82%, 50%, and 71% yields, respectively, and extention of one carbon unit on the ketone group of 17 and 18 will terminate the ergot alkaloid synthesis.

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7. Satisfactory result of elementary analysis was obtained for C,H,N.
8. IR (KBr) cm^{-1}: 1646, 1618, 1580. ^1H NMR (DMSO-d_6) δ: 2.23 (3H, s), 3.80 (2H, br.s), 6.56-7.03 (3H, m), 7.20 (br.s), 7.57 (br.t, J=1.5 Hz).
9. IR (KBr) cm^{-1}: 1747, 1668, 1643. ^1H NMR ($CDCl_3$) δ: 2.31 (3H, s), 3.89 (3H, s), 6.67 (d, J=17 Hz), 6.69 (d, J=4 Hz), 7.11 (d, J=7.5 Hz), 7.30 (dd, J=7.5, 7.5 Hz), 7.55 (d, J=4 Hz), 7.73 (d, J=17 Hz), 8.13 (d, J=7.5 Hz).
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11. MS *m/e*: 348 (M^+). IR (film) cm^{-1}: 1748. ^1H NMR ($CDCl_3$) δ: 1.16 (3H, s), 2.02 (2H, d, J=6 Hz), 3.70 (4H, s), 3.77 (3H, s), 3.96 (ddt, J=8,6,6 Hz), 4.43 (dd, J=12,8 Hz), 4.76 (dd, J=12,6 Hz), 6.48 (d, J=4 Hz), 6.81 (d, J=8 Hz), 7.02 (dd, J=8,8 Hz), 7.34 (d, J=4 Hz), 7.84 (d, J=8 Hz).
12. MS *m/e*: 290 (M^+). ^1H NMR ($CDCl_3$) δ: 1.14 (3H, s), 2.06 (2H, br.d, J=6 Hz), 3.68 (4H, s), 3.73-4.20 (1H, m), 4.46 (dd, J=12,8 Hz), 4.73 (dd, J=12,6 Hz), 6.30 (dd, J=3,2 Hz), 6.52-6.97 (4H, m), 8.08 (br.s, NH).
13. ^1H NMR (DMSO-d_6) δ: 0.86 (3H, s), 1.90 (dd, J=14,3 Hz), 2.47 (dd, J=14,6 Hz), 3.27-3.58 (4H, m), 4.56 (dd, J=6,3 Hz), 6.54-6.95 (3H, m), 7.28 (br.s, which became sharp by addition of D_2O), 7.82 (1H, s).
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15. MS *m/e*: 330 (M^+). IR (KBr) cm^{-1}: 1702. ^1H NMR ($CDCl_3$) δ: 1.46 (3H, s), 1.96 (2H, d, J=6 Hz), 2.82 (dd, J=16,3.5 Hz), 3.10-3.42 (1H, m), 3.21 (br.dd, J=16, 3.5 Hz), 3.55 (3H, s), 4.02 (4H, s), 4.42-4.69 (1H, m), 4.90 (br.d, J=9 Hz), 6.77-7.20 (4H, m), 8.36 (s, NH).
16. MS *m/e*: 330 (M^+). IR (KBr) cm^{-1}: 1705. ^1H NMR ($CDCl_3$) δ: 1.45 (3H, s), 2.14 (2H, d, J=6 Hz), 2.87 (dd, J=16,6 Hz), 3.14 (dd, J=16,4 Hz), 3.28-3.50 (1H, m), 3.61 (3H, s), 4.01 (4H, s), 4.29-4.62 (1H, m), 6.77-7.21 (4H, m), 8.34 (s, NH).
17. MS *m/e*: 300 (M^+). ^1H NMR ($CDCl_3$) δ: 1.43 (3H, s), 1.90 (dd, J=14,4.5 Hz), 2.19 (dd, J=14,6 Hz), 2.24 (6H, s), *ca.* 2.24-3.19 (3H, m), 3.28-3.57 (1H, m), 4.00 (4H, s), 6.69-6.82 (1H, m), 6.89-7.18 (3H, m), 8.18 (br.s, NH).
18. MS *m/e*: 300 (M^+). ^1H NMR ($CDCl_3$) δ: 1.30 (3H, s), 1.64 (dd, J=15,9 Hz), 2.33-2.70 (2H, m), 2.40 (6H, s), 2.80 (ddd, J=12.5,3,1.5 Hz), 3.13 (dd, J=13.5,3 Hz), 3.51 (ddd, J=9, 2.5, 1.5 Hz), 3.84-4.07 (4H, m), 6.79-7.19 (4H, m), 7.98 (br.s, NH).

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