A NOVEL SYNTHESIS OF (±)-ISOCHANOCLAVINE-I

Toshiko Kiguchi, Naoko Kuninobu, Takeaki Naito, and Ichiya Ninomiya*
Kobe Women's College of Pharmacy, Motoyamakita, Higashinada,
Kobe 658, Japan

Abstract —— Total synthesis of (±)-isochanoclavine-I (**9**) was achieved via the route involving fragmentation reaction of the 3-aminoalcohol **4**.

As a part of our general project toward the development of practical and divergent synthetic route for the ergot alkaloids[1] starting from a common intermediate **1**, we have now succeeded in the total synthesis of (±)-isochanoclavine-I[2] which has a 6,7-secoergoline type[3] of structure. The key step in our synthesis is the fragmentation reaction of 3-aminoalcohol derivatives[4] whose potentiality as a synthetic reaction had been already shown in the benzo[f]quinoline system as described in the previous paper.[5]

The starting compound for the study of fragmentation reaction, the 8-methyl-glycol **3** was synthesized from the known key intermediate **1** which had been obtained by reductive photocyclization of enamide[1] and successfully used as a common intermediate in the total synthesis of ergoline type of alkaloids.[1]
The lactam **1** was metalated with 2 equiv. of lithium diisopropylamide (-78°C, THF) and then treated with excess methyl iodide (from -78°C to 0°C) to give the desired 3a-methyl-lactam **2**[6] in 70% yield. The stereochemistry of **2** as having cis-anti-11c,11b-trans configuration was deduced by the comparison of its nmr spectrum with that of the starting lactam **1** and also by the observation of nuclear Overhauser effect between 3a-methyl group and 11c-hydrogen. Ring opening of the dihydrofuran ring of **2** by the two-step method[1] involving ozonolysis and lithium aluminum hydride reduction gave the debenzoylated 3-aminoalcohol **3**[7] in 61% yield. Selective acetylation of **3** on the primary hydroxyl group in addition to nitrogen was performed by treatment with acetic anhydride in pyridine at 20°C to afford the corresponding N,O-diacetate **4**[8] in 93% yield.

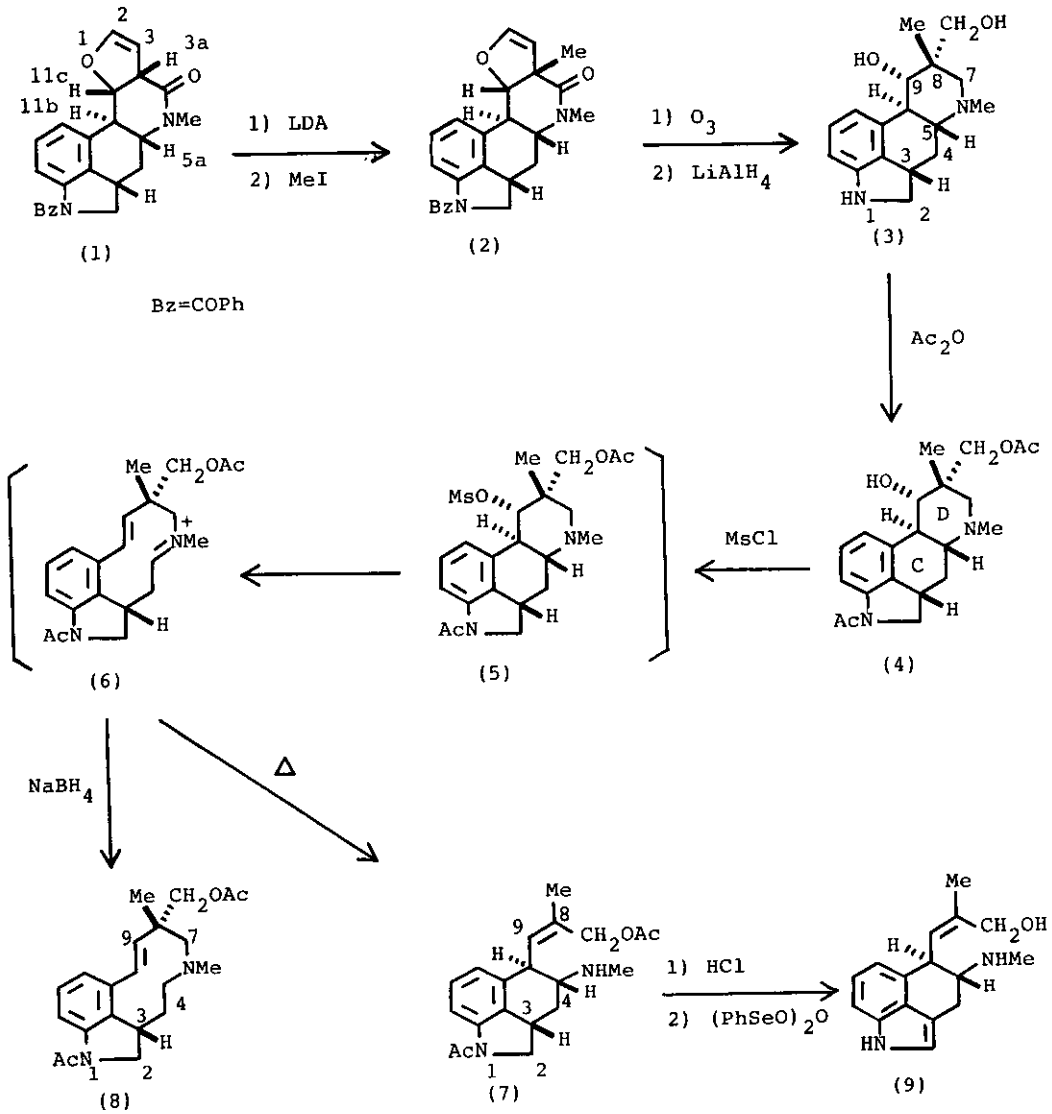
With this N,O-diacetate **4** as the starting compound, we have investigated the fragmentation reaction *via* its 9-mesylate. As described in the previous paper,[5] mesylation of 3-aminoalcohols was expected to proceed smoothly to give the corresponding mesylates which however, depending on the substituents on the ring D, were known to undergo further fragmentation even under the mesylating condition without forming any detectable amount of mesylates. Actually, treatment of the diacetate **4** with an equivalent amount of methanesulfonyl chloride (mesyl chloride) recovered only the starting compound **4**, while similar treatment with an excessive amount of mesyl chloride gave an intractable mixture.

