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A Concise Total Synthesis of (±)-*cis*- and (±)-*trans*-Clavicipitic Acids by Combinational Use of Directed Lithiation and Fluoride Ion-Induced Elimination-Addition Reaction of 1-(Triisopropylsilyl)gramine Derivatives

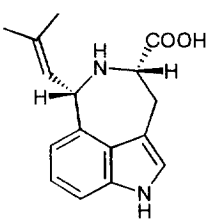
Masatomo Iwao*[a] and Fumito Ishibashi[b]

[a]Faculty of Liberal Arts and [b]Faculty of Fisheries, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852, Japan

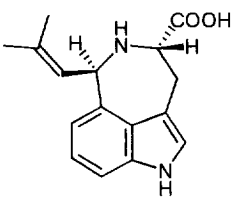
Abstract: A six-step total synthesis of (±)-clavicipitic acid (**1**) from 1-(triisopropylsilyl)gramine (**2**) was achieved by combinational use of 4-selective lithiation of **2** and fluoride ion-induced elimination-addition reaction of 4-[(*E*)-3-hydroxy-3-methyl-1-butenyl]-1-(triisopropylsilyl)gramine (**7**) as key reactions. Separation of *cis*- and *trans*-diastereomers (**1a** and **1b**) were easily accomplished by simple fractional crystallization and column chromatography. The overall yields of **1a** and **1b** from **2** were 21% and 17%, respectively. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Clavicipitic acid (**1**) has been isolated as a mixture of *cis*- and *trans*-diastereomers (**1a** and **1b**) from cultures of *Claviceps* strain SD58[1a,d] or *Claviceps fusiformis* 139/2/1G.[1b,c] The unusual azepinoindole structure was proposed by King and Waight[1b,c] based on nmr analysis of the *N*-acetyl methyl ester derivative and confirmed later by Floss and Clardy[1d] by single-crystal X-ray analysis of the *trans*-diastereomer (**1b**). These amino acids have been regarded as the derailment products in the normal biosynthesis of ergot alkaloids.[1d] Due to their unique structures and poor availability by fermentation process, a number of synthetic methods have been reported[2] during a period of the first total synthesis by Kozikowski in 1982[2a] and the most recent asymmetric synthesis by Yokoyama and Murakami in 1995.[2i]

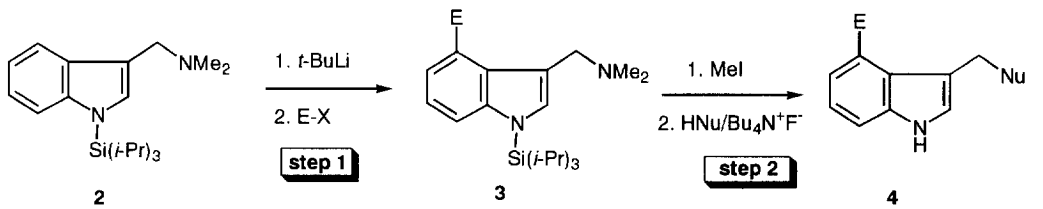


1a

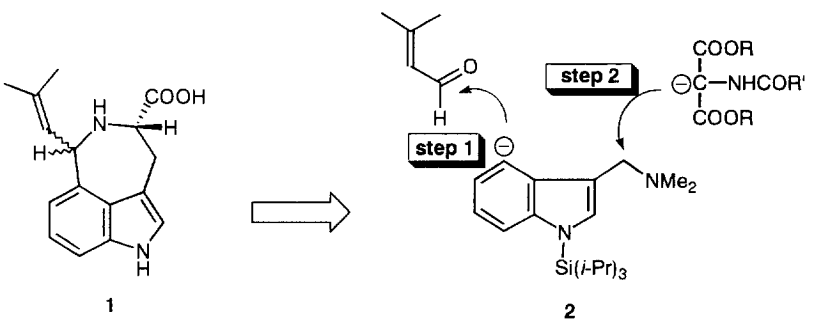


1b

Recently, we have developed highly efficient procedure for the synthesis of 3,4-differentially substituted indole derivatives.[3,4] The strategy comprises two sequential steps: 1) C-4 selective functionalization of the indole ring *via* directed lithiation of 1-(triisopropylsilyl)gramine (**2**) to produce **3** (**step 1**)[3] ; 2) functionalization of C-3 side chain by quaternization of **3** followed by fluoride ion-induced elimination-addition reaction with nucleophiles (**step 2**)[4] (**Scheme 1**). In this paper, we describe a concise total synthesis of (±)-clavicipitic acid (**1**) based upon this strategy. The requisite substituents at 4- and 3-positions of the indole ring of **1** would be introduced by the reaction of the lithiated **2** with 3-methyl-2-butenal (**step 1**), followed by fluoride ion-induced elimination-addition reaction of the adduct with aminomalonate derivatives (**step 2**) (**Scheme 2**).



