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Total Synthesis of Clavicipitic Acid and Aurantioclavine: Stereochemistry of Clavicipitic Acid Revisited

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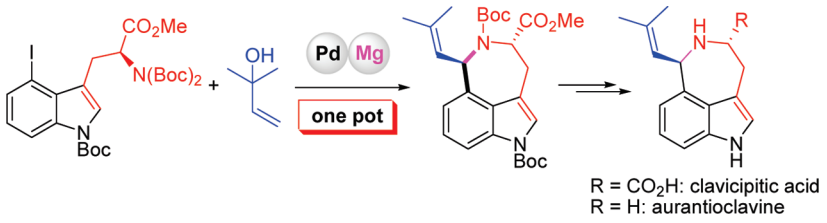

The stereocontrolled total synthesis of clavicipitic acid and aurantioclavine from a common azepino-[5,4,3-*cd*]-indole intermediate is reported. This key azepinoindole nucleus was constructed via a one-pot Heck/Boc-deprotection/aminocyclization process from the 4-iodotryptophan derivative, which was assembled by a Pd-catalyzed indole synthesis procedure. After two or three additional deprotection steps from the azepinoindole intermediates, (−)-*trans*- and (−)-*cis*-clavicipitic acid were prepared. The syntheses of both (−)- and (+)-aurantioclavine were achieved with the same azepinoindole intermediates utilizing the Barton decarboxylation reaction as the key step to remove the stereohindered carboxylic acid. During the course of our synthesis, mis-assigned configurations of the synthesized clavicipitic acids and their derivatives in the literature were identified. Extensive studies including 2D-NMR study, X-ray diffraction analysis, titration experiment, and R_f value comparison unambiguously confirmed the new configuration assignment. The *trans* and *cis* configuration assignments of the synthesized clavicipitic acids and their derivatives in the past literature should be switched.

Introduction

Clavicipitic acid[1−4] and aurantioclavine[5−7] (Figure 1) are unique members of the 3,4-disubstituted indole alkaloids characterized by the novel azepino[5,4,3-*cd*]-indole ring system. The azepinoindole framework was also found in complex fungal metabolite communesins.[8]

Clavicipitic acid, first isolated from the cultures of *Claviceps* strain SD58 or *Claviceps fusiformis* as a mixture of *trans*-**1a** and *cis*-**1b** diastereomers, was considered as the derailed product of ergot alkaloid biosynthesis.[1] However, no satisfactory NMR spectra were obtained during their isolation because of their low solubility in the commonly used organic

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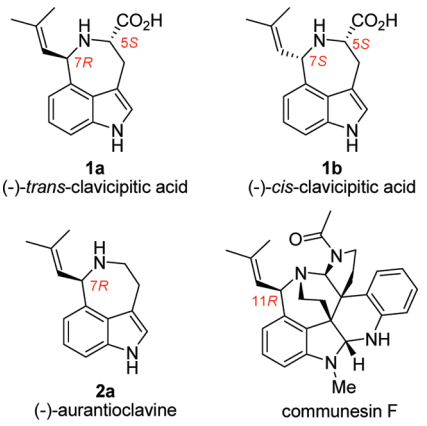

FIGURE 1. Structures of some naturally occurring azepino[5,4,3-*cd*]-indoles.

solvents and the lack of modern instrumentation. The relative configuration of one diastereomer of clavicipitic acid with a lower R_f value [$CHCl_3$−MeOH−concd NH_4OH (75:25:1), 1 day old] was determined to be *trans* by X-ray diffraction analysis.[1b]

(−)-Aurantioclavine, another structurally related ergot alkaloid bearing a single stereocenter, was first isolated from *Penicillium aurantiovirens* in 1981.[5] From the biosynthesis point of view, 4-(γ,γ-dimethylallyl)-tryptophan might be the common precursor of aurantioclavine and clavicipitic acid.[5,9] Moreover, it was proposed that aurantioclavine might serve as an intermediate in the biosynthesis of fungal communesin.[8c,d] So far, three racemic[6] and two enantioselective syntheses[7] of aurantioclavine have been achieved, and the absolute configuration of (−)-aurantioclavine was determined to be 7*R* by Stoltz and co-workers in 2008.[7a]

The synthesis of these 3,4-disubstituted indole alkaloids was an arduous task.[10] Generally speaking, two main strategies are available, relying either on direct functionalization at the less reactive 4-position of an existing indole nucleus or on functionalization at the 3-position of the preexisting 4-substituted indoles, which are usually prepared from simple aromatic precursors via indole synthesis.[11] However, only a few methods have been reported for the direct construction of optically pure 4-substituted tryptophan derivatives.[12]

Recently, a useful method for the synthesis of functionalized indoles via a Pd-catalyzed annulation reaction was developed by Zhu and Jia, which has been successfully applied to the construction of 4-substituted indoles, especially optically pure 4-substituted tryptophan derivatives.[3f,13] These 4-substituted tryptophan derivatives could serve as useful precursors for the synthesis of 3,4-disubstituted indole alkaloids, and we have reported an efficient total synthesis of clavicipitic acid taking advantage of this strategy.[3f] However, in our previous synthesis, Heck reaction of 4-chlorotryptophan derivative with 2-methyl-3-buten-2-ol required strict exclusion of oxygen and moisture and was carried out in a relatively dilute solution in the presence of an expensive phosphine ligand. All of these special requirements made the operation inconvenient. In order to overcome the operational limitations, we investigated another route to the key azepino[5,4,3-*cd*]-indole nucleus using a one-pot Heck/Boc-deprotection/aminocyclization process starting from 4-iodotryptophan derivatives. In addition, the synthesis of (−)- and (+)-aurantioclavine was also achieved from the same azepinoindole intermediates by utilizing the Barton decarboxylation reaction as the key step. Furthermore, our synthesis revealed that the reported relative configurations of synthesized clavicipitic acids and their derivatives are mis-assigned. Extensive structural analysis confirmed the correct configuration assignment.

Results and Discussion

Retrosynthetic Analysis of Clavicipitic Acid and Aurantioclavine. Our synthetic design is shown in Scheme 1. Both clavicipitic acid **1** and aurantioclavine **2** could be synthesized from the properly protected azepinoindole intermediate **3**. In our previous synthesis, intermediate **3** was constructed step by step via a Heck reaction with **5** followed by $Mg(ClO_4)_2$-mediated diastereoselective intramolecular S_N2'-type aminocyclization. We envisioned that direct transformation of **5** to this azepinoindole intermediate **3** could also be achieved in a cascade catalysis manner or one-pot process. Meanwhile, considering the low reactivity of the 4-chlorotryptophan derivative in Heck reaction, intermediate **5** with more reactive substitutions (X = OTf or I) at the 4-position were designed. These 4-substituted tryptophan derivatives (**5**) could be obtained by the reaction of corresponding 3-substituted *o*-iodoaniline **7** with the known chiral aldehyde **6**.

Attempted Synthesis of 4-Hydroxytryptophan Derivatives. Since Heck reaction could be carried out with the more reactive OTf substitution under ligand-free conditions, the synthesis of 4-hydroxytryptophan derivatives was first tried. Although 4-methoxytryptophan derivative was obtained in modest 55% yield,[13a,b] all three *o*-iodoaniline substrates **8a**−**c** failed to produce the desired tryptophan derivatives under the same conditions (Scheme 2).

