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journal or publication title	Heterocycles
volume	37
number	2
page range	719-724
year	1994-01-01
URL	http://hdl.handle.net/2297/4331

doi: <https://doi.org/10.3987/com-93-s96>

SYNTHESES OF (±)-CLAVICIPITIC ACID AND ITS DERIVATIVES¹

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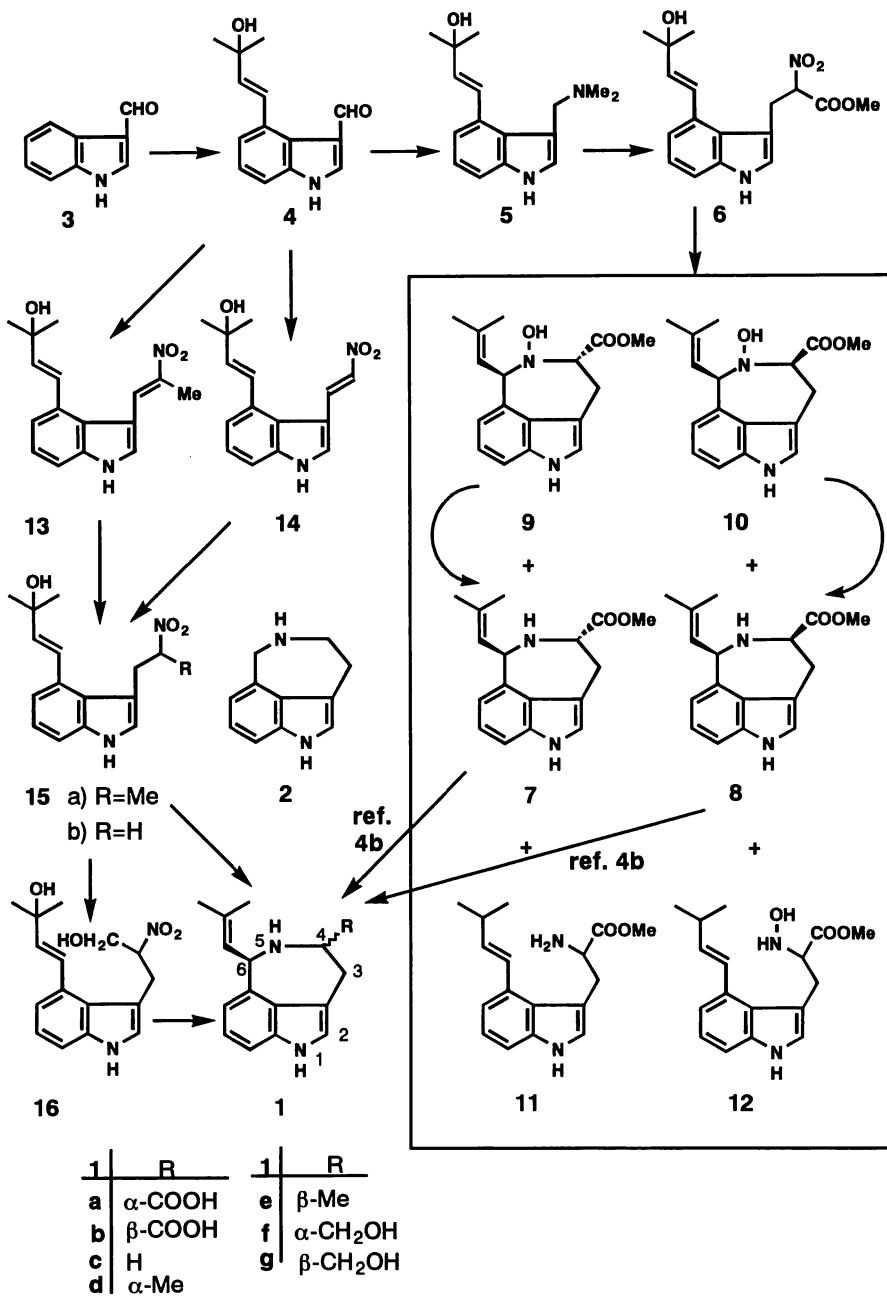
Abstract----A formal total synthesis of (±)-clavicipitic acid was achieved in five steps from indole-3-carboxaldehyde. Syntheses of (±)-4-cyano-, (±)-4-methyl-, and (±)-4-hydroxymethyl-6-(2-methyl-1-propen-1-yl)-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indoles are also reported.

Clavicipitic 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 ((±)-**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 (±)-**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 rate⁷ of the present synthesis of (±)-**1a** and (±)-**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

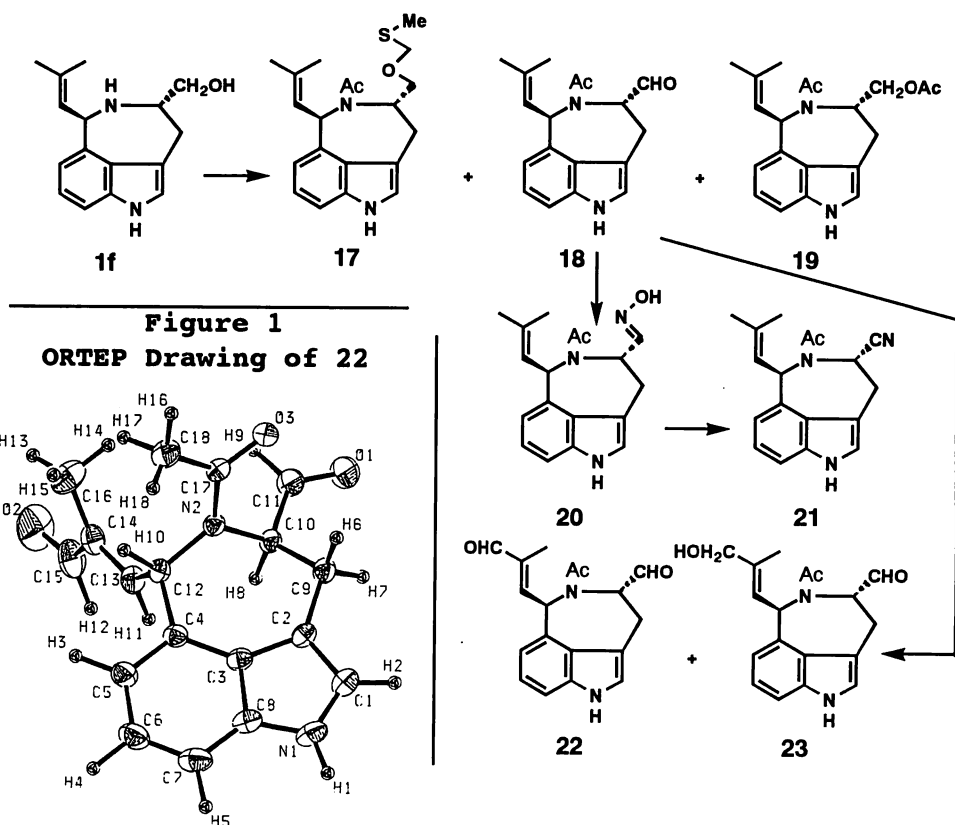
Scheme 1



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 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.

ACKNOWLEDGMENTS

The authors express their gratitude to Dr. M. Natsume (Research Foundation, Itsuu Laboratory) for kindly providing us with spectra of **7** and **8**. This work is supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan, which is gratefully acknowledged.

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Received, 29th September, 1993