Total Synthesis without Protection: Three-Step Synthesis of Optically Active Clavicipitic Acids by a Biomimetic Route

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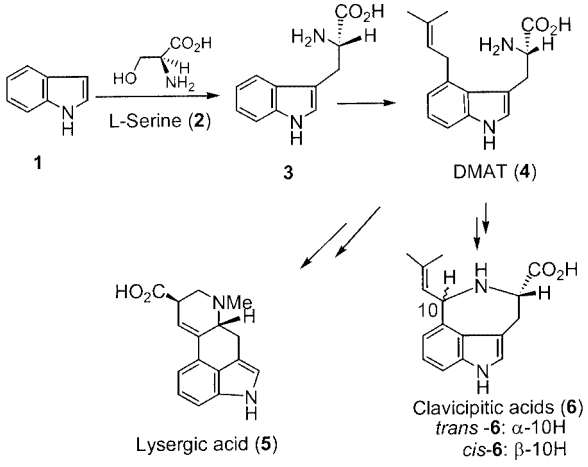
Keywords: Heck reaction / Tryptophan / Protecting groups / Clavicipitic acids / Total synthesis

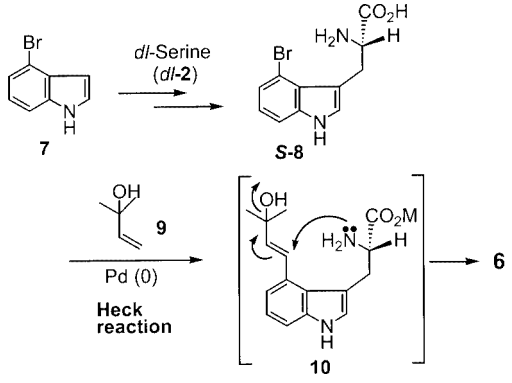
A three-step synthesis of a mixture of optically active *cis*- and *trans*-clavicipitic acids **6**, which are ergot alkaloids, was achieved, starting from 4-bromoindole (**7**) and *dl*-serine (*dl*-**2**). This short synthesis was made possible by omitting the protection and deprotection steps from the synthetic route. The key step was the spontaneous cyclization of 4-vinyltryptophan (**10**) formed from the Heck reaction of 4-bromotryptophan (**8**) with 2-methyl-3-buten-2-ol (**9**) in aqueous media. During this investigation, we also found that the palladium-catalyzed reaction of **8** with **9** showed an interesting pH dependence; under strongly basic conditions, the Heck reaction occurred to give a C^4-vinylated product **10**, whereas an *N*-allylated product **19b** was formed under neutral or weakly basic conditions.

Introduction

In biological systems, the syntheses of the compounds essential for life are accomplished efficiently and cleanly via enzymatic catalysis. Therefore, one of the most attractive goals for a synthetic chemist is to develop a synthetic pathway similar to the biosynthetic one, but without the use of enzymes. One of the most important aspects of creating a biomimetic synthesis is that the use of protecting groups should be avoided. In this paper, we report[1] the biomimetic synthesis of optically active clavicipitic acid (**6**), which is an ergot alkaloid, biosynthesized from indole (**1**) and L-serine (L-**2**) via L-tryptophan (**3**) and γ,γ-dimethylallyltryptophan (**4**, DMAT)[2] (Scheme 1). The synthetic outline is as follows (Scheme 2): 1) two-step synthesis of enantiomerically pure 4-bromotryptophan (***S*-8**) from 4-bromoindole (**7**) and *dl*-serine (*dl*-**2**); 2) Heck reaction of ***S*-8** with 2-methyl-3-buten-2-ol (**9**), followed by spontaneous cyclization of the resulting 4-vinyltryptophan (**10**). The outstanding features of this route are that it requires only three steps, and that it uses the reaction of free amino acids without protecting groups. Although numerous chemical transformations of amino acids have been reported,[3] most of them have been performed with protected amino acids,[4] in order to avoid side reactions.



Scheme 1. Biosynthetic pathway of the ergot alkaloids



Scheme 2. Three-step synthesis of clavicipitic acid (**6**)

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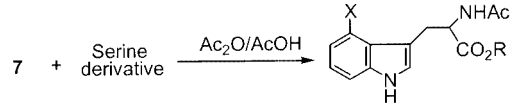
Results

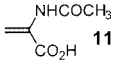
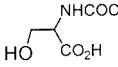
Synthesis of Enantiomerically Pure (*S*)-4-Bromotryptophan (*S*-8)

Following Snyder's procedure[5] for the direct synthesis of *N*-acetyltryptophan (*dl*-**12a**) from indole (**1**) and *N*-acetyldehydroalanine (**11**), we heated a mixture of 4-bromindole (**7**) and **11** in AcOH in the presence of Ac_2O at 80 °C for 1.5 h, and, after esterification of the resulting acid **12b** with $(CH_3)_3SiCHN_2$, the product was isolated as the methyl ester **12c** (Table 1). The 36%[6] yield of **12c** (run 1) was much lower than the yield of 58% reported by Snyder,[5] and was unsatisfactory. However, when *dl*-serine (**2**) was used instead of **11**, the yield of **12c** increased to 58% (run 2). The yield was further improved to 63% by the use of *N*-acetylserine (*dl*-**13**) (run 3). Although the yield was almost satisfactory for synthetic use, **13** is much more expensive than *dl*-**2**. We thought that the lower yield in run 2 compared to run 3 might be due to decomposition of **2** prior to the formation of *dl*-*N*-acetylserine (*dl*-**13**). Therefore, *dl*-**13** was prepared in situ by reaction with Ac_2O at a lower temperature (45 °C, 5 h) prior to the addition of 4-bromoindole (**7**). The yield from this reaction was an improved 73% (run 4).

Table 1. Tryptophan synthesis by the reaction of 4-bromoindole (**7**) with serine derivatives

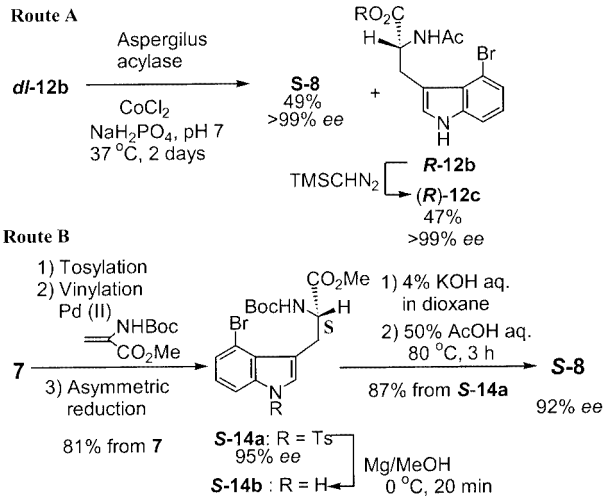


***dl*-12a** (X = H, R = H), ***dl*-12b** (X = Br, R = H)
***dl*-12c** (X = Br, R = CH_3)

Run	Serine Derivatives	Yield **12c** (%)	Run	Serine Derivatives	Yield **12c** (%)
1	 **11**	36	3	 *dl*-**13**	63
2	*dl*-**2**	58	4	*dl*-**2***	73

* *dl*-**2** was heated with Ac_2O at 50 °C for 5 h prior to the addition.

