# TOTAL SYNTHESIS OF (±)-CLAVICIPITIC ACIDS I AND II**

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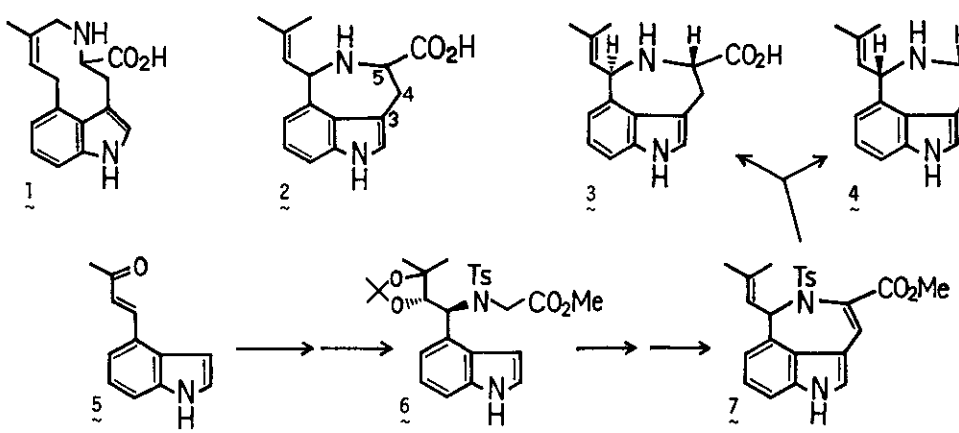
*Abstract* —— Ergot alkaloids, clavicipitic acids (3 and 4) were synthesized respectively in racemic forms from 4-(3-oxo-1-butenyl)-indole (5) by way of 6 and 7. Names of clavicipitic acids I and II were proposed for 3 and 4.

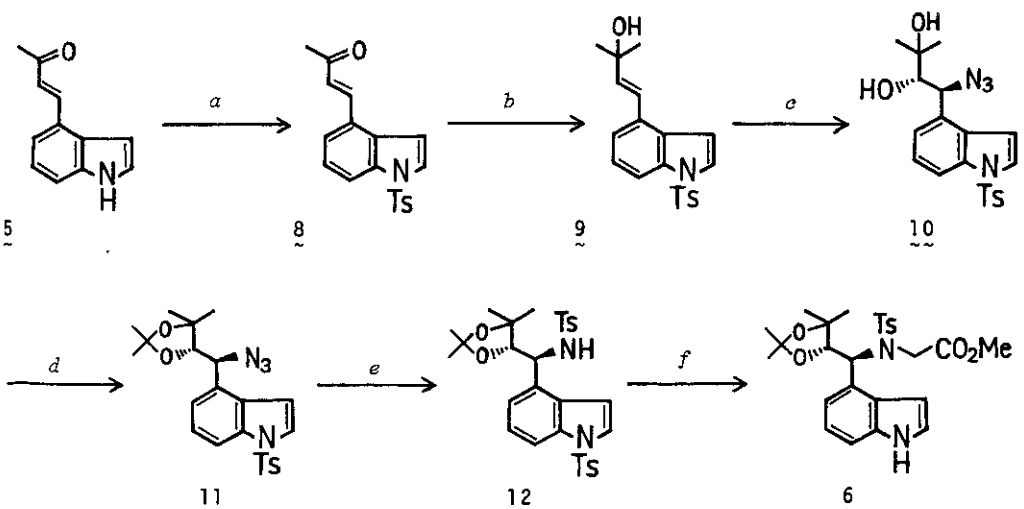
Clavicipitic acid, a metabolite of *Claviceps* strain SD 58[1] or *Claviceps fusiformis* 139/2/1G,[2] was originally assumed to be a single compound with a tentative structure (1),[1] but later on, its structure was revised to 2,[2] and furthermore, the acid itself was shown to be actually a mixture of two diastereoisomers concerning the side chain in 2.[3] Final proof that clavicipitic acid was composed of two compounds having structures (3) and (4) was obtained by the X-ray crystallographic study on a major component (3),[4] exhibiting a biogenetically unique structure where the N(b)-function of tryptophan participated with the isoprene unit in forming a nitrogen-containing seven-membered ring. As a continuation of our synthetic study on ergot alkaloids, we investigated the construction of this particular ring and achieved the first total synthesis of (±)-3 and (±)-4** in pure forms, respec-