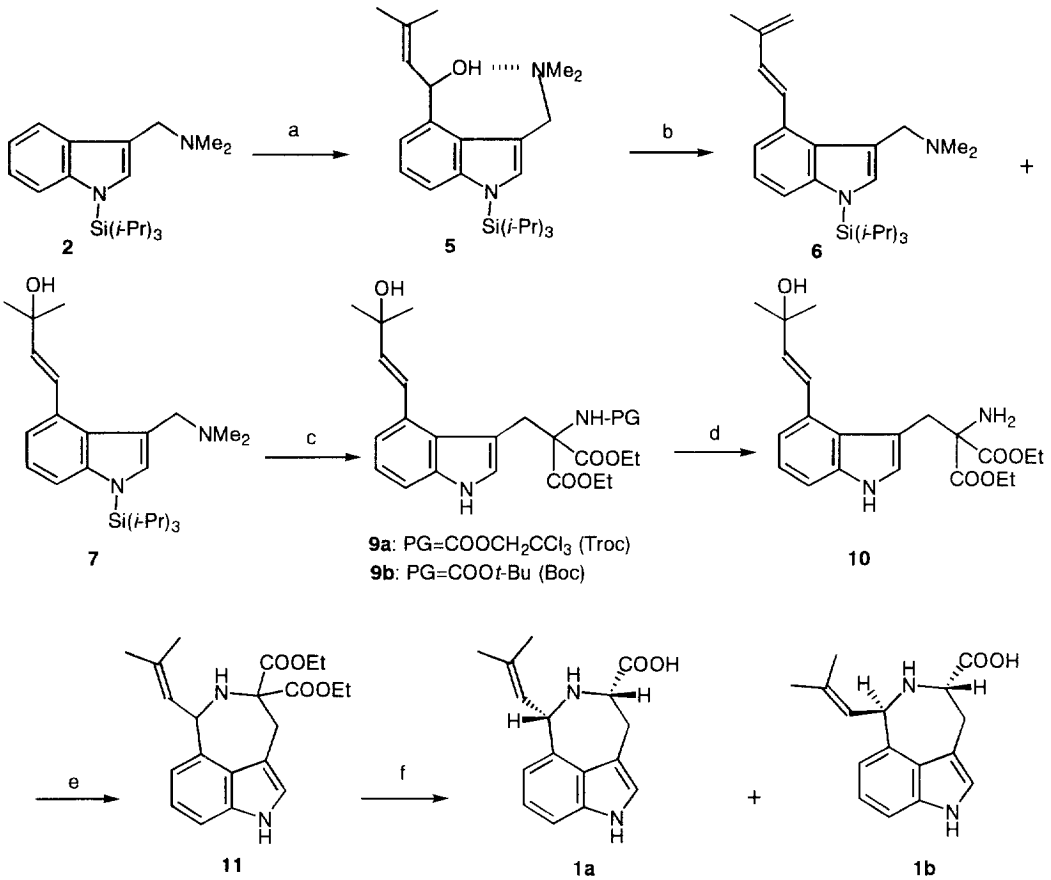
Scheme 1



Scheme 2

RESULTS AND DISCUSSION

The total synthesis was shown in **Scheme 3**. 1-(Triisoprpylsilyl)gramine (**2**) was lithiated under the standard conditions[3] (1.2 equiv *t*-BuLi, ether, 0 °C, 1h) and the resultant 4-lithio species was reacted with 3-methyl-2-butenal to give the alcohol **5** in 82% yield. For the subsequent fluoride ion-induced elimination-addition reaction,[4] **5** was reacted with 10 equiv of MeI in benzene at room temperature for 24 h to produce its methiodide. However, the reaction was sluggish and the starting material **5** was recovered in 75% yield. The failure of quaternization is attributable to rather tight intramolecular hydrogen bonding between hydroxyl group and gramine-nitrogen as shown in structure **5**. The presence of the hydrogen bonding was clearly indicated by the nmr spectrum of **5**, in which C-3 methylene protons absorbed non-equivalently at 3.47 and 4.17 ppm as two sets of doublet (J=12.8 Hz). These unusual absorptions must be caused by the hydrogen bonding-induced restricted rotation of the methylene group.