The *N*-acetyl group can be used in a kinetic resolution to obtain optically active 4-bromotryptophan (***S*-8**); treatment of *N*-acetylamino acids with acylase for this purpose is well established[7] as a practical and economical method in amino acid synthesis. *N*-Acetyl-4-bromotryptophan (*dl*-**12b**)[8] was treated with commercially available *Aspergillus* acylase at pH 7.5 for 3 days at 37 °C. Although the reaction proceeded smoothly, purification of the resulting ***S*-8** was difficult, because of its high polarity. Various purification methods, including the use of acidic or basic ion-exchange resins, dialysis membranes, and isoelectric precipitation, failed to separate **8** from the inorganic salts and enzymes. Finally, we found that octadecylsilyl-silica (ODS-silica) gel column chromatography was very effective for the purification of **8** on a small scale (100 mg), giving enantiomerically pure ***S*-8** (> 99% *ee*) in 49% yield as the unprotected form; enantiomerically pure ***R*-12b** was obtained as a methyl ester (***R*-12c**) (> 99% *ee*) in 47% yield (Scheme 3, Route A). Thus, enantiomerically pure ***S*-8** was obtained in 36% overall yield from **7**. ODS-silica gel, however, is too expensive to be used in large-scale synthesis. Therefore, in laboratory scale reactions (ca. 1 g scale), we used inexpensive cellulose gel (Cellulofine® GH-25) and polystyrene resin (Diaion® SP-207) for the purification of ***S*-8**, and this resulted in a reasonable isolated yield (30%).

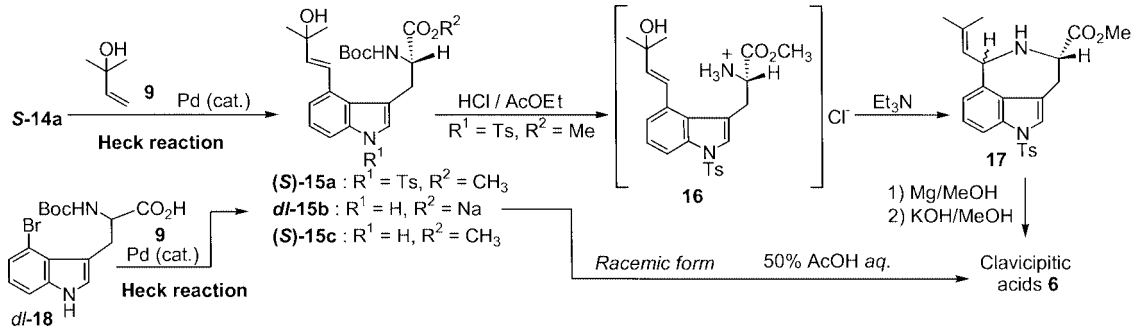


Scheme 3. Synthesis of optically active 4-bromotryptophan (***S*)-8**

Optically active ***S*-8** was also synthesized by another route, using conventional protection−deprotection methodology (Scheme 3, Route B). We have already reported the synthesis[9] in three steps from 4-bromoindole of almost enantiomerically pure (95% *ee*), fully protected *N*-Boc-1-tosyl-4-bromotryptophan methyl ester (***S*-14a**). ***S*-14a** was detosylated by treatment with Mg/MeOH, and the resulting ester **14b** was hydrolyzed with 4% aq. KOH in dioxane. This was followed by heating with 50% AcOH at 80 °C for 3 h to give ***S*-8** in 87% overall yield from ***S*-14a**, with slight racemization (92% *ee*). All spectral and physical data for the products from the two routes were completely identical.

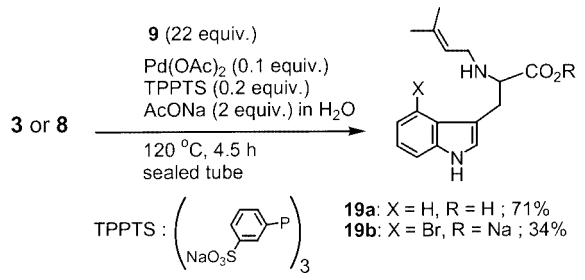
Reaction of (*S*)-4-Bromotryptophan (*S*-8) and 2-Methyl-3-buten-2-ol (9)

We have already reported[9] the four-step synthesis of optically active *cis*- and *trans*-clavicipitic acids (**6**) from (*S*)-*N*-Boc-1-tosyl-4-bromotryptophan methyl ester (***S*-14a**) via 4-vinyltryptophan (**15a**) (Scheme 4). The key step of this route was the one-pot transformation of **15a** to **17** by deprotection of the Boc group and subsequent cyclization of the amine **16**. Although this synthesis is similar to biosynthesis of **6** (Scheme 1) and is efficient compared to another reported synthesis,[10] three out of the four steps in this route are deprotection steps. We considered that if the Heck reaction were possible with unprotected 4-bromotryptophan (**8**), spontaneous cyclization of the resulting 4-vinylated product **10** should occur, to produce **6** in one pot (Scheme 2).



Scheme 4. Synthesis of clavicipitic acids (**6**) by protected route

At first, we attempted the reaction in organic solvents; a mixture of 4-bromotryptophan (**8**), $Pd(OAc)_2$, PPh_3, and **9** was heated in a polar organic solvent such as dioxane or DMF. However, these reactions gave complex mixtures, as the free amino acid (**8**) was scarcely soluble in the solvents used. Next, the reaction was carried out in aqueous solution using a phase-transfer catalyst, according to the method of Jeffery.[11] The reaction of *dl*-**8** with **9** in the presence of K_2CO_3, PPh_3, and nBu$_4$NBr in H_2O at 90 °C for 5 h yielded an unknown product, which gave a negative ninhydrin test, along with recovered starting material (**8**, 28%). We then changed the phosphane ligand to the water-soluble phosphane ligand TPPTS,[12] instead of using a phase-transfer catalyst. Disappointingly, the sodium salt of the *N*-allylated product **19b** was obtained in 34% yield as the sole product, along with starting material (**8**, 38%), after separation by ODS-silica gel column chromatography (Scheme 5). This reaction was repeated with L-tryptophan (**3**) under the same reaction conditions, and the *N*-allylated product **19a** was produced in 71% yield.

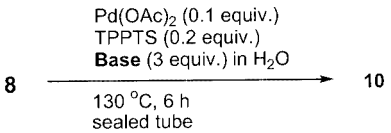


Scheme 5. Palladium-catalyzed *N*-allylation of 4-bromotryptophan (*dl*-**8**) with 1,1-dimethylallyl alcohol (**9**)

These results clearly show that the amino group must be protected. Therefore, we carried out the reaction of *dl*-*N*-Boc-4-bromotryptophan (*dl*-**18**) with **9** in the presence of a catalytic amount of $Pd(OAc)_2$, TPPTS, and $NaHCO_3$ (3 equiv.) at 100 °C for 5 h in H_2O, and the expected 4-vinylated product *dl*-**15b** was formed in 70% yield (Scheme 4). Since spontaneous cyclization of **16** had already been achieved by deprotection of the Boc group of (***S***)-**15a** followed by neutralization, the sodium salt (*dl*-**15b**) was treated with 50% aq. AcOH at 80 °C for 3 h. Cyclization occurred as expected, simultaneously with deprotection of the Boc group, to give a mixture of *cis*- and *trans*-**6** in one pot, in 76% yield.

These results indicated that if the reaction of the free amino acid **8** could be made to work, then the clavicipitic acids **6** might be obtained in a one-pot synthesis. Consequently, the Heck reaction of **8** was attempted again under different reaction conditions. According to Bumagin,[13] the palladium-catalyzed carbonylation of *p*-iodoaniline could be made to work by changing the base from AcONa to K_2CO_3 in aqueous DMF solution; therefore, we carried out the reaction using K_2CO_3 as a base. Surprisingly, the reaction proceeded smoothly to give the desired product **10** [M = K] in 91% yield (Table 2, run 3), which was stable enough to be isolated as its potassium salt by ODS-silica gel column chromatography. The structure was confirmed after conversion into **15c** by BOC-protection of the amine and esterification with $TMSCHN_2$, by comparison with an authentic sample of **15c** (see Exp. Sect.). We attempted this reaction using a variety of bases. $NaHCO_3$ gave a complex mixture (run 1), and Na_2CO_3 gave 51% of the desired product (run 2). A strong base (NaOH) gave 91% of **10** [M = Na] (run 4), and a weak organic base (Et_3N) gave 55% of the desired product along with tryptophan (**3**, 38%) and recovered starting material **8** (8%) (run 5). These results clearly reveal that the strength of base used affects the preference as to which is the reactive site in the starting molecule.

