Syntheses of (±)-clavicipitic acid and its derivatives

SYNTHESES OF (±)-CLAVICIPITIC ACID AND ITS DERIVATIVES[1]

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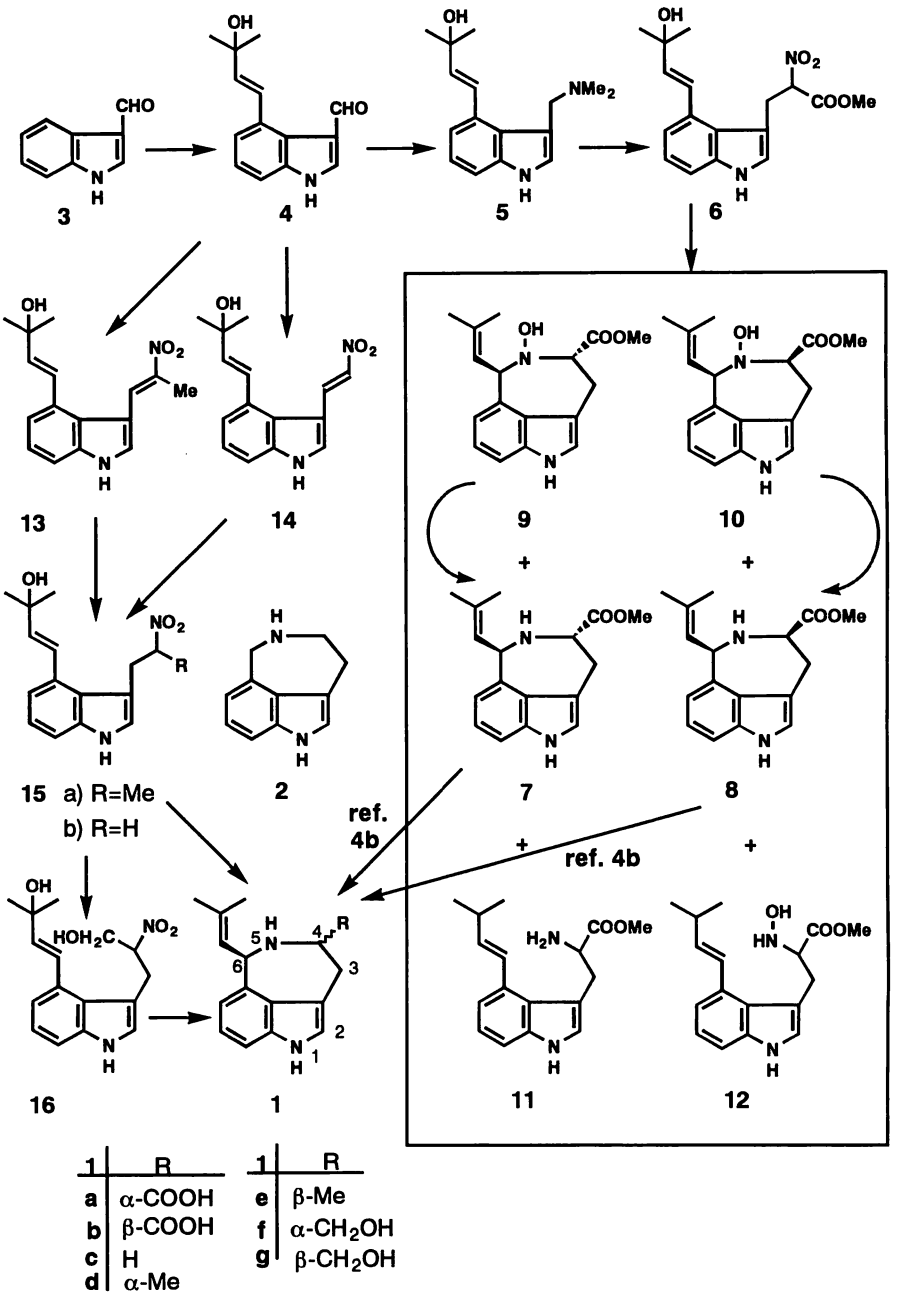
Abstract----A formal total synthesis of (±)-clavicipitic acid was achieved in five steps from indole-3-carboxaldehyde. Syntheses of (±)-4-cyano-, (±)-4-methyl-, and (±)-4-hydroxymethyl-6-(2-methyl-1-propen-1-yl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles are also reported.

