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SHORT-STEP SYNTHESIS OF THE ERGOT ALKALOIDS, (±)-NORCHANOCLAVINE-I, (±)-CHANOCLAVINE-I, (±)-ISOCHANOCLAVINE-I, AND (±)-AGROCLAVINE[1)]

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The simple total synthesis of the ergot alkaloids, (±)-norchanoclavine-I, (±)-chanoclavine-I, (±)-isochanoclavine-I, and (±)-agroclavine was achieved by a practical and common synthesis method. A new regio-selective oxidation of the Z-methyl group of the isoprenyl system with selenium dioxide is described.

KEYWORDS ——— (±)-norchanoclavine-I; (±)-norisochanoclavine-I; (±)-chanoclavine-I; (±)-isochanoclavine-I; (±)-agroclavine; ergot alkaloid; total synthesis; common synthesis method; new oxidation

We have been attempting to develop a common and practical synthesis method that would be widely applicable to various ergot alkaloids and their analogs by changing reagents without changing the reaction types, which would require alteration of the apparatus or plant for each step. Now, we have established such a synthesis method and succeeded in the simple and practical total synthesis of the ergot alkaloids, (±)-norchanoclavine-I (8a), (±)-chanoclavine-I (10a), (±)-isochanoclavine-I (10b), and (±)-agroclavine (11) and the related (±)-norisochanoclavine-I (8b).

4-Iodo-3-indolecarbaldehyde (2), prepared in a one-pot operation in 72% yield from 3-indolecarbaldehyde (1) as reported previously,[2)] reacted with 2-methoxy-2-methyl-3-buten-1-ol[3)] in DMF in the presence of tetra-n-butylammonium bromide[4)] and a catalytic amount of $Pd(OAc)_2$ at 100°C to afford 4-(3-hydroxymethyl-3-methoxy-1-buten-1-yl)-3-indolecarbaldehyde (3a, mp 78-80°C) in 92% yield. The aldol condensation reaction of 3a with nitromethane gave the corresponding nitrovinyl compound (4a, mp 164-165°C) in 99% yield. The subsequent reduction of 4a with $NaBH_4$ in MeOH afforded the nitroethyl compound (5a, mp 125.5-126.5°C) in 94% yield. Adding $NaBH_4$ to a solution of 5a in MeOH and subsequently treating the resultant nitronate with aqueous HCl[2,5)] produced three stereoisomers; E-4,5-trans-[6a)] (6a, mp 156-156.5°C), Z-4,5-trans-[6b)] (6b, mp 179-180°C), and E-4,5-cis-configurational isomer[6c)] (7, mp 134-135°C) in 31%, 8%, and 5% yields, respectively. As expected, these compounds (6a, 6b, and 7) were produced directly from 4a in almost the same yields by reducing the nitrovinyl moiety with $NaBH_4$ in MeOH, followed by treatment with aqueous HCl.[2,5)]

Reduction of 6a with zinc amalgam in MeOH-HCl achieved the first synthesis of (±)-norchanoclavine-I[7)] (8a, mp 182-183°C) in 98% yield (five steps from 1 with 20% overall yield). Methoxycarbonylation of 8a with methyl chloroformate yielded the corresponding carbamate (9a, oil) in 92% yield. Further reduction of 9a with $LiAlH_4$ in THF afforded (±)-chanoclavine-I[8)] [10a, mp 194-195°C (dec.)] in 96% yield. Thus,

the simple total synthesis of 10a was achieved in seven steps from 1 with an overall yield of 19%.

Similarly, the synthesis of (±)-norisochanoclavine-I (8b, mp 196-197°C) was achieved by reducing 6b with zinc amalgam in MeOH-HCl in 96% yield. Essentially the same reaction sequences as described for 10a converted 8b into the corresponding carbamate (9b, oil) and (±)-isochanoclavine-I[9] [10b, mp 200-201°C (dec.)] in 88% and 78% yields, respectively. Their structures were unequivocally confirmed by leading 10b to (±)-agroclavine[10]. [11, mp 189-191°C (dec.)] in 64% yield by the reaction with thionyl chloride.[11]

Thus, we developed a common and practical, short-synthesis method for ergot alkaloids as shown in the general formulae in Chart 1. When 2-methyl-3-buten-2-ol was used as an olefin component in the second step, (±)-6,7-secoagroclavine (10c) was produced,[2] while using 2-methoxy-2-methyl-3-buten-1-ol produced various ergot alkaloids (8a, 10a, 10b, and 11).

Next, 4,5-trans-5-(2-methyl-1-propen-1-yl)-4-nitro-1,3,4,5-tetrahydrobenz[cd]-indole (6c) was prepared in four steps with an overall yield of 42% from 1,[2] then oxidized with selenium dioxide in dioxane-water to produce directly 6a and the corresponding formyl compound (6d, mp 192-194°C) in 36% and 19% yields, respectively. These compounds were readily interconverted either by the reduction of 6d with $NaBH_4$ or by the oxidation of 6a with pyridinium chlorochromate in 93% or 55% yields, respectively. Interestingly, we found recently that the oxidation of (±)-6,7-secoagroclavine[2] (10c) with selenium dioxide[12] in dioxane at 100°C produced directly (±)-isochanoclavine-I (10b) in 35% yield and recovered 10c in 51% yield. This stereochemistry can be explained by the coordination of the amino group to selenium, putting selenium dioxide close to the 2-methyl group. With these findings in hand, we can now produce (±)-isochanoclavine-I (10b) in eight steps with 13% overall yield from 1.