Table 2. Results of Heck reaction of 4-bromotryptophan (**8**) with 1,1-dimethylallyl alcohol (**9**)



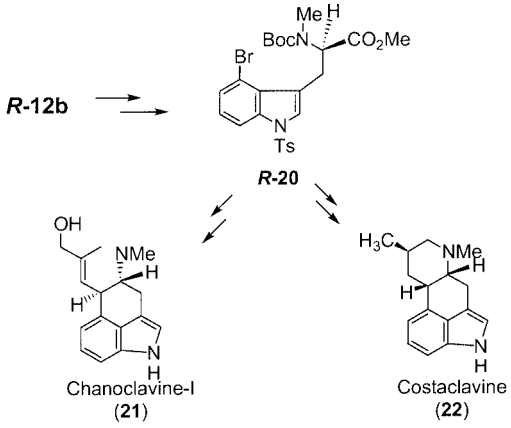
Run	Base	**10**	Other products (%)
1	$NaHCO_3$	-	many products
2	Na_2CO_3	51	**8** (38)
3	K_2CO_3	91	
4	NaOH	91	
5	Et_3N	55	**8** (8) + **3** (38)

We had obtained the pure potassium salt of **10** [M = K] in good yield. Treatment of **10** with 50% AcOH (50 °C, 3 h) resulted in a smooth cyclization, giving **6** in 78% yield as a isomeric mixture. Next, we attempted the one-pot synthesis of optically active **6**. After optically active ***S*-8** (92% *ee*) underwent the Heck reaction, the reaction mixture was acidified with 50% aq. AcOH and warmed to 50 °C for 3 h. The one-pot reaction proceeded smoothly to give an isomeric mixture of the natural products **6**[14] in 61% yield (Scheme 2). After esterification with $(CH_3)_3SiCHN_2$, each isomer was isolated as its methyl ester by silica gel column chromatography, and the optical purities of these compounds were determined by HPLC. Surprisingly, this one-pot process did not cause any racemization, in spite of the strong basic conditions used in the Heck reaction (K_2CO_3 in H_2O at 130 °C for 2 h).

Discussion

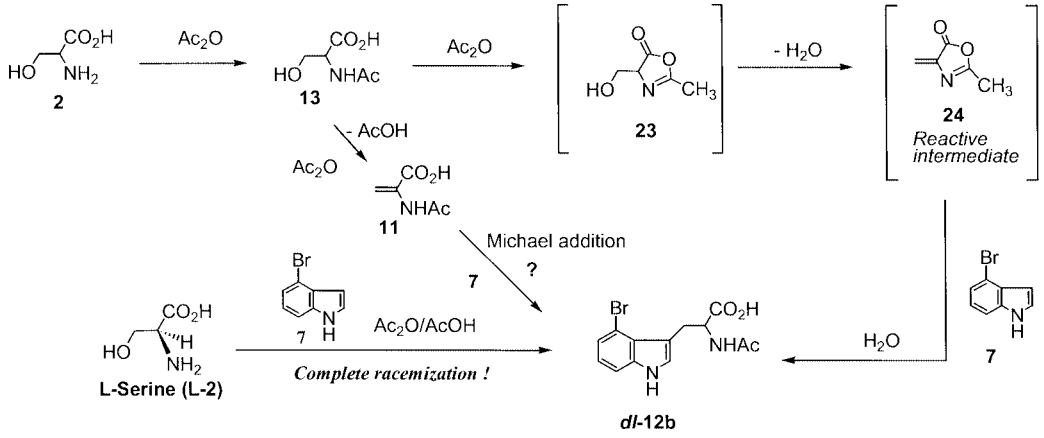
Synthesis of Optically Active 4-Bromotryptophan (*S*-8)

There have been several reports[15] on the direct synthesis of tryptophan (**3**) from indole (**1**) and serine (**2**) or its analogues. The aims of those reports were to mimic the biosynthesis. However, the yield and enantiomeric excess from the methods described above were far from satisfactory (3% yield, 35% *ee*) and this procedure cannot be used for practical synthesis. In the present study, we have succeeded in developing a practical synthesis of enantiomerically pure (***S*)-8** starting from 4-bromoindole (**7**) and *dl*-serine (*dl*-**2**) (Table 1 and Route A in Scheme 3). Although ***S*-8** could be synthesized by another route in higher overall yield (67%) by protecting all the reactive functional groups (route B in Scheme 3), it should be emphasized that the former route required only two steps and did not involve any expensive reagents. In the latter route, four out of the six steps were protection and deprotection procedures, and several expensive reagents (an equimolar amount of $Pd(OAc)_2$, rhodium catalyst, and optically active ligand) were required. Furthermore, (*R*)-*N*-acetyl-4-bromotryptophan (***R*-12b**), which was obtained as a by-product (Scheme 3, Route A), was transformed[16] into enantiomerically pure ***R*-20**, which is an important intermediate for the synthesis of ergot alkaloids, such as chanoclavine-I (**21**)[17a] and costaclavine (**22**)[17b] (Scheme 6).



Scheme 6. Synthesis of optically active ergot alkaloids

Scheme 7 shows a plausible mechanism for the formation of *N*-acetyl-4-bromotryptophan (**12b**) from 4-bromoindole (**7**) and serine (**2**). Since reaction with L-serine (L-**2**) resulted in complete racemization of **12b**, direct nucleophilic substitution at the hydroxyl carbon can be excluded. The reaction seems to be a simple acid-catalyzed Michael addition of **7** to *N*-acetyldehydroalanine (**11**), which might be formed in situ by the reaction of serine with Ac_2O, via *N*-acetylserine (**13**).[18] Although tryptophan synthesis by Michael addition of indole to a dehydroamino acid is already known,[19] in this reported case, special reaction conditions had to be designed in order to activate the double bond, as it was deactivated by the electron-donating acetamide group. It also has been reported that Michael addition of indole (**1**) to a reactive conjugated ketone such as methyl vinyl ketone required careful control of acidity to prevent side reactions such as dimerization or polymerization.[20] Johnson[21] reported that the mixed anhydrides of acrylic acid were reactive enough to undergo conjugate-addition, giving indole-3-propionic acid. Snyder[5] also reported that *N*-acetyldehydroalanine



Scheme 7. Plausible mechanism for the reaction of *N*-acetyl-4-bromotryptophan (*dl*-**12b**)

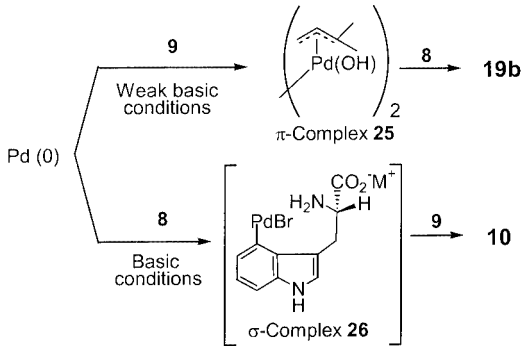
(**11**) did not react with indole in the absence of acetic anhydride. Our present study revealed that two equivalents of Ac_2O relative to **2** were required to make the reaction proceed, while one equivalent of Ac_2O was enough to make the reaction proceed with *N*-acetylserine (**13**). After the first equivalent of Ac_2O reacts with **2**, the second equivalent reacts with the carboxyl group of **13**, causing spontaneous formation of the oxazolone **23** and dehydration to form the conjugated oxazolone **24**,[22] a species which might be a key intermediate in this reaction. Since the double bond of **24** should be more reactive than that of **11**, bearing in mind the strong electron-withdrawing effect of the oxazolone group, Michael addition to this compound would occur smoothly. The complete racemization of **12b** when L-**2** was used suggests that the asymmetric center was converted into an sp^2 carbon during the reaction. A more detailed investigation of the mechanism of this reaction based on reactions conducted under various conditions, and its application to the syntheses of other tryptophan derivatives will be reported in a later paper.

