

TOTAL SYNTHESIS OF (±)-6,7-SECOAGROCLAVINE[†]

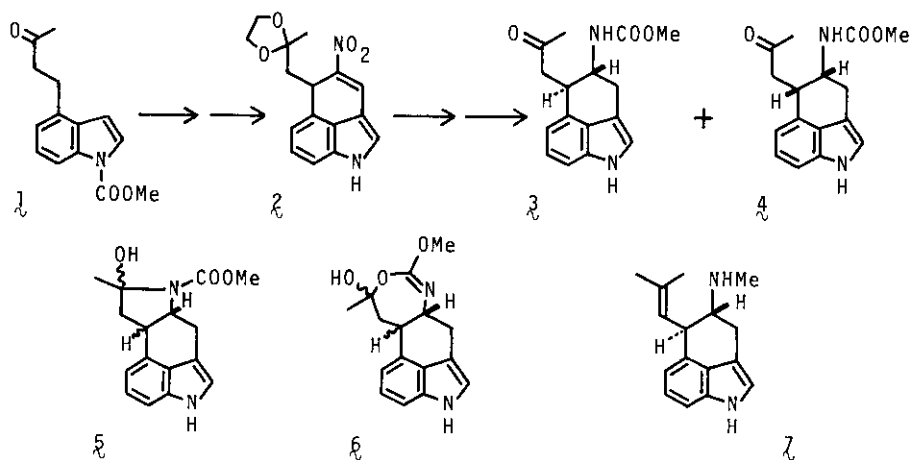
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Abstract: An ergot alkaloid, 6,7-secoagroclavine was synthesized in racemic form from 1-methoxycarbonylpyrrole in 15 steps.

In the previous communication,¹ we reported a synthesis of 8-oxo-6,7-seco-ergoline derivatives **3** and **4**, from 1-methoxycarbonyl-4-(3-oxo-1-butyl)indole² (**1**) by way of a tricyclic indole derivative **2**. For the goal of the ergot alkaloid synthesis, it is necessary to introduce one carbon unit into the ketone group of **3** and **4**. However, an intramolecular participation of the carbamate function prevented the carbanion attack to the ketone group, and either the recovery of **3** and **4** or the formation of an unstable compound, probably **5** or **6**, was observed in the reaction with the Grignard or Wittig reagent. This difficulty was overcome by modification of the carbamate group in **1** to N-methyl-benzyloxycarbonyl group (*vide infra*), and we wish to report here the first total synthesis of 6,7-secoagroclavine (**7**), which was isolated from *Claviceps purpurea*, strain AA-218.³

