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

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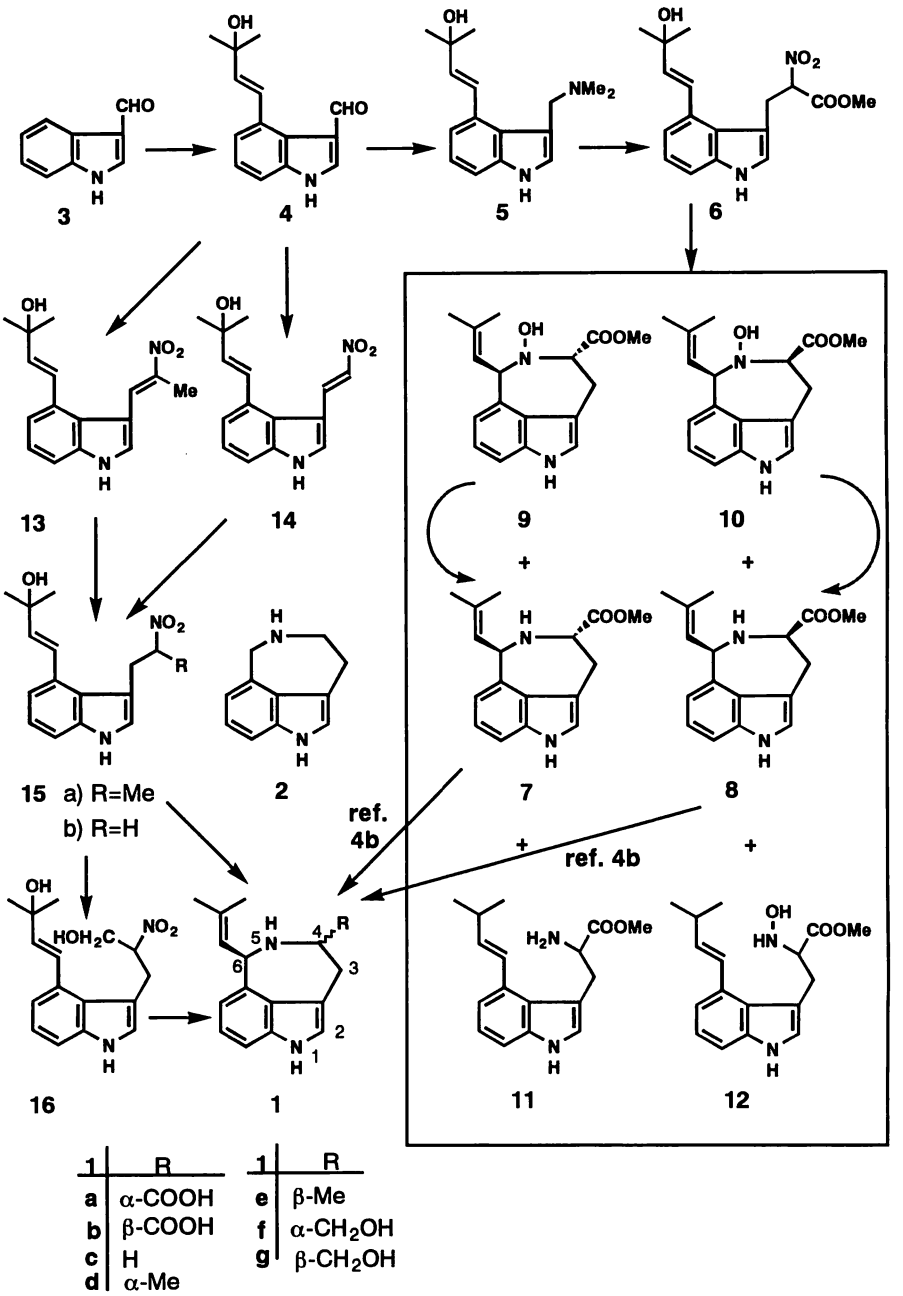
Abstract----A formal total synthesis of (±)-clavicipitic acid was achieved in five steps from indole-3-carboxaldehyde. Syntheses of (±)-4-cyano-, (±)-4-methyl-, and (±)-4-hydroxymethyl-6-(2-methyl-1-propen-1-yl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles are also reported.