Scheme 3

Reagents and conditions: (a) (i) *t*-BuLi, ether, 0°C, 1h; (ii) $Me_2C{=}CHCHO$. (b)85% H_3PO_4, dioxane, rt, 15 min. (c) (i) MeI, benzene, rt, 15h; (ii) TrocNHCH(COOEt)$_2$ **8a** or BocNHCH(COOEt)$_2$ **8b**, $Bu_4N^+F^-$, THF, rt, 30 min. (d) For **9a**: Zn dust, THF, 1M KH_2PO_4, rt, 6h. (e) PPTS, CH_2Cl_2, reflux, 4h. (f) (i) 2M KOH, MeOH, rt, 6h; (ii) 2M HCl; (iii) aq EtOH, reflux, 2h.

In order to break the hydrogen bonding, **5** was submitted to acid-catalyzed allylic rearrangement.[5a-c] When **5** was treated with 85% phosphoric acid in dioxane[5c] at room temperature for 30 min, the rearranged alcohol **7** was obtained in 86% yield together with a small amount (8%) of the diene **6**. Compound **7**, as expected, was smoothly quaternized with 2 equiv of MeI at room temperature in 99% yield. The resulted methiodide was reacted with diethyl *N*-(2,2,2-trichloroethoxycarbonyl)aminomalonate (**8a**)[6] or diethyl *N*-(*tert*-butoxycarbonyl)aminomalonate (**8b**)[7] in the presence of 1.5 equiv of tetrabutylammonium fluoride (TBAF) in THF at room temperature for 30 min to give **9a** or **9b** in 93% or 95% yield, respectively. These fluoride ion-induced elimination-addition reactions proceeded much more smoothly and in higher yields, compared with classical gramine-substitution reactions.[8] Attempted deprotection of *tert*-butoxycarbonyl (Boc) group from **9b**

under acidic conditions such as 2M HCl in dioxane or 98% HCOOH produced complex mixtures probably due to instability of allylic alcohol or indole portion of **9b** under the reaction conditions. On the other hand, deprotection of 2,2,2-trichloroethoxycarbonyl (Troc) group from **9a** went smoothly under the standard conditions[9] (Zn dust, THF, 1M KH_2PO_4) to furnish amino-alcohol **10** in 91% yield. Dehydrative cyclization of **10** into the azepinoindole **11** was accomplished in an excellent yield (95%) by heating **10** with catalytic amount of pyridinium *p*-toluenesulfonate (PPTS)[10] in refluxing CH_2Cl_2.

The conversion of **11** to (±)-clavicipitic acid (**1**) has been reported by Matsumoto, *et al.*[2e] Since details of the experiment and the specified yield are not available from their communication, we examined this final transformation by ourselves to achieve the total synthesis. Thus **11** was hydrolyzed with 2M KOH in MeOH at room temperature for 6 h. After acidification with 2M HCl, the resulting malonic acid derivative was decarboxylated by heating in aqueous ethanol to give (±)-clavicipitic acid (**1**) in 95% yield. The *cis* and *trans* ratio was estimated to be approximately 3:2 by comparison of 400 MHz ^{1}H-nmr spectrum of this product with those of authentic samples.[11]

The major drawback of the synthetic routes[2a,c,d,e,g] which pass through the malonic ester intermediates such as **11** seems to be difficulty in the separation of each diastereomers of clavicipitic acid at the final stage. Fortunately, however, we found out these isomers were easily separable by a combination of simple fractional crystallization from MeOH[12] and column chromatography. The pure (±)-*cis*-clavicipitic acid (**1a**) and (±)-*trans*-clavicipitic acid (**1b**) were isolated in 38% and 30% yields, respectively by using this procedure.