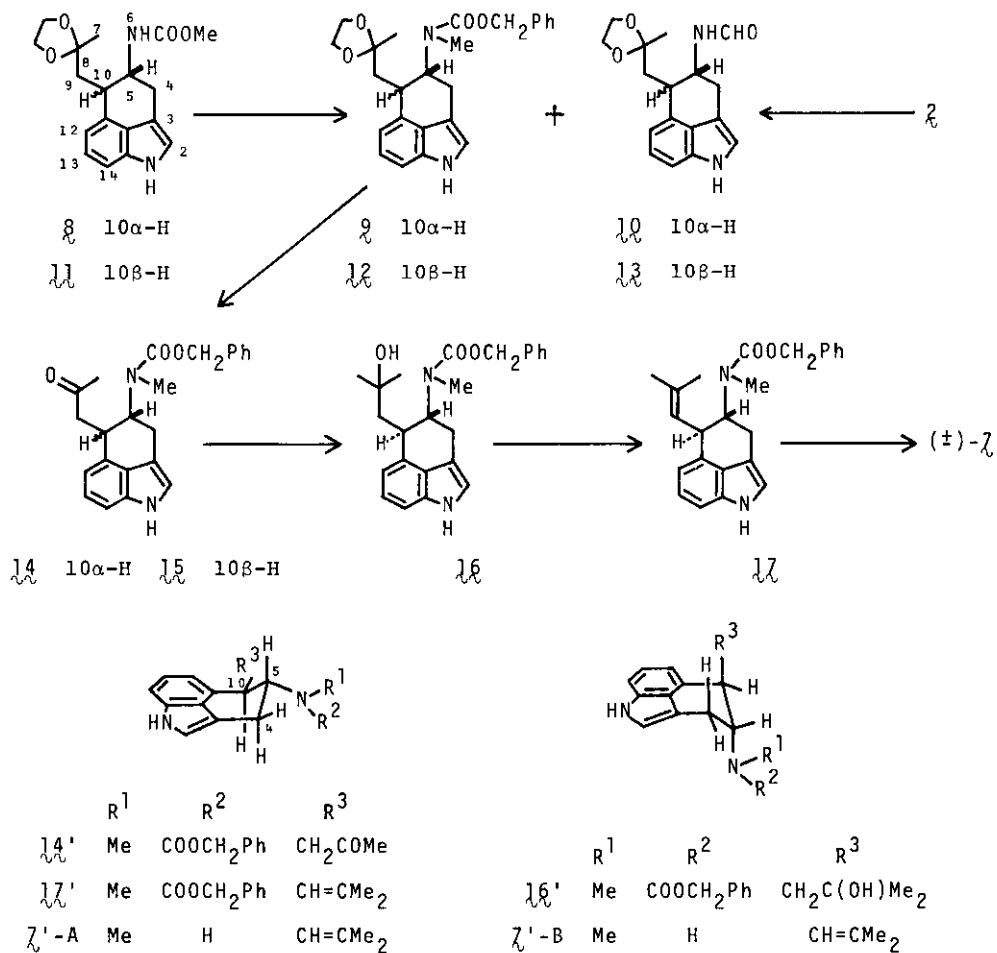


[†] Dedicated to the memory of the late Prof. Eiji Ochiai, who aroused our interest in the synthetic work of the ergot alkaloids.

The ethylene ketal derivative¹ **8** was reduced with LiAlH₄ in refluxing THF for 0.5 hr and the resulting mixture was immediately treated with ClCOOCH₂Ph in CH₂Cl₂ in the presence of Et₃N. **9**,^{4,5} mp 152-153.5°, was obtained in 55% yield, together with the formation of **10**⁶ (35% yield) as a by-product. The same series of reactions were applied to the corresponding 5,10-cis compound¹ **11**; and **12**⁷ and **13**⁸ were obtained in 67% and 18% yields, respectively. ¹H NMR spectra of **10** and **13** demonstrated the presence of NHCHO function and preparation of **10** (31% yield) and **13** (38% yield) from the nitro derivative¹ **2** by reduction with LiAlH₄ in refluxing THF, followed by formylation with HCOOH-Ac₂O confirmed their structures. Of these, **13** was subjected to the prolonged heating (7 hr) with LiAlH₄ in THF, followed by the treatment with ClCOOCH₂Ph in the presence of Et₃N to give **12** in 20% yield and the starting material **13** in 28% yield. This fact implied exceptional resistance of **13** to the LiAlH₄ reduction and explained the existence of **10** and **13** during the conversion of **8** and **11** into **9** and **12**.

Removal of the ethylene ketal group from **9** and **12** was readily carried out by stirring in acetone in the presence of TsOH at room temperature and **14**⁹ and **15**¹⁰ were obtained in 81% and 89% yields, respectively. In the ¹H NMR spectrum of **14**, the coupling constant between H-5 at δ 4.47 and H-10 at δ 3.87 was observed to be 10.5 Hz and this fact provided us with a direct evidence for the trans nature of two side chains on the ring C, as illustrated in the formula **14'**. Grignard reaction of **14** with MeMgI proceeded without trouble and **16**¹¹ was obtained in 87% yield. Judging from the ¹H NMR spectrum of **16** showing H-5 at δ 4.73 as a doublet of double doublet with J=5.5, 5.5, 5.5 Hz, the structure **16'** having two side chains in the diaxial relationship was assigned to the Grignard reaction product. Dehydration from **16** was readily achieved by refluxing C₆H₆ solution of **16** in the presence of TsOH and **17**¹² was isolated as the sole product in 83% yield. Again, the structure **17'** was suggested by ¹H NMR signals of H-5 at δ 4.48 and H-10 at δ 4.06, possessing J_{5,10}=10 Hz. Elimination of the N-protecting group was effected by treatment of **17** with Na in liquid NH₃. (±)-**7**,¹³ mp 202-205°, was finally obtained in 80% yield and identical with 6,7-secoagroclavine by comparison of the behavior on TLC,¹⁴ and spectral data (UV, IR,¹⁵ MS, ¹H NMR) with those of the natural specimen, which was kindly supplied by Dr. Horwell.

