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Efficient Total Synthesis of (−)-*cis*-Clavicipitic Acid

Zhengren Xu,[†] Qingjiang Li,[†] Lihe Zhang,[†] and Yanxing Jia*[,†,‡]

[†]*State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, 38 Xueyuan Road, Beijing 100191, China, and* [‡]*State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China*

yxjia@bjmu.edu.cn

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An efficient total synthesis of (−)-*cis*-clavicipitic acid has been achieved in seven linear steps (42% overall yield) from the known compound **6**. The present synthesis features a palladium-catalyzed indole synthesis to provide the optically pure 4-chlorotryptophan derivative and a Heck reaction using aryl chloride as partner. It has also been discovered that the key azepinoindole nucleus could be stereoselectively constructed via a $Mg(ClO_4)_2$-mediated intramolecular aminocyclization.

Clavicipitic acid, a derailment product of ergot alkaloid biosynthesis, has been isolated as a mixture of *cis*-**1a** and *trans*-**1b** diastereomers (Figure 1) from cultures of the *Claviceps* strain SD58 or *Claviceps fusiformis*. The proportions of **1a** and **1b** depend on the specific microorganism from which it was isolated.[1,2] The unique tricyclic azepinoindole structure was proposed by King and Waight on the basis of extensive NMR studies and confirmed by Floss and Clardy via single-crystal X-ray analysis of the *trans*-diastereomer.[3]

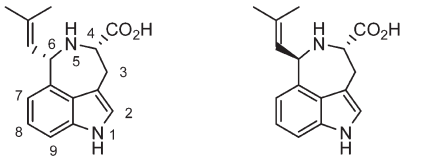

FIGURE 1. Structures of (−)-clavicipitic acid.

Due to its unique structure, clavicipitic acid has received considerable attention from synthetic chemists over the past three decades, and a number of novel synthetic strategies have been developed.[4−6] In all of its enantioselective syntheses, the chief obstacles have been the synthesis of optically pure 4-substituted tryptophan derivatives and the stereoselective construction of the C6 center. In this context, the key optically pure 4-substituted tryptophan derivatives have been formed from a preexisting 4-substituted indole, followed by introduction of the chiral amino acid moiety via asymmetric reduction,[5a] enzymatic resolution,[5b,c] Schöllkopf's amino acid synthesis,[5d] or asymmetric phase-transfer catalytic alkylation.[5e] In 2007, Park and co-workers reported the first stereocontrolled synthesis of the C6 center using palladium-catalyzed intramolecular aminocyclization.[5e] Herein, we report a highly efficient enantioselective synthesis of (−)-*cis*-clavicipitic acid by utilizing a palladium-catalyzed indole synthesis for the rapid construction of the key optically pure 4-chlorotryptophan derivative, a palladium-catalyzed Heck reaction using aryl chloride as partner, and a one-pot $Mg(ClO_4)_2$-mediated tandem deprotection/aminocyclization reaction for stereoselective construction of the key azepinoindole nucleus.

Our retrosynthetic analysis is outlined in Scheme 1. It was envisioned that clavicipitic acid **1** should be formed by diastereoselective intramolecular aminocyclization of **2**, which could be obtained from a Pd-catalyzed Heck reaction of aryl chloride **3** by using bulky, electron-rich phosphine ligands.[7] The optically pure **3** could be directly formed by the palladium-catalyzed reaction of **4** and **5**.[8]

Our total synthesis of clavicipitic acid commenced with 1-chloro-2-iodo-3-nitrobenzene **6** (Scheme 2), which was prepared from commercially available 1-chloro-3-nitrobenzene following literature procedures.[9] Reduction of the nitro group of **6** with $SnCl_2 \cdot 2H_2O$ in EtOH gave 3-chloro-2-iodoaniline **4**

