Pergamon

Tetrahedron 55 (1999) 10989–11000

TETRAHEDRON

A Formal Synthesis of Optically Active Clavicipitic Acids, Unusual Azepinoindole-type Ergot Alkaloids

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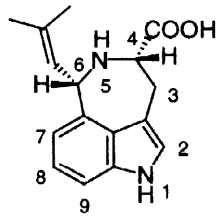
Received 9 June 1999; accepted 19 July 1999

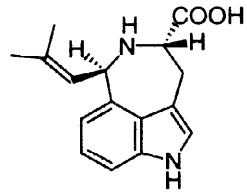
Abstract: An enantioselective synthesis of (-)-*cis*- and (-)-*trans*-clavicipitic acid methyl esters (**15a,b**) has been achieved. The key steps of the synthesis were 1) C-4 selective functionalization of the indole ring *via* directed lithiation of 1-(triisopropylsilyl)gramine (**2**), and 2) stereoselective alkylation of the lithiated (2*R*)-(-)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (Schöllkopf's bislactim ether) (**4**) with 1-*t*-butoxycarbonyl-3-chloromethyl-4-[(*E*)-3-methoxy-3-methyl-1-butenyl]indole (**10**). The diastereoselectivity of the latter reaction was found to be highly dependent on the coordinating ability of solvents or additives. The optically active amino-alcohol **13**, prepared by the mild acid hydrolysis of the alkylation product **11a**, was successfully converted to the azepinoindoles **14a, b** by PPTS-catalyzed dehydrative cyclization. During the course of the final deprotection of *N*-Boc group, an interesting *cis-trans* isomerization between **15a** and **15b**, which proceeded *via* acid-catalyzed ring opening and recyclization at C-6, was observed.

INTRODUCTION

Clavicipitic acids are unusual azepinoindole-type ergot alkaloids isolated as a mixture of *cis*- and *trans*-isomers (**1a** and **1b**) from culture of *Claviceps* strain SD58[1a,d] or *Claviceps fusiformis* 139/2/1G.[1b,d] The unique tricyclic structures of **1a,b** have received considerable attention by synthetic chemists and, therefore, a number of unique synthetic strategies have been developed.[2] Recently, we have reported a concise total synthesis of racemic clavicipitic acids[2j] by using a highly efficient method for the preparation of 3,4-disubstituted indoles developed in our laboratories.[3] In this paper, we report an enantioselective formal synthesis of clavicipitic acids based upon this methodology.



1a



1b

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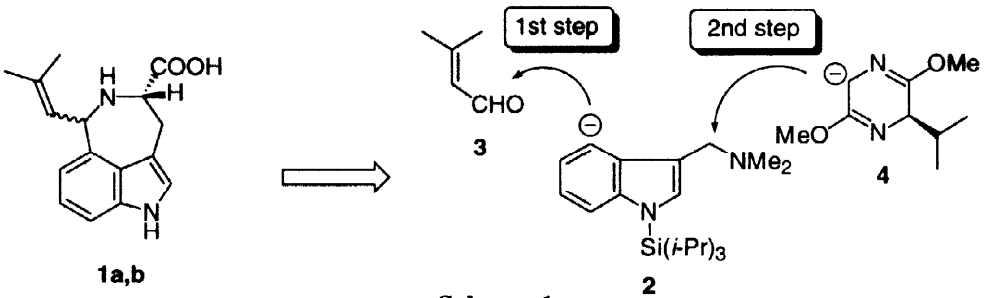
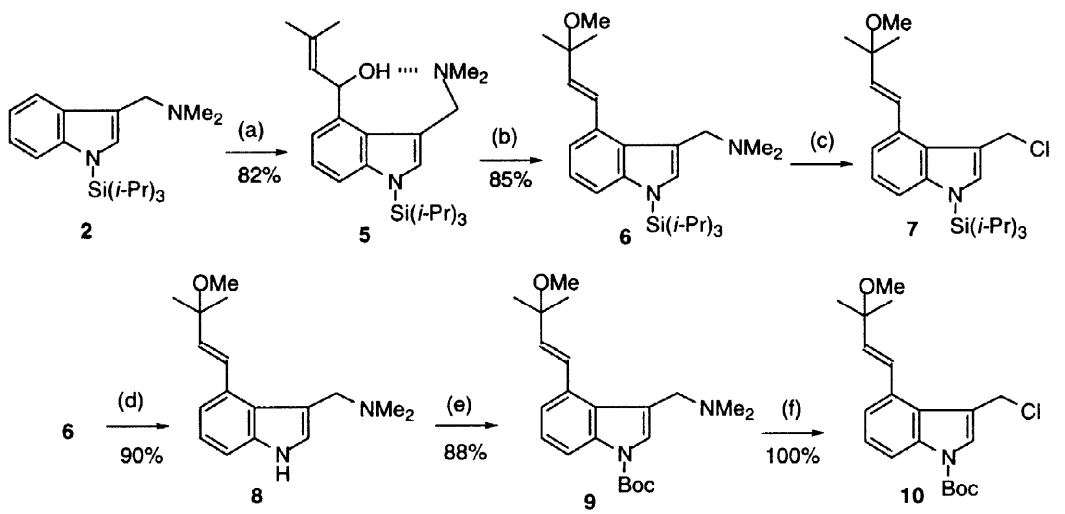
We planed to synthesize optically active **1a,b** by combined use of C-4 selective functionalization of the indole ring *via* directed lithiation of 1-(triisopropylsilyl)gramine (**2**)[3a] (1st step), and Schöllkopf's amino acid synthesis[4] using bislactim ether **4** (2nd step) as key reactions (**Scheme 1**).