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

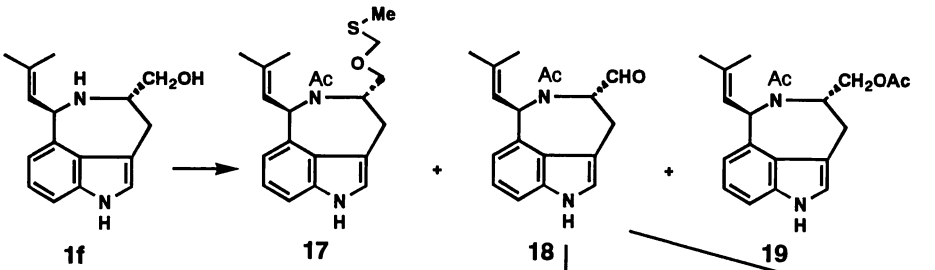
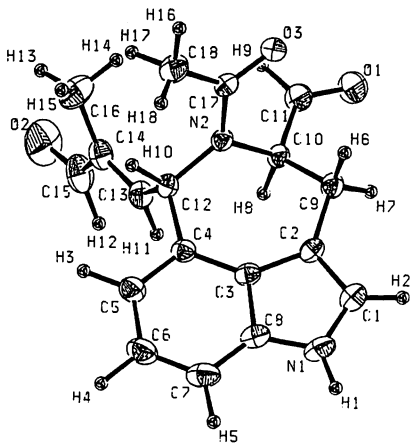


Figure 1
ORTEP Drawing of 22



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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REFERENCES AND NOTES

1. Dedicated to Prof. A. R. Katritzky on the occasion of his 65th birthday. This is partly reported, Abstracts of Papers, 87th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Toyama, Oct. 1992, p. 14. a) This report is Part 67 of a series entitled "The Chemistry of Indoles". b) Part 66: F. Yamada, K. Kobayashi, A. Shimizu, N. Aoki, and M. Somei, *Heterocycles*, 1993, **36**, 2783.
2. J. E. Robbers and H. G. Floss, *Tetrahedron Lett.*, 1969, 1857; J. E. Robbers, H. Otsuka, H. G. Floss, E. V. Arnold, and J. Clardy, *J. Org. Chem.*, 1980, **45**, 1117 and references cited therein.
3. A. G. Kozlovskii, T. F. Soloveva, V. G. Sakharovskii, and V. M. Adanin, *Dokl. Akad. Nauk SSSR*, 1981, **260**, 230; V. G. Sakharovskii, A. V. Aripovskii, M. B. Saru, and A. G. Kozlovskii, *Khim. Prir. Soedin*, 1983, 656.
4. a) A. P. Kozikowski and M. Okita, *Tetrahedron Lett.*, 1985, **26**, 4043 and references cited therein; b) H. Muratake T. Takahashi, and M. Natsume, *Heterocycles*, 1983, **20**, 1963. Reported mp of **7** was lower than our sample, but spectral data were identical; c) M. Matsumoto, H. Kobayashi, and N. Watanabe, *ibid.*, 1987, **26**, 1197; d) P. J. Harrington, L. S. Hegedus, and K. F. McDaniel, *J. Am. Chem. Soc.*, 1987, **109**, 4335 and references cited therein; e) D. A. Boyles and D. E. Nichols, *J. Org. Chem.*, 1988, **53**, 5128.
5. a) Five step synthesis of **1c**: F. Yamada, Y. Makita, T. Suzuki, and M.

Somei, *Chem. Pharm. Bull.*, 1985, **33**, 2162; b) L. S. Hegedus, J. L. Toro, W. H. Miles, and P. J. Harrington, *J. Org. Chem.*, 1987, **52**, 3319.

6. We have already succeeded in the simple five step total synthesis of (±)-, (+)-, and (-)-6,7-secoagroclavines: a) K. Nakagawa and M. Somei, *Heterocycles*, 1991, **32**, 873; b) M. Somei and F. Yamada, *ibid.*, 1984, **32**, 5064. Introduction of 2-methyl-3-buten-2-ol into the 4-position of indole: M. Somei and M. Tsuchiya, *Chem. Pharm. Bull.*, 1981, **27**, 3145.
7. Definition of the originality rate: M. Somei, *Yuki Gosei Kagaku Kyokai Shi*, 1982, **40**, 387; M. Somei, *Yakugaku Zasshi*, 1988, **108**, 361.
8. M. Somei, F. Yamada, and K. Naka, *Chem. Pharm. Bull.*, 1987, **35**, 1322. See also reference 6.
9. M. Somei, F. Yamada, Y. Karasawa, and C. Kaneko, *Chemistry Lett.*, 1981, 615.
10. M. Somei, Y. Karasawa, and C. Kaneko, *Chemistry Lett.*, 1980, 813; *idem*, *Heterocycles*, 1981, **16**, 941.
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.
12. F. Yamada, T. Hasegawa, M, Wakita, M. Sugiyama, and M. Somei, *Heterocycles*, 1986, **24**, 1223. See also reference 5a.
13. A. K. Sinhababu and R. T. Borchardt, *Tetrahedron Lett.*, 1983, **24**, 227.
14. Synthesis of optically active 4,6-*trans*-4-hydroxymethyl-6-(2-methyl-1-propen-1-yl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole was reported: M. F. Semmelhack, P. Knochel, and T. Singleton, *Tetrahedron Lett.*, 1993, **34**, 5051.
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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