

SYNTHESES OF (\pm)-CLAVICIPITIC ACID AND ITS DERIVATIVES¹

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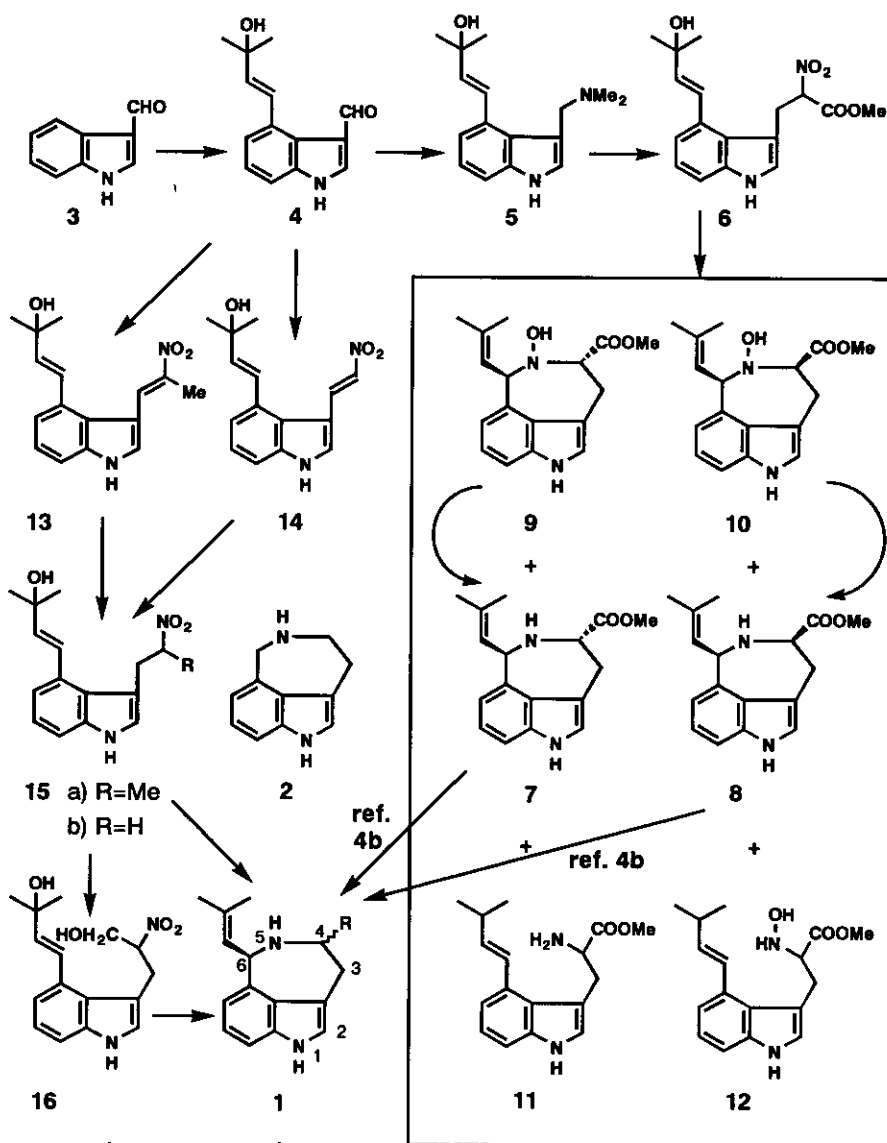
Abstract---A formal total synthesis of (\pm)-clavicipitic acid was achieved in five steps from indole-3-carboxaldehyde. Syntheses of (\pm)-4-cyano-, (\pm)-4-methyl-, and (\pm)-4-hydroxymethyl-6-(2-methyl-1-propen-1-yl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indoles are also reported.

