SYNTHESIS OF AN INTERMEDIATE TO THE TETRACYCLIC ERGOT ALKALOIDS

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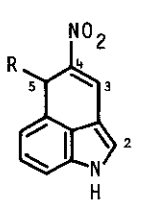
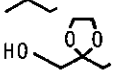
Abstract: 4-Nitro-5-[3-hydroxy-2-(1,3-dioxolan-2-ylidene)propyl]-5*H*-benz[c,d]indole (1b) was synthesized from 4-(1-methoxycarbonyl-2-pyrrolyl)crotonaldehyde (7) as a useful intermediate to the tetracyclic ergot alkaloids.

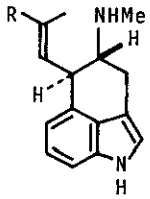
4-Nitro-5*H*-benz[c,d]indole derivative 1a is an important precursor[1] for synthesis of the ergot alkaloids and we have reported the total synthesis of 6,7-seco-agroclavine[2] (2a), chanoclavine-I[3] (2b), and dihydrosetoclavine[3] (3), utilizing 1a as the common intermediate for further derivatization. Parallel to this investigation, we planned to prepare the hydroxyl derivative of 1a in order to make an approach to ergot alkaloids having more complex structure, such as elymoclavine (4) and lysergic acid (5), and in this communication, we wish to describe a thirteen step synthesis of 1b, starting from 1-methyoxycarbonylpyrrole (6).

4-(1-Methoxycarbonylpyrrolyl)crotonaldehyde (7), obtained by one-pot reaction[4] from 6, was reacted with the Grignard reagent derived from acetonide of 4-bromo-1,2-butanediol and the condensation product 8 was oxidized with pyridinium chlorochromate (PCC) to an enone 9, which was cyclized to 4-alkylindole derivative 10 in the presence of $SnCl_4$, accompanied by the cleavage of the acetonide group.



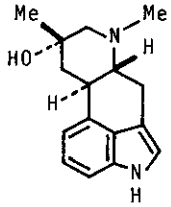
1a R= 

1b R= HO 



2a R=Me

2b R=$HOCH_2$



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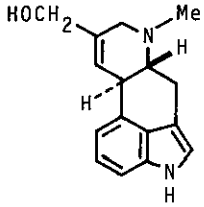

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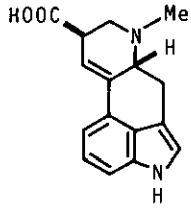

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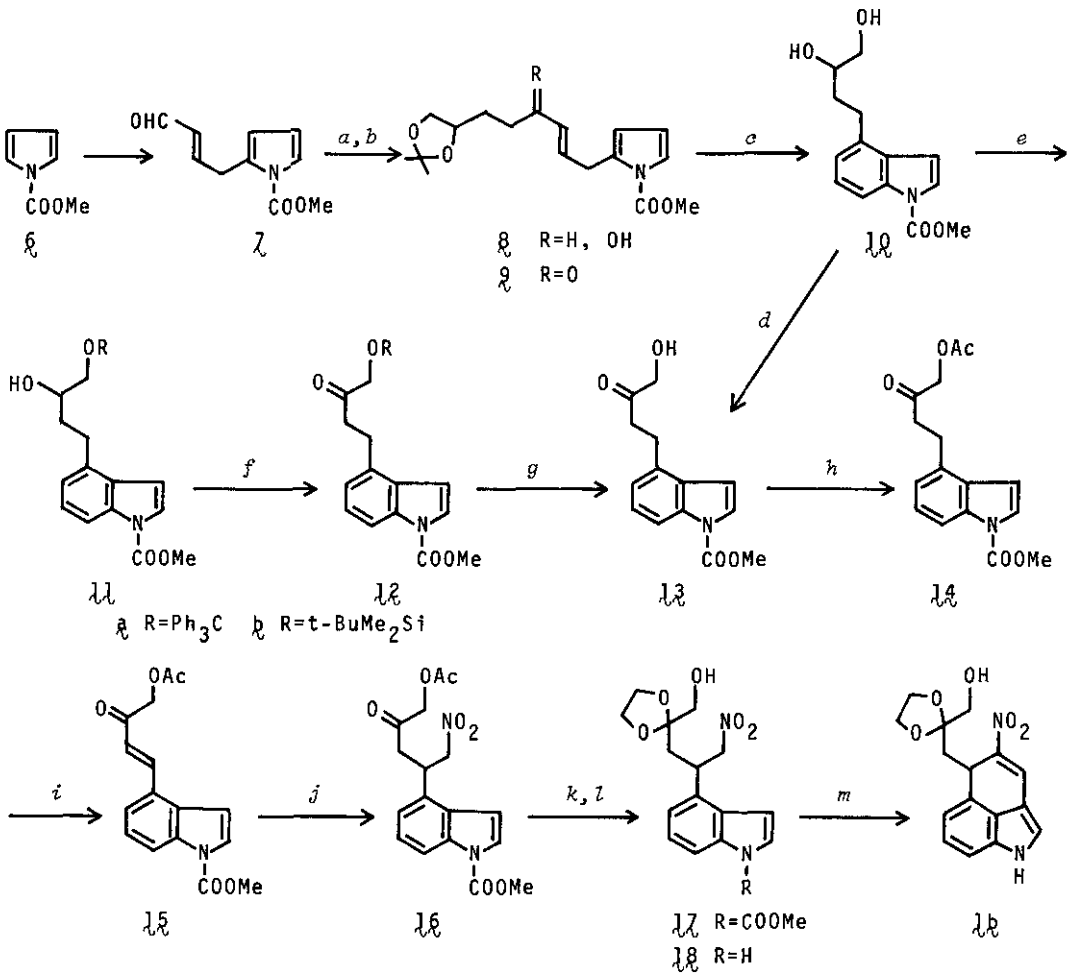
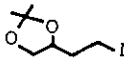