Synthesis of Optically Active Clavicipitic Acids (6)

The one-pot transformation of free 4-bromotryptophan (***S*-8**) into the clavicipitic acids (**6**), as shown in Scheme 2, involves three important new features: 1) the sequential reaction of unprotected amino acid functional groups; 2) a controlled chemoselective reaction that only occurs in aqueous solution, and 3) no racemization, in spite of the strongly basic conditions in the Heck reaction.

There have been few reports of consecutive reactions of free amino acids, such as that which led to **6** in one pot via the spontaneous cylcization of **10**. For example, Casalnuovo[23] reported the palladium-catalyzed alkynylation of 2-iodotyrosine using TPPTS in aqueous media, leading initially to the expected alkyne, which then cyclized in situ to give the benzofuran derivative. Another example involves the participation of unprotected functional groups of amino acids, as reported by Brewster.[24] He described the deamination of free optically active amino acids to give the hydroxy acid with complete net retention, due to anchimeric assistance by the carboxyl group. Our present work has demonstrated that unprotected functional groups can be effectively utilized in a one-pot reaction and that the design of a very short synthesis may be possible by omitting the protection and deprotection steps.

The second feature is a palladium-catalyzed chemoselective reaction of 4-bromotryptophan (**8**). Changing the pH affected which site in the molecule was reactive; *N*-allylation occurred under weakly basic conditions (Scheme 5), while the Heck reaction occurred selectively under strongly basic conditions (Table 2). It should be emphasized that this reaction only occurred when water was used as the solvent. It is very interesting that pH plays a critical role in the chemoselectivity of palladium-catalyzed reactions in aqueous media. It is well known that the Heck reaction[25] occurs faster in water than in organic solvents, whereas palladium-catalyzed *N*-allylation with allyl alcohol in water has not been reported. A Lewis acid[26a,26b] or highly activated palladium catalyst[26c] has been required for the reaction to proceed in an organic solvent. Our results reveal that *N*-allylation is also accelerated in water. The intermediates for *N*-allylation and C^4-vinylation (Heck reaction) were known to be the π-allyl palladium complex **25** and σ-complex **26**, respectively (Scheme 8). In order to explain this selectivity, Pd^0 should react selectively with allyl alcohol to form **25**[27] under weakly basic conditions, whereas under more strongly basic conditions, **26** should be formed before **25**. It is not clear at present why the formation of the π-allyl palladium complex **25** and σ-complex **26** could be pH dependent in water. We are currently investigating the reaction of aromatic bromides containing an amino group, such as bromoanilines and bromobenzylamine.



Scheme 8. Intermediates for the palladium-catalyzed reaction of 4-bromotryptophan (**8**)

The third interesting feature was the absence of the racemization of amino acids. During the Heck reaction, racemization did not occur, in spite of the strongly basic conditions (3 equiv. of K_2CO_3 at 130 °C, for 5 h). The results prompted us to investigate the racemization of amino acids under basic conditions, and the extent of racemization in water was compared to that in organic solvent. The experimental details already have been reported.[28] From this study, we found that free amino acids in water possessed interesting properties. Free amino acids were more stable in water than in polar organic solvents and they also did not racemize under basic conditions in water.

Conclusion

We have succeeded in developing a three-step synthesis of optically active clavicipitic acids (**6**) following a route very similar to the biosynthetic pathway. This route: 1) is the first practical synthesis of tryptophan from indole and serine, which mimics tryptophan biosynthesis; 2) provides a unique one-pot reaction sequence leading to the clavicipitic acids; 3) allows a chemoselective palladium-catalyzed reaction (i.e. either *N*-allylation or the Heck reaction) of free 4-bromotryptophan in aqueous solution, with the choice of reactive site in the starting material being determined by the pH; and 4) makes use of the fact that water suppresses

the racemization and decomposition of free amino acids under strongly basic conditions.

We believe that the reactions of unprotected amino acids would provide the possibility, not only of significantly shortening synthetic routes through omission of the protection and deprotection steps,[29] but also of creating new synthetic reactions under aqueous conditions. The present investigation might be one of the most successful examples in such methodology.

Experimental Section

General Remarks: All reagents and solvents were obtained commercially and used as received, unless otherwise indicated. Acylase (from *Aspergillus genus*) was purchased from Tokyo Kasei Kogyo Co., LTD (TCI), and was used without purification. All melting points were determined on a Yanagimoto micro-melting hot stage apparatus and are uncorrected. IR spectra were recorded as KBr tablets (unless otherwise stated) on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on a JEOL GX-400 (400 MHz) spectrometer (unless otherwise stated) with tetramethylsilane as the internal reference. The following abbreviations are used: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quadruplet; m, multiplet; br, broad; dif, diffuse; Ar, aromatic. EI Mass spectra were measured with a JEOL JMS-01SG-2 or JMS-AM-II-50 spectrometer using a direct inlet system. FAB Mass spectra were measured with a JEOL JMS-600H spectrometer using a direct inlet system. ESI Mass spectra were measured with a Thermoquest LCQ-10 spectrometer. Optical rotations were measured with the JASCO DIP-1000. Separations were performed using Kieselgel 60 (70−230 mesh, Merck) for silica gel column chromatography, Chromatorex® (Fuji Silysia Chemical Ltd.) for ODS-silica gel column chromoatography, Diaion® SP-207 (Mitsubishi Chemical) for synthetic absorbent chromatography, Celurofine® GH-25C (Biochemicals) for cellulose column chromatography, and Kieselgel® GF 254 for thin layer chromatography (TLC). Synthetic resin, SP-207, was extensively washed with MeOH and H_2O before use.

Supporting Information: ^{1}H NMR spectra of **6**, (***S***)-**8**, **10**, *dl*-**12b**, *dl*-**15b**, **18**, **19a**, and **19b** (see also the footnote on the first page of this article).

***dl*-*N*-Acetyl-4-bromotryptophan Methyl Ester (*dl*-12c). Reaction of 4-Bromoindole (7) with *N*-Acetyldehydroalanine (11):** A mixture of 4-bromoindole (**7**) (199 mg, 1.0 mmol), *N*-acetyldehydroalanine (**11**) (259 mg, 2.0 mmol), and Ac_2O (0.40 mL, 4 mmol) in AcOH (1.2 mL) was heated at 80 °C for 1.5 h under argon. The mixture was basified with 30% KOH in an ice-bath and washed with organic solvent (EtOAc/benzene, 1:1). The aqueous layer was acidified with conc. HCl and extracted three times with EtOAc. The combined organic layers were washed with H_2O and brine, and dried with $MgSO_4$. After evaporation of solvent and azeotropic removal of AcOH with benzene, the resulting brown solid was dissolved in EtOAc (4 mL) and MeOH (2 mL). 2.0 M Trimethylsilyldiazomethane ($TMSCHN_2$, 5.5 mmol, 2.7 mL) in hexane was added to this solution, and the resulting mixture was kept for 30 min at room temperature. Then, AcOH was added to quench the reaction, and the solution was diluted with water. The aqueous layer was extracted three times with EtOAc, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and dried with $MgSO_4$. After evaporation of the solvent, the resulting brown oil (313 mg) was subjected to silica gel chromatography (benzene/acetone, 3:1) to give 124 mg of **12c** (36% yield) of a pale yellow solid, which was recrystallized from EtOAc/hexane to give white needles, m.p. 197−198 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.89 (s, 3 H) , 3.45 (dd, *J* = 15.0, 8.0 Hz, 1 H), 3.63 (dd, *J* = 15.0, 5.4 Hz, 1 H), 3.71 (s, 3 H), 4.95 (ddd, *J* = 8.0, 8.0, 5.4 Hz, 1 H), 6.07 (br. d, *J* = 8.0 Hz, 1 H), 6.99 (t, *J* = 8.0 Hz, 1 H), 7.09 (d, *J* = 2.4 Hz, 1 H), 7.26 (d, *J* = 8.0 Hz, 1 H), 7.27 (d, *J* = 8.0 Hz, 1 H), 8.34 (br. s, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3379, 3317, 1735 cm^{-1}. FAB-MS: *m*/*z* = 339 [M^+ + H] (70%), 341 [M^+ + H + 2] (65%), 119 (base peak). $C_{14}H_{15}N_2O_3Br$ (339.18): calcd. C 49.58, H 4.46, N 8.26; found C 49.56, H 4.47, N 8.30.

