Communications to the Editor

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A PRACTICAL SYNTHESIS OF THE ERGOT ALKALOID (±)-6,7-SECOAGROCLAVINE[1)]

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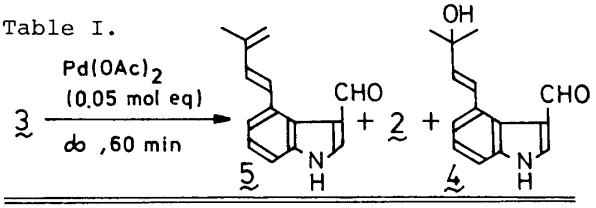
A convenient, short synthesis of (±)-6,7-secoagroclavine is developed having a 36% overall yield, high regio- and stereo-selectivity, and using no protecting groups.

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.

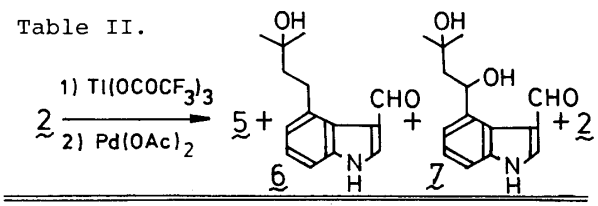
Readily available 3-formylindole (2) was converted regio-selectively to 3-formyl-4-iodoindole (3) in 72% yield by the one pot thallation-iodination method.[2)] The compound (3) was then treated with 2-methyl-3-buten-2-ol in the presence of a catalytic amount of $Pd(OAc)_2$ in DMF and NEt_3 to afford an 83% yield of 1-(3-formylindol-4-yl)-3-methyl-1-buten-3-ol[3a)] (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[4)] 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[3b)] (5), -butan-3-ol[3c)] (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.

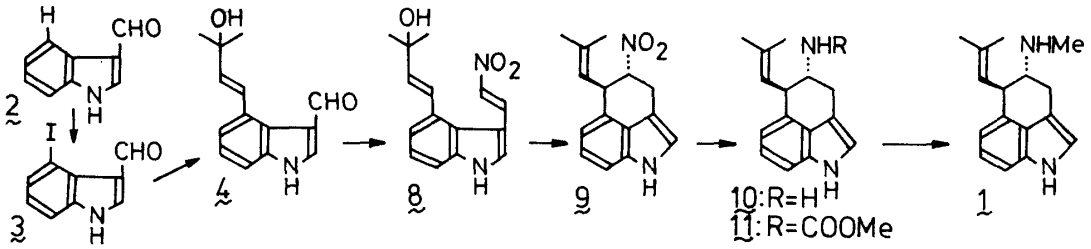


Run	Reaction time (min)	Additives	Yield (%) of 5	6	7	2
1	30	-	Major	9	11	19
2	30	H_2O	23	13	32	Trace
3	10	-	18	19	39	Trace
4	5	-	11	15	34	6

1,3-diol[3d] (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[3e] (8) in 98% yield. Treatment of 8 with $NaBH_4$ 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-tetrahydobenz[cd]indole[3f] (9) in 71% yield. Reduction of 9 with amalgamated zinc in 2N-HCl in MeOH produced the corresponding 4,5-trans-amino compound[3g] (10) as a single product in 96% yield. Methoxycarbonylation of 10 with methylchloroformate gave a 93% yield of the corresponding carbamate[3h] (11). The carbamate (11) was finally reduced with $LiAlH_4$ in refluxing THF to afford a 98% yield of (±)-6,7-secoagroclavine (1), which was identical with the sample prepared before.[5]

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 KBr pellets and the oily compounds for films and absorption bands are shown in cm^{-1}. The ^{1}H-NMR spectra were taken in deuterated-chloroform (d-C) or -methanol (d-M) and the chemical shifts are reported in ppm (δ) from TMS. a) mp 134-137°C (dec.). IR: 3310, 1640, 1578. ^{1}H-NMR (10% d-M in d-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}H-NMR (d-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}H-NMR (d-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}H-NMR (d-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}H-NMR (d-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}H-NMR (d-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}H-NMR (d-C): 1.81 (3H, d, J=1 Hz), 1.85 (3H, d, J=1 Hz), 1.65-2.28 (2H, br s, 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}H-NMR (d-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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