6 7 8 R=H, OH 9 R=O 10 11 a R=Ph_3C b R=t-$BuMe_2Si$ 12 13 14 15 16 17 R=COOMe 18 R=H 19

a.  MgBr, THF, r.t., quant. Y. *b*. PCC, NaOAc, CH_2Cl_2, r.t., 75%. *c*. $SnCl_4$, $ClCH_2CH_2Cl$, ice-cooling, 20 min., 58%. *d*. Ag_2CO_3-celite, C_6H_6, reflux, 40%; or $(n\text{-}Bu_3Sn)_2O\cdot Br_2$, CH_2Cl_2, r.t., 43%. *e*. Ph_3CCl, DMAP, Et_3N, CH_2Cl_2, r.t., 91%; or t-$BuMe_2SiCl$, DMAP, Et_3N, CH_2Cl_2, r.t., 81%. *f*. $CrO_3\cdot 2Py$, CH_2Cl_2, r.t., 12a 85%, 12b 78%. *g*. 10% HCl, $CHCl_3$, reflux, 90%. *h*. Ac_2O, Py, r.t., 87%. *i*. NBS, Bz_2O_2, CCl_4, reflux and then Al_2O_3, 63%. *j*. $MeNO_2$, 18-crown-6, KF, MeCN, reflux, 88.5%. *k*. $HOCH_2CH_2OH$, p-TsOH·H_2O, C_6H_6, reflux, 62%. *l*. KOH, MeOH-H_2O (9:1), r.t., 82%. *m*. $POCl_3$-DMF, ice-cooling→ r.t. and then KOH-H_2O, r.t., 66%.

Regioselective oxidation of the secondary alcohol of 10 was first studied using either Fétizon's reagent[5] (Ag_2CO_3-celite) or $(n\text{-}Bu_3Sn)_2O\cdot Br_2$.[6] Presence of the COOMe group at the indole nitrogen generally made the indole ring relatively stable to the oxidizing reagent, but in either case, reaction was not so clean as

to be used for the preparative purpose, and formation of the expected α-ketol derivative 13 was observed in 40% or 43% yield after PLC separation. In the actual synthetic route, a conventional way was adopted for the preparation of 13. 10 was converted to the trityl derivative 11a by the aid of dimethylaminopyridine[7] (DMAP) and the oxidation with Collins' reagent, followed by acid hydrolysis of 12a afforded 13 in 70% yield calculated from 10.

The next step is an introduction of a double bond in the side chain. Ideally, the protected α-ketol derivative 12a should be a compound for further transformation to an α-hydroxy enone derivative, but unfortunately, steric congestion of the big protecting group enabled the compound 12a intact to the dehydrogenation reagents such as NBS and DDQ. t-Butyldimethylsilyl derivative 12b was prepared in the analogous manner.[8] However, 12b was also found to be inert to the above reagents, so that the acetate 14 was subjected to the treatment with NBS. Satisfactory result was obtained after passing through alumina column[1] and 15 was produced in a good yield.

Succeeding steps were completely analogous to the preparation of 1a, and carried out without difficulty. Conjugate addition of nitromethane into 15, ethylene ketal formation accompanied by the hydrolysis of acetyl group (16→17), alkaline hydrolysis of methoxycarbonyl moiety (17→18), and the Vilsmeier reaction furnished 1b as orange-colored prisms. Characterization of crystalline compounds in the present synthesis is exemplified in the Note.[9]

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REFERENCES AND NOTES

1. M. Natsume and H. Muratake, *Heterocycles*, 14, 445 (1980).
2. M. Natsume and H. Muratake, *Heterocycles*, 14, 1101 (1980).
3. M. Natsume and H. Muratake, *Heterocycles*, 16, 375 (1981).
4. M. Natsume and H. Muratake, *Tetrahedron Lett.*, 3477 (1979).
5. M. Fétizon, M. Golfier, and J.-M. Louis, *J.C.S. Chem. Commun.*, 1102 (1969).
6. Y. Ueno and M. Okawara, *Tetrahedron Lett.*, 4597 (1976).
7. S.K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 95 (1979).

