JOC*Note*

Enantioselective Synthesis of (−)-*cis*-Clavicipitic Acid

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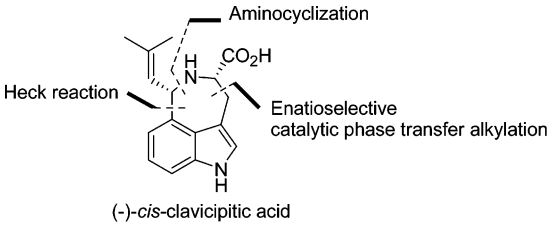
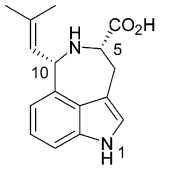


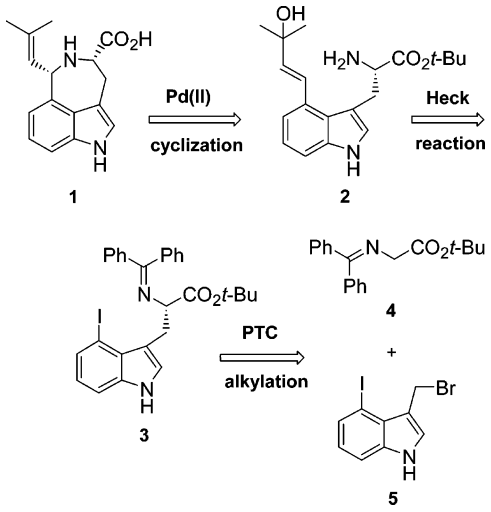
An enantioselective synthetic method for (−)-*cis*-clavicipitic acid (**1**) was reported. **1** was obtained in 10 steps (99% ee and 20% overall yield) from 1*H*-indole-3-carboxylic acid methyl ester (**9**) via asymmetric phase-transfer catalytic alkylation and diastereoselective Pd(II)-catalyzed intramolecular aminocyclization as key steps.

Clavicipitic acid (**1**), an ergot alkaloid isolated from SD58 and *Claviceps fusiformis*, has a unique tricyclic azepinoindole skeleton.[1] There are two chiral centers (C(5) and C(10)) in **1** but a mixture of diastereomers bearing C(5*S*) was naturally obtained. **1** is regarded as a derailed product at high pH environmental condition in the clavine alkaloid biosynthetic pathway.[2]



Because of the low amount of production of **1**, a systematic evaluation of its biological activities has not been extensively performed. As a part of our program to study the biological activity of **1**, we need to develop an efficient synthetic method. So far there have been several enantioselective synthetic methods, but the chemical yield or enantioselectivities were not suitable for large-scale preparation and the stereocontrolled synthesis of the C(10)-position was not reported.[3,4] In this note, we report a new efficient enantioselective synthesis of (−)-*cis*-clavicipitic acid via asymmetric phase-transfer catalytic alkylation for C(5*S*) chirality and diastereoselective Pd(II)-catalyzed intramolecular aminocyclization for C(10*S*) chirality.

SCHEME 1



Recently, we developed the asymmetric phase-transfer alkylation of the *N*-(diphenylmethylene)glycine *tert*-butyl ester (**4**) in the presence of *cinchona* alkaloid-derived quaternary ammonium salts, and successfully applied them to the enantioselective synthesis of natural and non-natural α-amino acids.[5] As shown in the retrosynthetic analysis (Scheme 1), the enantioselective phase-transfer catalytic alkylation was employed as the key step for the introduction of the 5*S* chirality in **1** and the construction of the azepinoindole ring system was planned by a Pd(0)-catalyzed Heck reaction,[4a] followed by diastereoselective