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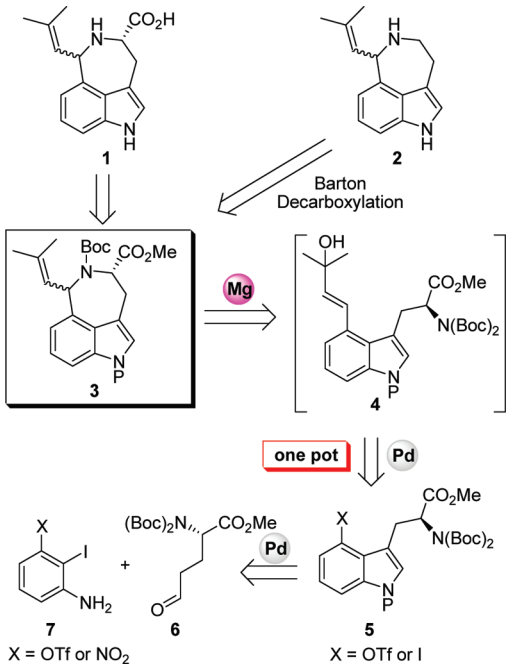
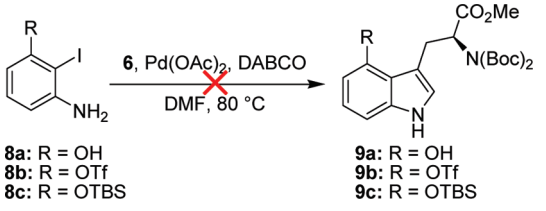
SCHEME 1. Retrosynthetic Analysis of Clavicipitic Acid (1) and Aurantioclavine (2)

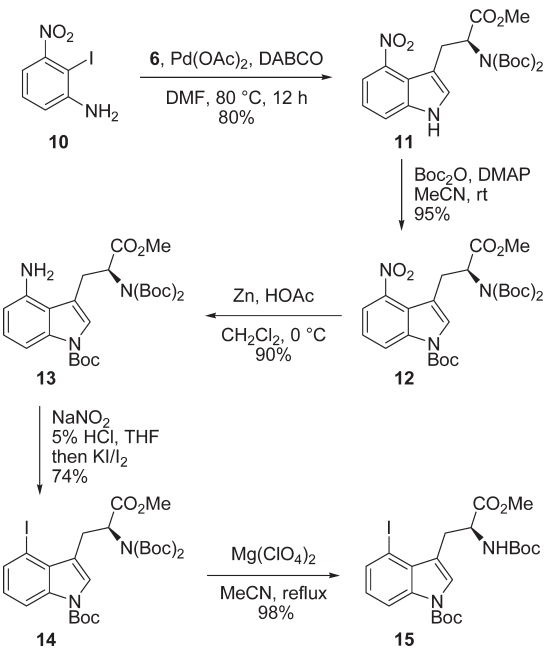


SCHEME 2. Attempted Synthesis of 4-Hydroxytryptophan Derivatives



Synthesis of 4-Iodotryptophan Derivatives. Our synthetic route to the 4-iodotryptophan derivatives **14** and **15** is shown in Scheme 3. Direct coupling of 3-nitro-2-iodoaniline **10**[14] with (*S*)-2-*N*,*N*-di-*tert*-butoxycarbonyl-5-oxopentane **6**[15] under standard Pd-catalyzed indole synthesis conditions afforded the optically pure 4-nitrotryptophan derivative **11** in 80% yield. Boc protection of the indole nitrogen and nitro reduction afforded the 4-aminotryptophan derivative **13**. Diazotization of **13** followed by the classical iodination process with KI provided **14** in low yield, accompanied with a substantial amount of the deiodinated product. However, we found that, by iodination with KI in the presence of 1 equiv of I_2, the desired 4-iodotryptophan derivative **14** was obtained in 74% yield, together with 15% deiodinated product.[13h,16] It was difficult to separate these two compounds at this stage. Selective partial deprotection of the di-Boc with $Mg(ClO_4)_2$[17] afforded **15**, which could be separated from its deiodinated product by careful chromatography.

SCHEME 3. Synthesis of 4-Iodotryptophan Derivatives



One-Pot Synthesis of the Azepinoindole Nucleus. Both 4-iodotryptophan intermediates **14** and **15** can be converted to **17** using the traditional two-step synthesis approach.[3e,f] However, it is also possible to employ the potentially more efficient cascade catalysis or one-pot process to carry out the synthesis.[18] The results of various reaction conditions are shown in Table 1.[19]

Since both the Heck reaction and aminocyclization could be promoted by palladium catalysis,[3e,4a,20] initial attempts to convert **15** to **17** were conducted in a cascade catalysis manner. However, only the Heck product **16** was obtained in most cases (Table 1, entries 1 and 2). Adding additional palladium catalyst ($Pd(OAc)_2$ or $PdCl_2(CH_3CN)_2$) to the reaction mixture after the Heck reaction was also tried. However, the desired **17** could be obtained in very low yield. It seems that the presence of base severely inhibits the catalysis cycle of this aminocyclization reaction.

We then turned our attentions to the one-pot process, which could also improve the reaction yield. There are a variety of available conditions for arylation of allylic alcohols,[3a,e,f,4a] and those conducted in air under ligand-free conditions are especially attractive.[21] Thus, we performed experiments to combine the Heck reaction with our previously developed $Mg(ClO_4)_2$-mediated Boc-deprotection/aminocyclization

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(19) There are three advantages for choosing **15** as the model rather than **14**, as **15** could be directly obtained in its pure form by careful chromatography whereas **14** could not. Meanwhile, the R_f values of the starting material **14** and products **17a**/**17b** are almost the same, and last, **15** is a suitable model substrate for Pd-catalyzed cascade Heck/aminocyclization reactions though it is not successful.
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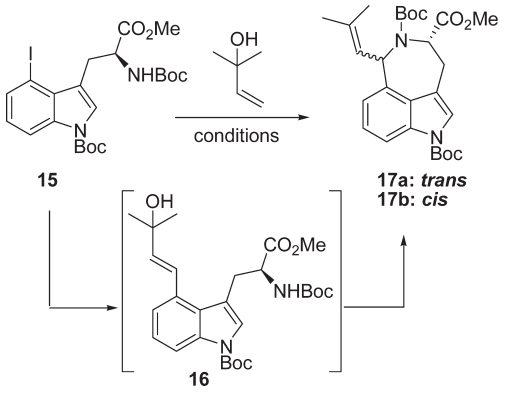
TABLE 1. Optimization of the Reaction Conditions for Azepinoindole Synthesis



entry	conditions[a]	product	yield (%)[b]
1	$Pd(OAc)_2$, K_2CO_3, DMF[c]	**16**	85
2	$Pd(OAc)_2$, Ag_2CO_3, PhH	**16**	95
3	$Pd(OAc)_2$, Ag_2CO_3, $Mg(ClO_4)_2$, PhH	**17**[e]	41
4	$Pd(OAc)_2$, Ag_2CO_3, $Mg(ClO_4)_2$, MeCN	*d*	
5	$Pd(OAc)_2$, Ag_2CO_3, PhH, then $Mg(ClO_4)_2$	**17**[e]	64
6	$Pd(OAc)_2$, Ag_2CO_3, MeCN, then $Mg(ClO_4)_2$	**17**[e]	84
7	$Pd(OAc)_2$, Ag_2CO_3, PhH, then MeCN, $Mg(ClO_4)_2$	**17**[e]	94

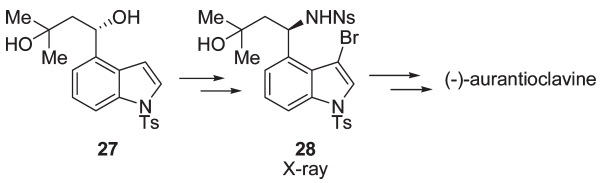
[a] 1.0 equiv of **15**, 10 equiv of 2-methyl-3-buten-2-ol, 0.10 equiv of $Pd(OAc)_2$, 0.6 equiv of Ag_2CO_3, 1.2 equiv of $Mg(ClO_4)_2$. [b] Isolated yield. [c] 3.0 equiv of K_2CO_3, 45 equiv of 2-methyl-3-buten-2-ol, under argon. [d] Starting material recovered. [e] *trans*:*cis* = 5:1.

process[3f] in a one-pot manner. Control experiments indicated that benzene was the best solvent for the Heck reaction, and acetonitrile was the optimal media for the aminocyclization process. Initial experiments showed that adding $Mg(ClO_4)_2$ together with palladium catalyst to the reaction mixture yielded the desired azepinoindole product **17** in only 41% yield when benzene was used as the solvent (entry 3). No reaction was observed when acetonitrile was used as the solvent, resulting in the recovery of the starting material (entry 4). When $Mg(ClO_4)_2$ was added after the completion of Heck reaction to avoid the possible interference with the Heck reaction, more desirable results were obtained. Under this condition, the desired product **17** was obtained in 64% yield when benzene was used as the solvent, together with about 15% dehydration product (entry 5), and the desired product was obtained in 84% yield (entry 6) when acetonitrile was used as the solvent. The best yield (entry 7) was achieved when **15** and 2-methyl-3-buten-2-ol were treated with 10% $Pd(OAc)_2$ and 0.6 equiv of Ag_2CO_3 in refluxing benzene for 2 h, followed by addition of acetonitrile and 1.2 equiv of $Mg(ClO_4)_2$ and stirring for an additional 2 h at reflux. The desired azepinoindole derivative **17** was obtained in 94% overall yield in this one-pot process, with a comparable *trans* to *cis* ratio (5:1) as reported.[3e,f]