Reaction of 7 with *dl*-*N*-Acetylserine (*dl*-13): A mixture of **7** (50 mg, 0.26 mmol), *dl*-*N*-acetylserine (*dl*-**13**) (68 mg, 0.52 mmol), and Ac_2O (0.01 mL, 1.1 mmol) in AcOH (0.9 mL) was heated at 80 °C for 1.5 h under argon. The work-up and esterification procedure was carried out as above to give crude *dl*-**12c** (66 mg) as a brown solid that was purified as above to give 55 mg (63% yield) as pale yellow solid.

Reaction of 7 with *dl*-Serine (*dl*-2): A mixture of *dl*-**2** (165 mg, 1.5 mmol) and Ac_2O (0.3 mL, 3.0 mmol) in AcOH (1.8 mL) was heated at 45 °C for 5 h. **7** (106 mg, 0.54 mmol) was added to the resulting clear solution, and the mixture was heated at 80 °C for 1.5 h. The work-up, esterification, and purification procedure was carried out as above to give *dl*-**12c** (133 mg, 73% yield) as a pale yellow solid.

***dl*-*N*-Acetyl-4-bromotryptophan (*dl*-12b):** A mixture of *dl*-**2** (2.64 g, 25 mmol) and Ac_2O (5.0 mL, 49 mmol) in AcOH (15 mL) was heated at 80 °C for 1.5 h. **7** (2.4 g, 12.3 mmol) was added to the resulting clear solution, and the mixture was heated at 80 °C for 1.5 h. The reaction mixture was basified with 30% NaOH and washed with benzene three times. The aqueous layer was acidified with conc. HCl, and extracted with organic solvent (EtOAc/benzene, 2:1) three times. The combined organic layers were washed with H_2O and brine and dried with $MgSO_4$. After evaporation of the solvent, the resulting brown solid (3.67 g) was subjected to neutralized silica gel chromatography [300 g, benzene/EtOAc (1:5) → EtOAc] to give **12b** in the EtOAc fraction as a pale brown viscous oil (2.81 g, 71%). ^{1}H NMR ([D_6]DMSO, 400 MHz): δ = 1.78 (s, 3 H), 3.07 (dd, *J* = 15.0, 8.0 Hz, 1 H), 3.54 (dd, *J* = 15.0, 5.0 Hz, 1 H), 4.55 (ddd, *J* = 10.0, 8.0, 5.0 Hz, 1 H), 6.96 (t, *J* = 8.0 Hz, 1 H), 7.17 (d, *J* = 8.0 Hz, 1 H), 7.23 (d, *J* = 2.0 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 8.16 (d, *J* = 7.8 Hz, 1 H), 11.19 (br. s, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3320, 1733, 1640 cm^{-1}. EI-MS: *m*/*z* = 324 [M^+] (1.4%), 326 [M^+ + 2] (1.3%), 208 (base peak). $C_{13}H_{13}N_2O_3Br$ (325.16): calcd. C 48.02, H 4.03, N 8.62; found C 48.06, H 4.05, N 8.52%.

Kinetic Resolution of *dl*-*N*-Acetyl-4-bromotryptophan (*dl*-12b): A solution of *dl*-**12b** (151 mg, 0.46 mmol), acylase (61.1 mg), and $CoCl_2 \cdot 6H_2O$ (6.5 mg, 0.02 mmol) in 20 mM NaH_2PO_4 buffer (pH 7.51) (30 mL) was shaken at 37 °C for 48 h. The reaction mixture was acidified with 5% HCl and washed three times with benzene-EtOAc (1:1). The combined organic layers were washed with H_2O, followed by drying with $MgSO_4$. Evaporation of the solvent gave crude ***R*-12b** (78.3 mg), which was esterified with 2.0 M $TMSCHN_2$ and purified by silica gel chromatography, as described for the synthesis of *dl*-**12c**, to give ***R*-12c** (74 mg, 47%), with an optical purity of > 99% *ee* by HPLC analysis using a chiral column [SUMIPAX OA-4600 (SCAS), hexane/*i*PrOH/AcOH, 100:20:1]; m.p. 198−202 °C, $[\alpha]_D^{22}$ = −16.2 ($CHCl_3$, *c* = 0.26). All spectroscopic data were identical with *dl*-**12c**. $C_{14}H_{14}N_2O_3Br$ (339.18): calcd. C 49.58, H 4.46, N 8.26; found C 49.64, H 4.45, N 8.24.

The aqueous layer was neutralized with 30% NaOH, the solution was reduced to ca. 5 mL by evaporation under reduced pressure and then subjected to ODS-silica gel column chromatography (20 g). After removal of inorganic salts by eluting with H_2O, ***S*-8** was obtained at the ratio of H_2O/MeOH (3:1) as a pale brown solid (68.3 mg, 49%), which was > 99% *ee* by HPLC analysis using a chiral column [Chirabiotic T (Astec), EtOH/H_2O/AcOH, 100:100:1]; m.p. 262−263 °C, $[\alpha]_D^{22}$ = −64.1 (AcOH, *c* = 0.304). ^{1}H NMR ([D_6]DMSO, 400 MHz): δ = 2.91 (dd, *J* = 15.2, 10.0 Hz, 1 H), 3.54 (dd, *J* = 15.2, 4.4 Hz, 1 H), 3.73 (dd, *J* = 10.0, 4.4 Hz, 1 H), 6.96 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.16 (d, *J* = 8.4 Hz, 1 H), 7.29 (d, *J* = 2.0 Hz, 1 H), 7.35 (d, *J* = 8.4 Hz, 1 H) ppm. IR (KBr): ṽ = 3413, 1653 cm^{-1}. ESI-MS: *m*/*z* = 283 (M^+ + H), 285 [(M^+ +2)+H]. $C_{11}H_{11}N_2O_2Br$ (283.12): calcd. C 46.66, H 3.92, N 9.89; found C 46.40, H 4.08, N 9.63.

Large-Scale Preparation of (*S*)-4-Bromotryptophan (*S*-8): After *dl*-**12b** (832 mg, 2.56 mmol) was dissolved in 1.0 N NaOH (2 mL), the solution was diluted with 20 mM NaH_2PO_4 (pH 7.66, 160 mL). Acylase (86.6 mg, 2598 units) and $CoCl_2$·$6H_2O$ (19.8 mg, 0.07 mmol) were added to this solution. The resulting pale red solution (pH 7.5) was shaken at 37 °C for 72 h. The reaction mixture was acidified with conc. HCl and washed with benzene/EtOAc (1:1) three times. The aqueous layer was neutralized with 30% NaOH and reduced to 50 mL, then subjected to cellulose column chromatography (Cellulofine® GH-25-C, 350 mL), eluting with H_2O. The fraction containing ***S*-8** was concentrated to 50 mL and subjected to SP-207 column chromatography (200 mL), eluting with H_2O/EtOH (3:1) to give pure ***S*-8** as a pale yellow solid (302 mg, 42%).

The combined organic layers were washed with H_2O and dried with $MgSO_4$. Evaporation of the solvent gave crude ***R*-12b** (415 mg), which was esterified with 2.0 M $TMSCHN_2$ and purified by silica gel chromatography, as described for the synthesis of *dl*-**12b**, to give ***R*-12b** (392 mg, 45%), with an optical purity of > 99% *ee* by HPLC analysis using a chiral column [SUMIPAX OA-4600 (SCAS), hexane/*i*PrOH/AcOH, 100:20:1].

