

Total syntheses of (\pm)-agroclavine- I ,
(\pm)-6-nor-chanoclavine- II , and (\pm)-chanoclavin- II

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| メタデータ | 言語: eng 出版者: 公開日: 2017-10-03 キーワード (Ja): キーワード (En): 作成者: メールアドレス: 所属: |
| URL | http://hdl.handle.net/2297/4309 |

TOTAL SYNTHESSES OF (±)-AGROCLAVINE-I, (±)-6-NOR-
 CHANOCCLAVINE-II, AND (±)-CHANOCCLAVINE-II¹

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Abstract ——— The first total syntheses of (±)-6-nor-
 chanoclavine-II and (±)-chanoclavine-II are achieved. Total
 synthesis of (±)-agroclavine-I is also reported.

In the previous papers,² we have established a practical and common synthetic method for ergot alkaloids. The community of the synthetic method is now successfully extended to total syntheses of (±)-agroclavine-I (8),³ (±)-6-nor-chanoclavine-II (11),⁴ and (±)-chanoclavine-II (13).⁵ In this communication, we describe these results in detail.

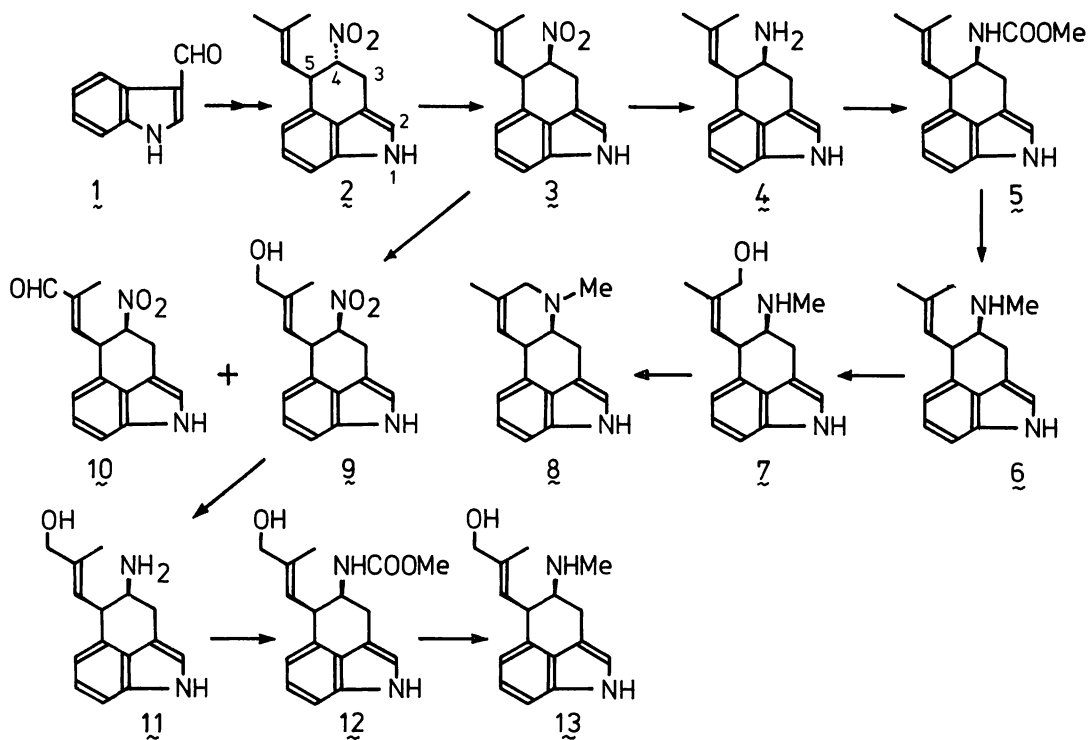
First, 4,5-trans-4-nitro-5-(2-methyl-1-propen-1-yl)-1,3,4,5-tetrahydrobenz[cd]indole (2) was prepared in four steps in 42% overall yield starting from 3-indolecarbaldehyde (1) as reported previously.² Subsequent treatment of 2 with sodium methoxide in methanol and protonation with 10% aqueous acetic acid readily inverted the stereochemistry of the carbon-4 bound to the nitro group to afford 4,5-cis-4-nitro-5-(2-methyl-1-propen-1-yl)-1,3,4,5-tetrahydrobenz[cd]indole (3)^{6a} in 85% yield together with the recovery of 2 in 8% yield.