In a CDCl₃ solution, 6,7-secoagroclavine existed as two conformers of slow equilibrium, **7'**-A and **7'**-B, the former being predominant, since ¹H NMR spectrum



exhibited two types of H-10 signals at the same chemical shift and the double resonance technique revealed that the H-10 of $\text{17}'\text{-B}$ coupled only with the vinyl proton of the dimethylallyl system. In CD₃OD, H-10 was observed as a simple double doublet ($J=10, 7.5$ Hz) at δ 3.93, implying that secoagroclavine was present mostly in the conformation of $\text{17}'\text{-A}$ in this solvent.

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REFERENCES AND NOTES

1. M. Natsume and H. Muratake, *Heterocycles*, 14, 445 (1980).
2. M. Natsume and H. Muratake, *Tetrahedron Lett.*, 3477 (1979).
3. D.C. Horwell and J.P. Verge, *Phytochemistry*, 18, 519 (1979); *Chem. Abst.*, 91, 157970m (1979). The structure of 6,7-secoagroclavine was erroneously printed in these Journals and Dr. Horwell informed me that he already put forward the correction of its structure to the Editor of *Phytochemistry*.
4. Satisfactory result of elementary analysis was obtained for C,H,N.
5. MS m/e : 420 (M^+). IR (KBr) cm^{-1} : 3425, 1680. 1H NMR¹⁶ ($CDCl_3$, 60°) δ : 1.41 (3H, s), 2.14 (2H, d, $J=4.5$ Hz), 2.80 (3H, s), 3.04 (2H, d, $J=7.5$ Hz), 3.27 (1H, dt, $J=7.5, 4.5$ Hz), 3.90 (4H, br s), 4.63 (1H, dt, $J=7.5, 7.5$ Hz), 5.17 (2H, s), 6.79 (1H, br s), 7.03-7.43 (3H, m), 7.33 (5H, s), 7.93 (1H, br s).
6. MS m/e : 300 (M^+). IR (KBr) cm^{-1} : 3320, 1660. 1H NMR ($CDCl_3$) δ : 1.44 (3H, s), 1.95 (2H, d, $J=6$ Hz), 2.82 (1H, dd, $J=16.5, 4.5$ Hz), 3.22 (1H, dd, $J=16.5, 4.5$ Hz), 3.26 (1H, dt, $J=4.5, 6$ Hz), 4.03 (4H, br s), 4.92 (1H, dddd, $J=9, 4.5, 4.5, 4.5$ Hz), 5.76 (1H, br d, 9 Hz, $NHCHO$), 6.80-7.27 (4H, m), 7.85 (1H, s, CHO), 8.39 (1H, br s).
7. MS m/e : 420 (M^+). IR (KBr) cm^{-1} : 3360, 1680. 1H NMR ($CDCl_3$) δ : 1.36 (3H, s), 2.10 (2H, d, $J=5$ Hz), 2.63 (3H, s), 3.08 (2H, d, $J=5.5$ Hz), 3.60 (1H, dt, $J=5, 5$ Hz), 3.86 (4H, br s), 4.76 (1H, dt, $J=5, 5.5$ Hz), 5.17 (2H, s), 6.77 (1H, br s), 6.87-7.47 (3H, m), 7.33 (5H, s), 8.21 (1H, br s).
8. MS m/e : 300 (M^+). IR (KBr) cm^{-1} : 3420 (sh), 3330, 1665. 1H NMR ($CDCl_3$) δ : 1.46 (3H, s), *ca.* 1.90-2.36 (2H, m), 2.91 (1H, dd, $J=15.5, 5.5$ Hz), 3.19 (1H, dd, $J=15.5, 3.5$ Hz), 3.27-3.53 (1H, m), 4.03 (4H, br s), 4.67-5.00 (1H, m), 5.31-6.53 (1H, m, $NHCHO$), 6.80-7.28 (4H, m), 8.03 and 8.27 (1H, s each, CHO, rotational isomers), 8.20 (1H, br s).
9. MS m/e : 376 (M^+). IR (KBr) cm^{-1} : 3400, 1692. 1H NMR ($CDCl_3$, 60°) δ : 2.12 (3H, s), 2.54-3.27 (4H, m), 2.81 (3H, s), 3.87 (1H, ddd, $J=10.5, 5, 5$ Hz), 4.47 (1H, ddd, $J=10.5, 10.5, 6$ Hz), 5.15 (2H, s), 6.57-6.83 (2H, m), 6.94-7.42 (2H, m), 7.30 (5H, s), 8.01 (1H, s).
10. MS m/e : 376 (M^+). IR (KBr) cm^{-1} : 3450-3350, 1695. 1H NMR ($CDCl_3$) δ : 2.04 (3H, s), 2.69 (3H, s), 2.77 (2H, d, $J=7$ Hz), 3.14 (2H, d, $J=6$ Hz), 4.04 (1H, dt, $J=5, 7$ Hz), 4.70 (1H, dt, $J=5, 6$ Hz), 5.15, (2H, s), 6.66-6.89 (2H, m), 6.94-7.43 (2H, m), 7.31 (5H, s), 8.14 (1H, br s).
11. MS m/e : 392 (M^+). IR (KBr) cm^{-1} : 3430, 3350 (sh), 1675. 1H NMR ($CDCl_3$,

