

## Communications to the Editor

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A PRACTICAL SYNTHESIS OF THE ERGOT ALKALOID (±)-6,7-SECOAGROCLAVINE<sup>1)</sup>

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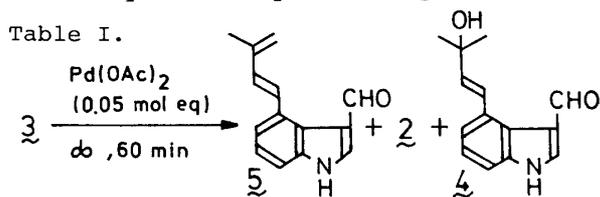
A convenient, short synthesis of (±)-6,7-secoagroclavine is developed having a 36% overall yield, high regio- and stereo-selectivity, and using no protecting groups.

KEYWORDS ——— ergot alkaloid; (±)-6,7-secoagroclavine; short synthesis; regio-selective synthesis; stereo-selective synthesis

We report here a practical method for synthesizing ergot alkaloid (±)-6,7-secoagroclavine (1). This method consists of seven steps starting from 3-formylindole (2). It gives a 36% overall yield, is highly regio- and stereo-selective and uses no protecting groups.

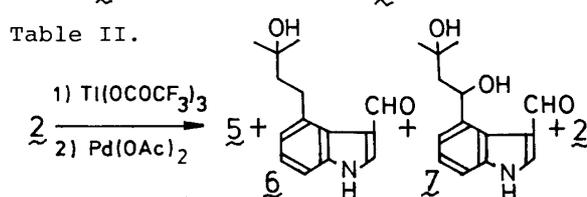
Readily available 3-formylindole (2) was converted regio-selectively to 3-formyl-4-iodoindole (3) in 72% yield by the one pot thallation-iodination method.<sup>2)</sup> The compound (3) was then treated with 2-methyl-3-buten-2-ol in the presence of a catalytic amount of Pd(OAc)<sub>2</sub> in DMF and NEt<sub>3</sub> to afford an 83% yield of 1-(3-formylindol-4-yl)-3-methyl-1-buten-3-ol<sup>3a)</sup> (4). The yield of 4 changed dramatically depending on the reaction temperature as described in Table I. It should be noted that when the one pot thallation-palladation method<sup>4)</sup> was applied to 2 with 2-methyl-3-buten-2-ol as an olefin component, the desired compound (4) was not formed, instead 1-(3-formylindol-4-yl)-3-methyl-1,3-butadiene<sup>3b)</sup> (5), -butan-3-ol<sup>3c)</sup> (6), and -butan-

Table I.



Run	Reaction temp. (°C)	Yield (%) of		
		5	2	4
1	160-170	36	0	0
2	120-130	16	26	28
3	110-120	13	21	57
4	100-110	3	Trace	83
5	90-100	Quantitative recovery		

Table II.

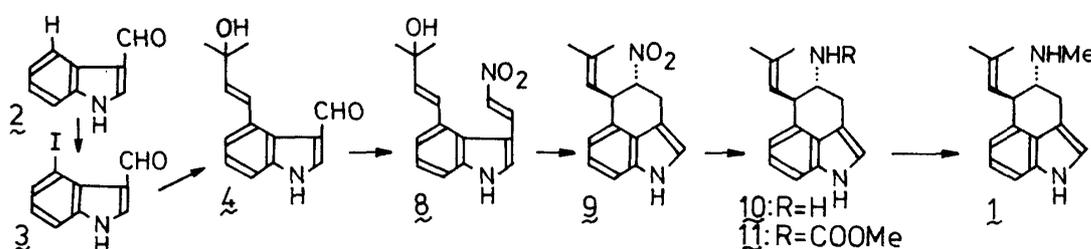


Run	Reaction time (min)	Additives	Yield (%) of			
			5	6	7	2
1	30	-	Major	9	11	19
2	30	H <sub>2</sub> O	23	13	32	Trace
3	10	-	18	19	39	Trace
4	5	-	11	15	34	6

1,3-diol<sup>3d)</sup> (7) were produced. The results are summarized in Table II.

The aldol condensation reaction of 4 with nitromethane afforded 1-[3-(2-nitrovinyl)indol-4-yl]-3-methyl-1-buten-3-ol<sup>3e)</sup> (8) in 98% yield. Treatment of 8 with  $\text{NaBH}_4$  in MeOH, followed by 2N-HCl, effected the reduction of the nitrovinyl moiety and successive cyclization to give stereo-selectively 4,5-*trans*-5-(2-methylpropen-1-yl)-4-nitro-1,3,4,5-tetrahydrobenz[cd]indole<sup>3f)</sup> (9) in 71% yield. Reduction of 9 with amalgamated zinc in 2N-HCl in MeOH produced the corresponding 4,5-*trans*-amino compound<sup>3g)</sup> (10) as a single product in 96% yield. Methoxycarbonylation of 10 with methylchloroformate gave a 93% yield of the corresponding carbamate<sup>3h)</sup> (11). The carbamate (11) was finally reduced with  $\text{LiAlH}_4$  in refluxing THF to afford a 98% yield of (+)-6,7-secoagroclavine (1), which was identical with the sample prepared before.<sup>5)</sup>

Thus, the shortest and most practical method for synthesizing 1 was established. Since this method can be carried out in a multi-gram scale, the alkaloid (1) and its synthetic intermediates are now readily available.