With the compound (3) in hand, the syntheses of 8, 11, and 13 were carried out by employing our general synthetic operations.² Thus, reduction of 3 with zinc amalgam in aqueous hydrochloric acid (HCl) gave the corresponding amine (4)^{6b} in 98% yield. Treatment of 4 with methyl chloroformate (ClCOOMe) in methylene chloride (CH₂Cl₂) in the presence of triethylamine (NEt₃) afforded 66% yield of the desired carbamate (5).^{6c} Reduction of 5 with lithium aluminum hydride (LiAlH₄) in absolute tetrahydrofuran (THF) gave (±)-5-epi-6,7-secoagroclavine (6)^{6d} in 91% yield. Subsequent regioselective oxidation of Z-methyl⁷ in the isobutenyl group at the 5-position was attained by the treatment of 6 with selenium dioxide (SeO₂) in dioxane and water to

produce *Z*-4,5-*cis*-5-(2-hydroxymethyl-1-propen-1-yl)-4-methylamino-1,3,4,5-tetrahydrobenz[cd]indole [7, (±)-isochanoclavine-II]^{6e} in 34% yield. Cyclization of **7** with phosphorus oxychloride in the presence of potassium carbonate⁸ produced (±)-agroclavine-I (**8**)^{3,6f} in 87% yield. Proton nuclear magnetic resonance (¹H-NMR) spectrum of **8** was identical with that of the authentic (±)-agroclavine-I, which was synthesized by Ninomiya and co-workers.^{3b}

On the other hand, oxidation of **3** with SeO₂ in dioxane and water gave *E*-4,5-*cis*-5-(2-hydroxymethyl-1-propen-1-yl)-4-nitro-1,3,4,5-tetrahydrobenz[cd]indole (**9**)^{6g} and *E*-4,5-*cis*-3-(4-nitro-1,3,4,5-tetrahydrobenz[cd]indol-5-yl)-2-methylacrylic aldehyde (**10**)^{6h} in 31% and 4% yields,⁷ respectively, together with the recovery of **3** in 62% yield. Reduction of **9** with zinc amalgam in aqueous HCl afforded (±)-6-nor-chanoclavine-II (**11**)^{4,6i} in 94% yield. Treatment of **11** with ClCOOMe in CH₂Cl₂ in the presence of NEt₃ afforded 92% yield of the corresponding carbamate (**12**).^{6j} Finally, reduction of **13** with LiAlH₄ in absolute THF afforded (±)-chanoclavine-II (**13**)^{6k} in 69% yield. ¹H-NMR spectrum of **13** was identical with that of the natural alkaloid, reported in the literature.⁵

Thus, the first and simple total syntheses of **11** and **13** were accomplished.



ACKNOWLEDGEMENT

The authors express their cordial gratitude to Prof. I. Ninomiya, Kobe Women's College of Pharmacy, for giving us the $^1\text{H-NMR}$ spectrum of (\pm)-agroclavine-I.