Alternative Synthesis of (*S*)-4-Bromotryptophan (*S*-8) from (*S*)-4-Bromo-*N*-(*tert*-butoxycarbonyl)-1-tosyltryptophan Methyl Ester (*S*-14a)

(*S*)-4-Bromo-*N*-(*tert*-butoxycarbonyl)tryptophan Methyl Ester (14b): Mg ribbon (1.50 g, 62 mmol) was added to MeOH (19 mL) at 0 °C. After hydrogen gas began to be evolved, a solution of ***S*-14a**[9] (95% *ee*, 623 mg, 1.13 mmol) in MeOH (15 mL) was added at the same temperature, and the resulting mixture was vigorously stirred until the starting material disappeared (20 min). Then the reaction mixture was quenched with saturated NH_4Cl, and extracted with EtOAc three times. The combined organic layers were washed with saturated $NaHCO_3$ and brine, and dried with $MgSO_4$. After evaporation of the solvent, the resulting residue was subjected to silica gel column chromatography to give pure (***S***)-4-bromo-*N*-(*tert*-butoxycarbonyl)tryptophan methyl ester (**14b**, 431 mg, 96%) as a colorless solid. The optical purity was 95% by HPLC analysis using a chiral column [CHIRALPAK AS (Daicel), hexane/*i*PrOH, 3:1]; m.p. 135−139 °C. $[\alpha]_D^{20}$ = −11.0 ($CHCl_3$, *c* = 2.2). ^{1}H NMR (CD_3OD, 400 MHz): δ = 1.32 (s, 9 H), 3.04 (dd, *J* = 15.0, 10.0 Hz, 1 H), 3.46 (dd, *J* = 15.0, 5.0 Hz, 1 H), 3.60 (s, 3 H), 4.30−4.40 (m, 1 H), 6.97 (t, *J* = 7.5 Hz, 1 H), 7.18 (d, *J* = 7.5 Hz, 1 H), 7.24−7.28 (m, 2 H), 7.37 (d, *J* = 7.5 Hz, 1 H) ppm. IR (KBr): ṽ = 3333, 1730. 1689 cm^{-1}. FAB-MS: *m*/*z* = 396 (M^+] (20%), 398 [M^+ +2] (18%), 210 (base peak). $C_{17}H_{21}N_2O_4Br$ (397.26): calcd. C 51.40, H 5.33, N 7.05; found C 51.29, H 5.13, N 7.03.

(*S*)-4-Bromotryptophan (*S*-8): The above ester **14b** (497 mg, 1.25 mmol) was dissolved in dioxane (7.8 mL), and a 10% KOH/MeOH solution (5.8 mL) was added. The mixture was kept at room temperature for 1.5 h. After this time, the mixture was poured into ice-water, and acidified with AcOH. The solution was extracted with EtOAc three times, and the combined organic layers were washed with water and dried with $MgSO_4$. After evaporation of the solvent, the (*S*)-4-bromo-*N*-(*tert*-butoxycarbonyl)tryptophan (***S*-18**) was obtained as a white solid (472 mg). It was dissolved in 50% aqueous AcOH (31 mL) and heated at 80 °C for 3 h. Evaporation of the solvent gave pure ***S*-8** as a white solid (319 mg, 90% overall yield from the ester), with an optical purity of 92% *ee*, as determined by HPLC.

Palladium Catalyzed *N*-Allylation of 4-Bromotryptophan (8) with 2-Methyl-3-buten-2-ol (9): A mixture of ***dl*-8** (50 mg, 0.177 mmol), **9** (400 μL, 5.6 mmol), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol), TPPTS (20 mg, 0.035 mmol), and AcONa (25 mg, 0.38 mmol) in H_2O (1.5 mL) was heated at 120 °C for 4.5 h in a sealed tube. The solvent was removed under reduced pressure, and the resulting residue was dissolved in a small amount of AcOH and subjected to ODS-silica gel column chromatography (10 g). A solvent gradient, starting with H_2O and with increasing proportions of MeOH, was used as eluent. When the eluent was H_2O/MeOH (3:1), the starting material **8** (19 mg, 35% recovery) was eluted. The second fraction (H_2O/MeOH, 2:1) gave crude *dl*-4-bromo-*N*-(3-methyl-2-buten-1-yl)tryptophan (**19b**), which was washed with CH_3CN to give a colorless solid (22 mg, 34% yield). m.p. 186−188 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ = 1.54 (s, 3 H), 1.67 (s, 3 H), 3.30 (m, 1 H), 3.48 (d, *J* = 7.0 Hz, 2 H), 3.75 (dd, *J* = 15.0, 6.0 Hz, 1 H), 4.04 (dd, *J* = 9.0, 6.0 Hz, 1 H), 5.05 (t, *J* = 7.0 Hz, 1 H), 6.97 (t, *J* = 8.0 Hz, 1 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H) ppm. IR (Nujol): ṽ = 3208, 1626 cm^{-1}. FAB-MS: *m*/*z* = 351 [M^+] (80%), 353 [M^+ +2] (85%), 69 (base peak). $C_{16}H_{18}BrN_2NaO_2$·$2.1H_2O$ (411.06): calcd. C 46.64, H 5.67, N 6.80; found C 46.23, H 5.45, N 6.99.

Palladium Catalyzed *N*-Allylation of Tryptophan (3) with 2-Methyl-3-buten-2-ol (9): A mixture of **3** (97 mg, 0.49 mmol), **9** (1.1 mL 11 mmol), $Pd(OAc)_2$ (11 mg, 0.049 mmol), TPPTS (56 mg, 0.098 mmol), and AcONa (80 mg, 0.98 mmol) in H_2O (2.0 mL) was heated at 120 °C for 5 h in a sealed tube. The work-up and isolation procedure was carried out as above to give pure *N*-(3-methyl-2-buten-1-yl)tryptophan (**19a**) (93 mg, 71%) as colorless needles. m.p. 224−225 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ = 1.53 (s, 3 H), 1.68 (s, 3 H), 3.21 (dd, *J* = 16.0, 6.0 Hz, 1 H), 3.44−3.54 (m, 3 H), 3.84 (dd, *J* = 9.0, 4.0 Hz, 1 H), 5.03 (t, *J* = 7.0 Hz, 1 H), 7.04 (t, *J* = 7.0 Hz, 1 H), 7.12 (t, *J* = 7.0 Hz, 1 H), 7.21 (s, 1 H), 7.36 (d, *J* = 7.0 Hz, 1 H), 7.67 (d, *J* = 7.0 Hz, 1 H) ppm. IR (KBr): ṽ = 3280, 1607 cm^{-1}. FAB-MS: *m*/*z* = 273 [M^+] (base peak). $C_{16}H_{20}N_2O_2$·H_2O (290.36): calcd. C 66.19, H 7.64, N 9.65; found C 66.20, H 7.23, N 9.61.

***dl*-4-Bromo-*N*-(*tert*-butoxycarbonyl)tryptophan (18):** A mixture of *dl*-4-bromo-*N*-(*tert*-butoxycarbonyl)tryptophan methyl ester (40 mg, 0.10 mmol) and KOH (50 mg, 0.84 mmol) in MeOH (0.45 mL) and dioxane (0.6 mL) was stirred for 1.5 h at room temperature. The reaction mixture was poured into the ice water, acidified with AcOH and extracted with EtOAc three times. The combined organic layers were washed with water and dried with $MgSO_4$. After evaporation of the solvent, *dl*-4-bromo-*N*-(*tert*-butoxycarbonyl)tryptophan (**18**) was obtained as a colorless amorphous powder (38 mg, 99%). ^{1}H NMR ([D_6]DMSO, 100 °C, 400 MHz): δ = 1.28(s, 9 H), 3.10 (dd, *J* = 15.0, 10.0 Hz, 1 H), 3.54(dd, *J* = 15.0, 5.0 Hz, 1 H), 4.34 (ddd, *J* = 10.0, 8.0, 5.0 Hz, 1 H), 6.37 (br. s, 1 H), 6.93 (t, *J* = 7.5 Hz, 1 H), 7.14 (d, *J* = 7.5 Hz, 1 H), 7.21 (d, *J* = 2.0 Hz, 1 H), 7.34 (d, *J* = 7.5 Hz, 1 H),

10.9 (br. s, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3418, 1696 cm^{-1}. FAB-MS: *m*/*z* = 382 [M^+] (11%), 384 [M^+ + 2] (9%), 57 (base peak). $C_{16}H_{19}N_2O_4 \cdot 0.3H_2O$ (388.65): calcd. C 49.45, H 5.08, N 7.21; found C 49.23, H 4.71, N 7.00.