Scheme 1

RESULTS AND DISCUSSION

The syntheses of 4-substituted 3-chloromethylindoles **7** and **10**, the substrates for the alkylation of bislactim ether **4**, were shown in **Scheme 2**. 1-(Triisopropylsilyl)gramine (**2**) was treated with *t*-BuLi in ether at 0°C for 1 h and the resulting 4-lithio species was reacted with 3-methyl-2-butenal (**3**) to give the hydrogen-bonded amino alcohol **5** in good yield.[2j] Methanolysis of **5** in the presence of anhydrous phosphoric acid produced **6** *via* S_N1' reaction in 85% yield. This compound was treated with 1 equivalent of isopropyl chlorocarbonate in toluene for 10 min at room temperature to generate the chloride **7**.[5] This chloride, however, was extremely unstable and decomposed to intractable tarry material during evaporation of the solvent. Although, we attempted to use a freshly generated toluene solution of **7** for the alkylation of **4**, we could isolate none of the expected coupling product.

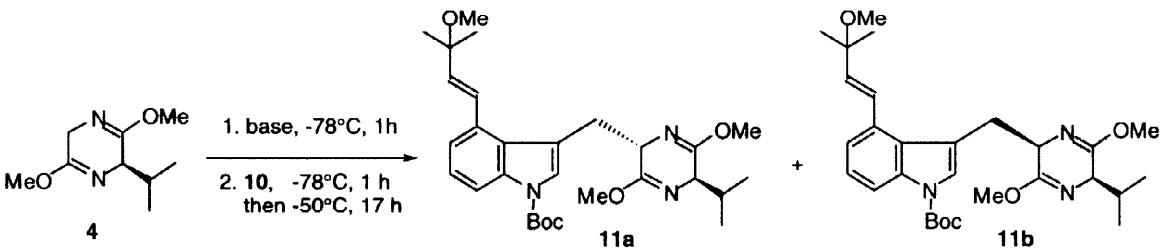


Reagents and conditions: (a) (i) *t*-BuLi, ether, 0°C, 1h; (ii) Me_2C=CHCHO. (b) anhy H_3PO_4, MeOH, rt, 1 h. (c) ClCOO-*i*-Pr, toluene, rt, 10 min. (d) TBAF, rt, 30 min. (d) $(Boc)_2O$, DMAP, Et_3N, THF, rt, 1.5 h. (f) ClCOOEt, toluene, rt, 10 min.

Scheme 2

The lability of **7** was assumed to be due to rapid elimination of chloride ion by electronic assistance of indole nitrogen, followed by decomposition of the generated 3-methyleneindolenine-type intermediate.[6] Therefore, we planed to synthesize the chloride **10** in which indole nitrogen was protected by electron-withdrawing *t*-butoxycarbonyl (Boc) group. Thus, compound **6** was treated with tetrabutylammonium fluoride (TBAF) to give deprotected **8**, which was then reacted with $(Boc)_2O$ in the presence of 4-(dimethylamino)pyridine (DMAP) and triethylamine to afford the *N*-Boc gramine **9**. Treatment of **9** with ethyl chlorocarbonate in toluene cleanly furnished the chloride **10**[5] as white solid in quantitative yield after evaporation of the solvent. As expected, this compound was much more stable than **7** and could be efficiently elaborated in further reactions.

Table 1. Diastereoselective Alkylation of Bislactim Ether **4** with Chloride **10**



entry	base[a]	solvent	additive	**11a** : **11b**[b]	yield (%)[c]	% ee **11a**[d]
1	BuLi	THF	—	2.5 : 1	68	—
2	BuLi	Et_2O	—	1 : 1	23	—
3	BuLi	DME	—	20 : 1	53	—
4	BuLi	THF	TMEDA	>30 : 1	71	89
5	BuLi	THF	HMPA	20 : 1	75	—
6	BuLi	THF	LiCl	6.5 : 1	70	—
7	LDA	THF	—	—	0	—
8	MeLi	THF	—	—	0	—
9	BuLi	THF	TMEDA	>30:1	66	96

a) Reagents ratio; **10** : **4** : base = 1.0 : 1.1 : 1.2 (entries 1-8); 1.00 : 1.15 : 1.10 (entry 9). b) Diastereomeric ratio was estimated by ^{1}H-NMR analysis. c) Combined yield (**11a** + **11b**). d) Enantiomeric excess was determined after hydrolysis.

The results of the coupling of **4** with **10** were summarized in **Table 1**. The bislactim ether **4** was metalated under the standard conditions[4] (BuLi/THF/-78°C/1 h) and subsequently alkylated with the freshly prepared chloride **10** (-78°C/1 h then -50°C/17 h) (entry 1). The alkylation products **11a,b** were isolated as a mixture by flash chromatography in 68% yield and the diastereomeric ratio was estimated to be 2.5:1 by

integration of isopropyl absorptions in the ^{1}H-NMR spectrum [δ 0.68 (*trans*); δ 0.46 (*cis*)]. This result was very surprising for us because the diastereoselectivity of the alkylation of **4** with common alkyl halides has been reported to be generally very high (de>95%).[4] We, therefore, tested a variety of conditions to improve the diastereoselectivity and also to clarify the origin of this unusually poor result. When diethyl ether was used as a solvent instead of THF, the stereoselectivity was changed for the worse (1:1) (entry 2). On the other hand, the use of 1,2-dimethoxyethane (DME) as a solvent improved the diastereomeric ratio dramatically to 20:1(entry 3). These results suggested that the solvent of chelating ability such as DME could regenerate the inherent reactivity of the lithiated **4**. In fact, when TMEDA was used as a chelating additive in THF, the best *trans* selectivity (>30:1) was achieved (entry 4). The addition of HMPA proved to be also effective (entry 5). However, the effect of LiCl[8] as an additive was not remarkable (entry 6). We also tested the effects of bases, however none of the coupling products were isolated when LDA or MeLi was employed as the base (entries 7,8).

A reasonable explanation for the dramatic change of the stereoselectivity is as follows.[7] In ether or THF, the Boc-carbonyl of the substrate **10** may coordinate to the lithium of the aza-enolate **12** from the less congested bottom side as shown in **Figure 1**. The poor *trans* selectivity in these solvents could be caused by this coordination because the molecular modeling of this adduct showed that the bottom side of **12** is efficiently sielded by a bulky *t*-butyl group. In the presence of a solvent (DME) or additives (TMEDA or HMPA) having strong coordinating ability, such coordination with the substrate is no more significant and, therefore, **12** reacts in usual manner with **10** to give the *trans* product **11a** in high stereoselectivity.