In conclusion, we have achieved a six-step total synthesis of (±)-*cis*-clavicipitic acid (**1a**) and (±)-*trans*-clavicipitic acid (**1b**) from easily prepared starting material **2** in 21% and 17% overall yields, respectively. The abbreviated steps and excellent overall yields demonstrated the potential of our methodology for the preparation of 3,4-disubstituted indoles.[3,4] Further application for the synthesis of optically active clavicipitic acids is in progress in our laboratories.

EXPERIMENTAL

General. Melting points were determined with a Yanagimoto micromelting points apparatus and are uncorrected. Ir spectra were recorded with JASCO IR-810 or A-100 spectrometer. ^{1}H Nmr spectra were obtained with JEOL JNM-GX400 (400 MHz) machine using TMS as an internal standard. Mass spectra were recorded with JEOL JMS-DX303 spectrometer. Elemental analyses were performed at the microanalytical laboratory in Nagasaki University. For flash chromatography, FL60D silica gel (Fuji Silysia) was used, except otherwise mentioned. Dry ether and THF were distilled from Na-benzophenone ketyl under N_2 before use.

1-(Triisopropylsilyl)gramine (2). Under an atmosphere of Ar, powdered gramine (17.43 g, 100 mmol) was added portionwise at 0°C to a stirred suspension of NaH (4.40 g of 60% dispersion in mineral oil, 110 mmol, prewashed with dry pentane) in dry THF (200 mL) over 20 min. After stirring at the same temperature for 3 h, triisopropylsily chloride (20.25 g, 105 mmol) was added dropwise and the stirring at 0 °C was continued overnight. The reaction mixture was carefully quenched with water and the product was extracted with ether. The combined extracts were washed with water and brine solution, dried over Na_2SO_4, and evaporated. The residue was purified by distillation to give **3** as a slightly yellow oil (32.40 g, 98%): bp140-150 °C/0.3 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.14 (d, 18H, *J*=7.7 Hz), 1.70 (sept, 3H, *J*=7.7 Hz), 2.27 (s,

6H), 3.62 (s, 2H), 7.09-7.16 (m, 2H), 7.15 (s, 1H), 7.47 (m, 1H), 7.67 (m, 1H); ms *m/z* 330 (M^+). *Anal.* Calcd for $C_{20}H_{34}N_2Si$: C, 72.66; H, 10.37; N, 8.47. Found: C, 72.72; H, 10.31; N, 8.50.

4-(1-Hydroxy-3-methyl-2-butenyl)-1-(triisopropylsilyl)gramine (5). Under an atmosphere of Ar, *t*-BuLi (26 ml of 1.4 M solution in pentane, 36 mmol) was added dropwise to a stirred solution of **2** (9.92 g, 30 mmol) in dry ether (150 mL) at -78 °C. After being stirred for 15 min, dry ice-acetone bath was removed and the mixture was allowed to warm to *ca.* 0 °C (20 min). The reaction flask was then immersed in an ice-water bath and kept for 1.5 h. After cooling to -78°C, a solution of 3-methyl-2-butenal (3.79 g, 45 mmol) in dry ether (9 mL) was added dropwise. After 30 min, dry ice-acetone bath was removed and the mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and, after dilution with water, the product was extracted with ether. The combined extracts were washed with water and brine solution, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over Chromatorex NH-DM1020 silica gel (Fuji Silisia) using hexane-ethyl acetate (10:1~5:1) as eluent to give 10.24 g (82% yield) of **5** as a colorless viscous oil, which on standing solidified. Recrystallization from pentane afforded colorless fine needles, mp 99-100 °C; ir (KBr) 3125 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.13 (d, 18H, *J*=7.7 Hz), 1.68 (s, 3H), 1.69 (sept, 3H, *J*=7.7 Hz), 1.84 (s, 3H), 2.24 (s, 6H), 3.47 (d, 1H, *J*=12.8 Hz), 4.17 (d, 1H, *J*=12.8 Hz), 5.79 (d, 1H, *J*=7.7 Hz), 5.90 (d, 1H, *J*=7.7 Hz), 7.05 (dd, 1H, *J*=8.4 and 7.0 Hz), 7.09 (s, 1H), 7.12 (d, 1H, *J*=7.0 Hz), 7.38 (d, 1H, *J*=8.4 Hz); ms *m/z* 414 (M^+). *Anal.* Calcd for $C_{25}H_{42}N_2OSi$: C, 72.41; H, 10.21; N, 6.75. Found: C, 72.30; H, 10.16; N, 6.80.