***dl*-4-(3-Hydroxy-3-methyl-1-buten-1-yl)-*N*-(*tert*-butoxycarbonyl)-tryptophan, Sodium Salt (*dl*-15b):** A mixture of the above acid **18** (62 mg, 0.16 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), TPPTS (18 mg, 0.031 mmol), $NaHCO_3$ (39.4 mg, 0.47 mmol), and 2-methyl-3-buten-2-ol (**9**) (0.72 mL, 6.9 mmol) in H_2O (0.72 mL) was heated at 100 °C for 5 h. Then, the reaction mixture was directly subjected to ODS-silica gel column chromatography to remove inorganic salts by eluting with H_2O. Then, elution with MeOH gave the crude vinylated product (*dl*-**15b**, 55 mg), which was purified using preparative TLC (CH_2Cl_2/MeOH, 5:1) to give pure *dl*-**15b** as pale yellow solid (47 mg, 70%). m.p. 164−171 °C. ^1H NMR ([D_6]DMSO, 100 °C, 400 MHz): δ = 1.00−1.40 (m, 15 H), 2.70 (m, 1 H), 3.46 (dd, *J* = 15.0, 3.0 Hz, 1 H), 3.95 (dt, *J* = 9.0, 3.0 Hz, 1 H), 6.12 (d, *J* = 16.0 Hz, 1 H), 6.92 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.95 (t, *J* = 8.0 Hz, 1 H), 7.05 (br. s, 1 H), 7.17 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.48 (d, *J* = 16.0 Hz, 1 H), 10.32 (br. s, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3410, 1607 cm^{-1}. FAB-MS: *m*/*z* = 411 [M^+] (95%, base peak). $C_{21}H_{27}N_2O_5Na \cdot 2H_2O$ (446.47): calcd. C 56.49, H 7.00, N 6.27; found C 56.48, H 6.85, N 6.15.

***dl*-Clavicipitic Acids (6) from *dl*-15b:** A solution of *dl*-**15b** (14.1 mg, 0.0343 mmol) in 50% aqueous AcOH (3.0 mL) was heated at 80 °C for 3 h. After the starting material had disappeared (3 h), as monitored by HPLC [Supelcosil LC-ABZ (SUPELCO), 20 mM $NaHPO_4/CH_3CN$, 5:1], the reaction mixture was directly subjected to ODS-silica gel column chromatography using gradient elution from H_2O to MeOH. A mixture of *cis*- and *trans*-clavicipitic acids (*dl*-**6**) was obtained at the fraction of H_2O/MeOH (2:1), as pale yellow solid (7.0 mg, 76%), which was recrystallized from H_2O/MeOH to give pale yellow prisms. decomp. 278−282 °C. ^1H NMR (CD_3OD, 400 MHz): δ = 1.85 (s, [*cis*], 3 H), 1.90 (s, [*cis*], 3 H) 1.92 (s, [*trans*], 3 H), 1.93 (s, [*trans*], 3 H), 3.13 (dd, *J* = 20.0, 14.0 Hz [*trans*], 1 H), 3.35 (dd, *J* = 20.0, 14.0 Hz [*cis*], 1 H), 3.72 (dd, *J* = 14.0, 2.0 Hz [*cis*], 1 H), 3.76 (dd, *J* = 14.0, 2.0 Hz [*trans*], 1 H), 3.95 (br. d, *J* = 14 Hz [*trans*], 1 H), 4.19 (dd, *J* = 15.0, 2.0 Hz [*cis*], 1 H), 5.30 (br. d, *J* = 11.0 Hz [*cis*], 1 H), 5.49 (br. d, *J* = 11.0 Hz [*trans*], 1 H), 5.55 (br. d, *J* = 11.0 Hz [*trans*], 1 H), 5.85 (d, *J* = 11.0 Hz [*cis*], 1 H), 6.79 (d, *J* = 9.0 Hz [*cis*], 1 H), 6.82 (d, *J* = 9.0 Hz [*trans*], 1 H), 7.03 (t, *J* = 9.0 Hz [*cis*], 1 H), 7.07 (t, *J* = 9.0 Hz [*trans*], 1 H), 7.13 (s, [*cis*], 1 H), 7.17 (s, [*trans*], 1 H), 7.26 (d, *J* = 9.0 Hz [*cis*], 1 H), 7.29 (d, *J* = 9.0 Hz [*trans*], 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3700−2800, 1625 cm^{-1}. EI-MS: *m*/*z* = 270 [M^+] (54%),44 (base peak). $C_{16}H_{18}N_2O_2 \cdot H_2O$ (288.24): calcd. C 66.65, H 6.99, N 9.72; found C 66.98, H 6.76, N 9.01.

***dl*-4-(3-Hydroxy-3-methyl-1-buten-1-yl)tryptophan Potassium Salt (10) [M = K]:** A mixture of *dl*-**8** (13.2 mg, 0.047 mmol), $Pd(OAc)_2$ (1.3 mg, 0.0058 mmol), TPPTS (5.2 mg, 0.0091 mmol), K_2CO_3 (9.5 mg, 0.0687 mmol), and 2-methyl-3-buten-2-ol (**9**, 100 μL, 0.597 mmol) in H_2O (0.2 mL) was heated at 130 °C for 6 h in a sealed tube. After the starting material had disappeared (3 h), as monitored by HPLC [Supelcosil LC-ABZ (SUPELCO), 20 mM Na_2HPO_4/CH_3CN, 5:1], the reaction mixture was directly subjected to ODS-silica gel column chromatography using gradient elution from H_2O to MeOH. *dl*-4-(3-Hydroxy-3-methyl-1-buten-1-yl)tryptophan potassium salt (*dl*-**10**, M = K) was obtained at the fraction of H_2O/MeOH (2:1), as a pale yellow amorphous solid (13.8 mg, 91%). ^1H NMR (CD_3OD, 400 MHz): δ = 1.39 (s, 3 H), 1.40 (s, 3 H), 2.86 (dd, *J* = 16.0, 12.0 Hz, 1 H), 3.68 (d, *J* = 12.0 Hz, 1 H), 3.74 (d, *J* = 16.0 Hz, 1 H), 6.19 (d, *J* = 16.0 Hz, 1 H), 7.0−7.1 (m, 2 H), 7.15 (s, 1 H), 7.24 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.44 (d, *J* = 16.0 Hz, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3418, 1625 cm^{-1}. FAB-MS: *m*/*z* = 311 [M^+ + Na] (25%), 177 (base peak).

