

## SYNTHESIS OF AN INTERMEDIATE TO THE TETRACYCLIC ERGOT ALKALOIDS

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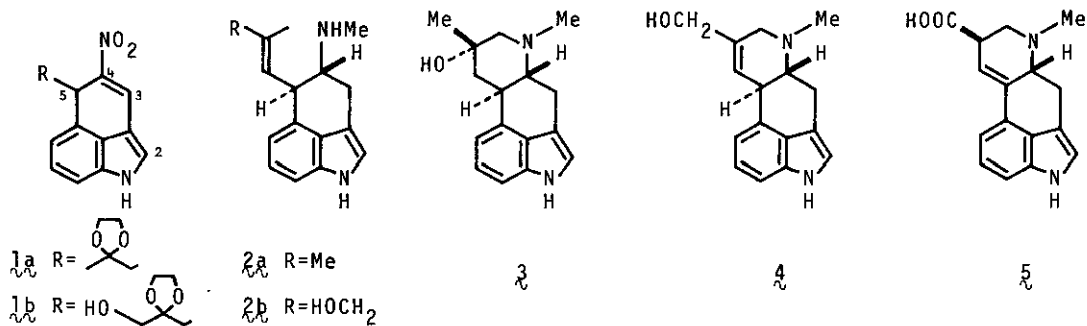
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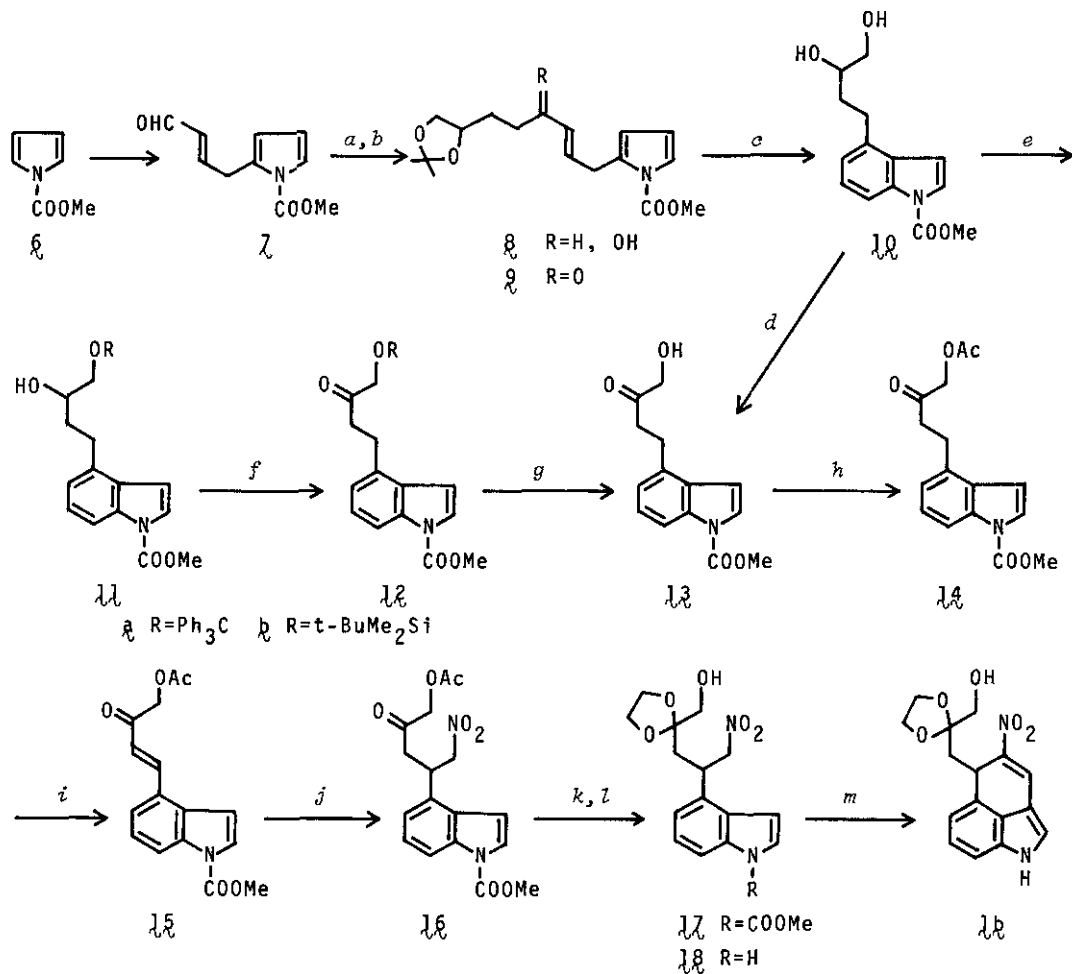
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*Abstract:* 4-Nitro-5-[3-hydroxy-2-(1,3-dioxolan-2-ylidene)propyl]-5H-benz[c,d]indole (**1b**) was synthesized from 4-(1-methoxycarbonyl-2-pyrrolyl)crotonaldehyde (**7**) as a useful intermediate to the tetracyclie ergot alkaloids.

4-Nitro-5H-benz[c,d]indole derivative **1a** is an important precursor<sup>1</sup> for synthesis of the ergot alkaloids and we have reported the total synthesis of 6,7-seco-agroclavine<sup>2</sup> (**2a**), chanoclavine-I<sup>3</sup> (**2b**), and dihydrosetoclavine<sup>3</sup> (**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-methoxycarbonylpyrrole (**6**).