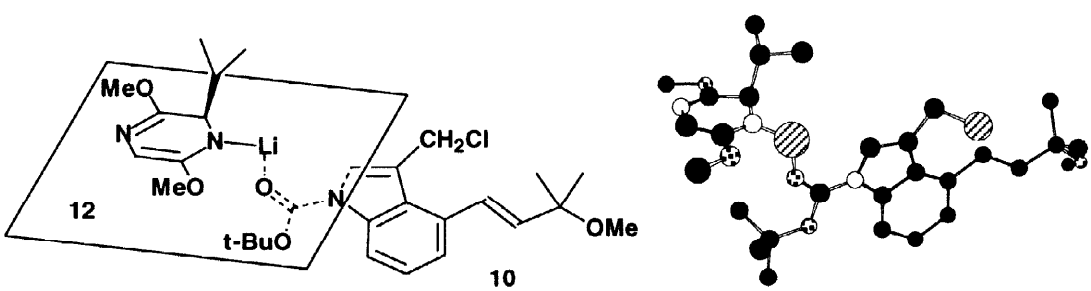
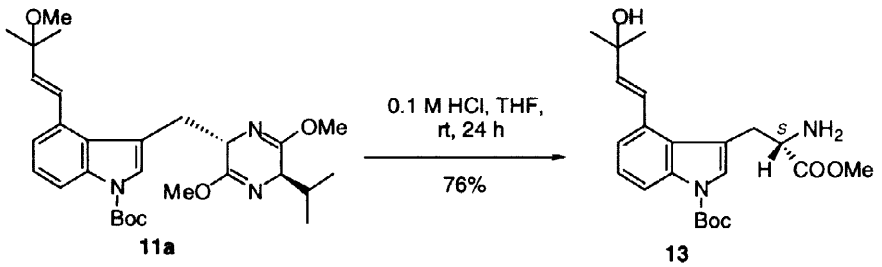


Figure 1. Molecular Modeling of Aza-enolate **12** Coordinated with *N*-Boc-indole **10**

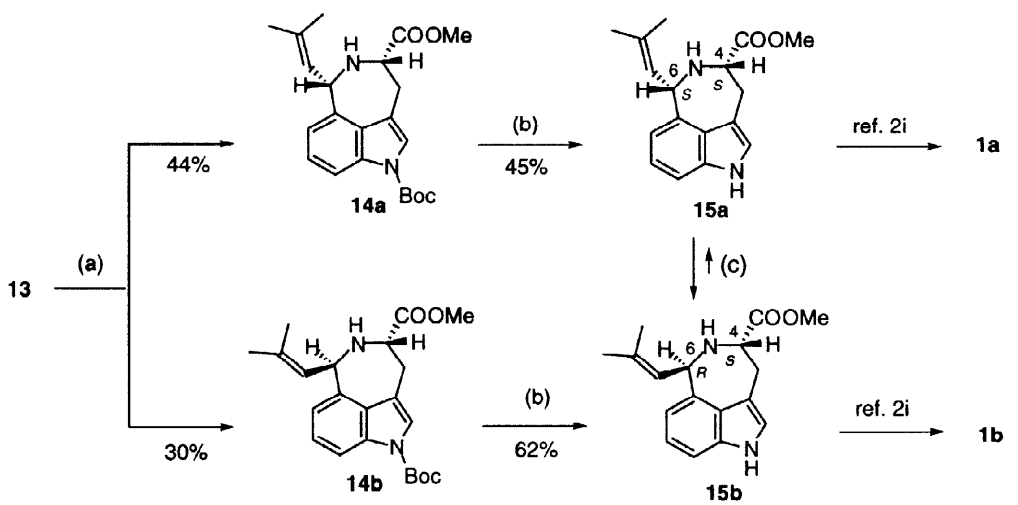
The diastereomeric mixture **11a,b** prepared under the conditions shown in entry 4 was rechromatographed to remove minor *cis* isomer **11b**. The pure **11a** thus obtained was treated with 0.1 M aq HCl in THF to give the amino ester **13** in 76% yield (**Scheme 3**). The enantiomeric excess (ee) of **13** was estimated to be 89% by chiral stationary phase HPLC analysis. We assumed that somewhat lower ee of **13** compared to the typical ee (>95%) of this type reactions could be due to partial racemization of **4** *via* dianion formation with excess of BuLi under the metalation conditions (**10** : **4** : BuLi = 1.0 : 1.1 : 1.2). Thus, we reexamined the coupling reaction using slightly excess of **4** against BuLi (**10** : **4** : BuLi = 1.00 : 1.15 : 1.10) (entry 9, **Table 1**). As we expected, the ee of **13** derived from **11a** prepared under these conditions was found to be satisfactory (96%).

The conversion of **13** to optically active clavicipitic acid methyl esters (**15a,b**) is shown in **Scheme 4**. Dehydrative cyclization of **13** was successfully conducted by refluxing a diluted dichloromethane solution of **13** and pyridinium *p*-toluenesulfonate (PPTS) for 7 days. After chromatographic purification, *cis* **14a** and *trans*

14b were obtained in 44% and 30% yields, respectively. The optical purity of both **14a** and **14b** did not decrease during this cyclization (96% ee). Although we tested the cyclization in refluxing benzene or chloroform in order to accelerate the reaction, yields of **14a,b** were decreased considerably and the diene derivative[2i,j] generated by simple dehydration at C-4 side chain was obtained as a major product.