Syntheses of (−)-*trans*- and (−)-*cis*-Clavicipitic Acid and Reassignment of the Configurations of the Synthesized Clavicipitic Acids and Their Derivatives. The total synthesis of clavicipitic acid was carried out as shown in Scheme 4. Under the optimal conditions, the tri-Boc-protected **14** was transformed to the desired azepinoindole product **17** in a one-pot Heck/Boc-deprotection/aminocyclization reaction in 90% overall yield, with a *trans* to *cis* ratio of 5:1. The two diastereomers *trans*-**17a** and *cis*-**17b** were separated at this stage by careful flash chromatography, and these two compounds could be easily converted to (−)-*trans*- and (−)-*cis*-clavicipitic acid, respectively, following our previous approach.[3f]

In our previous paper, the relative configuration of the major diastereomer **17a** was assigned as *cis* by comparing the NMR spectra of compounds **18a** and **1a** with those in literature.[3f] However, on the basis of the *cis* assignment, the absolute configuration of (−)-aurantioclavine **2a**, prepared from this major diastereomer (vide infra), should be assigned as 7*S*, which was opposite to that assigned by Stoltz.[7a] The 7*R* assignment of (−)-aurantioclavine **2a** has been confirmed via X-ray diffraction with an advanced intermediate by Stoltz.[22,23] Meanwhile, the minor diastereomer **17b** could be transformed to the (+)-aurantioclavine **2b**. Apparently, no epimerizations have occurred at C-7 in our synthesis of both enantiomers of aurantioclavine, and the stereocenter at C-5 is retained during the transformation of the starting amino acid to clavicipitic acid. Therefore, we suspected that the relative configurations of the synthesized clavicipitic acids and their derivatives assigned in our previous paper

(22) Though the assignment of the absolute configuration in **27** was based on their model of the oxidative process (see refs 7a and 23), Prof. Stoltz has obtained single crystal X-ray diffraction data on the advanced intermediate **28**, for which no inversion of the stereocenter occurred during its transformation to (−)-aurantioclavine. (Personal communation with Prof. Brian M. Stoltz.) Prof. Ellman has achieved the second enantioselective total synthesis of (−)-aurantioclavine recently, taking advantage of the asymmetric alkenylation of *N*-*tert*-butanesulfinyl imines, which allows the same absolute configuration assignment as that of Stoltz (see ref 7b).



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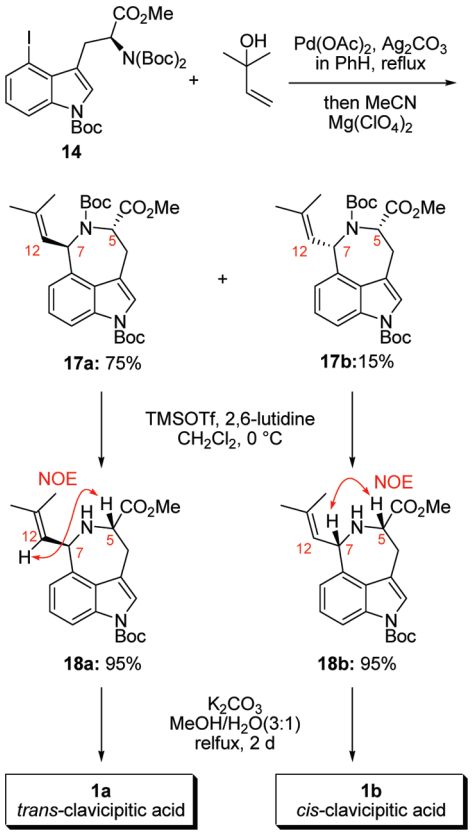
SCHEME 4. Synthesis of Clavicipitic Acid



as well as those reported in the literature had been mis-assigned,[2b,d,f,g,3a,3c−3g,4a] and their *trans* and *cis* configuration assignments should be switched.

To verify our suspicion, detailed 2D-NMR analysis of **17a,b** and **18a,b** were carried out. Although the NOESY results of **17a** and **17b** seemed to support the configuration assignments in our previous paper,[3f] further HSQC results showed that our previous assigment was wrong, because the downfield signals (δ 6.41, 6.15 for **17a**, and δ 6.42, 6.03 for **17b**) were arbitrarily attributed to the vinylic protons (H-12). In fact, these signals should be assigned to the benzylic protons (H-7) after detailed HSQC analysis, and this re-interpretation resulted in the opposite configuration assignments for **17a** and **17b**. Clearer NOESY spectra were obtained with **18a** and **18b** (Scheme 4). The cross peak between H-5 (δ 4.11) and H-12 (δ 5.40) of **18a** indicated the *trans* configuration of H-5 and H-7, and correlation between H-5 (δ 3.82) and H-7 (δ 4.87) of **18b** revealed their *cis* configuration.

To obtain a definitive proof for the reassignments, we made efforts to crystallize some advanced intermediates for X-ray diffraction analysis. However, our attempts to obtain suitable single crystals of the intermediates **17** and **18**, as well as aurantioclavine **2a,b** and their derivatives, were not successful.

Literature survey showed that clavicipitic acid methyl ester **23** could be recrystallized from benzene−hexane to form pale yellow prisms.[2d,3a,3d] We thought it might be a good candidate substrate for crystallization. Thus, we synthesized **23** from 4-nitrotryptophan derivative **11** following a similar sequence as described for **18a** (Scheme 5). Tosylation of **11** gave 1*N*-tosyl-4-nitrotryptophan derivative **19**. Nitro reduction followed by iodination of the resultant 4-amino-tryptophan derivative afforded the desired 4-iodotryptophan derivative **20** according to Knochel's procedure,[24] together with 10−20% mono-Boc product; no deiodinated product was detected under these conditions. Treating the crude products with Boc_2O and DMAP in acetonitrile yielded **20** in 67% overall yield from **19**. The one-pot Heck/Boc-deprotection/aminocyclization process was also used for the synthesis of 1*N*-tosyl-azepinoindole intermediates *trans*-**21a** and *cis*-**21b**, with a ratio of 3:1, in 95% overall yield. Deprotection of the Boc of *trans*-**21a** with TMSOTf, followed by detosylation afforded *trans*-**23a**, which upon alkaline hydrolysis gave the *trans*-clavicipitic acid **1a** according to the literature procedure.[3a] Following the same procedures, *cis*-**21b** was converted to *cis*-**23b** and *cis*-clavicipitic acid **1b.**

Both *trans*-**23a** and *cis*-**23b** produced single crystals suitable for X-ray diffraction analysis, which showed that their relative configurations were opposite to those assigned in the literature.[2d,3a,3d] Furthermore, we also obtained a single crystal of **1b**, and the X-ray diffraction results showed that its *cis* configuration is consistent with our new assignment. In addition, the molecule crystallizes as a zwitterion, and there are many hydrogen bonds in the crystal structure (see Supporting Information). All these results confirmed the reassigned relative configurations of synthesized clavicipitic acids and their derivatives.[25] Because X-ray analysis defines only the relative configurations, the absolute configurations shown above are based on the fact that no epimerization of C-5 has occurred during the transformation of the starting L-amino acid to clavicipitic acid. Our assignments are in accord with those assigned by biosynthetic study[1b] and enantioselective synthesis.[3]