We have then investigated direct formation of the desired allyl acetate **7** from the N,O-diacetate **4** by the fragmentation reaction *via* the presumed mesylate **5**. According to the procedure exploited on the benzo[f]quinolines,[5] the diacetate **4** was treated with mesyl chloride (20 equiv.) in pyridine at 20°C for 2.5 h and then diethylamine (20 equiv.) was added to the reaction mixture at room temperature in order to quench unreacted mesyl chloride. The reaction mixture was diluted with anhydrous ethanol and heated at 50°C for 3 h to complete the fragmentation reaction of the presumed mesylate **5**. Thereby the desired allyl acetate **7**[9] was obtained in 56% isolated yield.

Furthermore, treatment of the above reaction mixture, which was obtained from the diacetate **4**, mesyl chloride, pyridine, and diethylamine at 20°C, in the presence of sodium borohydride in anhydrous ethanol gave the ten-membered amine **8**[10] in 59% yield. The reaction course for the conversion of the diacetate **4** to the desired acetate **7** was established as in the case of the benzo[f]quinoline system.[5] That is, fragmentation reaction of the mesylate **5** would first form the ring-opened intermediate **6**, which would then undergo aza-Cope rearrangement to give the acetate **7** while the ten-memberd amine **8** would be formed by reduction of iminium bond in **6**.

Hydrolysis of the diacetate **7** by heating in methanol containing conc. hydrochloric acid at 80°C followed by dehydrogenation[11] with phenylseleninic anhydride in the presence of 3 equivs. of indole and triethylamine in THF afforded the indole derivative **9** (mp 190-192°C(H_2O-MeOH))(lit.,[2b] mp 200-201°C) in 83% yield. The nmr and ir spectra of the synthetic compound **9** were identical with those of the authentic sample of (±)-isochanoclavine-I provided by Professor Somei.

Thus, we have succeeded in the total synthesis of (±)-isochanoclavine-I by applying the fragmentation reaction of the 3-aminoalcohol derivative.



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6. Mp 210-212°C(MeOH-Et_2O). Ir($CHCl_3$)cm^{-1}:1638. Nmr($CDCl_3$)δ:6.39(1H, d, J = 2.5 Hz, 2-H), 5.37(1H, d, J = 2.5 Hz, 3-H), 4.45(1H, d, J = 10.5 Hz, 11c-H), 3.60 (1H, ddd, J = 12.5, 10.5, and 3 Hz, 5a-H), 3.08(3H, s, NMe), and 1.45(3H, s, 3a-Me).
7. Mp 222-225°C(decomp.)(MeOH). Ir(nujol)cm^{-1}:3276. Nmr(DMSO-d_6)δ:3.72(2H, br s, 8-C$\underline{H}_2$OH), 2.80(1H, t, J = 10.5 Hz, 10-H), 2.23(3H, s, NMe), 1.94(1H, br t, J = 10.5 Hz, 5-H), and 0.92(3H, s, 8-Me).
8. Mp 226-228.5°C(CH_2Cl_2-Et_2O). Ir($CHCl_3$)cm^{-1}:1732 and 1650. Nmr($CDCl_3$)δ:4.60 and 4.42(2H, ABq, J = 11 Hz, C$\underline{H}_2$OAc), 3.61(1H, d, J = 11 Hz, 9-H), 2.99(1H, br t, J = 10 Hz, 10-H), 2.31(3H, s, NMe), 2.24(3H, s, NAc), 2.11(3H, s, OAc), and 1.08(3H, s, 8-Me).
9. Mp 117-119.5°C(Me_2CO). Ir($CHCl_3$)cm^{-1}:1724 and 1656. Nmr($CDCl_3$)δ:5.37(1H, br d, J = 10 Hz, 9-H), 4.96 and 4.64 (2H, ABq, J = 13 Hz, C$\underline{H}_2$OAc), 3.84(1H, t, J = 10 Hz, 10-H), 2.89(1H, br t, J = 10 Hz, 5-H), 2.62(3H, s, NMe), and 1.89 (3H, d, J = 1 Hz, 8-Me).
10. Mp 133.5-135.5°C(MeOH-Et_2O). Ir($CHCl_3$)cm^{-1}:1730 and 1652. Nmr($CDCl_3$)δ:6.67 (1H, d, J = 17 Hz, 10-H), 5.71(1H, d, J = 17 Hz, 9-H), 4.60 and 4.40(2H, ABq, J = 13 Hz, C$\underline{H}_2$OAc), 2.44(3H, s, NMe), and 1.25(3H, s, 8-Me).
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