Scheme 3



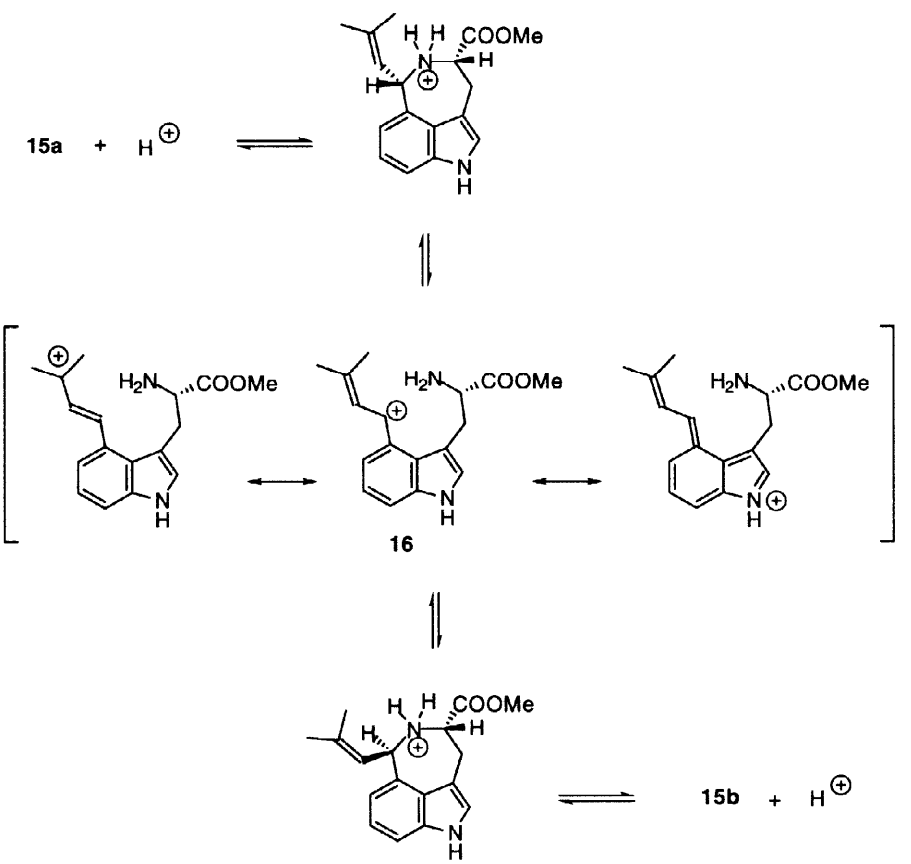
Reagents and conditions: (a)PPTS, CH_2Cl_2, reflux, 7 days. (b) silica gel, 0.2 mm, 55 °C, 24 h. (c) PPTS, CH_2Cl_2, reflux.

Scheme 4

The final deprotection of Boc group from indole nitrogen was proved to be somewhat tricky. When **14a** was treated with 1:1 mixture of trifluoroacetic acid and dichloromethane for 30 min at room temperature, only a complex mixture was obtained. This result indicated that the deprotection must be carried out under much milder conditions. Thus, we tested the silica gel-catalyzed thermolytic deprotection devised by Wensbo.[9] When **14a** was adsorbed on silica gel and the mixture was heated *in vacuo* at 55 °C for 24 h, *cis*-clavicipitic acid methyl ester (**15a**) (96% ee) was obtained in 45% yield, accompanied by epimerized *trans* isomer **15b** (15% yield, 78% ee) and starting material **14a** (10%). Similar thermolysis of **14b** afforded *trans*-clavicipitic acid methyl ester (**15b**) (62% yield, 96% ee), epimerized **15a** (4% yield, 83% ee), and unchanged **14b** (10%).

Single recrystallization of **15a,b** afforded optically pure samples (>99% ee). The spectroscopic data and specific rotations of **15a,b** thus synthesized were identical with those reported for optically pure *cis*- and *trans*-clavicipitic acid methyl esters reported by Yokoyama and Murakami.[2i,10] Since alkaline hydrolysis of these methyl esters without racemization has been reported by the same authors,[2i] this therefore represents a formal enantioselective synthesis of *cis*- and *trans*-clavicipitic acids (**1a,b**).

Finally, we wish to discuss briefly about an interesting epimerization observed at the final deprotection step. The absolute configurations of the epimerized *trans***15b** (4*S*, 6*R*) and *cis***15a** (4*S*, 6*S*) elucidated by chiral stationary phase HPLC analyses revealed that the inversion occurred mainly at C-6. This unusual epimerization may proceed by an acid-catalyzed ring opening and recyclization mechanism *via* the resonance-stabilized carbocation intermediate **16** (**Scheme 5**). The following experiments supported this mechanism. Treatment of *cis***15a** (>99% ee) with catalytic amount of PPTS in refluxing dichloromethane for 5 h afforded epimerized *trans***15b** (>99% ee) and unreacted *cis***15a** (>99% ee) in 69% and 18% yields, respectively. On the other hand, treatment of *trans***15b** (>99% ee) with PPTS under similar conditions afforded only 4% yield of *cis***15a** (>99% ee) and recovered *trans***15b** (>99% ee) in 91% yield. These experiments clearly indicated that *cis***15a** is thermodynamically less stable and easily isomerized to more stable *trans***15b** by the proposed mechanism.



Scheme 5

EXPERIMENTAL

General. Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were recorded with a Perkin Elmer System 2000 FT-IR spectrometer or a JASCO FT/IR-420 spectrometer. ^{1}H-NMR spectra were obtained with Varian Gemini-200 or -300 or JEOL JMS-GX 400 machine using TMS as an internal standard. Mass spectra (MS) were recorded with JEOL JMS-DX303 spectrometer. HPLC analyses for determination of enantiomeric excess were performed with Shimazu LC-6A using Chiralpak AD column produced by Daicel Chemical Industries. Optical rotations were measured on a JASCO DPI-1000 digital polarimeter at ambient temperature. Elemental analyses were performed at the microanalytical laboratory in Nagasaki University. Dry diethyl ether and THF were distilled from Na-benzophenone ketyl under N_2 before use. Dry DME and toluene were distilled over powdered CaH_2 and kept over MS 4A. (2*R*)-(-)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine was purchased from Merck and used after distillation. BuLi was purchased from Aldrich and titrated with 2,5-dimethoxybenzyl alcohol before use.