4-(3-Methyl-1,3-butadienyl)-1-(triisopropylsilyl)gramine (6) and 4-[(*E*)-3-Hydroxy-3-methyl-1-butenyl]-1-(triisopropylsilyl)gramine (7). To a stirred solution of **5** (7.67 g, 18.5 mmol) in dioxane (74 mL) was added dropwise 85% H_3PO_4 (7.4 mL) at 16 °C (water bath temperature) over 5 min. After being stirred for 30 min, the reaction mixture was poured into water (300 mL), and the whole was made basic with solid $NaHCO_3$ with vigorous stirring. The products were extracted three times with ether, and the combined extracts were washed with water and brine solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed over Chromatorex NH-DM1020 silica gel (Fuji Silisia) using hexane-ethyl acetate (5:1) as eluent to give 0.58 g (8%) of **6**, mp 89.5-91 °C (pentane); ^1H nmr ($CDCl_3$) δ 1.13 (d, 18H, *J*=7.7 Hz), 1.69 (sept, 3H, *J*=7.7 Hz), 2.07 (approx. s with fine coupling, 3H), 2.26 (s, 6H), 3.56 (s, 2H), 5.02 (s, 1H), 5.09 (approx. s with fine coupling, 1H), 6.87 (d, 1H, *J*=16 Hz), 7.09 (s, 1H), 7.10 (dd, 1H, *J*=8.1 and 7.7 Hz), 7.32 (d, 1H, *J*=7.7 Hz), 7.36 (d, 1H, *J*=8.1 Hz), 7.76 (d, 1H, *J*= 16 Hz); ms *m/z* 396 (M^+). *Anal.* Calcd for $C_{25}H_{40}N_2Si$: C, 75.70; H, 10.16; N, 7.06. Found: C, 75.83; H, 10.19; N, 7.08. Further elution with hexane-ethyl acetate (5:1~2:1) afforded 6.60 g (86%) of **7** as a colorless viscous oil; ir (neat) 3400 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.13 (d, 18H, *J*=7.7 Hz), 1.47 (s, 6H), 1.68 (sept, 3H, *J*=7.7 Hz), 2.25 (s, 6H), 3.56 (s, 2H), 6.32 (d, 1H, *J*=16 Hz), 7.08 (s, 1H), 7.09 (dd, 1H, *J*=8.1 and 7.7 Hz), 7.23 (d, 1H, *J*=7.7 Hz), 7.36 (dd, 1H, *J*=8.1 and 0.7 Hz), 7.72 (d, 1H, *J*=16 Hz); ms m/z 414 (M^+). *Anal.* Calcd for $C_{25}H_{42}N_2OSi$: C, 72.41; H, 10.21; N, 6.75. Found: C, 72.44; H, 10.36; N, 6.48.

Diethyl *N*-(2,2,2-Trichloroethoxycarbonyl)aminomalonate (8a). To a stirred suspension of diethyl aminomalonate hydrochloride (10.58 g, 50 mmol) and 2,2,2-trichloroethyl chloroformate (11.02 g, 52 mmol) in CH_2Cl_2 (200 mL) was added triethylamine (16.7 mL, 120 mmol) over 10 min at 0°C. The mixture

was stirred for 2 h at room temperature and diluted with water. Organic layer was separated, washed with water and brine solution, dried over Na_2SO_4, and evaporated. The residue was purified by bulb to bulb distillation to give 15.92 g (91%) of **9a** as colorless liquid, bp 150 °C (oven temperature)/0.5 mmHg; ir (neat) 3410, 3330, 1760, 1730 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.31 (t, 6H *J*=7 Hz), 4.24-4.34 (m, 4H), 4.75 (s, 2H), 5.00 (d, 1H, *J*=7.7 Hz), 6.05 (br d, 1H). *Anal.* Calcd for $C_{10}H_{14}Cl_3NO_6$: C, 34.26; H, 4.02; N, 4.00; Cl, 30.34. Found: C, 34.13; H, 3.92; N, 3.97; Cl, 30.11.