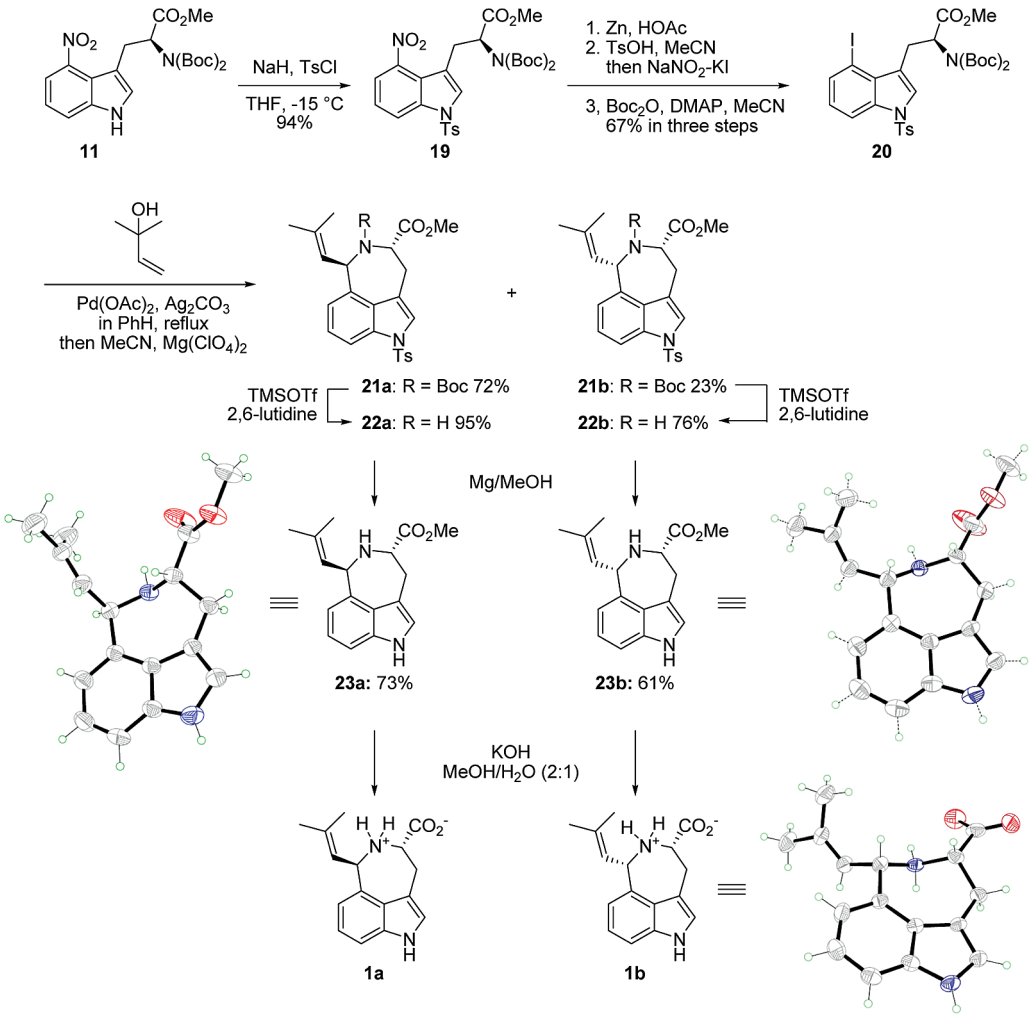
All of this evidence, including 2D-NMR study and X-ray diffraction analysis, unambiguously confirmed that the relative configurations of clavicipitic acids and their derivatives were mis-assigned in the literature since they were first synthesized and that their *trans* and *cis* configuration assignments should be switched on the basis of our results.

However, it is still not clear where and how the mis-assignment occurred. We started by checking the NMR spectra of the *trans*- and *cis*-clavicipitic acid. The NMR spectra to distinguish the *trans*- and *cis*-clavicipitic acids and their methyl esters were first reported by Natsume. Although their relative configuration assignments were based on comparison of R_f values on TLC [silica gel GF_{254}, $CHCl_3$−MeOH−concd NH_4OH (75:25:1)] with the natural mixtures (*cis*- and *trans*-form) of clavicipitic acids, the NMR data of clavicipitic acids reported therein were different from those reported later.[2d] Therefore, researchers cannot rely on this first set of NMR data for structural identification. The NMR data of *trans*- and *cis*-clavicipitic acids in neutral CD_3OD were given by Matsumoto, which were consistent with those reported subsequently.[2f] The relative configurations of their products were confirmed by direct comparison with Natsume's synthesized samples (pure *cis*- and *trans*-form). Thus, all of the relative configurations

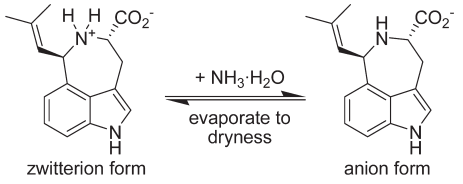
(24) (a) Krasnokutskaya, E. A.; Semenischeva, N. I.; Filimonov, V. D.; Knochel, P. *Synthesis* **2007**, 81–84. (b) Li, B. T. Y.; White, J. M.; Hutton, C. A. *Aust. J. Chem.* **2010**, *63*, 438–444.

(25) The relative configurations of clavicipitic acids and their derivatives in literature are reinvestigated; see Supporting Information for details.

SCHEME 5. Synthesis of Clavicipitic Acid from 1*N*-Tosyl Tryptophan Derivative



SCHEME 6. Different Forms of Clavicipitic Acid



of the synthesized clavicipitic acids and their derivatives assigned thereafter were based on comparison with these NMR data.[2b,c,g,3,4a]

It is well-known that amino acids such as clavicipitic acid exist in different forms at different pH level (Scheme 6), and their NMR spectra vary with the forms. In order to figure out the cause of the mis-assignment, a titration experiment on the NMR of clavicipitic acid was carried out (Table 2, see Supporting Information for detailed spectra),[26] aiming to reproduce the spectra reported by Natsume. Indeed, when diluted ammonia was added to a solution of clavicipitic acid in *d*-methanol, the signals of H-5 and H-7 shifted to the higher field gradually. Finally, spectra of clavicipitic acid similar to those reported by Natsume were observed.[2d] These results indicate that the spectra of clavicipitic acids obtained by Natsume are probably in the anionic form.

To understand why the mis-assignment still occurred when the TLC R_f values of the synthesized clavicipitic acids were compared with these of the natural clavicipitic acids, we carried out detailed TLC analysis of our synthesized clavicipitic acids. Since it was difficult to define the so-called "1-day old" $CHCl_3$−MeOH−concd NH_4OH developing system in the literature,[1b−d] a freshly prepared $CHCl_3$−MeOH−concd NH_4OH (75:25:1) system was used. To our surprise, *trans*-clavicipitic acid, either in zwitterion form (in neutral methanol) or in anion form (in basic ammonia-containing methanol), showed identical R_f values on TLC and moved more quickly than *cis*-clavicipitic acid, which was opposite to that developed by the 1-day old system. It is easy to understand the zwitterion form will be converted to the anion form in the presence of ammonia, but it is difficult to explain the R_f change. We then removed the ammonia from the developing system and found that when developed by a $CHCl_3$−MeOH (75:25) system without ammonia, *trans*-clavicipitic acid, in both zwitterion and anion forms, showed identical R_f values on TLC and moved more slowly than *cis*-clavicipitic acid, which was the same as that developed by the 1-day old system

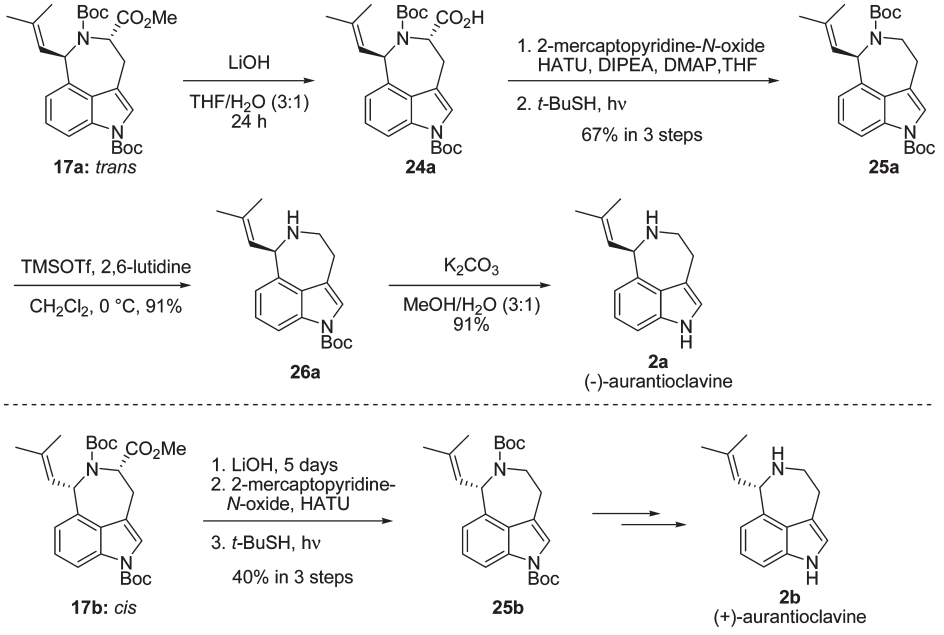
(26) Although Matsumoto had discovered that the NMR spectra of clavicipitic acid were different in neutral and basic *d*-methanol, no detailed data were reported (see ref 2f).