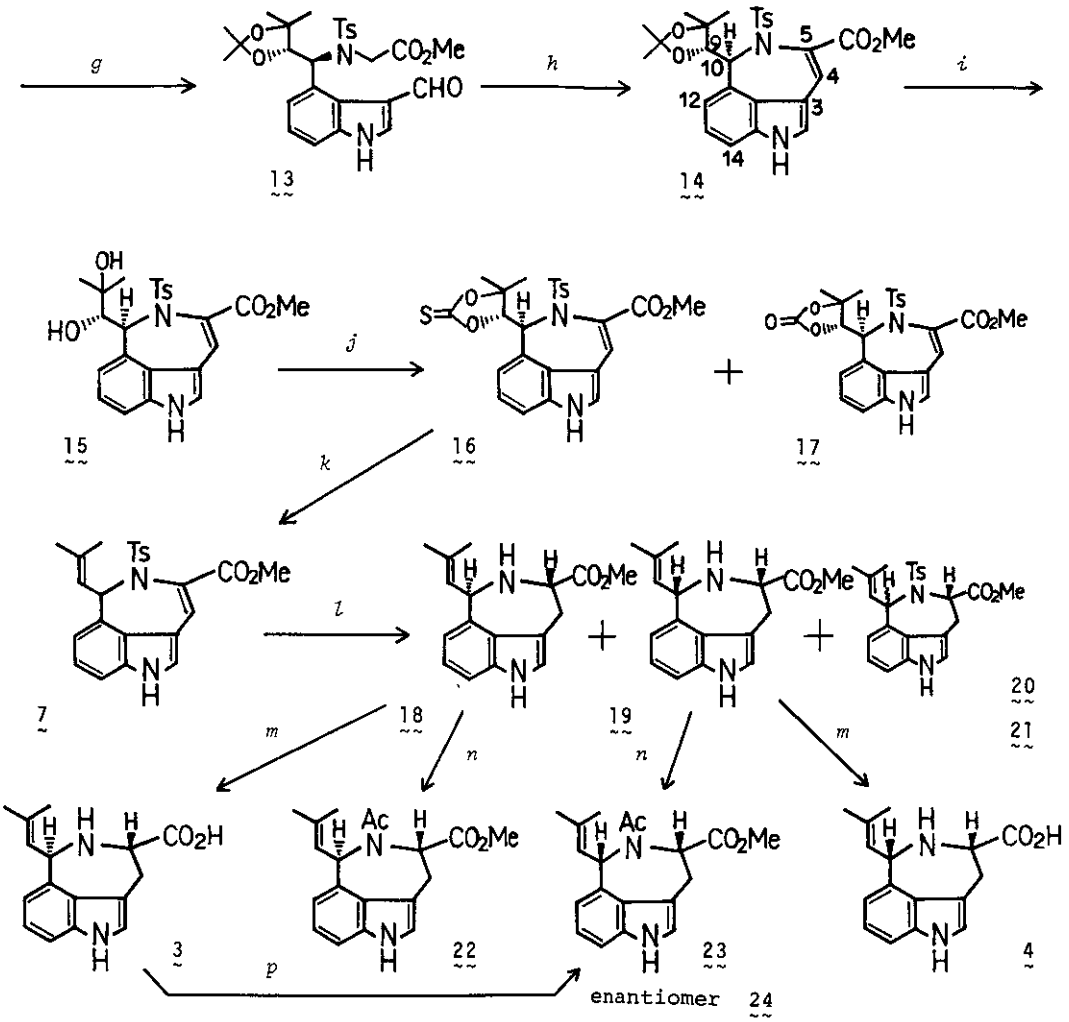
tively,[5] according to our synthetic plan, i.e., (i) introduction of a glycine moiety into the readily available compound (5) leading to 6, (ii) Vilsmeier reaction on 6 followed by ring closure and formation of the dimethylvinyl side chain to afford 7, and (iii) removal of the tosyl group accompanied by reduction of the double bond producing (±)-3 and (±)-4.[6]

The compound (5), obtained by our synthetic procedure,[7] was tosylated for the sake of stabilizing the indole portion against oxidation and an acid treatment. The Grignard reagent prepared from MeI was applied to the tosylate (8) and subsequent oxidation of 9 with *m*-chloroperbenzoic acid, followed by opening of an epoxide ring with $NaN_3$ afforded an α-glycol derivative (10), whose regiochemistry was confirmed by consumption of $NaIO_4$. The diol group, which was arranged to be the double bond on the side chain of the final compound was once protected by an acetonide exchange reaction, and the azide function of 11 was converted to the N-tosylglycine ester moiety according to the conventional steps by way of 12, providing the first objective (6) after removal of the indole protecting group.

