Total syntheses of (±)-agroclavine-?, (±)-6-nor-chanoclavine-?, and (±)-chanoclavin-?

TOTAL SYNTHESES OF (±)-AGROCLAVINE-I, (±)-6-NOR-CHANOCLAVINE-II, AND (±)-CHANOCLAVINE-II[1]

Masanori Somei,* Fumio Yamada, and Yoshihiko Makita
Faculty of Pharmaceutical Sciences, Kanazawa University
13-1 Takara-machi, Kanazawa 920, Japan

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.

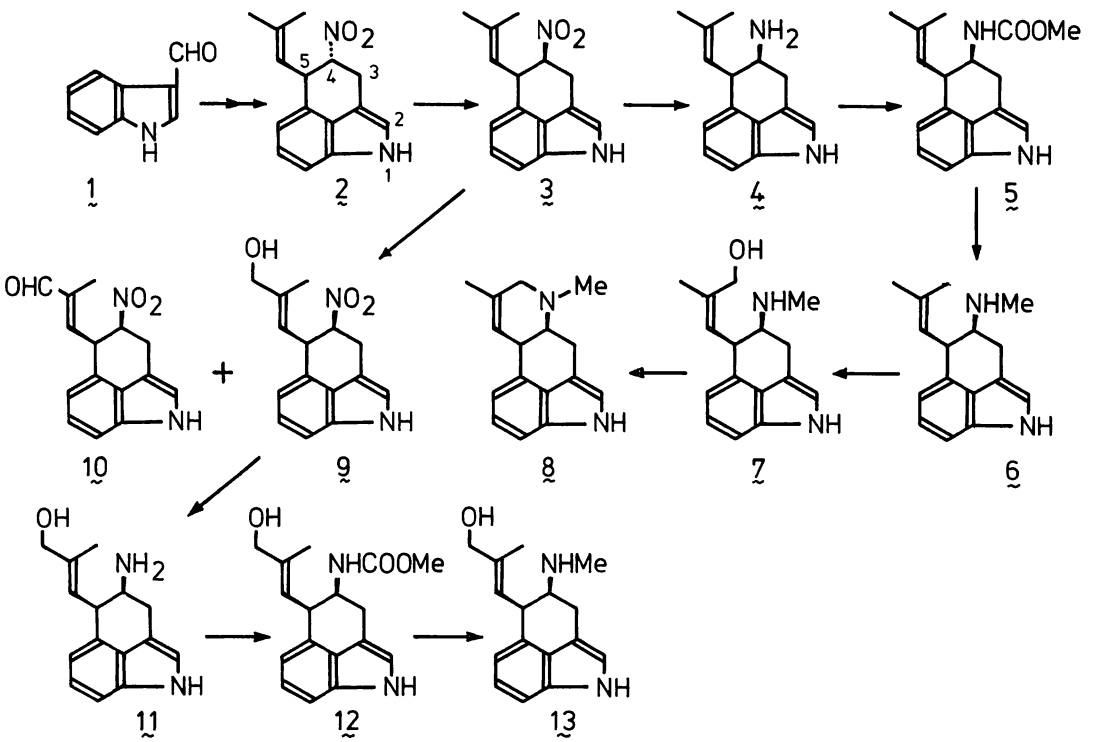
First, 4,5-trans-4-nitro-5-(2-methyl-1-propen-1-yl)-1,3,4,5-tetrahydrobenz[cd]indole (2) was prepared in four steps in 42% overall yield starting from 3-indolecarbaldehyde (1) as reported previously.[2] Subsequent treatment of 2 with sodium methoxide in methanol and protonation with 10% aqueous acetic 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 (CH_2Cl_2) in the presence of triethylamine (NEt_3) afforded 66% yield of the desired carbamate (5).[6c] Reduction of 5 with lithium aluminum hydride ($LiAlH_4$) in absolute tetrahydrofuran (THF) gave (±)-5-epi-6,7-secoagroclavine (6)[6d] in 91% yield. Subsequent regioselective oxidation of Z-methyl[7] in the isobutenyl group at the 5-position was attained by the treatment of 6 with selenium dioxide (SeO_2) 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 carbonate[8] produced (±)-agroclavine-I (8)[3,6f] in 87% yield. Proton nuclear magnetic resonance (^{1}H-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 SeO_2 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 CH_2Cl_2 in the presence of NEt_3 afforded 92% yield of the corresponding carbamate (12).[6j] Finally, reduction of 13 with $LiAlH_4$ in absolute THF afforded (±)-chanoclavine-II (13)[6k] in 69% yield. ^{1}H-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.



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3. As far as we know, two groups succeeded in the total synthesis of (±)-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, 1378cm^{-1}. ^{1}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}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}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}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}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}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}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}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}H-NMR (pyridine-d_5)δ: 2.06 (3H, d, J=1.0Hz), 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}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}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.

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