4-(1-Methoxycarbonylpyrrolyl)crotonaldehyde (**7**), obtained by one-pot reaction<sup>4</sup> 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<sub>4</sub>, accompanied by the cleavage of the acetonide group.





a.  $\text{O}(\text{CH}_2)_3\text{MgBr}$ , THF, r.t., quant. Y. b. PCC, NaOAc,  $\text{CH}_2\text{Cl}_2$ , r.t., 75%.  
 c.  $\text{SnCl}_4$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ , ice-cooling, 20 min., 58%. d.  $\text{Ag}_2\text{CO}_3$ -celite,  $\text{C}_6\text{H}_6$ , reflux, 40%; or  $(\text{n-Bu}_3\text{Sn})_2\text{O}\cdot\text{Br}_2$ ,  $\text{CH}_2\text{Cl}_2$ , r.t., 43%. e.  $\text{Ph}_3\text{CCl}$ , DMAP,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , r.t., 91%; or  $\text{t-BuMe}_2\text{SiCl}$ , DMAP,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , r.t., 81%. f.  $\text{CrO}_3\cdot 2\text{Py}$ ,  $\text{CH}_2\text{Cl}_2$ , r.t.,  $\text{12a}$  85%,  $\text{12b}$  78%. g. 10% HCl,  $\text{CHCl}_3$ , reflux, 90%. h.  $\text{Ac}_2\text{O}$ , Py, r.t., 87%. i. NBS,  $\text{Bz}_2\text{O}_2$ ,  $\text{CCl}_4$ , reflux and then  $\text{Al}_2\text{O}_3$ , 63%. j.  $\text{MeNO}_2$ , 18-crown-6, KF, MeCN, reflux, 88.5%. k.  $\text{HOCH}_2\text{CH}_2\text{OH}$ , p-TsOH $\cdot\text{H}_2\text{O}$ ,  $\text{C}_6\text{H}_6$ , reflux, 62%. l. KOH, MeOH- $\text{H}_2\text{O}$  (9:1), r.t., 82%. m.  $\text{POCl}_3$ -DMF, ice-cooling  $\rightarrow$  r.t. and then KOH- $\text{H}_2\text{O}$ , r.t., 66%.

Regioselective oxidation of the secondary alcohol of  $\text{10}$  was first studied using either Fétizon's reagent<sup>5</sup> ( $\text{Ag}_2\text{CO}_3$ -celite) or  $(\text{n-Bu}_3\text{Sn})_2\text{O}\cdot\text{Br}_2$ .<sup>6</sup> 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  $\alpha$ -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<sup>7</sup> (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  $\alpha$ -ketol derivative  $12a$  should be a compound for further transformation to an  $\alpha$ -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.<sup>8</sup> 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<sup>1</sup> and  $15$  was produced in a good yield.

Succeeding steps were completely analogous to the preparation of  $13$ , 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  $19$  as orange-colored prisms. Characterization of crystalline compounds in the present synthesis is exemplified in the Note.<sup>9</sup>

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

9.  $\lambda_{\text{max}}$ : mp 79.5-80.5° ( $\text{C}_6\text{H}_6$ ). Anal.  $\text{C}_{14}\text{H}_{17}\text{NO}_4$ : C, H, N. IR (KBr): 1755  $\text{cm}^{-1}$ . PMR (90 MHz,  $\text{CDCl}_3$ ) ppm: 1.79 (2H, ddd,  $J=6, 6, 6$  Hz), 2.68-3.18 (2×OH, exchangeable with  $\text{D}_2\text{O}$ ), 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).

$\lambda_{\text{max}}$ : mp 152-153° ( $\text{CHCl}_3$ -ether). Anal.  $\text{C}_{33}\text{H}_{29}\text{NO}_4$ : C, H, N. IR (KBr): 1738, 1715  $\text{cm}^{-1}$ . PMR (90MHz,  $\text{CDCl}_3$ ) 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).

$\lambda_{\text{max}}$ : mp 92-93° ( $\text{C}_6\text{H}_6$ -ether). Anal.  $\text{C}_{14}\text{H}_{15}\text{NO}_4$ : C, H, N. IR (KBr): 1755, 1725  $\text{cm}^{-1}$ . PMR (90 MHz,  $\text{CDCl}_3$ ) 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  $\text{D}_2\text{O}$ ), 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).

$\lambda_{\text{max}}$ : mp 74.5-75° ( $\text{CHCl}_3$ -ether). Anal.  $\text{C}_{16}\text{H}_{17}\text{NO}_5$ : C, H, N. IR (KBr): 1760 (sh), 1745 (sh), 1725  $\text{cm}^{-1}$ . PMR (90 MHz,  $\text{CDCl}_3$ ) 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).

$\lambda_{\text{max}}$ : mp 92-93° ( $\text{CHCl}_3$ -ether). Anal.  $\text{C}_{16}\text{H}_{15}\text{NO}_5$ : C, H, N. IR (KBr): 1740, 1675, 1620  $\text{cm}^{-1}$ . PMR (90 MHz,  $\text{CDCl}_3$ ) 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,  $-\text{CO}-\text{CH}=\text{CH}-$ ), 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,  $-\text{CO}-\text{CH}=\text{CH}-$ ), 8.29 (d,  $J=6$  Hz, H-7).

$\lambda_{\text{max}}$ : mp 213-215° (decomp.) (acetone). Anal.  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5$ : C, H, N. IR (KBr): 1580  $\text{cm}^{-1}$ . PMR (90 MHz,  $\text{DMSO}-d_6$ ) 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  $\text{D}_2\text{O}$ ,  $\text{HOCH}_2-$ ), 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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