Clavicipitic acid[2] (a mixture of **1a** and **1b**, Scheme 1) and aurantioclavine[3] (**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 groups[4] have achieved total synthesis of the former alkaloid ((±)-**1a,b**), and two groups[5] 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 (±)-**1a** and (±)-**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 rate[7] of the present synthesis of (±)-**1a** and (±)-**1b** is 86%.

The first step is the one pot preparation[6] of 4-(3,3-dimethylallyl)indole-3-carboxaldehyde (**4**) from indole-3-carboxaldehyde (**3**) in 49% yield

Scheme 1


OH
CHO
NMe2
NO2
COOMe
3
4
5
6
Me
13
14
R
15 a) R=Me
b) R=H
2
9
10
7
8
ref. 4b
ref. 4b
HOH2C
16
1
H2N
HN
11
12
1 R
a α-COOH
b β-COOH
c H
d α-Me
1 R
e β-Me
f α-CH2OH
g β-CH2OH

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 $NaBH_4$ in MeOH and aqueous 50% Me_2NH at room temperature produced the desired **5**[6,9] in 69% yield. As the third step, alkylation method[10] 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 $TiCl_3$. 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-1*H*-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 $NaBH_4$.[13] While, treatment of **15b**, prepared in 71% yield by the reduction of **14**[6b] with $NaBH_4$, 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

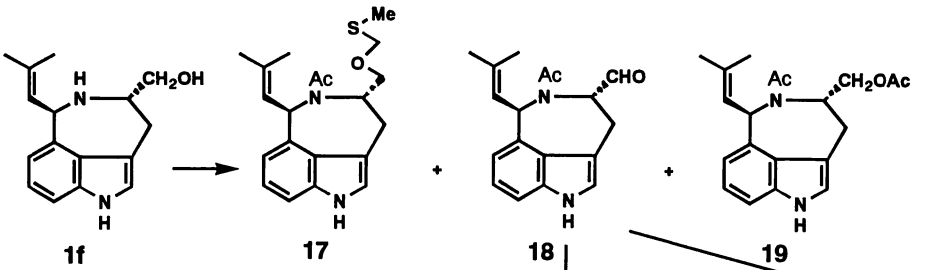
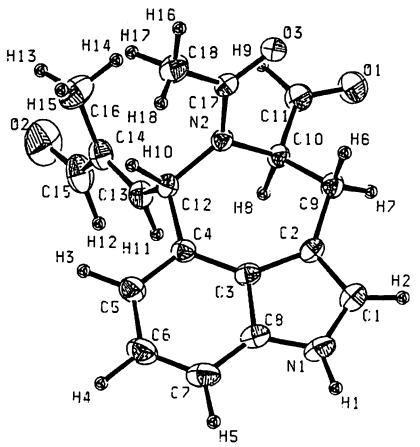


Figure 1
ORTEP Drawing of 22



Although oxidation of (±)-**1f** was expected to give (±)-**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**, (±)-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 ((±)-**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 SeO_2 in refluxing dioxane was found to produce **22**[11s] and **23**[11t] in 53 and 4% yields, respectively. The compound (**22**) was suitable prisms 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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11. All new compounds gave satisfactory spectral and elemental analysis data for crystals or high resolution mass data for oils. a) mp 134.0-136.0°C; b) mp 157.0-159.0°C; c) mp 145.5-147.5°C; d) mp 170.0°C (decomp.); e) mp 208.0°C (decomp.); f) mp117.5-119.0°C; g) mp 143.0-145.0°C; h) mp 175.0-176.5°C; i) mp 199.5-201.5°C; j) mp 158.0-159.0°C; k) mp 238.0-240.0°C; l) mp 203.5-205.0°C; m) mp 105.5-106.0°C; n) mp 113.0-114.0°C; o) oil; p) mp 133.5-137.0°C; q) oil; r) mp 208.5-209.5°C; s) mp 142.5-144.5°C; t) oil. Stereochemical assignments for **1d-g** were made by nOe experiment in nmr spectroscopy.
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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)Å, β=112.07(2)°, V=1876.0(9)Å^3, Z=4 and Dc=1.099g/cm^3. The reflection data were collected on a Rigaku AFC-5 diffractometer for $3°<2\theta<55°$ using Mo Kα radiation (λ=0.71069Å) and the ω-2θ scan speed of 6°/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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