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3. As far as we know, two groups succeeded in the total synthesis of (\pm)-agroclavine-I: a) A.P. Kozikowski and P.D. Stein, J. Am. Chem. Soc., 107, 2569 (1985); b) T. Kiguchi, C. Hashimoto, and I. Ninomiya, Heterocycles, 23, 2891 (1985). Formal total synthesis: W.J. Wheeler, Tetrahedron Lett., 27, 3469 (1986). Isolation: V.G. Sakharovsky and A.G. Kozlovsky, Tetrahedron Lett., 25, 109 (1984).
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6. a) mp 147.0-148.0°C. IR (KBr): 3381, 1620, 1606, 1526, 1444, 1378 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.67 (3H, d, $J=1.2$ Hz), 1.83 (3H, d, $J=1.5$ Hz), 3.33 (1H, dd, $J=15.4$ and 5.3 Hz), 3.59 (1H, ddd, $J=15.4$, 10.0, and 1.5 Hz), 4.73 (1H, dd, $J=10.3$ and 4.4 Hz), 4.96 (1H, ddd, $J=10.0$, 5.3, and 4.4 Hz), 5.13 (1H, br d, $J=10.3$ Hz), 6.75-6.98 (1H, m), 6.92 (1H, br s), 7.00-7.25 (2H, m), 7.98 (1H, br s). b) mp 113.0-114.0°C. IR (KBr): 2920, 1598, 1572, 756 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.69 (2H, br s, NH_2), 1.81 (3H, d, $J=1.2$ Hz), 1.85 (3H, d, $J=1.2$ Hz), 2.81 (1H, ddd, $J=15.2$, 7.3, and 1.0 Hz), 3.05 (1H, ddd, $J=15.2$, 4.4, and 1.0 Hz), 3.44 (1H, ddd, $J=7.3$, 4.4, and 3.5 Hz), 3.98 (1H, dd, $J=10.0$ and 3.5 Hz), 5.27 (1H, br d, $J=10.0$ Hz), 6.70-6.91 (1H, m), 6.83 (1H, br s), 6.97-7.19 (2H, m), 8.03 (1H, br s). c) mp 139.0-141.0°C. IR (KBr): 3320, 1683, 1669, 1533 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.79 (1H, d, $J=2.0$ Hz), 1.81 (1H, d, $J=1.5$ Hz), 2.87 (1H, dd, $J=15.5$ and 7.0 Hz), 3.11 (1H, dd, $J=15.5$ and 4.2 Hz), 3.61 (3H, s), 4.05 (1H, dd, $J=9.8$ and 3.7 Hz), 4.30 (1H, dddd, $J=9.5$, 7.0, 4.2, and 3.7 Hz), 4.75 (1H, br d, $J=9.5$ Hz), 5.21 (1H, br d, $J=9.8$ Hz), 6.68-6.92 (1H, m), 6.85 (1H, br s), 6.96-7.25 (2H, m), 7.93 (1H, br s). d) M. Somei, F. Yamada, Y. Karasawa, and C. Kaneko, Chemistry Lett., 1981, 615. mp 177.0-178.0°C. IR (KBr): 3140, 3090, 1661, 1616, 1437 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.57 (1H, s, NH), 1.73 (3H, d, $J=1.2$ Hz), 1.89 (3H, d, $J=1.2$ Hz), 2.51 (3H, s), 2.77 (1H, ddd, $J=15.4$, 10.3, and 1.5 Hz), 2.93-3.22 (2H, m), 4.14 (1H, dd, $J=10.3$ and 3.7 Hz), 5.21 (1H, br d, $J=10.3$ Hz), 6.69-6.87 (1H, m), 6.81 (1H, br s), 6.91-7.15 (2H, m), 8.01 (1H, br s, NH). e) oil. IR (film): 3250, 1617, 1604, 1445 cm^{-1} . $^1\text{H-NMR}$ (pyridine- d_5) δ : 1.92 (3H, d, $J=1.2$ Hz), 2.49 (3H, s), 2.89 (1H, dd, $J=15.4$ and 11.2 Hz), 3.06-3.35 (2H, m), 4.46 (1H, d, $J=12.1$ Hz), 4.54 (1H, dd, $J=10.3$ and 3.7 Hz), 4.78 (1H, d, $J=12.1$ Hz), 5.54 (1H, d, $J=10.3$ Hz), 6.98 (1H, d, $J=6.7$ Hz), 7.05-7.27 (2H, m), 7.34 (1H, d, $J=7.8$ Hz), 11.50 (1H, br s, NH). f) mp 157.0-158.0°C. IR (KBr): 3400, 3100, 2860, 1618, 1607, 1444 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.63 (3H, br s), 2.56 (3H, s), 2.78 (1H, ddd, $J=15.0$, 10.0, and 1.5 Hz), 2.98 (1H, dd, $J=15.0$ and 4.5 Hz),