Introduction of a formyl function was readily carried out by treatment of 6 with Vilsmeier-Haack reagent, and the following cyclization was achieved only by a reaction condition, refluxing gently a benzene solution of 13 with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)[8] for 15 h until the ratio of the newly formed compound (14) and the starting material (13) was almost 1:1, when the reaction mixture was checked by TLC. The desired compound (14) was obtained as colorless prisms, mp 242-243.5°C (decomp.) [IR (KBr) $cm^{-1}$: 3340, 1710, 1612, 1593; $^1H$ NMR ($CDCl_3$, 90 MHz) δ: 1.07, 1.24, 1.40, 1.53 (12H, s each), 2.09 (3H, s, $SO_2C_6H_4\underline{Me}$), 3.91 (1H, d,




5 8 9 10 11 12 6




*a*: TsCl, $K_2CO_3$ in MeCOEt, reflux, 96%. *b*: MeMgI in $Et_2O$-THF, 0°C, 70%. *c*: (i) *m*-$ClC_6H_4CO_3H$ in $CH_2Cl_2$, 0°C→r.t.; (ii) $NaN_3$ in dioxane-$H_2O$, reflux, 78%. *d*: $Me_2C(OMe)_2$, *p*-TsOH, r.t., 93%. *e*: (i) $H_2$, $PtO_2$ in MeOH, r.t.; (ii) TsCl, $Et_3N$ in $ClCH_2CH_2Cl$, reflux, 79%. *f*: (i) $BrCH_2COOMe$, $K_2CO_3$ in DMF, r.t.; (ii) 20% KOH in MeOH-DME-$H_2O$ (2:1:1); (iii) $CH_2N_2$ in MeOH-$Et_2O$, 70%. *g*: $POCl_3$-DMF in $Et_2O$-DMF, 0°C→r.t., 70%. *h*: DBU in $C_6H_6$, gentle reflux, 49% (conversion Y.: 83%). *i*: *ca.*1% HCl in MeOH-THF-$H_2O$, r.t., 88%. *j*: $S{=}CCl_2$, 4-dimethylaminopyridine in $CH_2Cl_2$, r.t., 16: 62%, 17: 17%. *k*: $(MeO)_3P$, reflux, 88%. *l*: *hν*, $NaBH_4$, $Na_2CO_3$, MeOH-DME-$H_2O$ (4:2:1), -70°--66°C. *m*: *ca.* 4% KOH in MeOH-$H_2O$ (2:1). *n*: $Ac_2O$ in pyridine, r.t. *p*: $Ac_2O$ in MeOH, 30-35°C.