4-[(*E*)-3-Methoxy-3-methyl-1-butenyl]-1-(triisopropylsilyl)gramine (6). To a stirred solution of **5**[2j] (13.83 g, 33 mmol) in methanol (340 mL) was added dropwise anhydrous H_3PO_4 (16 mL) at room temperature over 10 min. After being stirred for 1 h, the reaction mixture was poured into a solution of $NaHCO_3$ (30 g) in water (770 mL) with vigorous stirring. The product was extracted twice with CH_2Cl_2, 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-AcOEt (20:1) as an eluent to give 12.04 g (85%) of **6** as colorless oil; IR: (neat) 2949, 1558, 1467, 1420, 1377, 1364, 1305, 1257, 1237, 1178, 1154, 1135, 1071, 1046, 1014, 900, 885, 852, 766, 745, 708, 690, 664, 648 cm^{-1}; ^{1}H-NMR (200 MHz) ($CDCl_3$) δ 1.13 (d, 18H, *J*=7.7 Hz), 1.44 (s, 6H), 1.69 (sept, 3H, *J*=7.7 Hz), 2.26 (s, 6H), 3.26 (s, 6H), 3.54 (s, 3H), 6.15 (d, 1H, *J*=16.1 Hz), 7.09 (s, 1H), 7.10 (dd, 1H, *J*=8.4, 7.3 Hz), 7.27 (d, 1H, *J*=7.3 Hz), 7.38 (d, 1H, *J*=8.4 Hz), 7.68 (d, 1H, *J*=16.1 Hz). *Anal.* Calcd for $C_{26}H_{44}N_2OSi$: C, 72.84; H, 10.34; N, 6.53. Found: C, 72.91; H, 10.54; N, 6.39.

3-Chloromethyl-4-[(*E*)-3-methoxy-3-methyl-1-butenyl]-1-(triisopropylsilyl)indole (7). A mixture of **6** (423 mg, 1.0 mmol) and isopropyl chlorocarbonate (139 μL, 1.0 mmol) in benzene-d_6 (4 mL) was stirred at room temperature for 10 min. ^{1}H-NMR spectrum (200 MHz) of this mixture indicated a quantitative formation of **7** [δ 0.94 (d, 18H, *J*=7.3 Hz), 1.36 (sept, 3H, *J*=7.7 Hz), 1.49 (s, 6H), 3.23 (s, 3H), 4.85 (s, 2H), 6.30 (d, 1H, *J*=16.1 Hz), 7.07 (s, 1H), 7.18 (dd, 1H, *J*=7.7, 7.3 Hz), 7.32 (d, 1H, *J*=7.7 Hz), 7.38 (d, 1H, *J*=7.3 Hz), 7.71 (d, 1H, *J*=16.1 Hz)] and isopropyl *N,N*-dimethylcarbamate [δ 1.11 (d, 6H, *J*=6.3 Hz), 2.47 (br s, 3H), 2.63 (br s, 3H), 5.04 (sept, 1H, *J*=6.3 Hz)]. Evaporation of the solvent, however, resulted in the formation of intractable tarry material.

4-[(*E*)-3-Methoxy-3-methyl-1-butenyl]gramine (8). To a stirred solution of **6** (12.02 g, 28 mmol) in THF (70 mL) was added dropwise tetrabutylammmonium fluoride (36 mL of 1.0 M THF solution, 36 mmol) over 8 min. After stirring for 30 min, water was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted twice with ether. The combined extract was washed twice with water and then with brine solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed

over Chromatorex NH-DM1020 silica gel (Fuji Silisia) using hexane-AcOEt (1:1) as an eluent to give 6.05 g (90%) of **8**, mp 126.5-127.5 °C (ether-hexane); IR (KBr) 3147, 3104, 2978, 2945, 2815, 1456, 1248, 1168, 1070, 996 cm^{-1}; ^{1}H-NMR (400 MHz) ($CDCl_3$) δ 1.44 (s, 6H), 2.27 (s, 6H), 3.26 (s, 3H), 3.55 (s, 2H), 6.16 (d, 1H, *J*=16.1 Hz), 7.08 (d, 1H, *J*=2.6 Hz), 7.15 (t, 1H, *J*=7.7 Hz), 7.25-7.28 (m, 2H), 7.68 (d, 1H, *J*=16.1 Hz), 8.05 (br s, 1H). *Anal.* Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 74.87; H, 8.88; N, 10.16.

1-*t*-Butoxycarbonyl-4-[(*E*)-3-methoxy-3-methyl-1-butenyl]gramine (9). Under ice-water cooling, a solution of compound **8** (5.70 g, 21 mmol) in THF (90 mL) was added dropwise over 10 min to a stirred solution of di-*t*-butyl dicarbonate (5.50g, 25 mmol), 4-(dimethylamino)pyridine (257 mg, 2.1 mmol), triethylamine (3.5 mL, 25 mmol) in THF (50 mL). After stirring for 1.5 h at room temperature, water was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted twice with ether. The combined extract was washed three times with water and then with brine solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed over Chromatorex NH-DM1020 silica gel (Fuji Silisia) using hexane-AcOEt (5:1) as an eluent to give 6.83 g (88%) of **9**, mp 87-88 °C (CH_2Cl_2-hexane); IR (KBr) 2975, 2816, 2777, 1739, 1457, 1422, 1381, 1347, 1285, 1254, 1159, 1091, 856, 770, 748, 704 cm^{-1}; ^{1}H-NMR (200 MHz) ($CDCl_3$) δ 1.43 (s, 6H), 1.67 (s, 9H), 2.28 (s, 6H), 3.26 (s, 3H), 3.48 (s, 2H), 6.15 (d, 1H, *J*=16.2 Hz), 7.26 (dd, 1H, *J*=8.1, 7.2 Hz), 7.37 (d, 1H, *J*=7.2 Hz), 7.46 (s, 1H), 7.65 (d, 1H, *J*=16.2 Hz), 8.08 (br d, 1H, *J*=8.1 Hz). *Anal.* Calcd for $C_{22}H_{32}N_2O_3$: C, 70.94; H, 8.66; N, 7.52. Found: C, 70.98; H, 8.67; N, 7.38.