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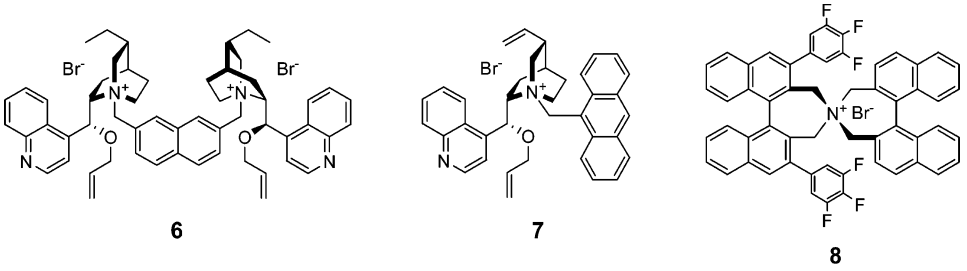
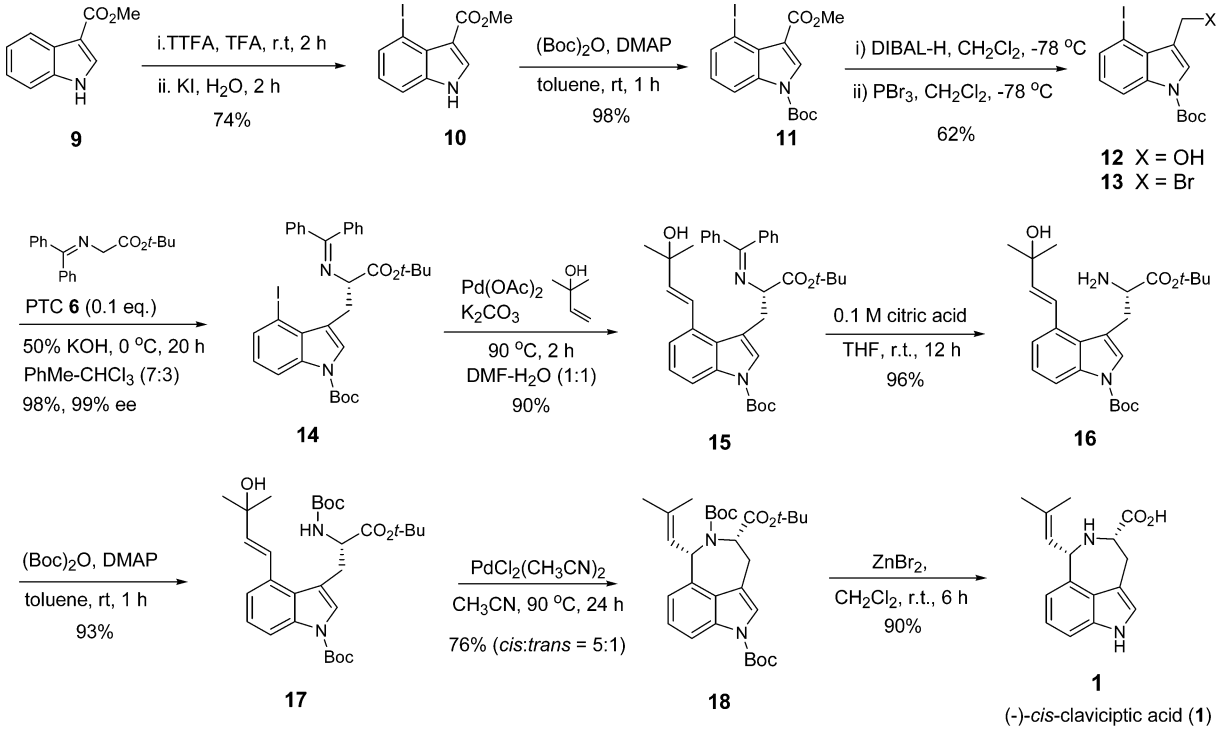


FIGURE 1. Chiral phase-transfer catalyst.

SCHEME 2



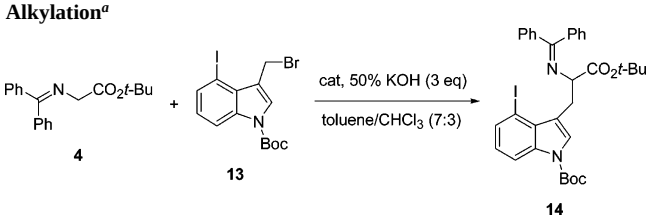
intramolecular aminocyclization induced by C(5*S*) chirality for the introduction of the C(10*S*) chirality.[4b]

First, the alkylating agent **13** for the asymmetric phase-transfer catalytic alkylation was prepared in 4 steps from 1*H*-indole-3-carboxylic acid methyl ester (**9**). The addition of thallium(III) trifluoroacetate in a TFA solution of **9**, followed by the treatment of potassium iodide afforded **10** (74%). The *N*-Boc protection of indole **10** with $(Boc)_2O$ in the presence of DMAP gave **11** (98%). The reduction of methyl ester of **11** with DIBAL-H, followed by benzylic bromination with PBr_3 provided the alkylating agent **13** (62%).