3.07 (2H, br s), 3.24-3.49 (1H, m), 3.78-4.08 (1H, m), 5.48 (1H, br s), 6.74-6.98 (1H, m), 6.79 (1H, br s), 6.98-7.18 (2H, m). g) mp 132.0-134.0°C. IR (KBr); 3496, 3246, 1607, 1535, 1370 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.86 (3H, d, $J=1.5$ Hz), 3.37 (1H, dd, $J=16.0$ and 5.5 Hz), 3.62 (1H, ddd, $J=16.0$, 10.3, and 1.7 Hz), 3.94 (2H, br s), 4.81 (1H, dd, $J=10.3$ and 4.5 Hz), 5.02 (1H, ddd, $J=10.3$, 5.5, and 4.5 Hz), 5.46 (1H, dq, $J=10.3$ and 1.5 Hz), 6.84 (1H, dd, $J=5.8$ and 2.2 Hz), 6.96 (1H, br s), 7.04-7.28 (2H, m), 8.03 (1H, br s). h) oil. IR (film): 1676 (br), 1636, 1544 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.96 (3H, d, $J=1.5$ Hz), 3.32-3.84 (2H, m), 4.89-5.21 (2H, m), 6.41 (1H, br d, $J=10.2$ Hz), 6.83 (1H, dd, $J=6.2$ and 1.5 Hz), 7.01 (1H, br s), 6.92-7.34 (2H, m), 8.15 (1H, br s, NH), 9.23 (1H, s). i) mp 208.0-210.0°C (dec.). IR (KBr): 3150, 1614, 1597, 1572, 1420 cm^{-1} . $^1\text{H-NMR}$ (pyridine- d_5) δ : 2.06 (3H, d, $J=1.0$ Hz), 2.98 (1H, dd, $J=15.3$ and 7.3 Hz), 3.19 (1H, dd, $J=15.3$ and 3.9 Hz), 3.50-3.77 (1H, m), 4.28 (1H, dd, $J=9.8$ and 3.9 Hz), 4.34 (2H, s), 6.05 (1H, br d, $J=9.8$ Hz), 7.01 (1H, d, $J=6.8$ Hz), 7.09-7.46 (3H, m), 11.55 (1H, br s). j) oil. IR (film): 3350, 1695 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.86 (3H, d, $J=1.2$ Hz), 2.91 (1H, dd, $J=15.5$ and 6.3 Hz), 3.14 (1H, dd, $J=15.5$ and 4.5 Hz), 3.60 (3H, s), 4.07 (2H, s), 4.14 (1H, dd, $J=9.8$ and 3.7 Hz), 4.20-4.57 (1H, m), 4.89 (1H, br d, $J=9.5$ Hz), 5.56 (1H, br d, $J=9.8$ Hz), 6.64-6.96 (2H, m), 7.00-7.31 (2H, m), 8.04 (1H, br s). k) mp 86.0-88.0°C (recrystallized from CHCl_3). IR (KBr): 3190, 1620, 1605, 1440 cm^{-1} . $^1\text{H-NMR}$ (pyridine- d_5) δ : 2.12 (3H, d, $J=1.0$ Hz), 2.47 (3H, s), 2.95 (1H, dd, $J=15.5$ and 10.0 Hz), 3.10-3.38 (2H, m), 4.28 (2H, s), 4.43 (1H, dd, $J=10.2$ and 3.8 Hz), 6.03 (1H, d, $J=10.2$ Hz), 6.98-7.44 (4H, m), 11.54 (1H, br s).

7. The differences in the direction of oxidation with SeO_2 would be explained by the formation of a complex with the methylamino group in the compound (6), where the SeO_2 lie in the vicinity of Z-methyl group. See also reference 2.
8. Combination of these reagents was first applied for the synthesis of benzo[c]-phenanthridine alkaloids by H. Ishii and co-workers: H. Ishii, I.-S. Chen, S. Ueki, T. Masuda, K. Morita, and T. Ishikawa, Symposium Papers, The 28th Symposium on the Chemistry of Natural Products, Sendai, October 1986, p. 457.

Received, 10th December, 1986