#### REFERENCES AND NOTES

- 1) This report is part XXIII of a series entitled "The Chemistry of Indoles." Part XXII: see reference 2.
- 2) M. Somei, F. Yamada, M. Kunimoto, and C. Kaneko, *Heterocycles*, **22**, 797 (1984).
- 3) All melting points are uncorrected. All oily compounds gave satisfactory high mass data and crystalline compounds afforded acceptable combustion data. The IR spectra of the crystalline compounds were recorded in  $\text{KBr}$  pellets, and the oily compounds for films and absorption bands are shown in  $\text{cm}^{-1}$ . The  $^1\text{H-NMR}$  spectra were taken in deuterated-chloroform ( $d\text{-C}$ ) or -methanol ( $d\text{-M}$ ) and the chemical shifts are reported in ppm ( $\delta$ ) from TMS. a) mp 134-137°C (dec.). IR: 3310, 1640, 1578.  $^1\text{H-NMR}$  (10%  $d\text{-M}$  in  $d\text{-C}$ ): 1.48 (6H, s), 6.19 (1H, d,  $J=16$  Hz), 6.91-7.38 (3H, m), 7.75 (1H, s), 7.78 (1H, d,  $J=16$  Hz), 9.65 (1H, s); b) Unstable prisms. mp 169-173°C (dec.). IR: 3100, 1636, 1597, 1560.  $^1\text{H-NMR}$  ( $d\text{-M}$ ): 2.10 (3H, s), 4.99 (2H, br s), 6.74 (1H, d,  $J=16$  Hz), 6.86-7.50 (3H, m), 7.93 (1H, s), 8.12 (1H, d,  $J=16$  Hz), 9.59 (1H, s); c) mp 156-158°C (dec.). IR: 3375, 3160, 1655.  $^1\text{H-NMR}$  ( $d\text{-M}$ ): 1.30 (6H, s), 1.60-1.96 (2H,  $A_2B_2$ ,  $A_2$  part), 3.13-3.46 (2H,  $A_2B_2$ ,  $B_2$  part), 6.80-7.40 (3H, m), 7.92 (1H, s), 9.70 (1H, s); d) mp 194-195°C. IR: 3380, 3100, 1634.  $^1\text{H-NMR}$  ( $d\text{-M}$ ): 1.23 (3H, s), 1.43 (3H, s), 1.73-2.10 (2H, m), 5.91 (1H, dd,  $J=8$  and 5 Hz), 7.00-7.43 (3H, m), 8.01 (1H, s), 9.56 (1H, s); e) mp 171-173°C. IR: 3455, 1616, 1575, 1485, 1308.  $^1\text{H-NMR}$  ( $d\text{-M}$ ): 1.48 (6H, s), 6.16 (1H, d,  $J=15$  Hz), 6.90-7.40 (4H, m), 7.58 (1H, d,  $J=13$  Hz), 7.83 (1H, s), 8.55 (1H, d,  $J=13$  Hz); f) mp 163-165°C. IR: 3410, 1540, 1442, 1345.  $^1\text{H-NMR}$  ( $d\text{-C}$ ): 1.76 (3H, d,  $J=1.6$  Hz), 1.81 (3H, d,  $J=1.6$  Hz), 3.48 (2H, d,  $J=7$  Hz), 4.30-4.96 (2H, m), 5.11 (1H, d,  $J=10$  Hz), 6.63-7.20 (4H, m), 7.90 (1H, br s, NH); g) mp 121.5-123°C. IR: 3400 (br), 3100 (br), 1593, 1444.  $^1\text{H-NMR}$  ( $d\text{-C}$ ): 1.81 (3H, d,  $J=1$  Hz), 1.85 (3H, d,  $J=1$  Hz), 1.65-2.28 (2H, br s,  $\text{NH}_2$ ), 2.58-3.35 (3H, m), 3.61 (1H, dd,  $J=9$  and 7 Hz), 5.10 (1H, br d,  $J=9$  Hz), 6.55-6.88 (2H, m), 6.91-7.21 (2H, m), 7.84 (1H, br s, NH); h) Viscous oil. IR: 3410, 3325, 1697, 1512.  $^1\text{H-NMR}$  ( $d\text{-C}$ ): 1.73 (3H, d,  $J=1$  Hz), 1.86 (3H, d,  $J=1$  Hz), 2.76 (1H, dd,  $J=15.5$  and 5 Hz), 3.22 (1H, dd,  $J=15.5$  and 4 Hz), 3.56 (3H, s), 3.69-4.32 (2H, m), 4.46-4.82 (1H, br s, NH), 5.01 (1H, br d,  $J=10$  Hz), 6.59-6.89 (2H, m), 6.96-7.19 (2H, m), 7.89 (1H, br s, NH).
- 4) M. Somei, T. Hasegawa, and C. Kaneko, *Heterocycles*, **20**, 1983, 1983.
- 5) M. Somei, F. Yamada, Y. Karasawa, and C. Kaneko, *Chemistry Letters*, **1981**, 615.

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