Diethyl *N*-(*tert*-Butoxycarbonyl)aminomalonate (8b). To a stirred suspension of diethyl aminomalonate hydrochloride (10.58 g, 50 mmol) and di-*tert*-butyl dicarbonate (11.35 g, 52 mmol) in CH_2Cl_2 (200 mL) was added triethylamine (8.4 ml, 60 mmol) at room temperature, and the mixture was stirred overnight. Similar workup and purification as described for **8a** provided 11.96 g (87%) of **8b** as colorless liquid, bp 120 °C (oven temperature)/0.2 mmHg; ir (neat) 3425, 3360, 1755, 1740, 1720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.30 (t, 6H, *J*=7 Hz), 1.45 (s, 9H), 4.21-4.32 (m, 4H), 4.94 (d, 1H, *J*=7.7 Hz), 5.56 (br d, 1H). *Anal.* Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.29; H, 7.46; N, 5.00.

Diethyl ({4-[(*E*)-3-Hydroxy-3-methyl-1-butenyl]-1*H*-indol-3-yl}methyl)[(2,2,2-trichloroethoxycarbonyl)amino]malonate (9a). To a stirred solution of **7** (5.74 g, 13.8 mmol) in benzene (100 mL) was added MeI (3.91 g, 27.6 mmol). The mixture was stirred at ambient temperature overnight and evaporated under reduced pressure. The residue was dried *in vacuo* to give 7.63 g (99%) of the methiodide as a white powder which was used for next reactions without further purifications.

To a stirred suspension of the methiodide (5.57 g, 10.0 mmol) and **8a** (3.86 g, 11.0 mmol) in THF (50 mL) was added TBAF (15 mL of 1M THF solution, 15 mmol). After 30 min, THF was removed under reduced pressure and the residue was partitioned between ether and water. The organic layer was washed with water (four times) and brine solution, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel using hexane-ethyl acetate (2:1) as an eluent to give 5.27 g (93%) of **9a**, mp 121-123 °C (ether-pentane); ir (KBr) 3520, 3415, 1750, 1735, 1720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.17 (t, 6H, *J*=7 Hz), 1.50 (s, 6H), 2.43 (br s, 1H), 4.04 (s, 2H), 4.11-4.26 (m, 4H), 4.67 (s, 2H), 6.17 (d, 1H, *J*=16 Hz), 6.38 (br s, 1H), 7.04 (d, 1H, *J*=2.4 Hz), 7.06 (d, 1H, *J*=7.3 Hz), 7.12 (dd, 1H, *J*=8.1 and 7.3 Hz), 7.25 (dd, 1H, *J*=8.1 and 1.1 Hz), 7.34 (d, 1H, *J*=16 Hz), 8.12 (br s, 1H); ms *m/z* 564 (M^+) and 562 (M^+). *Anal.* Calcd for $C_{24}H_{29}Cl_3N_2O_7$: C, 51.12; H, 5.18; N, 4.97; Cl, 18.86. Found: C, 51.10; H, 5.08; N, 4.86; Cl, 18.88.

Diethyl [(*tert*-Butoxycarbonyl)amino]({4-[(*E*)-3-hydroxy-3-methyl-1-butenyl]-1*H*-indol-3-yl}methyl)malonate (9b). This compound was prepared in a similar manner as described for **9a** by using **8b** as an aminomalonate in 95% yield, mp 124-125 °C (ether-pentane); ir (KBr) 3405, 3350, 3200, 1765, 1720, 1690 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.13 (t, 6H, *J*=7 Hz), 1.38 (br s, 9H), 1.50 (s, 6H), 2.48 (br s, 1H), 3.98 (br s, 2H), 4.04-4.12 (m, 2H), 4.12-4.25 (br m, 2H), 5.93 (br s, 1H), 6.16 (br d, 1H, *J*=16 Hz), 7.06 (d, 1H, *J*=7.7 Hz), 7.08 (br s, 1H), 7.11 (t, 1H, *J*=7.7 Hz), 7.24 (dd, 1H, *J*=7.7 and 1.1 Hz), 7.38 (d, 1H, *J*=16 Hz), 8.13 (br s, 1H); ms *m/z* 488 (M^+). *Anal.* Calcd for $C_{26}H_{36}N_2O_7$: C, 63.92; H, 7.43; N, 5.73. Found: C, 63.98; H, 7.47; N, 5.70.