TABLE 2. pH Dependence of Chemical Shifts of H-5, H-7, and H-12 in Clavicipitic Acid[a]

	trans-clavicipitic acid (**1a**)[d]				*cis*-clavicipitic acid (**1b**)[e]		
ammonia (μL)[b,c]	$\delta_{H\text{-}5}$[f]	$\delta_{H\text{-}7}$[f]	$\delta_{H\text{-}12}$[f]	ammonia (μL)[b,c]	$\delta_{H\text{-}5}$[f]	$\delta_{H\text{-}7}$[f]	$\delta_{H\text{-}12}$[f]
0	4.30	5.94	5.49	0	4.14	5.63	5.57
60	4.04	5.60	5.48	20	3.79	5.19	5.54
120	4.01	5.52	5.47	60	3.68	5.06	5.53
180	3.98	5.47[g]	5.47[g]	100	3.62	4.99	5.51
240	3.95	5.41	5.46	140	3.59	4.93	5.50
300	3.93	5.39	5.46	180	3.55	4.89	5.49
h	3.91	5.30	5.53	*h*	3.67	4.96	5.53

[a]Selected data are shown. [b]15 μL of concentrated ammonia (25−28%) dissolved in 1.0 mL D_2O. [c]20 μL per time. [d]Approximately 6 mg in 0.6 mL of neutral CD_3OD. [e]Approximately 4 mg in 0.6 mL neutral CD_3OD. [f]In ppm. [g]Appeared as a singlet. [h]Data reported by Natsume, see ref 2d.

SCHEME 7. Total Synthesis of Aurantioclavine



in the literature.[1b] We previously found that the anion form of our synthesized clavicipitic acid was switched to the zwitterion form after the ammonia-containing solvent was removed.[27] Therefore, these TLC results clearly demonstrated that *trans*-clavicipitic acid moved more quickly in the anion form and more slowly in the zwitterion form than *cis*-clavicipitic acid in its corresponding forms. We concluded that it is likely the evaporation of ammonia from the 1-day old $CHCl_3$−MeOH−ammonia system in the isolation paper caused the mis-assignment of configuration. When an ammonia-containing system was used in Natsume's report, the *trans*-clavicipitic acid, which moved more quickly, was misassigned the *cis*-form.

Total Synthesis of (−)- and (+)-Aurantioclavine. As shown in Scheme 7, hydrolysis of *trans*-**17a** with LiOH afforded the carboxylic acid **24a**. Attempts to esterify this hindered carboxylic acid with 2-mercaptopyridine-*N*-oxide using known DCC or mixed anhydride methods were not successful.[28] In most cases, the starting acid **24a** was recovered from the crude reaction mixtures after radical trapping, which involved the incomplete formation of the Barton ester. Inspired by the use of Garner's uronium salt reagent for preparing the hindered Barton esters,[29] we found that the thiohydroxamate ester could be formed by direct coupling **24a** with 2-mercaptopyridine-*N*-oxide using HATU in the presence of Hünig's base and DMAP in THF. After 4 h of stirring in the dark, *t*-BuSH was added, and the resulting reaction mixture was irradiated with a sunlight lamp for 30 min. The desired decarboxylated product **25a** was obtained in 67% overall yield over three steps. Finally, deprotection of the two Boc groups in **25a** gave natural product (−)-aurantioclavine **2a** without any racemization. The NMR data and the optical rotation ($[\alpha]_D$ −36, *c* 1.00, $CHCl_3$) of our synthesized (−)-aurantioclavine were essentially identical to those reported (lit.[5] $[\alpha]_D$ −34, *c* 1.25, $CHCl_3$).[5,7]

Similarly, *cis*-**17b** could also be transformed to (+)-aurantioclavine **2b** following the same synthetic sequence, albeit at a much slower rate (5 days) in the saponification reaction and in relative lower overall yield (40%). Meanwhile, partial

(27) The NMR spectra of clavicipitic acid recovered from the titration experiment after removal of the basic solvent were identical with those in the zwitterion form.

(28) (a) Crich, D. *Aldrichimica Acta* **1987**, *20*, 35–42. (b) Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479–5486. (c) Barton, D. H. R.; Ferreira, J. A. *Tetrahedron* **1996**, *52*, 9367–9386. The following mixed anhydride method was also tried: (d) Zhang, F.; Jia, Y. *Tetrahedron* **2009**, *65*, 6840–6843. (e) Sakakura, A.; Kawajiri, K.; Ohkubo, T.; Kosugi, Y.; Ishihara, K. *J. Am. Chem. Soc*. **2007**, *129*, 14775–14779.

(29) Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K. *J. Org. Chem*. **1998**, *63*, 5732–5733.

epimerization at the C-5 position was found when *cis*-**17b** was hydrolyzed under basic conditions in such a long period. However, this epimerization would not affect the chiral center of final product, since the chirality at C-5 would disappear after the removal of the carboxyl group in the next step. The NMR data of the synthesized (+)-aurantioclavine matched those reported,[5−7] and the optical rotation of the synthesized (+)-aurantioclavine ($[\alpha]_D$ +37, *c* 1.18, $CHCl_3$) was essentially the same in absolute value but in the opposite direction to that of (−)-aurantioclavine reported in the isolation paper.[5]

In conclusion, the stereocontrolled total syntheses of (−)-*trans*, (−)-*cis*-clavicipitic acid, together with (−)- and (+)-aurantioclavine from the common azepinoindole intermediate, have been achieved. The synthetic procedure features a Pd-catalyzed indole synthesis of the optically pure 4-nitrotryptophan derivative, a one-pot Heck/Boc-deprotection/aminocyclyzation sequence for the construction of azepinoindole nucleus, and a Barton decarboxylation reaction to remove the stereohindered carboxylic acid. Furthermore, the relative configurations of the synthesized clavicipitic acids and their derivatives are reassigned on the basis of our extensive structural analysis.