8. For the silylation step see S.K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 99 (1979).

9. 10: mp 79.5-80.5° (C_6H_6). Anal. $C_{14}H_{17}NO_4$: C, H, N. IR (KBr): 1755 cm^{-1}. PMR (90 MHz, $CDCl_3$) ppm: 1.79 (2H, ddd, J=6, 6, 6 Hz), 2.68-3.18 (2×OH, exchangeable with D_2O), 2.85 (dt, J=13.5, 6 Hz), 3.05 (dt, J=13.5, 6 Hz), 3.30-3.88 (3H, m), 4.00 (s, COOMe), 6.66 (d, J=4 Hz), 7.04 (d, J=7 Hz), 7.22 (dd, J=7, 7 Hz), 7.54 (d, J=4 Hz), 8.02 (d, J=7 Hz).

12a: mp 152-153° ($CHCl_3$-ether). Anal. $C_{33}H_{29}NO_4$: C, H, N. IR (KBr): 1738, 1715 cm^{-1}. PMR (90MHz, $CDCl_3$) ppm: 2.77-3.24 (4H, m), 3.74 (2H, s), 4.01 (s, COOMe), 6.62 (d, J=4 Hz, H-3), 7.01 (d, J=8 Hz, H-5), 7.13-7.54 (Tr and H-6), 7.57 (d, J=4 Hz, H-2), 8.05 (d, J=8 Hz, H-7).

13: mp 92-93° (C_6H_6-ether). Anal. $C_{14}H_{15}NO_4$: C, H, N. IR (KBr): 1755, 1725 cm^{-1}. PMR (90 MHz, $CDCl_3$) ppm: 2.77 (2H, br. t, J=7 Hz), 3.04 (t, J=5 Hz, OH), 3.19 (2H, br. t, J=7 Hz), 4.03 (s, COOMe), 4.14 (2H, d, J=5 Hz, s with D_2O), 6.37 (d, J=4 Hz), 7.02 (d, J=7 Hz), 7.24 (dd, J=7, 7 Hz), 7.60 (d, J=4 Hz), 8.06 (d, J=7 Hz).

14: mp 74.5-75°($CHCl_3$-ether). Anal. $C_{16}H_{17}NO_5$: C, H, N. IR (KBr): 1760 (sh), 1745 (sh), 1725 cm^{-1}. PMR (90 MHz, $CDCl_3$) ppm: 2.17 (s, Ac), 2.67-2.86 (2H, m), 3.04-3.24 (2H, m), 4.02 (s, COOMe), 4.57 (2H, s), 6.58 (d, J=4 Hz), 6.98 (d, J=7.5 Hz), 7.20 (dd, J=7.5, 7.5 Hz), 7.54 (d, J=4 Hz), 8.01 (d, J=7.5 Hz).

15: mp 92-93° ($CHCl_3$-ether). Anal. $C_{16}H_{15}NO_5$: C, H, N. IR (KBr): 1740, 1675, 1620 cm^{-1}. PMR (90 MHz, $CDCl_3$) ppm: 2.23 (s, Ac), 4.07 (s, COOMe), 4.96 (2H, s), 6.88 (d, J=4 Hz, H-3), 6.92 (d, J=16.5 Hz, -CO-C<u>H</u>=CH-), 7.22 (d, J=4 Hz, H-2), 7.30 (d, J=6 Hz, H-5), 7.52 (dd, J=6, 6 Hz, H-6), 8.10 (d, J=16.5 Hz, -CO-CH=C<u>H</u>-), 8.29 (d, J=6 Hz, H-7).

1b: mp 213-215° (decomp.)(acetone). Anal. $C_{16}H_{16}N_2O_5$: C, H, N. IR (KBr): 1580 cm^{-1}. PMR (90 MHz, DMSO-d_6) ppm: 2.15 (dd, J=15, 3 Hz) and 2.61 (dd, J=15, 6 Hz)(methylene), 3.03 (2H, d, J=3 Hz, s with D_2O, HOC<u>H</u>$_2$-), 3.19-3.87 (4H, m, ethylene ketal), 4.53 (t, J=3 Hz, exchangeable, OH), 4.89 (dd, J=6, 3 Hz, H-5), 6.98-7.21 (3H, m, H-6, H-7, and H-8), 7.65 (br. s, H-2), 8.16 (s, H-3), 11.49 (br. s, exchangeable, NH).

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