The phase-transfer catalytic alkylation was performed from **4** with 4-iodo-*N*-Boc-3-bromomethylindole (**13**) under phase-transfer catalytic reaction conditions of 50% aqueous KOH in toluene−chloroform (volume ratio = 7:3) at 0 °C (Scheme 2). We employed three representative catalysts (PTCs, **6**−**8**, Figure 1) which showed excellent catalytic efficiencies in the enantioselective catalytic alkylation **4**.[5d,6]

As shown in Table 1, very high enantioselectivities were observed in the case of both **6**[5d] (99% ee) and **7**[6a] (99% ee), but

TABLE 1. The Enantioselective Phase-Transfer Catalytic Alkylation[a]



no.	catalyst	time, h	yield,[b] %	ee,[c] % (config)[d]
1	**6**	12	97	99 (S)
2	**7**	12	85	99 (S)
3	**8**	12	69	65 (S)

[a] The reaction was carried out with 1.0 equiv of alkylating agent and 3.0 equiv of 50% KOH in the presence of catalyst (10 mol %) in toluene/$CHCl_3$ (7:3). [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis of **14**, using a chiral column (Chiralcel OD) with hexane/2-propanol as an eluent; in this case it was established by analysis of the racemate, of which the enantioisomers were fully resolved. [d] Absolute configuration was determined by comparison of the optical rotation of (−)-*cis*-clavicipitic acid (**1**) transformed from **14** with the reported value.[4b]

6 (97%) showed higher chemical yield compared to that of **7** (85%). The non-*cinchona* catalyst, **8**,[6b] afforded relatively poor results in both chemical yield and enantioselectivity. The enantiopurities were determined by chiral HPLC analysis with

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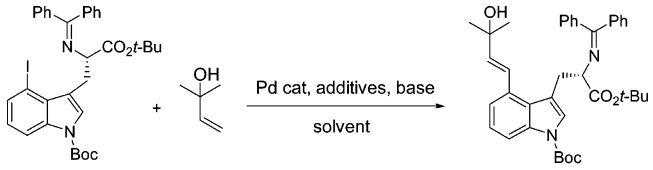
TABLE 2. The Synthesis of 15 with Use of the Heck Reaction[a]



14 **15**

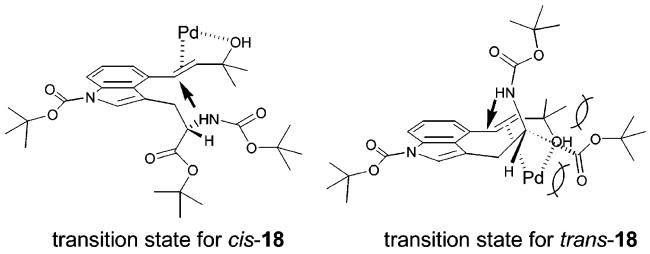
No.	catalyst	additives	base	solvent	temp, °C	time, h	yield,[b] %
1	$Pd(Ph_3P)_2Cl_2$	Ag_2CO_3 (1.0 equiv)	Et_3N (10 equiv)	DMF	100	3	21
2	$Pd(Ph_3P)_2Cl_2$	Ag_2CO_3 (1.0 equiv)	Et_3N (10 equiv)	toluene	110	3	N.R.
3	$Pd(Ph_3P)_2Cl_2$	Ag_2CO_3 (1.0 equiv)	K_2CO_3 (2 equiv)	DMF	100	6	53
4	$Pd(Ph_3P)_2Cl_2$	Ag_2CO_3 (1.0 equiv)	K_2CO_3 (2 equiv)	DMF/H_2O	90	3	52
5	$Pd(Ph_3P)_2Cl_2$		K_2CO_3 (2 equiv)	DMF/H_2O	90	3	54
6	$Pd(Ph_3P)_4$		K_2CO_3 (2 equiv)	DMF/H_2O	90	2	N.R
7	$Pd(DIPHOS)_2$		K_2CO_3 (2 equiv)	DMF/H_2O	90	3	65
8	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$		K_2CO_3 (2 equiv)	DMF/H_2O	90	3	42
9	$Pd(OAc)_2$		K_2CO_3 (2 equiv)	DMF/H_2O	90	2	90