1-(*t*-Butoxycarbonyl)-3-chloromethyl-4-[(*E*)-3-methoxy-3-methyl-1-butenyl]indole (10). To a solution of **9** (372 mg, 1.0 mmol) in dry toluene (4 mL) was added ethyl chlorocarbonate (96 μL, 1.0 mmol). The mixture was stirred at room temperature for 10 min and evaporated *in vacuo*. The residual white solid was evacuated under vacuum pump pressure for 4 h to give 364 mg (100%) of essentially pure **10**; ^{1}H-NMR (300 MHz) (C_6D_6) δ 1.34 (s, 9H), 1.42 (s, 6H), 3.19 (s, 3H), 4.47 (s, 2H), 6.21 (d, 1H, *J*=15.9 Hz), 7.21 (t, 1H, *J*=7.5 Hz), 7.31 (d, 1H, *J*=7.5 Hz), 7.45 (s, 1H), 7.48 (d, 1H, *J*=15.9 Hz), 8.43 (br d, 1H, *J*=7.5 Hz). This compound was used immediately for the next reaction without further purification due to its instability.

(2*R*,5*S*)-5-({1-(*t*-Butoxycarbonyl)-4-[(*E*)-3-methoxy-3-methyl-1-butenyl]indol-3-yl}methyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (11a) and (2*R*,5*R*)-5-({1-(*t*-Butoxycarbonyl)-4-[(*E*)-3-methoxy-3-methyl-1-butenyl]indol-3-yl}methyl)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (11b). *The synthesis was carried out under the conditions indicated in entry 9 of Table 1.* Under an atmosphere of Ar, BuLi (4.9 mL of 1.12 M solution in hexane, 5.5 mmol) was added dropwise to a stirred solution of (2*R*)-(-)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (**4**) (1.07 g, 5.8 mmol) in dry THF (20 mL) at -78 °C. After stirring for 1 h, TMEDA (1.0 mL, 6.6 mmol) was added to this solution and, after 30 min, a solution of the freshly prepared chloride **10** (1.82 g, 5.0 mmol) in THF (20 mL) was added dropwise over 10 min. The mixture was stirred for 1 h at -78 °C and then stirred for 17 h at -50 °C. The reaction mixture was quenched with aqueous NH_4Cl at -50°C and the product was extracted three times with ether. The combined extract was washed with brine solution, dried over Na_2SO_4, and evaporated. The

residue was purified by flash chromatography over neutral silica gel using hexane-AcOEt (20:1) as an eluent to give diastereomeric mixture of **11a** and **11b** (1.68g, 66% combined yield). This mixture was rechromatographed over neutral silica gel using CH_2Cl_2-AcOEt (20:1) as an eluent to give 1.58 g (62%) of the *trans* isomer **11a** as colorless oil, $[\alpha]_D$ -15.7° (c=1.50, EtOH); IR (neat) 2975, 1735, 1696, 1422, 1370, 1287, 1239, 1156, 1093, 1014, 858, 754, 669 cm^{-1}; ^{1}H-NMR (400 MHz) ($CDCl_3$) δ 0.68 (d, 3H, *J*=6.6 Hz), 1.02 (d, 3H, *J*=6.6 Hz), 1.43 (s, 3H), 1.44 (s, 3H), 1.64 (s, 9H), 2.22 (m, 1H), 3.03 (dd, 1H, *J*=15, 8 Hz), 3.29 (s, 3H), 3.57 (dd, 1H, *J*=15, 4 Hz), 3.59 (s, 3H), 3.73 (s, 3H), 3.86 (t, 1H, *J*=4 Hz), 4.29 (dt, 1H, *J*=8, 4 Hz), 6.08 (d, 1H, *J*=16.1 Hz), 7.20-7.27 (m, 2H), 7.46 (s, 1H), 7.49 (d, 1H, *J*=16.1 Hz), 8.10 (br d, 1H, *J*=7.3 Hz); MS *m/z* 511 (M^+); HRMS calcd for $C_{29}H_{41}N_3O_5$ 511.3046, found 511.3059. Further elution with the same eluent afforded 48 mg (2%) of the *cis* isomer **11b** as colorless oil, $[\alpha]_D$ +56.3° (c=1.93, $CHCl_3$); IR (neat) 2975, 1736, 1696, 1423, 1370, 1287, 1239, 1157, 1095, 1015, 858, 755, 666 cm^{-1}; ^{1}H-NMR (400 MHz) ($CDCl_3$) δ 0.46 (d, 3H, *J*=6.6 Hz), 1.01 (d, 3H, *J*=6.6 Hz), 1.44 (s, 3H), 1.45 (s, 3H), 1.64 (s, 9H), 2.10 (m, 1H), 2.98 (dd, 1H, *J*=15, 8 Hz), 3.26 (s, 3H), 3.60 (s, 3H), 3.62 (dd, 1H, *J*=15 and 4 Hz), 3.74 (s, 3H), 3.90 (t, 1H, *J*=4 Hz), 4.37 (dt, 1H, *J*=15, 4 Hz), 6.08 (d, 1H, 16.1 Hz), 7.20-7.26 (m, 2H), 7.48 (s, 1H), 7.52 (1H, d, *J*=16.1 Hz), 8.09 (br d, 1H, *J*=7.2 Hz); MS *m/z* 511 (M^+); HRMS calcd for $C_{29}H_{41}N_3O_5$ 511.3046, found 511.3053.