(*S*)-4-(3-Hydroxy-3-methyl-1-buten-1-yl)tryptophan Potassium Salt (*S*-10, M = K): A mixture of ***S*-8** (39.2 mg, 0.14 mmol, 92% *ee*), $Pd(OAc)_2$ (3.1 mg, 0.014 mmol), TPPTS (15.9 mg, 0.028 mmol), K_2CO_3 (27.3 mg, 0.20 mmol), and 2-methyl-3-buten-2-ol (**9**, 600 μL, 6.25 mmol) in H_2O (0.6 mL) was heated at 130 °C for 7 h in a sealed tube. Isolation was carried out as above to give (*S*)-4-(3-Hydroxy-3-methyl-1-buten-1-yl)tryptophan potassium salt (***S*-10**, M = K) as a pale yellow amorphous solid (40.2 mg, 89%), whose optical purity was 91% *ee*, as analyzed by HPLC after *tert*-butoxycarbonylation and esterification (see below). All spectroscopic data were identical with *dl*-**10**, [M = K] (see above) $[\alpha]_D^{20}$ = −75.4 (MeOH, *c* = 1.18). $C_{16}H_{19}KN_2O_3 \cdot 2.1H_2O$ (364.27): calcd. C 52.76, H 6.37, N 7.69; found C 52.59, H 6.23, N 7.68.

Determination of Optical Purity of *S*-10 [M = K]: A solution of Boc_2O (4.6 mg, 0.021 mmol) in 1,4-dioxane (50 μL) was added, with vigorous stirring, to a solution of ***S*-10** [M = K] (2.0 mg, 0.0061 mmol) and 1 M aqueous NaOH (25 μL) in 1,4-dioxane (50 μL) and H_2O (50 μL) at room temperature. After 1 h, the reaction was quenched by pouring into ice-water, and the mixture was extracted with EtOAc three times. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, and dried with $MgSO_4$. After evaporation of the solvent, a diethyl ether solution of CH_2N_2 (1.5 mL) was added to the resulting residue (8.9 mg) at 0 °C, and the mixture was allowed to stand for 15 min. After removal of the solvent, the product was purified by preparative TLC to a give pale yellow amorphous solid (2.1 mg, 85%), whose optical purity was 91% *ee*, as determined by HPLC analysis (CHIRALPAK AS, hexane/*i*PrOH, 7:1). All spectroscopic data were identical with authentic *dl*-4-(3-hydroxy-3-methyl-1-buten-1-yl)-*N*-(*tert*-butoxycarbonyl)tryptophan methyl ester (*dl*-**15c**) (see below).

***dl*-*N*-(*tert*-Butoxycarbonyl)-4-(3-hydroxy-3-methyl-1-buten-1-yl)-tryptophan Methyl Ester (*dl*-15c):** Mg ribbon (239 mg, 9.84 mmol) was added to MeOH (6.8 mL) and the mixture was stirred at room temperature. After hydrogen gas began to be evolved, a solution of *dl*-4-(3-hydroxy-3-methyl-1-buten-1-yl)-*N*-(*tert*-butoxycarbonyl)-1-tosyltryptophan methyl ester[9] (*dl*-**15a**, 201 mg, 0.362 mmol) in MeOH (15 mL) was added. Further Mg (225 mg and 230 mg) was added after 30 min and 1 h, respectively, and the reaction was stirred for a further 1 h at ambient temperature. After this time, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc three times. The combined organic layers were washed with saturated $NaHCO_3$ and brine and dried with $MgSO_4$. After evaporation of the solvent, the resulting residue (160 mg) was subjected to silica gel column chromatography (benzene/EtOAc, 4:1) to give the *dl*-**15c** (131 mg, 90%) as colorless solid, which was recrystallized from benzene/hexane to give colorless prisms, m.p. 74−84 °C. ^1H NMR (C_6D_6, 400 MHz): δ = 1.33 (s, 9 H), 1.50 (s, 3 H), 1.53 (s, 3 H), 3.03 (s, 3 H), 3.09 (dd, *J* = 14.0, 8.0 Hz, 1 H), 3.24−3.34 (m, 1 H), 4.92 (dd, *J* = 18.0, 8.0 Hz, 1 H), 5.16 (d, *J* = 8.0 Hz, 1 H), 6.37 (s, 1 H), 6.38 (d, *J* = 16.0 Hz, 1 H), 6.87 (br. s, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 16.0 Hz, 1 H) ppm. IR (KBr): ν̃: $\tilde{\nu}$ = 3391, 1694 cm^{-1}. FAB-MS: *m*/*z* = 402 [M^+] (18%), 69 (base peak). $C_{22}H_{30}N_2O_5$ (402.48): calcd. C 65.65, H 7.51, N 6.96; found C 65.57, H 7.57, N 6.77.

***dl*-Calvicipitic Acids (6) from *dl*-4-(3-Hydroxy-3-methyl-1-buten-1-yl)tryptophan Potassium Salt (*dl*-10, M = K):** A solution of *dl*-**10** [M = K] (13.8 mg, 0.0423 mmol) in 50% aqueous AcOH (2.0 mL)

was warmed at 50 °C for 3 h. After the starting material had disappeared (3 h), as monitored by HPLC [Supelcosil LC-ABZ (SUPELCO), 20 mM $NaHPO_4/CH_3CN$, 5:1], the reaction mixture was directly subjected to ODS-silica gel column chromatography using gradient elution from H_2O to MeOH. A mixture of *cis*- and *trans*-clavicipitic acids (*dl*-**6**) was obtained at the fraction of H_2O/MeOH (2:1), as a pale yellow solid (8.9 mg, 78%).

One-pot Synthesis of Optically Active Clavicipitic Acids (6) from (*S*)-4-Bromotryptophan (*S*-8): A mixture of ***S*-8** (26.1 mg, 0.092 mmol, 92% *ee*), $Pd(OAc)_2$ (2.2 mg, 0.0098 mmol), TPPTS (10.3 mg, 0.018 mmol), K_2CO_3 (19.2 mg, 0.14 mmol), and 2-methyl-3-buten-2-ol (**9**, 400 μL, 4.15 mmol) in H_2O (0.4 mL) was heated at 130 °C for 8 h in a sealed tube. After this time, the reaction mixture was allowed to cool to room temperature, 60% aqueous AcOH (1.6 mL) was added, and the resulting mixture was warmed at 60 °C for 2 h. After this time, the reaction mixture was directly subjected to ODS-silica gel column chromatography by gradient elution from H_2O to MeOH. A mixture of *cis* and *trans* clavicipitic acids (***S*-6**) was obtained at the fraction of H_2O/MeOH (2:1), as a pale yellow solid (15.1 mg, 61%). The optical purity of each isomer was analyzed by HPLC after esterification (see below), d.p. 253−260 °C (ref.[14] m.p. 262). $C_{16}H_{18}N_2O_2{\cdot}0.4H_2O$ (277.54): calcd. C 69.24, H 6.83, N 10.09; found C 69.45, H 6.98, N 9.73. All spectroscopic data were identical with *dl*-**6**.

Determination of Optical Purity of *cis* and *trans*-Clavicipitic Acids (6): A methanolic solution of the above isomeric mixture (23.1 mg, 0.086 mmol) was esterified with an ethereal solution of CH_2N_2. After evaporation of the solvent, each isomer was isolated by preparative TLC to give the pure *cis*- (1.7 mg) and *trans*- (2.8 mg) isomers as pale yellow needles. The optical purities of the isomers were 92% (*cis*) and 93% (*trans*), based on HPLC analysis (CHIRALPAK AS, hexane/*i*PrOH, 50:1). *trans*-Clavicipitic acid methyl ester; m.p. 144−148 °C (ref.[9] 158−160 °C). $[\alpha]_D^{22} = -116.3$ (EtOH, $c = 0.14$). [ref.[9] $[\alpha]_D^{22} = -129.1$ (EtOH, $c = 0.72$), > 99% *ee*]. All spectroscopic data were identical with reported *trans*-clavicipitic acid methyl ester.[9] *cis*-Clavicipitic acid methyl ester; m.p. 132−134 °C (ref.[9] 144−144.5 °C). $[\alpha]_D^{22} = -178.1$ (EtOH, $c = 0.09$). [ref.[2] $[\alpha]_D^{22} = -195.3$ (EtOH, $c = 0.39$), > 99% *ee*]. All spectroscopic data were identical with reported *cis*-clavicipitc acid methyl ester.[9]

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