

## Communications to the Editor

[Chem. Pharm. Bull.  
32(12)5064—5065(1984)]

# A PRACTICAL SYNTHESIS OF THE ERGOT ALKALOID ( $\pm$ )-6,7-SECOAGROCLAVINE<sup>1)</sup>

Masanori Somei\* and Fumio Yamada

Faculty of Pharmaceutical Sciences, Kanazawa University,  
13-1 Takara-machi, Kanazawa 920, Japan

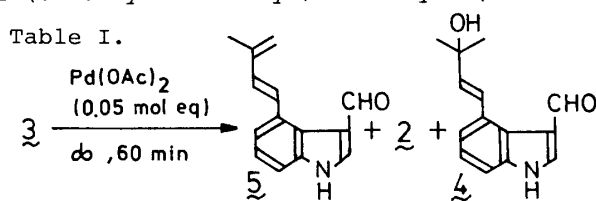
A convenient, short synthesis of ( $\pm$ )-6,7-secoagroclavine is developed having a 36% overall yield, high regio- and stereo-selectivity, and using no protecting groups.

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

We report here a practical method for synthesizing ergot alkaloid ( $\pm$ )-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.

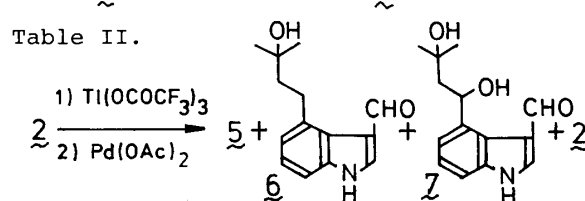
Readily available 3-formylindole (2) was converted regio-selectively to 3-formyl-4-iodoindole (3) in 72% yield by the one pot thallation-iodination method.<sup>2)</sup> The compound (3) was then treated with 2-methyl-3-buten-2-ol in the presence of a catalytic amount of Pd(OAc)<sub>2</sub> in DMF and 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.

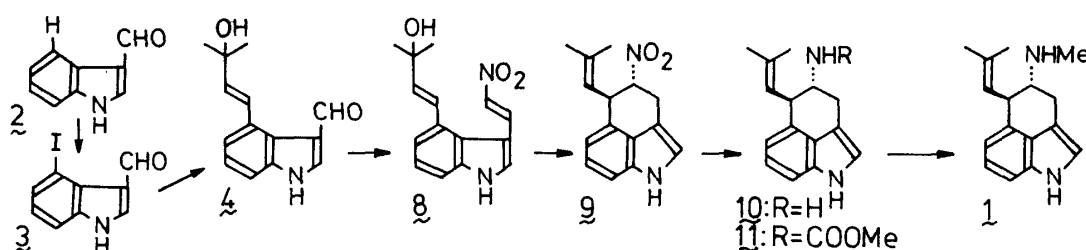


| Run | Reaction time (min) | Additives        | Yield (%) of |    |    |       |
|-----|---------------------|------------------|--------------|----|----|-------|
|     |                     |                  | 5            | 6  | 7  | 2     |
| 1   | 30                  | -                | Major        | 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 NaBH<sub>4</sub> 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 LiAlH<sub>4</sub> 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 KBr pellets, and the oily compounds for films and absorption bands are shown in cm<sup>-1</sup>. The <sup>1</sup>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. <sup>1</sup>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. <sup>1</sup>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. <sup>1</sup>H-NMR (d-M): 1.30 (6H, s), 1.60-1.96 (2H, A<sub>2</sub>B<sub>2</sub>, A<sub>2</sub> part), 3.13-3.46 (2H, A<sub>2</sub>B<sub>2</sub>, B<sub>2</sub> part), 6.80-7.40 (3H, m), 7.92 (1H, s), 9.70 (1H, s); d) mp 194-195°C. IR: 3380, 3100, 1634. <sup>1</sup>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. <sup>1</sup>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. <sup>1</sup>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. <sup>1</sup>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<sub>2</sub>), 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. <sup>1</sup>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.

(Received October 5, 1984)