Clavicipitic acid² (a mixture of **1a** and **1b**, Scheme 1) and aurantioclavine³ (**1c**) constitute one family of ergot alkaloids and they attracted much attention because they have 1,3,4,5-tetrahydroazepino[5,4,3-cd]indole (**2**) as a unique common skeleton. Thus far, five groups⁴ have achieved total synthesis of the former alkaloid ((\pm)-**1a,b**), and two groups⁵ for the latter (**1c**), but their syntheses are necessitated to carry out more than ten synthetic steps.^{4,5b}

In our continuing project^{5a,6} for simple syntheses of ergot alkaloids, we succeeded now in achieving five step total synthesis of (\pm)-**1a** and (\pm)-**1b**. It should be stressed that except the last hydrolysis step^{4b} we created suitable reactions for other four steps, and all steps can be practiced in the presence of air and moisture. Originality rate⁷ of the present synthesis of (\pm)-**1a** and (\pm)-**1b** is 86%.

The first step is the one pot preparation⁶ of 4-(3,3-dimethylallyl)indole-3-carboxaldehyde (**4**) from indole-3-carboxaldehyde (**3**) in 49% yield

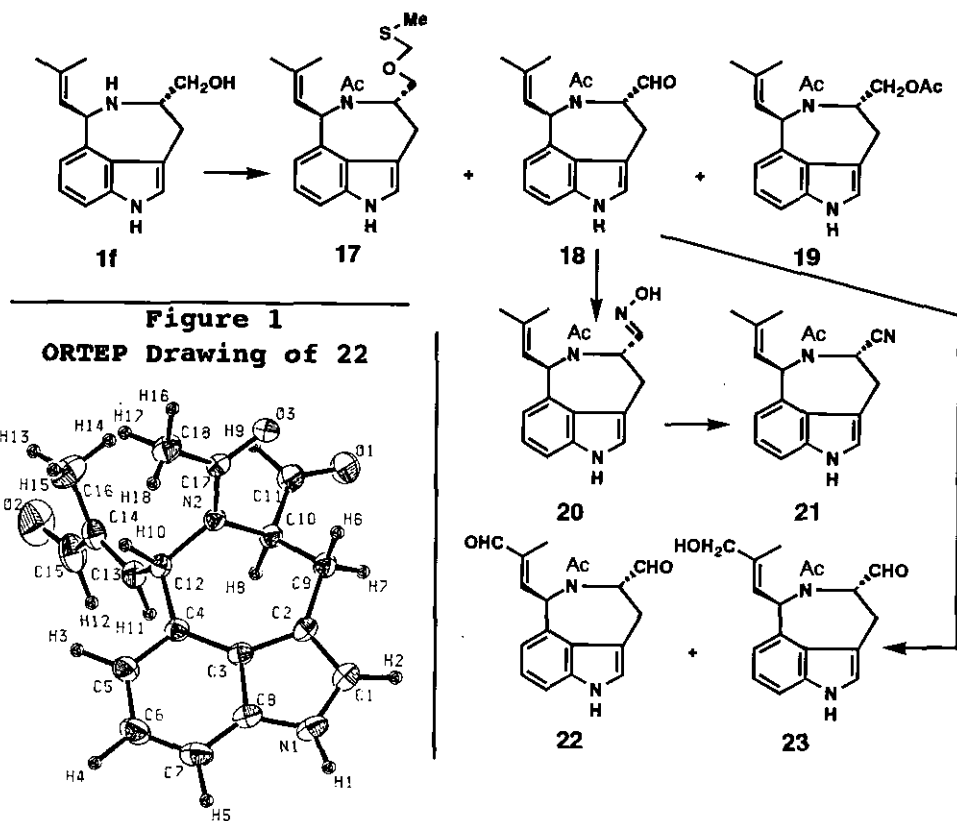
Scheme 1



according to tin-thall reaction.^{6,8} In the second step, gramine synthetic method^{1b} from indole-3-carboxaldehydes was applied. Thus, the treatment of **4** with NaBH₄ in MeOH and aqueous 50% Me₂NH at room temperature produced the desired **5**^{6,9} in 69% yield. As the third step, alkylation method¹⁰ of gramine in the presence of (nBu)₃P was applied to the reaction of **5** with methyl nitroacetate, resulting in the formation of the expected **6**^{11a} in 80% yield. As the fourth step, the reductive aminocyclization method^{5a,12} of nitro-olefins with Zn(Hg) in HCl and MeOH was applied to **6**. Consequently, (±)-4,6-trans-**11b** (**7**) and -cis-clavicipitic acid methyl ester^{11c} (**8**), the corresponding (±)-N-hydroxycompounds, (**9**)^{11d} and (**10**),^{11e} and noncyclized products, (**11**)^{11f} and (**12**),^{11g} were produced in 29, 22, 1, 3, 4, and 6% yields, respectively. The compound (**9**) was transformed to **7** in 66% yield by the reduction with aqueous TiCl₃. Under similar reduction conditions, **10** afforded **8** in 84% yield. Since both compounds, (**7**) and (**8**), were converted to the corresponding (±)-4,6-trans- ((±)-**1a**) and -cis-clavicipitic acid ((±)-**1b**) by M. Natsume and co-workers,^{4b} formal total syntheses of them were completed.