Methyl (*S*)-{1-(*t*-Butoxycarbonyl)-4-[(*E*)-3-hydroxy-3-methyl-1-butenyl]}-tryptophanate (13). A mixture of **11a** (1.50 g, 2.9 mmol), THF (20 mL), and 0.1 M aqueous HCl (60 mL) was stirred at room temperature for 24 h. The mixture was concentrated under reduced pressure, washed with ether, and made basic (pH 9) with conc. NH_4OH. The alkaline solution was extracted three times with ether. The combined extract was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography over silica gel using CH_2Cl_2-MeOH (20:1) as an eluent to give 0.90 g (76%) of **13**, mp 100.5-101 °C (ether-hexane); HPLC (hexane-*i*-PrOH=19:1) 96% ee; $[\alpha]_D$ +29.3° (c=2.34, $CHCl_3$); IR (KBr) 3419 (br) , 2976, 1733, 1646, 1423, 1373, 1355, 1300, 1286, 1256, 1160, 1094, 1049, 970, 754 cm^{-1}; ^{1}H-NMR (400 MHz) ($CDCl_3$) δ 1.42 (s, 6H), 1.66 (s, 9H), 2.2 (br, 3H), 2.89 (dd, 1H, *J*=14.3, 7.7 Hz), 3.43 (dd, 1H, *J*=14.3, 4.8 Hz), 3.75 (s, 3H), 3.78 (dd, 1H, *J*=7.7, 4.8 Hz), 6.26 (d, 1H, *J*=15.8 Hz), 7.23-2.29 (m, 2H), 7.33 (d, 1H, *J*=15.8 Hz), 7.42 (s, 1H), 8.09 (br d, 1H, *J*=7.3 Hz); MS *m/z* 402 (M^+); HRMS calcd for $C_{22}H_{30}N_2O_5$ 402.2155, found 402.2139.

Methyl (4*S*,6*S*)-1-(*t*-Butoxycarbonyl)-3,4,5,6-tetrahydro-6-(2-methyl-1-propenyl)-azepino[5,4,3-*cd*]indole-4-carboxylate (14a) and Methyl (4*S*, 6*R*)-1-(*t*-Butoxycarbonyl)-3,4,5,6-tetrahydro-6-(2-methyl-1-propenyl)azepino[5,4,3-*cd*]indole-4-carboxylate (14b). A mixed solution of **13** (858 mg, 2.13 mmol) and anhydrous pyridinium *p*-toluenesulfonate (535 mg, 2.13 mmol) in dry CH_2Cl_2 (213 mL) was refluxed for 7 days under Ar atmosphere. After cooling, CH_2Cl_2 was evaporated and the residue was partitioned between ether and aqueous $NaHCO_3$ solution. 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-AcOEt (5:1) to give *trans* **14b** (248 mg, 30%) as colorless oil; HPLC (hexane-*i*-PrOH=19:1) 96% ee; $[\alpha]_D$ -32.2° (c=0.51, $CHCl_3$); IR (neat) 3339, 2977, 1733, 1423, 1383, 1353, 1300, 1284, 1252, 1217, 1157, 1094, 1059, 856, 757, 667 cm^{-1}; ^{1}H-NMR (400 MHz) ($CDCl_3$) δ 1.66 (s, 9H), 1.82 (d, 3H, *J*=1.1 Hz), 1.87 (d, 3H, *J*=1.5 Hz), 3.01 (ddd, 1H,

J=15.8, 11.0, 1.8 Hz), 3.51 (ddd, 1H, *J*=15.8, 2.9, 1.1 Hz), 3.81 (s, 3H), 3.82 (dd, 1H, *J*=11.0, 2.9 Hz), 4.87 (d, 1H, *J*=8.8 Hz), 5.46 (d with fine coupling, 1H, *J*=8.8 Hz), 6.98 (d, 1H, J=7.7 Hz), 7.22 (dd, 1H, *J*=8.1, 7.7 Hz), 7.42 (br s, 1H), 8.07 (br d, 1H, *J*=8.1 Hz); MS *m/z* 384 (M^+); HRMS calcd for $C_{22}H_{28}N_2O_4$ 384.2049, found 384.2040. Further elution with the same eluent afforded *cis* **14a** (364 mg, 44%) as colorless oil; HPLC (hexane-*i*-PrOH=19:1), 96% ee; $[\alpha]_D$ -82.5° (c=0.71, $CHCl_3$); IR (neat) 3341, 2977, 2930, 1732, 1427, 1385, 1370, 1351, 1284, 1252, 1158, 1098, 1055, 856, 783, 755, 666 cm^{-1}; ^{1}H-NMR (400 MHz) ($CDCl_3$) δ 1.66 (s, 9H), 1.80 (d, 3H, *J*=1.1 Hz), 1.83 (d, 3H, *J*=1.1 Hz), 3.20 (ddd, 1H, *J*=15.4, 11.4, 1.8 Hz), 3.37 (dd, 1H, *J*=15.4, 4.0 Hz), 3.78 (s, 3H), 4.11 (dd, 1H, *J*=11.4, 4.0 Hz), 5.30 (d, 1H, *J*=8.8 Hz), 5.40 (d with fine coupling, 1H, *J*=8.8 Hz), 6.92 (d, 1H, *J*=7.7 Hz), 7.19 (dd, 1H, *J*=8.1, 7.7 Hz), 7.40 (br s, 1H), 7.98 (br d, 1H, *J*=8.1 Hz); MS *m/z* 384 (M^+); HRMS calcd for $C_{22}H_{28}N_2O_4$ 384.2049, found 384.2048.