Experimental Section

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(4-nitro-1*H*-indol-3-yl)-propionic Acid Methyl Ester 11. A mixture of 3-nitro-2-iodoaniline **10** (792 mg, 3.0 mmol), (*S*)-2-*N*,*N*-di-*tert*-butoxycarbonyl-5-oxopentane **6** (518 mg, 1.5 mmol), and DABCO (990 mg, 4.5 mmol) in DMF (8.0 mL) was degassed for 20 min. $Pd(OAc)_2$ (34 mg, 0.15 mmol) was added to the reaction, and the resulting reaction mixture was heated at 80 °C under argon atmosphere for 12 h. The reaction mixture was then cooled to room temperature and diluted with water followed by extraction with EtOAc. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by FCC (PE−EtOAc, 2:1) afforded the starting aniline **10** (390 mg) and the desired product **11** (553 mg, 80% based on **6**) as yellowish powder: $[\alpha]_D^{23}$ −230.1 (*c* 1.00, $CHCl_3$); IR (KBr) 3307, 2981, 1780, 1748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.82 (br s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.09−7.14 (m, 2H), 5.42 (dd, J = 3.9, 11.4 Hz, 1H), 4.00 (dd, J = 3.9, 14.4 Hz, 1H), 3.78 (s, 3H), 3.25 (dd, J = 11.4, 14.4 Hz, 1H), 1.18 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 151.5, 142.3, 139.7, 130.2, 119.9, 119.1, 118.8, 117.9, 109.3, 83.4, 59.5, 52.1, 27.8, 27.3; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{29}N_3O_8Na$ $(M + Na)^+$ 486.1847, found 486.1842.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(4-nitro-1*N*-*tert*-butoxycarbonyl-indol-3-yl)propionic Acid Methyl Ester 12. To a stirring solution of **11** (1.23 g, 2.65 mmol) and DMAP (65 mg, 0.53 mmol) in dry CH_3CN (20 mL) was added Boc_2O (693 mg, 3.18 mmol). The resulting reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and purified by FCC (PE−EtOAc, 4:1) to give **12** (1.42 g, 95%) as yellowish foam: $[\alpha]_D^{23}$ −140.0 (*c* 1.00, $CHCl_3$); IR (KBr) 2981, 1748, 1716, 1526 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.53 (s, 1H), 7.36 (t, J = 8.4 Hz, 1H), 5.29 (dd, J = 4.8, 10.8 Hz, 1H), 3.76−3.81 (m, 1H), 3.76 (s, 3H), 3.35 (dd, J = 10.8, 14.7 Hz, 1H), 1.65 (s, 9H), 1.20 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 151.8, 148.5, 143.1, 137.9, 130.0, 123.4, 122.6, 120.7, 120.0, 114.7, 84.8, 82.7, 58.1, 52.1, 27.8, 27.7, 27.5; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{37}N_3O_{10}Na$ $(M + Na)^+$ 586.2371, found 586.2374.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(4-amino-1*N*-*tert*-butoxycarbonyl-indol-3-yl)propionic Acid Methyl Ester 13. To a stirring suspension of **12** (3.09 g, 5.48 mmol) and zinc dust (24.95 g, 383.8 mmol) in DCM (59.0 mL) at 0 °C was added dropwise glacial acetic acid (5.9 mL). The resulting reaction mixture was stirred at 0 °C for another 20 min. The mixture was filtered and washed with DCM. The combined filtrates were washed sequentially with satd aq $NaHCO_3$ and brine, and the organic layer was dried over Na_2SO_4. Purification by FCC (PE−EtOAc, 4:1) afforded the desired product **13** (2.63 g, 90%) as white foam: $[\alpha]_D^{23}$ −84.0 (*c* 1.00, $CHCl_3$); IR (KBr) 3426, 2980, 2935, 1793, 1742, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 1H), 7.22 (s, 1H), 7.05 (t, J = 8.1 Hz, 1H), 6.49 (d, J = 8.1 Hz, 1H), 5.37 (dd, J = 4.2, 9.6 Hz, 1H), 4.04 (br s, 2H), 3.75 (s, 3H), 3.67 (dd, J = 4.2, 15.3 Hz, 1H), 3.34 (dd, J = 9.6, 15.3 Hz, 1H), 1.62 (s, 9H), 1.31 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 151.8, 149.6, 140.2, 137.4, 125.4, 123.6, 118.7, 116.0, 110.1, 107.0, 83.2, 83.0, 59.3, 52.3, 28.0, 27.8, 27.5; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{40}N_3O_8$ $(M + H)^+$ 534.2810, found 534.2814.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(4-iodo-1*N*-*tert*-butoxycarbonyl-indol-3-yl)propionic Acid Methyl Ester 14. To a solution of **13** (2.55 g, 4.78 mmol) in THF (37.0 mL) and 5% HCl (14.5 mL) was added $NaNO_2$ (759 mg, 11.0 mmol) portionwise at 0 °C, and the mixture was stirred at the same temperature for 20 min. Then the resultant solution was transferred to a solution of KI (4.76 g, 28.7 mmol) and I_2 (1.21, 4.77 mmol) in H_2O (100 mL) at 0 °C. The reaction mixture was stirred at room temperature for another 30 min after the addition was finished, which was then extracted with EtOAc. The combined organic phases were washed sequentially with satd $NaHSO_3$, satd $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and purified by FCC (PE−EtOAc, 5:1) to afford a mixture of **14** and the deiodinated byproduct (2.65 g in total), which was not separated at this stage. The ratio was determined to 5:1 by NMR analysis of the crude products. A pure sample of **14** could be obtained by Boc-reprotection of compound **15**, which could be separated with its deiodinated byproduct: $[\alpha]_D^{23}$ −77.1 (*c* 1.00, $CHCl_3$); IR (KBr) 2980, 2933, 1793, 1737, 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.37 (s, 1H), 6.95 (t, J = 8.1 Hz, 1H), 5.47 (dd, J = 4.5, 11.4 Hz, 1H), 4.18 (dd, J = 4.5, 15.0 Hz, 1H), 3.78 (s, 3H), 3.17 (dd, J = 11.4, 15.0 Hz, 1H), 1.62 (s, 9H) 1.28 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 151.7, 148.8, 136.5, 134.4, 130.9, 127.2, 125.6, 116.6, 115.3, 84.8, 84.1, 82.8, 58.7, 52.2, 28.0, 27.6, 25.4; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{37}IN_2O_8Na$ $(M + Na)^+$ 667.1487, found 667.1481.

(2*S*)-2-(*tert*-Butoxycarbonylamino)-3-(4-iodo-1*N*-*tert*-butoxycarbonyl-indol-3-yl)propionic Acid Methyl Ester 15. A solution of compound **14** with the deiodinated product (2.65 g, 5:1 ratio) and $Mg(ClO_4)_2$ (189 mg, 0.85 mmol) in CH_3CN (70 mL) was heated at 90 °C until the starting materials disappeared. The reaction mixture was cooled to room temperature, diluted with water, and extracted with EtOAc. The combined organic layers were washed with satd $NaHCO_3$ and brine and dried over Na_2SO_4. Purification by careful FCC (PE−EtOAc, 8:1) afforded the deiodinated byproduct (281 mg) and the desired product **15** (1.88 g) as white foam: $[\alpha]_D^{23}$ −16.8 (*c* 1.76, MeOH); IR (KBr) 3369, 2979, 1739, 1511, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), existing two rotamers, the main rotamer was shown, δ 8.23 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.51 (br s, 1H), 6.96 (t, J = 7.5 Hz, 1H), 5.09 (d, J = 8.4 Hz, 1H), 4.75 (br s, 1H), 3.74 (s, 3H), 3.62−3.74 (m, 1H), 3.22 (br t, J = 14.1 Hz, 1H), 1.64 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 155.2, 148.9, 136.4, 134.7, 130.8, 126.3, 125.6, 116.2, 115.3, 84.5, 84.2, 79.8, 53.8, 52.3, 28.5, 28.1, 28.0; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{30}IN_2O_6$ $(M + H)^+$ 545.1143, found 545.1150.

Allylic Alcohol 16. $[\alpha]_D^{23}$ −9.3 (*c* 2.02, MeOH); IR (KBr) 3476, 3372, 2975, 1731, 1505 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) two existing rotamers, the main rotamer is shown, δ 8.06 (d, J = 6.9 Hz, 1H), 7.43 (s, 1H), 7.20−7.25 (m, 3H), 6.29 (d, J = 15.6 Hz, 1H), 4.47 (dd, J = 5.4, 9.6 Hz, 1H), 3.68 (s, 3H), 3.37 (dd, J = 5.4, 15.0 Hz, 1H), 3.06 (dd, J = 9.6, 15.0 Hz, 1H), 1.65 (s, 9H), 1.44 (s, 6H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.6, 158.0, 150.9, 142.5, 137.8, 133.3, 128.6, 126.4, 125.7, 125.4, 122.3, 117.8, 115.4, 84.9, 80.7, 71.7, 55.5, 52.7, 31.1, 29.7, 28.7, 28.4, 28.1; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{38}N_2O_7Na$ $(M + Na)^+$ 525.2571, found 525.2576.