[a] The above reaction was allowed to stir with 45 equiv of 2-methylbut-3-en-2-ol and base in the presence of catalyst (0.1 equiv) in solvent until dark material was precipitated. [b] Isolated yields.

use of Chiralcel OD. The absolute configuration of **14** was determined as *S* by comparison of the optical rotation of the final product, (−)-*cis*-Clavicipitic acid {**1**, $[\alpha]^{25}_D$ −238 (*c* 0.2, EtOH)} transformed from **14** with the reported values {**1**, $[\alpha]^{25}_D$ −249 (EtOH)[4b]}.

We next investigated the Pd(0)-catalyzed Heck reaction of **14** to afford **15**. At the beginning, we adapted the previous Heck reaction condition for the synthesis of clavicipitic acid reported by Yokoyama et al. in 1995.[4a] The Heck reaction of **14** with $Pd(Ph_3P)_2Cl_2$ in the presence of Ag_2CO_3 under DMF solvent at 100 °C gave **15** in only 21% chemical yield (Table 2, entry 1). The Heck reaction conditions needed to be optimized by the variation of solvent, catalyst, and base. Toluene solvent showed no reaction but quite increased chemical yield could be observed by replacing Et_3N with K_2CO_3 (entry 3, 53%). The aqueous DMF solvent system, DMF−H_2O (volume ratio = 1:1), showed comparable chemical yield but two times faster reaction rate than the DMF only solvent system (entries 3 and 4). Interestingly, the removal of Ag_2CO_3 did not show any significant change in chemical yield (entries 4 and 5). We then moved our attention to optimize Pd(0) catalyst. An additional four kinds of Pd(0) catalysts were chosen and their catalytic efficiency was evaluated (entries 6−9). Among the used catalysts, $Pd(OAc)_2$ gave the highest chemical yield in the presence of K_2CO_3 under the 50% aqueous DMF solvent system to give **15** (entry 9, 90%).

Next, the benzophenone imine moiety of **15** was selectively hydrolyzed with 0.1 M citric acid to afford **16** (96%). The direct azepinoindole ring construction from **16** was attempted by acidic condition with PPTS in CH_2Cl_2, but only a diastereomeric mixture (1:1.2) of the corresponding *trans*-(5*S*,10*R*)-*N*(1)-Boc-clavicipitic acid *tert*-butyl ester and *cis*-(5*S*,10*S*)-*N*(1)-Boc-clavicipitic acid *tert*-butyl ester was obtained, respectively (data not shown). We speculate that the poor diastereoselectivity of the C(10)-position induced by C(5*S*) chirality might be due to the less steric hindered environment. So we finally employed Pd(II)-catalyzed intramolecular aminocyclization.[7] The *N*-Boc protection of **16** was performed with $(Boc)_2O$ in the presence of DMAP to give **17** (93%). The intramolecular aminocyclization of **17** was performed with $PdCl_2(CH_3CN)_2$ in CH_3CN solvent at 90 °C for 24 h, which could afford *cis*-**18** and *trans*-**18** at the ratio of 5 to 1, respectively.[8]



transition state for *cis*-**18** transition state for *trans*-**18**

FIGURE 2. Plausible transition state in the Pd(II)-catalyzed aminocyclization.