Methyl (4*S*,6*S*)-3,4,5,6-Tetrahydro-6-(2-methyl-1-propenyl)-1*H*-azepino[5,4,3-*cd*]-indole-4-carboxylate (15a). [(-)-*cis*-Clavicipitic Acid Methyl Ester]. A mixture of **14a** (300 mg, 0.78 mmol) and silica gel 60 (3.00 g) in CH_2Cl_2 (10 mL) was stirred at room temperature for 30 min. The solvent was evaporated and the residue was heated at 55 °C (bath temperature) under vacuum pump pressure for 24 h. After cooling, the residue was applied directly on a column of silica gel and eluted with hexane-AcOEt (2:1) to give 29 mg (10%) of the starting material **14a**, 32 mg (15%) of the epimerized *trans* **15b**, and 99 mg (45%) of the *cis* **15a**. HPLC analyses (hexane-*i*-PrOH=8:2 for **15a**; 9:1 for **15b**) indicated the optical purity of **15a** and **15b** thus obtained were 96% ee and 78% ee, respectively. Single recrystallization of the crude **15a** from benzene-hexane afforded optically pure (>99% ee) compound as slightly yellow prisms, mp 141-142.5 °C (lit.[2i], mp 144.0-145.5 °C); $[\alpha]_D$ -205.2° (c=0.88, EtOH) [lit.[2i], $[\alpha]_D$ -195.3° (EtOH)]; IR (KBr) 3323, 3168, 2890, 1732, 1434, 1363, 1275, 1233, 1219, 1126, 1050, 926, 834, 809, 782, 741 cm^{-1}; ^{1}H-NMR (400 MHz) ($CDCl_3$) δ 1.76 (d, 3H, *J*=1.1 Hz), 1.84 (d, 3H, *J*=1.1 Hz), 2.68 (br s, 1H), 3.21 (ddd, 1H, *J*=15.4, 11.4, 1.5 Hz), 3.42 (dd, 1H, *J*=15.4, 3.7 Hz), 3.76 (s, 3H), 4.17 (dd, 1H, *J*=11.4, 3.7 Hz), 5.35 (d, 1H, *J*=8.8 Hz), 5.45 (d with fine coupling, 1H, *J*=8.8 Hz), 6.77 (d, 1H, *J*=7.3 Hz), 6.86 (br s, 1H), 7.04 (t, 1H, *J*=7.3 Hz), 7.10 (d, 1H, *J*=7.3 Hz), 8.44 (br s, 1H). *Anal.* Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.61; H, 6.82; N, 9.60.

Methyl (4*S*,6*R*)-3,4,5,6-Tetrahydro-6-(2-methyl-1-propenyl)-1*H*-azepino[5,4,3-*cd*]-indole-4-carboxylate (15b). [(-)-*trans*-Clavicipitic Acid Methyl Ester]. A mixture of **14b** (216 mg, 0.56 mmol) and silica gel 60 (2.16 g) in CH_2Cl_2 (10 mL) was stirred at room temperature for 30 min. The solvent was evaporated and the residue was heated at 55 °C (bath temperature) under vacuum pump pressure for 24 h. After cooling, the residue was applied directly on a column of silica gel and eluted with hexane-AcOEt (2:1) to give 21 mg (10%) of the starting material **14b**, 98 mg (62%) of the *trans* **15b**, and 7 mg (4%) of the epimerized *cis* **15a**. HPLC analyses indicated the optical purity of **15b** and **15a** thus obtained were 96% ee and 83% ee, respectively. Single recrystallization of the crude **15b** from benzene-hexane afforded optically pure (>99% ee) compound as slightly yellow prisms, mp 161.5-162.5 °C (lit.[2i], mp 158-160 °C); $[\alpha]_D$ -130.9° (c=1.03, EtOH) [lit.[2i], $[\alpha]_D$ -129.1° (EtOH)]; IR (KBr) 3330, 3103, 2936, 1728, 1434, 1374, 1333, 1289, 1272, 1206, 1180, 1110, 1051, 980, 918, 861, 834 cm^{-1}; ^{1}H-NMR (400 MHz) ($CDCl_3$) δ 1.82 (d, 3H, *J*=1.5 Hz), 1.86 (d, 3H, *J*=1.5 Hz), 2.64 (br s, 1H), 3.04 (ddd, 1H, *J*=15.4, 11.7, 1.5 Hz), 3.52 (dd, 1H, *J*=15.4,

2.6 Hz), 3.80 (s, 3H), 3.83 (dd, 1H, *J*=11.7, 2.6 Hz), 4.87 (d, 1H, *J*=8.8 Hz), 5.49 (d with fine coupling, 1H, *J*=8.8 Hz), 6.83 (d with fine coupling, 1H, *J*=7.3 Hz), 6.92 (br s, 1H), 7.08 (dd, 1H, *J*=8.1, 7.3 Hz), 7.16 (d, 1H, *J*=8.1 Hz), 8.42 (br s, 1H). *Anal.* Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.80; H, 7.04; N, 9.85.

PPTS-Catalyzed Isomerization of (-)-*cis*-Clavicipitic Acid Methyl Ester (15a) to (-)-*trans*-Clavicipitic Acid Methyl Ester (15b). A solution of **15a** (17.5 mg, 0.06 mmol) (>99% ee) and PPTS (15 mg, 0.06 mmol) in CH_2Cl_2 (6 mL) was refluxed for 5 h. After cooling, saturated aqueous $NaHCO_3$ was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was chromatographed over silica gel using hexane-AcOEt (2:1) as an eluent to give 12.0 mg (69%) of the epimerized *trans* isomer **15b** and 3.2 mg (18%) of the starting material **15a**. HPLC analyses indicated the optical purity of both **15b** and **15a** thus isolated were >99% ee.

PPTS-Catalyzed Isomerization of (-)-*trans*-Clavicipitic Acid Methyl Ester (15b) to (-)-*cis*-Clavicipitic Acid Methyl Ester (15a). A solution of **15b** (22.1 mg, 0.077 mmol) (>99% ee) and PPTS (19 mg, 0.077 mmol) in CH_2Cl_2 (8 mL) was refluxed for 5 h. Similar work-up and purification as described above afforded 20.1 mg (91%) of the starting material **15b** and 0.8 mg (4%) of the isomerized *cis* isomer **15a**. HPLC analyses indicated the optical purity of both **15b** and **15a** thus isolated were >99% ee.

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10. The authors are grateful to Professor Yasuoki Murakami (Toho University) for his kind correspondence concerning HPLC conditions to determine enantiomeric excess of clavicipitic acid derivatives.