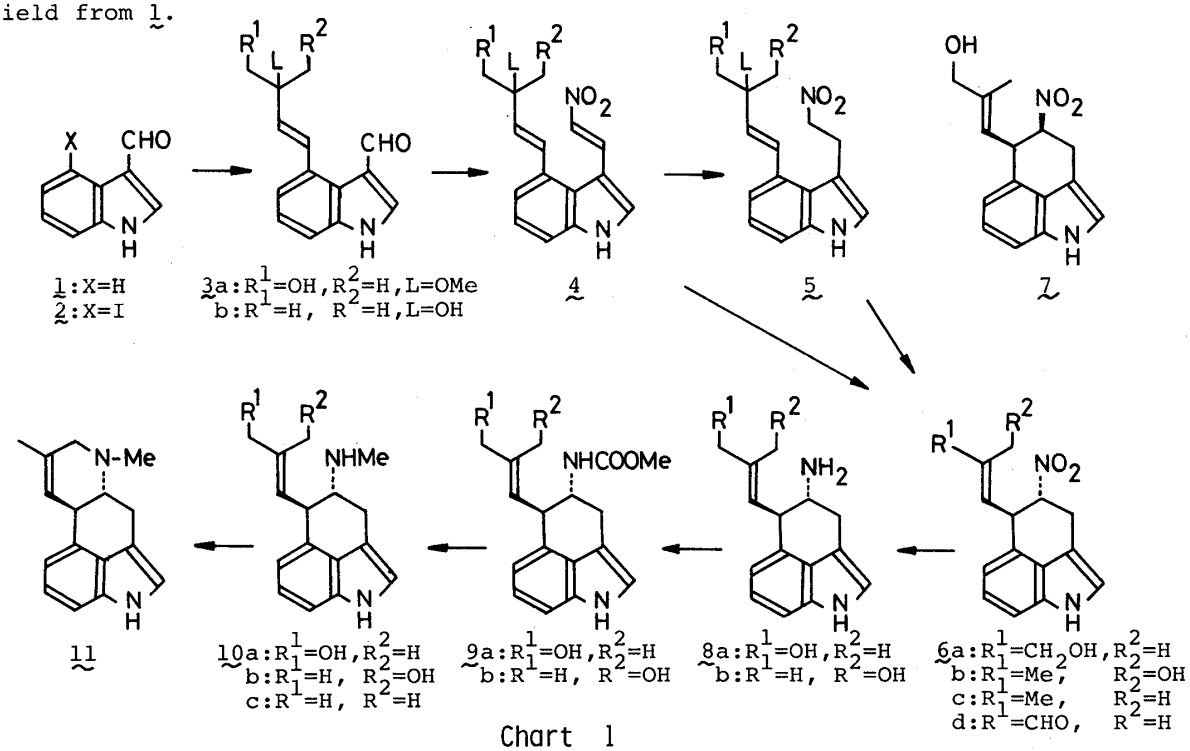

Chart 1

Synthetic (±)-chanoclavine-I and (±)-agroclavine were identical with the natural alkaloids as proved by TLC, MS, UV, and ^{1}H-NMR comparisons. The IR spectrum of (±)-chanoclavine-I was identical with that of the natural alkaloid.

Since agroclavine has already led to festuclavine,[13] costaclavine,[14] setoclavine,[15] and isosetoclavine,[15] formal synthesis of these alkaloids is also achieved. We have now established experimental procedures for the compound (6c) in large scale (10g-50g) preparation. Synthesis of analogs of the ergot alkaloids and their biological evaluation is currently in progress.

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3) This olefin was prepared by treating isoprene monooxide with HCl in MeOH. bp 46°C (10 mmHg). ^{1}H-NMR (CCl_4) δ: 1.2 (3H, s), 2.2 (1H, s, OH), 3.08 (3H, s), 3.25 (2H, s), 4.81-5.81 (3H, m).
4) T. Jeffery, J. Chem. Soc., Chem. Commun., 1984, 1287. Independently, we have also found the same effect of the phase transfer catalyst on both the thallation-palladation method and the Heck reaction; M. Somei, T. Hasegawa, T. Suzuki, and M. Wakita, Abstracts of Papers, The 105th Annual Meeting of Pharmaceutical Society of Japan, Kanazawa, April 1985, p. 679.
5) These results clearly demonstrate that this new reaction is versatile for such intra-molecular cyclization. Extension and application of the reaction to natural product synthesis is now in progress.
6) All compounds gave satisfactory combustion data. a) IR (KBr): 3520, 3250, 1540, 1345 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 1.81 (3H, d, J=1.5 Hz), 3.53 (2H, d, J=7.4 Hz), 4.09 (2H, s), 4.60 (1H, dd, J=9.5 and 9.7 Hz), 4.81 (1H, dt, J=9.7 and 7.4 Hz), 5.48 (1H, dq, J=9.5 and 1.5 Hz), 6.64-7.34 (4H, m), 9.16 (1H, br s); b) IR (KBr): 3540, 3270, 1540, 1366 cm^{-1}. ^{1}H-NMR (pyridine-d_5) δ: 2.07 (3H, d, J=1.5 Hz), 3.46-3.64 (2H, m), 4.51 (1H, d, J=12.5 Hz), 4.74 (1H, d, J=12.5 Hz), 4.96-5.22 (2H, m), 5.44 (1H, dq, J=8.5 and 1.5 Hz), 6.88-7.60 (4H, m), 11.84 (1H, br s); c) IR (KBr): 3480, 3250, 1535, 1368 cm^{-1}. ^{1}H-NMR (10% CD_3OD in $CDCl_3$) δ: 1.79 (3H, d, J=1.2 Hz), 3.06-3.76 (2H, m), 3.80 (2H, s), 4.70 (1H, dd, J=10 and 4.4 Hz), 4.74-5.10 (1H, m), 5.36 (1H, dq, J=10 and 1.2 Hz), 6.60-6.90 (2H, m), 6.90-7.30 (2H, m), 8.86 (1H, br s).
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