One-Pot Preparation of *trans*-(5*S*,7*R*)-1*N*,6*N*-Di-Boc-clavicipitic Acid Methyl Ester 17a and *cis*-(5*S*,7*S*)-1*N*,6*N*-Di-Boc-clavicipitic Acid Methyl Ester 17b. A suspension of **14** (198 mg, 0.307 mmol), 2-methyl-3-buten-2-ol (264 mg, 3.07 mmol), $Pd(OAc)_2$ (7.0 mg, 0.031 mmol), and Ag_2CO_3 (50.7 mg, 0.184 mmol) in benzene (2.0 mL) was heated at 90 °C for 1.5 h, and then CH_3CN (4.0 mL) was added followed by the addition of $Mg(ClO_4)_2$ (82.2 mg, 0.368 mmol). The resultant reaction mixture was stirred at 90 °C for an additional 3 h and cooled to room temperature. The insoluble material was filtrated and washed with EtOAc. The filtrate was evaporated to dryness and subjected to FCC (PE−EtOAc, 10:1), affording the desired *trans*-**17a** (112.3 mg, 75%), $[\alpha]_D^{23}$ −150 (*c* 1.00, $CHCl_3$), and *cis*-**17b** (23.0 mg, 15%), $[\alpha]_D^{23}$ 103 (*c* 1.00, $CHCl_3$).

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(4-nitro-1*N*-tosyl-indol-3-yl)propionic Acid Methyl Ester 19. To a solution of **11** (1.51 g, 3.26 mmol) in THF (25 mL) was added NaH (163 mg, 4.08 mmol, 60% oil dispersion) at −15 °C, and the mixture was stirred for 5 min. Then TsCl (652 mg, 3.42 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min. Saturated NH_4Cl, was added to the reaction followed by extraction with EtOAc. The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by FCC (PE−EtOAc, 4:1) afforded **19** (1.89 g, 94%) as white foam: $[\alpha]_D^{23}$ −146 (*c* 2.00, $CHCl_3$); IR (KBr) 2981, 1790, 1749, 1699, 1529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.58 (s, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 5.21 (dd, J = 4.8, 11.2 Hz, 1H), 3.76 (dd, J = 4.8, 14.8 Hz, 1H), 3.73 (s, 3H), 3.37 (dd, J = 11.2, 14.8 Hz, 1H), 2.32 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 151.6, 145.7, 143.3, 136.9, 134.3, 130.2, 130.1, 126.9, 123.6, 122.9, 120.4, 118.8, 116.3, 82.9, 57.9, 52.2, 27.9, 27.5, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{35}N_3O_{10}SNa$ $(M + Na)^+$ 640.1935, found 640.1927.

(2*S*)-2-(Di-*tert*-butoxycarbonylamino)-3-(4-iodo-1*N*-tosyl-indol-3-yl)propionic Acid Methyl Ester 20. A solution of (2*S*)-2-(di-*tert*-butoxycarbonylamino)-3-(4-amino-1*N*-tosyl-indol-3-yl)-propionic acid methyl ester (1.78 g, 3.03 mmol), prepared from **19** following the same procedure as that of **13**, was dissolved in acetonitrile (12 mL) and cooled to 10 °C, and then *p*-toluene sulfonic acid monohydrate (1.73 g, 9.09 mmol) was added to the resultant solution. After 5 min, a solution of $NaNO_2$ (469 mg, 6.80 mmol) and KI (1.29 g, 7.77 mmol) in water (2.5 mL) was added dropwise, and the mixture was stirred at 10 °C for a further 10 min, then warmed to room temperature, and stirred for further 2 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with satd $NaHSO_3$, satd $NaHCO_3$, and brine sequentially and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was dissolved in acetonitrile (15 mL), followed by addition of Boc_2O (331 mg, 1.52 mmol) and DMAP (17 mg, 0.14 mmol). The resultant reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure. Purification by FCC (PE−EtOAc, 5:1) afforded **20** (1.41 g, 66%) as white foam: $[\alpha]_D^{23}$ −72 (*c* 1.00, $CHCl_3$); IR (KBr) 2982, 1744, 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.41 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 6.91 (t, J = 8.0 Hz, 1H), 5.42 (dd, J = 4.4, 11.6 Hz, 1H), 4.11 (dd, J = 4.4, 15.2 Hz, 1H), 3.77 (s, 3H), 3.21 (dd, J = 11.6, 15.2 Hz, 1H), 2.32 (s, 3H), 1.26 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 151.5, 145.1, 135.4, 134.7, 131.0, 130.1, 127.3, 126.9, 125.5, 118.1, 113.4, 85.2, 83.0, 58.5, 52.3, 27.6, 25.3, 21.5; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{35}IN_2O_8SNa$ $(M + Na)^+$ 721.1051, found 721.1050.

***trans*-(5*S*,7*R*)-1*N*-Tosyl-6*N*-Boc-clavicipitic Acid Methyl Ester 21a.** $[\alpha]_D^{23}$ −135 (*c* 2.00, $CHCl_3$); IR (KBr) 2976, 2926, 1747, 1694, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) showed the presence of two rotamers in a ratio of 1/2, δ 7.87 (d, J = 8.0 Hz, 1H, minor), 7.85 (d, J = 7.6 Hz, 1H, major), 7.75 (d, J = 8.8 Hz, 2H, both), 7.41 (s, 1H, both), 7.20−7.23 (m, 3H, both), 6.99 (d, J = 7.6 Hz, 1H, major), 6.94 (d, J = 6.8 Hz, 1H, minor), 6.36 (d, J = 7.2 Hz, 1H, major), 6.09 (br s, 1H, minor), 5.21 (br s, 1H, minor), 5.12 (d, J = 6.8 Hz, 1H, major), 4.35 (br s, 1H, minor), 4.30 (dd, J = 2.8, 12.4 Hz, 1H, major), 3.72 (s, 3H, major), 3.71 (s, 3H, minor), 3.38−3.58 (m, 2H, both), 2.32 (s, 3H, major), 2.31 (s, 3H, minor), 1.85 (s, 3H, both), 1.74 (s, 3H, minor), 1.71 (s, 3H, major), 1.38 (s, 9H, major), 1.30 (s, 9H, minor); ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer shown, δ 171.2, 153.4, 144.8, 140.0, 138.0, 135.9, 135.1, 129.8, 126.8, 124.5, 124.2, 123.5, 123.2, 121.9, 118.4, 111.6, 80.9, 57.0, 55.6, 51.9, 28.2, 28.0, 25.5, 21.4, 18.7; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{34}N_2O_6S$-Na $(M + Na)^+$ 561.2030, found 561.2034.

***cis*-(5*S*,7*S*)-1*N*-Tosyl-6*N*-Boc-clavicipitic Acid Methyl Ester 21b.** $[\alpha]_D^{23}$ +63 (*c* 2.00, $CHCl_3$); IR (KBr) 2975, 2929, 1756, 1736, 1692, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) showed the presence of two rotamers in a ratio of 1/1, δ 7.74−7.83 (m, 3H × 2), 7.36 (d, J = 7.2 Hz, 1H × 2), 7.16−7.23 (m, 3H × 2), 7.05 (d, J = 7.2 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 6.36 (d, J = 7.6 Hz, 1H), 5.95 (d, J = 8.0 Hz, 1H), 5.32 (d, J = 8.0 Hz, 1H), 5.28 (d, J = 7.6 Hz, 1H), 5.15 (dd, J = 6.8, 12.0 Hz, 1H), 4.70 (dd, J = 5.2, 12.4 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.47−3.54 (m, 1H × 2), 3.34 (dd, J = 7.2, 16.4 Hz, 1H), 3.24 (dd, J = 5.2, 16.0 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 1.84 (s, 3H), 1.83 (s, 3H), 1.68 (s, 3H × 2), 1.32 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) both rotamers shown, δ 172.8, 172.5, 155.4, 154.7, 144.9, 144.8, 139.9, 139.3, 138.2, 137.6, 135.6, 135.4, 135.3, 135.2, 129.85, 129.80, 128.7, 128.5, 126.8, 126.7, 124.9, 124.4, 124.0, 122.6, 122.5, 122.0, 121.3, 120.8, 118.55, 118.49, 112.2, 80.6, 80.4, 59.8, 57.5, 57.0, 55.7, 52.1, 51.9, 28.1, 28.0, 27.1, 26.7, 25.5, 25.4, 21.4, 18.8, 18.6; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{34}N_2O_6SNa$ $(M + Na)^+$ 561.2030, found 561.2037.