Diethyl Amino({4-[(*E*)-3-hydroxy-3-methyl-1-butenyl]-1*H*-indol-3-yl}methyl)-malonate (10). Zinc dust (5 g), followed by 1M aqueous KH_2PO_4 (10 mL) were added to a stirred solution of **9a** (2.819 g, 5.00 mmol) in THF (50 mL) at room temperature. After being stirred vigorously for 6 h, zinc was removed by filtration through a pad of Celite. The filtrate was evaporated under reduced pressure, and the residue was partitioned between ether and water. The organic layer was separated, washed sequentially with water and brine solution, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel using hexane-ethyl acetate (1:1) as an eluent to give 1.764 g (91%) of **10**, mp 87-87.5 °C (ether-pentane); ir (KBr) 3500, 3375, 3230, 1750, 1725 cm^{-1}; ^1H nmr 1.24 (t, 6H, *J*=7 Hz), 1.47 (s, 6H), 2.00 (br s, 2H), 2.81 (br s, 1H), 3.73 (s, 2H), 4.22 (two sets of q, 4H, *J*=7 Hz), 6.18 (d, 1H, *J*=16 Hz), 7.06 (d, 1H, *J*=2.6 Hz), 7.10 (approx. dd with fine coupling, 1H, *J*=7.3 and 1.5 Hz), 7.14 (dd, 1H, *J*=7.7 and 7.3 Hz), 7.25 (dd, 1H, *J*=7.7 and 1.5 Hz), 7.55 (d, 1H, *J*=16 Hz), 8.16 (br s, 1H); ms *m/z* 388 (M^+). *Anal.* Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.26; N, 7.21. Found: C, 64.98; H, 7.21; N, 7.17.

Diethyl 3,4,5,6-Tetrahydro-6-(2-methyl-1-propenyl)-1*H*-azepino[5,4,3-*cd*]indole-4,4-dicarboxylate (11). A solution of **10** (728 mg, 1.87 mmol) and PPTS (94 mg, 0.37 mmol) in CH_2Cl_2 (20 mL) was heated under reflux for 4 h. After cooling, CH_2Cl_2 was evaporated and the residue was partitioned between ether and saturated aqueous $NaHCO_3$. The organic layer was separated, washed sequentially with water and brine, dried over Na_2SO_4, and evaporated. The residual solid was purified by flash chromatography over silica gel using hexane-ethyl acetate (2:1) as an eluent to give 656 mg (95%) of **11**, mp 125-126 °C (ethyl acetate-hexane) (lit.[2e] mp 125-126.5 °C); ir (KBr) 3310, 3220, 1745, 1715 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.22 (t, 3H, *J*=7 Hz), 1.25 (t, 3H, *J*=7 Hz), 1.74 (d, 3H, *J*=1.1 Hz), 1.87 (d, 3H, *J*=1.1 Hz), 3.09 (br s, 1H), 3.48 (d, 1H, *J*=15.5 Hz), 3.92 (dd, 1H, *J*=15.5 and 1.5 Hz), 4.11-4.31 (m, 4H), 5.30 (br d, 1H, *J*=8.8 Hz), 5.45 (dsept, 1H, *J*=8.8 and 1.1 Hz), 6.76 (dt, *J*=7.3 and 1.1 Hz), 6.92 (br s, 1H), 7.02 (dd, 1H, *J*=8.1 and 7.3 Hz), 7.14 (d, 1H, *J*=8.1 Hz), 7.97 (br s, 1H); ms *m/z* 370 (M^+). *Anal.* Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.10; H, 7.03; N, 7.67.

(±)-*cis*-Clavicipitic Acid (1a) and (±)-*trans*-Clavicipitic Acid (1b). A mixture of **11** (148 mg, 0.2 mmol) and 2M methanolic KOH (2 mL) was stirred at room temperature for 6 h. Methanol was removed under reduced pressure and the residue was dissolved in water (30 mL). The solution was adjusted to pH 3 with 2M aqueous HCl and the precipitated colorless crystalline solid, probably the dicarboxylic acid, was collected by filtration. This solid was suspended in a mixed solvent of ethanol (20 mL) and water (2 mL), and the mixture was refluxed for 2 h to effect decarboxylation. After cooling, the solvent was evaporated and the residue was dried *in vacuo* to give 103 mg (95%) of a diastereomeric mixture of **1a** and **1b** as colorless fine crystals. The ratio of **1a** to **1b** was estimated to be approximately 3:2 based upon ^1H nmr analysis (CD_3OD).