On the basis of the diastereoselectivity, the plausible transition state in the aminocyclization is proposed in Figure 2. The Pd(II) catalyst forms a complex with the allylic alcohol group in **17** from the upside, followed by the approach of C(5*S*)-BocNH from the downside to afford *cis*-**18**. In the case of *trans*-**18**, the Pd(II) catalyst should form a complex with the allylic alcohol group from the downside and C(5*S*)-BocNH approach from the upside to the allylic alcohol group, but there might be severe steric hindrance between C(5*S*)-$CO_2{}^t$Bu and the Pd(II)−allylic alcohol complex, which might give the *trans*-isomer as a minor product. The nonseparable diastereomeric mixture of **18** was directly adapted to hydrolysis without further separation. Since Shinohara et al. reported that a partial epimerization of the C(10)-position occurred during the thermolytic deprotection catalyzed by silica gel (SiO_2),[9] we need to find a milder reaction condition at low temperature. After several trials with various hydrolysis methods, we finally overcame the epimerization by using $ZnBr_2$.[10] **18** could be selectively converted to the (−)-

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(8) Since *cis*-**18** and *trans*-**18** were not separable, their ratio was confirmed by the ratio of *cis*-**1** and *trans*-**1** derived from the hydrolysis of the diastereomeric mixture of **18**.

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cis-clavicipitic acid (90%) by the treatment of $ZnBr_2$ in CH_2Cl_2 without any epimerization.[11]

In conclusion, (−)-*cis*-clavicipitic acid has been synthesized in 10 steps (20% overall yield, 99% ee) with asymmetric phase-transfer catalytic alkylation and diastereoselective Pd(2)-catalyzed intramolecular aminocyclization as key steps from 1*H*-Indole-3-carboxylic acid methyl ester (**9**). We believe the efficient synthetic method would facilitate the studies on the biological evaluation of (−)-*cis*-clavicipitic acid.

Experimental Section

Representative Procedure for the Enantioselective Phase-Transfer Catalytic Alkylation of 4 (14). To a mixture of **13** (29 mg, 0.067 mmol) and chiral catalyst **6** (6.6 mg, 0.0067 mmol) in solvent (dichloromethane:toluene = 3:7) (0.67 mL) was added *N*-(diphenylmethylene)glycine *tert*-butyl ester (**4**) (19.6 mg, 0.067 mmol). The reaction mixture was then cooled (0 °C), aq 50% KOH (13.7 mg, 0.24 mmol) was added, and the reaction mixture was stirred at 0 °C until starting material was consumed (8 h). The suspension was diluted with diethyl ether (20 mL), washed with water (2 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of residue by column chromatography on silica gel (hexanes:EtOAc = 10:1) afforded the desired product **14** (42 mg, 97% yield) as a pale yellow oil. The enantioselectivity was determined by chiral HPLC analysis (Chiralcel OD, hexanes:2-propanol = 500:2.5, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention times: *R* (minor) 19 min, *S* (major) 23.3 min, 98.8% ee).

Representative Procedure for the Pd(II)-Catalyzed Intramolecular Aminocyclization (18). To an acetonitrile solution of **17** (90 mg, 0.16 mmol) was added $PdCl_2(CH_3CN)_2$ (4 mg, 0.016 mmol) at room temperature. The reaction solution was allowed to stir at room temperature until the starting material was consumed. After cooling, the reaction mixture was quenched with water, diluted with ethyl acetate, washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes:EtOAc = 6:1) to afford inseparable mixture of diastereomer, *cis*-**18** and *trans*-**18** (5:1) (66 mg, 76% yield).

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Supporting Information Available: Spectroscopic characterizations of **1**and **10**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) No epimerization was confirmed by the hydrolysis of the *cis*-(5*S*,10*S*)-*N*(1)-Boc-clavicipitic acid *tert*-butyl ester and *trans*-(5*S*,10*R*)-*N*(1)-Boc-clavicipitic acid *tert*-butyl ester derived from **16** by the acidic cyclization with PPTS in CH_2Cl_2. The separable *cis*- and *trans*-isomer could be hydrolyzed to afford *cis*-**1** and *trans*-**1** without any epimerization by $ZnBr_2$ in CH_2Cl_2, respectively. The related scheme and procedure are provided in the Supporting Information.