***trans*-(5*S*,7*R*)-1*N*,6*N*-Di-Boc-clavicipitic Acid 24a.** To a stirring solution of **17a** (102 mg, 0.21 mmol) in 2.8 mL of THF/H_2O (3:1) was added $LiOH \cdot H_2O$ (26.5 mg, 0.63 mmol). Then the reaction was stirred at room temperature for 24 h until the starting material was consumed. An additional 2.0 mL of H_2O was added, and the pH was adjusted to 6−7 by adding 5% HCl. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude **24a** as white amorphous powder: ^1H NMR (400 MHz, DMSO-d_6) showed the presence of two rotamers in a ratio of 3/1, δ 8.29 (s, CO_2H), 7.96 (d, J = 8.4 Hz, 1H, major), 7.93 (d, J = 8.4 Hz, 1H, minor), 7.54 (s, 1H, major), 7.51 (s, 1H, minor), 7.22 (t, J = 8.4 Hz, 1H, major), 7.21 (t, J = 8.4 Hz, 1H, minor), 6.93 (d, J = 8.4 Hz, 1H, major), 6.91 (d, J = 8.4 Hz, 1H, minor), 6.29 (d, J = 7.6 Hz, 1H, major), 6.08 (br s, 1H, minor), 5.37 (br s, 1H, minor), 5.26 (d, J = 7.2 Hz, 1H, major), 4.46 (br s, 1H, minor), 4.36 (dd, J = 2.8, 12.0 Hz, 1H, major), 3.25−3.45 (m, 2H, both), 1.81 (s, 3H, both), 1.72 (s, 3H, minor), 1.69 (s, 3H, major), 1.59 (s, 9H, both), 1.32 (s, 9H, major), 1.25 (s, 9H, minor); ^{13}C NMR (100 MHz, $CDCl_3$), major rotamer shown, δ 172.0, 153.2, 148.8, 137.5, 137.4, 135.8, 126.6, 124.1, 123.4, 121.2, 116.8, 112.8, 83.5, 80.0, 79.2, 56.5, 55.3, 27.8, 27.7, 25.4,

18.5; HRMS (ESI) m/z calcd for $C_{26}H_{35}N_2O_6$ $(M + H)^+$ 471.2490, found 471.2490.

(−)-(7*R*)-1*N*,6*N*-Di-Boc-aurantioclavine 25a. A solution of the crude **24a** (from saponification of 102 mg **17a**), 2-mercaptopyridine-*N*-oxide (29.3 mg, 0.23 mmol), HATU (120 mg, 0.32 mmol), Hünig's base (DIPEA, 146 μL, 0.84 mmol), and DMAP (2.6 mg, 0.021 mmol) in THF (3.0 mL) was stirred at room temperature in dark (wrapped with aluminum foil) for 4 h. Then *tert*-butyl mercaptan (237 μL, 2.1 mmol) was added, and the resultant yellowish reaction mixture was irradiated with a 500 W sunlight lamp for 30 min. The solvent was removed under reduced pressure, and repeated preparative TLC (PE−EtOAc, 10:1) gave the desired **25a** (60 mg, 67%). Meanwhile, *tert*-butyl 2-pyridyl disulfide (26.6 mg) was also obtained at a R_f value very close to that of **25a**: $[\alpha]_D^{23}$ −194 (c 1.00, $CHCl_3$), [the antipode **25b**, $[\alpha]_D^{23}$ +180 (c 1.00, $CHCl_3$)]; IR (KBr) 2972, 2926, 1731, 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) showed the presence of two rotamers in a ratio of 1/1, δ 8.04−8.10 (m, 1H × 2), 7.37 (s, 1H × 2), 7.21−7.26 (m, 1H × 2), 6.99 (d, J = 7.2 Hz, 1H), 6.93 (d, J = 6.8 Hz, 1H), 6.48 (d, J = 7.2 Hz, 1H), 6.28 (d, J = 7.6 Hz, 1H), 5.27−5.32 (m, 1H × 2), 4.04 (d, J = 13.6 Hz, 1H), 3.88 (d, J = 13.6 Hz, 1H), 3.37−3.47 (m, 1H × 2), 3.12−3.25 (m, 1H × 2), 2.94−2.98 (m, 1H × 2), 1.86 (s, 3H × 2), 1.72 (s, 3H × 2), 1.65 (s, 9H × 2), 1.47 (s, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 154.4, 149.5, 137.9, 137.7, 136.6, 136.5, 136.3, 135.5, 127.3, 127.2, 125.3, 125.2, 124.1, 123.9, 122.7, 122.6, 121.7, 121.2, 119.3, 119.0, 113.2, 113.1, 83.3, 79.8, 79.4, 58.1, 57.0, 42.2, 41.8, 28.5, 28.4, 28.2, 27.6, 26.8, 25.6, 18.5, 18.4; HRMS (ESI) m/z calcd for $C_{25}H_{35}N_2O_4$ $(M + H)^+$ 427.2591, found 427.2584.

(−)-(7*R*)-1*N*-Boc-aurantioclavine 26a. To a stirring solution of **25a** (83 mg, 0.19 mmol) and 2,6-lutidine (102 mg, 0.95 mmol) in DCM (2.0 mL) at 0 °C was added TMSOTf (138 μL, 0.76 mmol) dropwise. The reaction mixture was stirred at 0 °C for 20 min, and satd NH_4Cl was added followed by extraction with EtOAc. The combined organic phases were washed with satd $NaHCO_3$ and brine and dried over Na_2SO_4. Purification by preparative TLC (DCM−MeOH, 20:1) afforded **26a** (56 mg, 91%) as colorless oil: $[\alpha]_D^{23}$ −50 (c 1.00, $CHCl_3$), [the antipode **26b**, $[\alpha]_D^{23}$ +44 (c 1.00, $CHCl_3$)]; IR (KBr) 3432, 2976, 2927, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.6 Hz, 1H), 7.39 (s, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 5.43 (d, J = 9.2 Hz, 1H), 4.90 (d, J = 9.2 Hz, 1H), 3.46−3.52 (m, 1H), 2.92−3.09 (m, 3H), 2.14 (br s, 1H), 1.85 (s, 3H), 1.83 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 138.7, 136.5, 133.8, 128.5, 127.3, 123.7, 122.3, 121.2, 120.2, 113.2, 83.2, 61.7, 47.7, 30.7, 28.2, 25.8, 18.3; HRMS (ESI) m/z calcd for $C_{20}H_{27}N_2O_2$ $(M + H)^+$ 327.2067, found 327.2059.

(−)-(7*R*)-Aurantioclavine 2a. To a stirring suspension of **26a** (49 mg, 0.15 mmol) and K_2CO_3 (62 mg, 0.45 mmol) in MeOH (2.7 mL) was added water (0.9 mL). The resultant reaction mixture was stirred at 100 °C for 12 h. The reaction was cooled to room temperature, diluted with satd $NaHCO_3$, extracted with EtOAc, and dried over Na_2SO_4. The solvent was removed under reduced pressure and purified by preparative TLC (PE−EtOAc−Et_3N, 25:35:1) to give (−)-aurantioclavine **2a** (31 mg, 91%): $[\alpha]_D^{23}$ −36 (c 1.00, $CHCl_3$), [lit.[5] $[\alpha]_D$ −34 (c 1.25, $CHCl_3$)], [its antipode (+)-aurantioclavine **2b**, $[\alpha]_D^{23}$ +37 (c 1.18, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.97 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H), 5.47 (dt, J = 1.2, 8.8 Hz, 1H), 4.91 (d, J = 8.8 Hz, 1H), 3.55−3.60 (m, 1H), 2.98−3.13 (m, 3H), 2.24 (br s, 1H), 1.86 (d, J = 1.2 Hz, 3H), 1.85 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 137.1, 133.2, 127.8, 125.4, 121.4, 121.0, 117.8, 115.6, 109.2, 62.6, 48.9, 30.9, 25.8, 18.3; HRMS (ESI) m/z calcd for $C_{15}H_{19}N_2$ $(M + H)^+$ 227.1543, found 227.1540

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Supporting Information Available: Experimental procedures and physical data for compounds **1a,b**, **8a−c**, **10**, **17a−18a**, **17b−18b**, **22a−23a**, **22b−23b**; copies of spectra for compounds **1a,b**, **2a**, **8a−c**, **10−16**, **17a−18a**, **17b−18b**, **19**, **20**, **21a−26a**, **21b−23b**; detailed NOESY correlation of **17a,b**, **18a,b**; CIF files and ORTEP drawing for **23a,b** and **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.