Further separation of **1a** and **1b** was carried out as follows. A suspension of this mixture (103 mg) in methanol (20 mL) was vigorously stirred at refluxing temperature for 1 h. After cooling, the insoluble solid (60 mg, **1a**:**1b** = *ca.* 7:1) was collected by filtration and recrystallized from methanol to give 38 mg (35 %) of analytically pure **1a** as colorless fine needles, mp 287-289 °C (dec) (determined in an evacuated small capillary) (lit.[2b] mp 284-288 °C); Rf 0.31 (silica gel 60 F_{254}, $CHCl_3$-MeOH-concd NH_4OH = 75:25:1, 1 day old); ir (KBr) 3420, 3160, 3310, 2930, 1620 cm^{-1}; ^1H nmr (CD_3OD) δ 1.88 (d, 3H, *J*=1.5 Hz), 1.94 (d, 3H, *J*=1.5 Hz), 3.41 (ddd, 1H, *J*=16.5, 12.5, 1.5 Hz), 3.72 (dd, 1H, *J*=16.5 and 3.7 Hz), 4.19 (dd, 1H, *J*=12.5, 3.7

Hz), 5.49 (dsept, 1H, *J*=9.2, 1.5 Hz), 5.91 (d, 1H, *J*=9.2 Hz), 6.84 (d, 1H, *J*=7.3 Hz), 7.09 (dd, 1H, *J*=8.1, 7.3 Hz), 7.21 (d, 1H, *J*=1.5 Hz), 7.33 (d, 1H, *J*=8.1 Hz); ms *m/z* 270 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.82; H, 6.75; N, 10.09. The filtrate of the methanol digestion was evaporated, and the residue was chromatographed over silica gel ($CHCl_3$-MeOH-concd NH_4OH = 80:20:1) to give 3 mg (3 %) of additional **1a** and 32 mg (30 %) of **1b**. Recrystallization of the latter sample from methanol produced analytically pure **1b** as colorless prisms, mp 266-268 °C (dec) (determined in an evacuated small capillary)[lit.[2b], mp 235-240 °C (dec)];[13] Rf 0.26 (silica gel 60 F_{254}, $CHCl_3$-MeOH-concd NH_4OH = 75:25:1, 1 day old); ir (KBr) 3420, 3230, 2980, 2930, 1620 cm^{-1}; ^1H nmr (CD_3OD) δ 1.95 (d, 3H, *J*=1.1 Hz), 1.99 (d, 3H, *J*=1.1 Hz), 3.21 (ddd, 1H, *J*=16.5, 11.7, 1.5 Hz), 3.84 (ddd, 1H, *J*=16.5, 3.3, 0.7 Hz), 4.13 (dd, 1H, *J*=11.7, 3.3 Hz), 5.57 (dsept, 1H, *J*=9.5, 1.1 Hz), 5.62 (d, 1H, *J*=9.5 Hz), 6.85 (dt, 1H, *J*=7.3, 1.1 Hz), 7.11 (dd, 1H, *J*=8.1 and 7.3 Hz), 7.24 (s, 1H), 7.37 (d, 1H, *J*=8.1 Hz); ms *m/z* 270 (M^+). *Anal.* Calcd for $C_{16}H_{18}N_2O_2 \cdot H_2O$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.50; H, 6.91; N, 9.54.

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11. The authors are grateful to Professor Masakatsu Matsumoto (Kanagawa University) for providing copies of 400 MHz ^1H nmr spectra of (±)-*cis*-clavicipitic acid and (±)-*trans*-clavicipitic acid.
12. *Cis* -**1a** is only sparingly soluble in hot MeOH, while *trans*-**1b** is well soluble.
13. Relatively large gap between the melting point of **1b** and the literature value is due to the difference of determination methods. Dr. H. Muratake (Research Foundation Itsuu Laboratory) kindly informed us that he measured the melting point by placing his sample between two cover glasses and heating it on a micro hot plate. We could not determine the accurate melting point by this way due to gradual decomposition of **1b** over 200 °C.

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