$J$= 8.5 Hz, H-9), 3.93 (3H, s, COOMe), 5.52 (1H, d, $J$=8.5 Hz, H-10), 6.67 and 7.32 ($A_2B_2$, $J$=8.5 Hz, $SO_2C_6\underline{H}_4Me$), 6.86-7.16 (m, H-2, H-12, H-13, and H-14), 8.03 (1H, s, H-4), 8.64 (1H, s, exchangeable with $D_2O$, NH)] in 49% yield (83% conversion yield calculated from the consumed starting material), accompanied by recovery of 13 in 41% yield. Prolonged heating, for example, for 38 h ruined a part of the product (14) resulting in the conversion yield of 67% with the recovery of 13 in 19% yield. In the case of 14, decrease of enamine character due to the indolylacrylic ester structure made it possible to undergo a drastic condition for the transformation of an α-glycol into a double bond.[9] Thus, the acetonide group in 14 was cleaved by acid treatment, and the resulting diol (15), mp 243-243.5°C (decomp.) was suspended in $CH_2Cl_2$ and reacted with thiophosgene in the presence of 4-dimethylaminopyridine at room temperature for 14 h. The thiocarbonate (16), mp 265-266°C (decomp.) was obtained in 62% yield, accompanied by formation in 17% yield of a by-product (17), which was converted back to 15 in 53% yield by treatment with $NaBH_4$ in refluxing MeOH.[10] The compound (7) having the correct carbon side chain was produced from 16 by refluxing it in neat trimethyl phosphite for 50 h as colorless prisms, mp 252-253°C (decomp.)[IR (KBr) $cm^{-1}$: 3375, 1720, 1613, 1596; $^1H$ NMR ($CDCl_3$, 90 MHz) δ: 1.58 (3H, s) and 1.90 (3H, s)(=$CMe_2$), 2.08 (3H, s, $SO_2C_6H_4\underline{Me}$), 3.83 (3H, s, COOMe), 4.77 (1H, br d, $J$=8 Hz, H-9), 5.97 (1H, d, $J$=8 Hz, H-10), 6.58 ($\underline{A}_2B_2$ part of tosyl protons, $J$=8 Hz), 6.88 (1H, dd, $J$=8, 4.5 Hz, H-13), 7.01-7.27 (5H, m, other aromatic protons), 7.85 (1H, s, H-4), 8.60 (1H, br s, NH)].

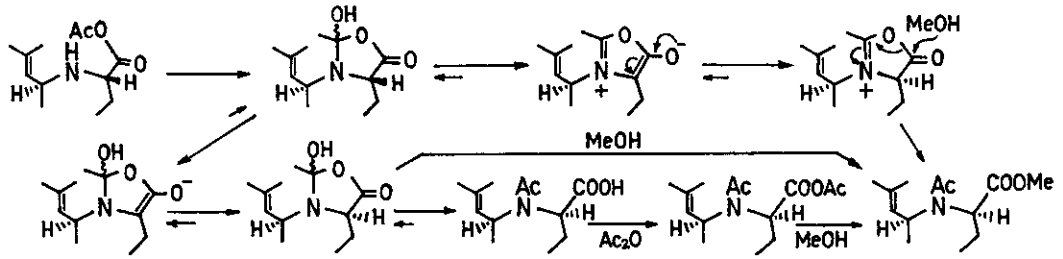
With the requisite compound (7) in hand, reductive cleavage of N-Ts function was investigated and the Umezawa's reaction condition[11] was found to be satisfactory in view of the result that a single operation not only removed the protecting group but also reduced simultaneously the stable conjugated double bond, whose reduction was otherwise unattainable. The compound (7) was dissolved in a solution of MeOH-DME-$H_2O$ containing almost equal amount of $NaBH_4$ and $Na_2CO_3$ and the mixture was irradiated using Toshiba 400P high pressure mercury lamp with Pyrex filter under $N_2$ atmosphere at -70--66°C for 10 min. The reaction mixture was separated by repeated preparative TLC to afford four derivatives,[6] i.e., 18, colorless prisms, mp 129-129.5°C [IR (KBr): 1733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 90 MHz) δ: 1.83 (3H, d, $J$=1.5 Hz) and 1.86 (3H, d, $J$=1.5 Hz)(=$CMe_2$), 2.26 (1H, br s, disappeared by addition of $D_2O$, aliphatic NH), 3.02 (1H, ddd, $J$=15.5, 12, 1.5 Hz, H-4), 3.53 (1H, dd, $J$=15.5, 3 Hz, H'-4), 3.79 (3H, s, COOMe), 3.82 (1H, dd, $J$=12, 3 Hz, H-5), 4.86 (1H, d, $J$=9 Hz, H-10), 5.48 (1H, br d, $J$=9 Hz, H-9), 6.73-7.25 (4H, m, aromatic

protons), 8.17 (1H, br s, indole NH)], 19, colorless prisms, mp 146-147.5°C [IR (KBr): 1734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 90 MHz) δ: 1.77 (3H, br s) and 1.84 (3H, br s) ($=CMe_2$), 1.96 (1H, br s, disappeared by addition of $D_2O$, aliphatic NH), 3.18 (1H, dd, *J*=15.5, 11 Hz, H-4), 3.45 (1H, dd, *J*=15.5, 4 Hz, H'-4), 3.75 (3H, s, COOMe), 4.16 (1H, dd, *J*=11, 4 Hz, H-5), 5.31 (1H, d, *J*=9 Hz, H-10), 5.46 (1H, br. d, *J*=9 Hz, H-9), 6.70-7.17 (4H, m, aromatic protons), 8.02 (1H, br s, exchangeable with $D_2O$, indole NH)], 20, colorless prisms, mp 195-197°C, and 21, colorless prisms, mp 202-204°C, in 46%, 20%, 10%, and 7% yields, respectively, the latter two compounds being diastereomers with respect to orientation of the side chains, whose stereochemistry remained uncharacterized.