- 60°) δ : 1.26 (3H, s), 1.36 (3H, s), 1.71 (1H, dd, $J=15$, 4.5 Hz), 1.91 (1H, dd, $J=15$, 6 Hz), 2.38-3.17 (OH), 2.57 (3H, s), 3.02 (1H, dd, $J=16.5$, 5.5 Hz), 3.17-3.48 (1H, m), 3.26 (1H, dd, $J=16.5$, 5.5 Hz), 4.73 (1H, ddd, $J=5.5$, 5.5, 5.5 Hz), 5.14 (2H, s), 6.78-7.42 (4H, m), 7.30 (5H, s), 8.09 (1H, br s).
12. MS m/e : 374 (M^+). IR (KBr) cm^{-1} : 3360, 1680, 1605. 1H NMR ($CDCl_3$, 60°) δ : 1.75 (3H, s), 1.80 (3H, s), 2.71-3.46 (2H, m), 2.90 (3H, s), 4.06 (1H, dd, $J=10$, 10 Hz), 4.48 (1H, ddd, $J=10$, 10, 6 Hz), 4.91-5.36 (3H, m), 6.64-6.87 (2H, m), 6.96-7.43 (2H, m), 7.30 (5H, br s), 7.92 (1H, br s).
13. MS m/e : 240 (M^+). UV (95% EtOH) nm: 222, 280, 292. IR ($CHCl_3$) cm^{-1} : 3510 (s), 3340 (w), 3080 (w), 3020 (m), 2980 (s), 2950 (s), 2875 (m), 2815 (m), 1675 (w), 1610 (m), 1478 (w), 1447 (s), 1418 (w), 1384 (w), 1380 (m), 1352 (w), 1340 (m), 1288 (m), 1268 (w), 1212 (sh), 1159 (w), 1140 (m), 1108 (w), 1092 (w), 1076 (m), 1053 (w), 1028 (w), 1007 (w), 965 (w), 875 (w), 840 (w), 820 (w). 1H NMR ($CDCl_3$) δ : 1.84 (3H, d, $J=1.5$ Hz, Me), 1.88 (3H, d, $J=1.5$ Hz, Me), 2.01 (1H, s, exchangeable, NH), 2.52 (3H, s, NMe), *ca.* 2.52-3.04 (2H, m, H-4_{ax.} and H-5), 3.08-3.50 (1H, m, H-4_{eq.}), 3.88 (br dd, $J=10$, 8 Hz) and 3.88 (d, $J=10$ Hz) (1H, H-10), 5.13 (1H, br d, $J=10$ Hz, $-CH=C$), 6.74 (1H, ddd, $J=4.5$ 3.5, 1 Hz, H-12), 6.84 (1H, br s, H-2), *ca.* 6.98-7.27 (2H, m, H-13 and H-14), 8.18 (1H, br s, exchangeable, indole NH).
14. Merck Silica Gel 60F₂₅₄. Dioxane:MeOH=2:0.5 afforded $R_f=0.25$, and $CHCl_3$: MeOH:conc.NH₄OH=46:5:0.5 afforded $R_f=0.44$ for both samples.
15. IR ($CHCl_3$) of natural $\bar{\nu}$ cm^{-1} : 3482 (s), 3320 (w), 3060 (w), 3010 (sh), 2920 (s), 2862 (sh), 2802 (m), 1675 (w), 1610 (m), 1477 (sh), 1445 (s), 1417 (w), 1385 (sh), 1378 (m), 1351 (sh), 1340 (m), 1288 (m), 1268 (m), 1210 (sh), 1159 (w), 1142 (m), 1108 (sh), 1096 (w), 1077 (m), 1053 (w), 1028 (w), 1007 (w), 965 (w), 875 (w), 840 (sh), 820 (w). A minor discrepancy at 2980-2920 cm^{-1} region may be attributable to the difference of resolution of the instruments.
16. All 1H NMR spectra were taken at 90 MHz.

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