Syntheses of (±)-4,6-trans-**11h** (**1d**) and -cis-4-methyl-**11i** (**1e**), and (±)-4,6-trans-**11j** (**1f**) and -cis-4-hydroxymethyl-6-(2-methyl-1-propen-1-yl)-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole^{11k} (**1g**) were readily achieved as follows. The aldol reaction of **4** with nitroethane afforded 88% yield of **13**,^{11l} and then **13** was converted to **15a**^{11m} in 77% yield by the reduction with NaBH₄.¹³ While, treatment of **15b**, prepared in 71% yield by the reduction of **14**^{6b} with NaBH₄, with formaldehyde in the presence of KO^tBu afforded **16**¹¹ⁿ in 58% yield. Subsequent amino-cyclization reaction of **15a** produced **1d** and **1e** in 26 and 17% yields, respectively. Compounds, (**1f**) and (**1g**),¹⁴ were also prepared in 38 and 17% yields, respectively, by the similar amino-cyclization of **16**.

Scheme 2



Although oxidation of (\pm)-**1f** was expected to give (\pm)-**1a**, this was not the case. Jones, Swern, or Moffatt oxidation of **1f** formed many products and tars, and 2-oxindole derivatives were only isolable products in low yields. Contrariwise, oxidation of **1f** with Ac_2O -DMSO produced **17**,^{11o} **18**,^{11p} and **19**,^{11q} in 22, 38, and 26% yields, respectively (Scheme 2). Starting from **18**, (\pm)-4,6-*trans*-4-cyano-6-(2-methyl-1-propen-1-yl)-3,4,5,6-tetrahydro-1*H*-azepino-[5,4,3-*cd*]indole ((\pm)-**21**) was prepared as follows. The reaction with NH_2OH in pyridine afforded the oxime (**20**), a mixture of *syn*- and *anti*-isomers, in 99% yield. Dehydration of **20** with Ac_2O at 115°C produced **21**^{11r} in 89% yield.

Interestingly, attempts to transform the formyl group of **18** into the

carboxyl group were unsuccessful under various reaction conditions and finally the treatment of 18 with SeO₂ in refluxing dioxane was found to produce 22^{11s} and 23^{11t} in 53 and 4% yields, respectively. The compound (22) was suitable for X-ray single crystallographic analysis.¹⁵ The ORTEP drawing of 22, shown in Figure 1, clearly shows that the approach of the oxidizing reagents from the top side to the formyl group at the 4-position is sterically hindered with the 2-methyl-1-propen-1-yl side chain and the down side with the N-acetyl group. This is probably the reason why the formyl group resisted to oxidation.

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 15. Crystal data for **22**. $C_{18}H_{18}N_2O_3$, $M=310.35$, monoclinic, space group $P2_1$, with unit cell dimensions, $a=15.764(5)$, $b=7.695(2)$, $c=16.689(4)\text{\AA}$, $\beta=112.07(2)^\circ$, $V=1876.0(9)\text{\AA}^3$, $Z=4$ and $D_c=1.099\text{g/cm}^3$. The reflection data were collected on a Rigaku AFC-5 diffractometer for $3^\circ < 2\theta < 55^\circ$ using Mo $K\alpha$ radiation ($\lambda=0.71069\text{\AA}$) and the ω - 2θ scan speed of $6^\circ/\text{min}$. The structure was solved by the direct method using the MITHRIL program and refined by full-matrix least squares. The final R value was 0.058 for 2392 independent reflections [$I > 3\sigma(I)$].

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