For completion of the total synthesis, both esters (18) and (19) were hydrolyzed with diluted KOH in MeOH-$H_2O$ at room temperature for 40 min, followed by treatment with ion-exchanger resin (IRC-50, $H^+$-form) in MeOH to furnish in a quantitative yield, respectively, (±)-clavicipitic acid I (3),[6] colorless prisms, mp 235-240°C (decomp.) [IR (KBr): 1643 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 400 MHz) δ: 1.87 (3H, br s) and 1.90 (3H, br s)($=CMe_2$), 3.00 (1H, ddd, *J*=16, 12, 1.5 Hz, H-4), 3.61 (1H, dd, *J*=12, 3 Hz, H-5), 3.67 (1H, dd, *J*=16, 3 Hz, H'-4), 4.96 (1H, d, *J*=9 Hz, H-10), 5.53 (br d, *J*=9 Hz, H-9), 6.72 (1H, d, *J*=7.5 Hz) and 7.22 (1H, d, *J*=8 Hz)(H-12, H-14), 6.99 (1H, dd, *J*=8, 7.5 Hz, H-13), 7.09 (1H, br. s, H-2)] and (±)-clavicipitic acid II (4),[6] colorless prisms, mp 284-288°C [IR (KBr): 1620 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 90 MHz) δ: 1.75 (3H, s) and 1.86 (3H, s)($=CMe_2$), 3.03 (1H, ddd, *J*=15.5, 12, 1.5 Hz, H-4), 3.58 (1H, dd, *J*=15.5, 3 Hz, H'-4), 3.91 (1H, dd, *J*=12, 3 Hz, H-5), 5.30 (1H, d, *J*=9 Hz, H-10), 5.53 (1H, br d, *J*=9 Hz, H-9), 6.66 (1H, d, *J*=7.5 Hz) and 7.16 (1H, d, *J*=7.5 Hz)(H-12, H-14), 6.94 (1H, dd, *J*=7.5, 7.5 Hz, H-13), 7.02 (1H, br s, H-2)], each of which exhibited identical Rf values on TLC [silica gel $GF_{254}$, $CHCl_3$-MeOH-conc. $NH_4OH$ (75:25:1)] with those of both the natural and synthetic mixtures of clavicipitic acids kindly provided by Professors Floss and Kozikowski. Our slowly moving acid, (±)-3 was determined to be the *trans* derivative, since Floss and Clardy carried out their X-ray structural determination on the compound having the low Rf value.[4]

Acetylation of 18 and 19 proceeded readily with $Ac_2O$ in pyridine at room temperature for 3 h to afford 22,[6] colorless glass, and 23,[6] mp 115-117°C in a quantitative yield, respectively, in contrast with the description of Waight and collaborators[3] that the acetylation of clavicipitic acids with $Ac_2O$ in MeOH gave rise to form in an excellent yield an N-acetyl methyl ester as a single compound, whose

$^1$H NMR spectrum in the literature resembled well that of our *cis* compound (23). Kozikowski and Greco also prepared the same N-acetyl methyl ester by repeating the above reaction on both their synthetic and natural clavicipitic acids.[5] Direct comparison of our compound (23) with Kozikowski's synthetic sample confirmed the identity in all respects [mp, TLC, MS, IR ($CHCl_3$) and $^1$H NMR ($CDCl_3$, 90 MHz) spectra], meaning that clavicipitic acid I (3) in the natural mixture might be isomerized during the $Ac_2O$-MeOH treatment to afford 24. This possibility was substantiated by our experiment that (±)-23 was in fact obtained in 62% yield from (±)-3 by reacting with $Ac_2O$ in MeOH at room temperature for 1 h. As the other N-acetyl methyl ester, (±)-22 was found to be thermally stable, tentative mechanisms for the rearrangement are considered as follows.

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