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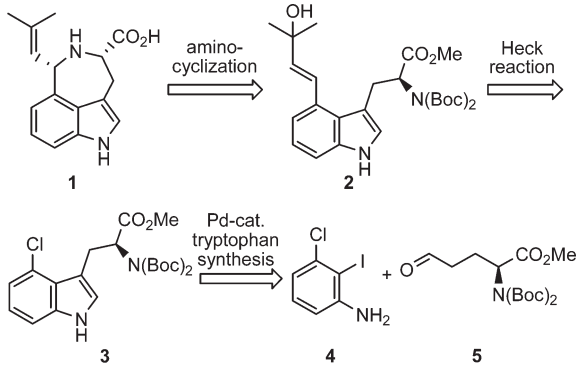
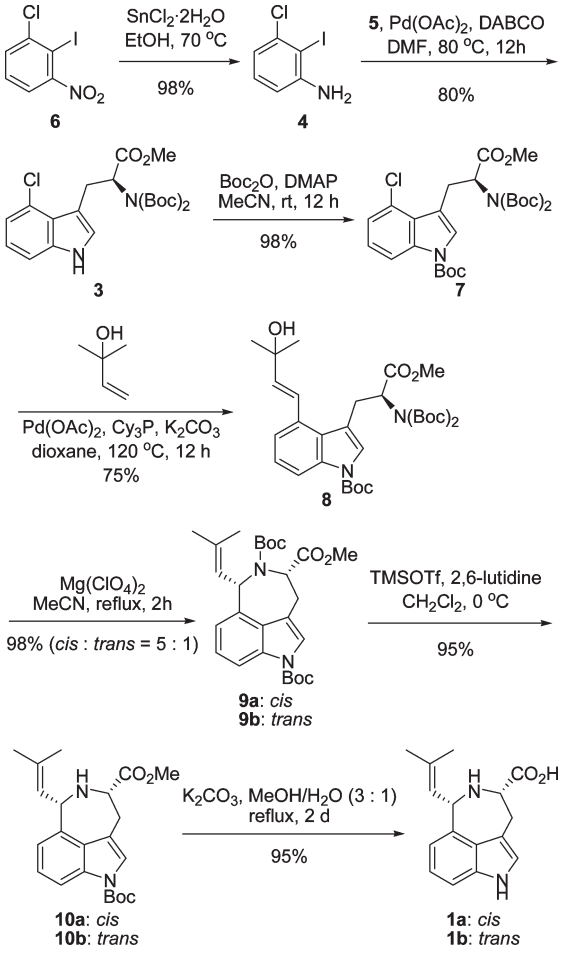
SCHEME 1. Retrosynthesis of Clavicipitic Acid

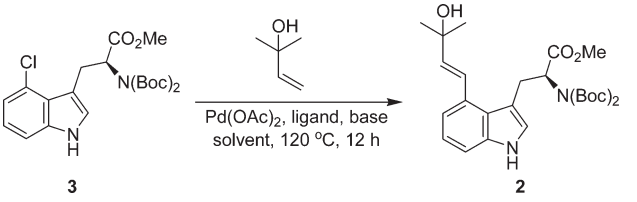


SCHEME 2. Total Synthesis of (−)-Clavicipitic Acid



in 98% yield.[10] Palladium-catalyzed reaction of **4** with (*S*)-2-*N*,*N*-di-*tert*-butoxycarbonyl-5-oxopentane **5**[11] according to the recently developed conditions afforded the protected 4-chlorotryptophan derivative **3** in 50% isolated yield.[12]

TABLE 1. Palladium-Catalyzed Vinylation of 3



entry	ligand	base	solvent	yield
1	(t-Bu_3P)HBF_4	K_2CO_3	dioxane	23
2	XPhos	K_2CO_3	dioxane	18
3	JohnPhos	K_2CO_3	dioxane	23
4	Cyclohexyl JohnPhos	K_2CO_3	dioxane	20
5	PCy_3	K_2CO_3	dioxane	48
6	PCy_3	t-BuOK	dioxane	45
7	PCy_3	Cs_2CO_3	dioxane	25
8	PCy_3	K_3PO_4	dioxane	26
9	PCy_3	K_2CO_3	DMSO	20
10	PCy_3	K_2CO_3	DMA	18
11	PCy_3	K_2CO_3	CH_3CN	23

[a] General reaction conditions: concentration 0.06 M in solvent, 0.10 equiv of $Pd(OAc)_2$, 0.20 equiv of ligand, 1.0 equiv of **3**, 50 equiv of 2-methyl-3-buten-2-ol, 1.2 equiv of base, 120 °C. [b] Isolated yield.

To our delight, the yield could be increased to 80% by using 2 equiv of **4**, 45% of which was recovered and could be reused.

The stage was now set for the investigation of the key Heck reaction of **3** with 2-methyl-3-buten-2-ol. Heck reactions of similar substrates, either 4-iodotryptophan derivative[5e] or 4-bromotryptophan derivatives,[5a−c,6a] have been achieved. However, aryl chlorides are generally unreactive under the conditions employed to couple bromides or iodides. Although remarkable progress has been achieved in the palladium-catalyzed Heck reaction of aryl chlorides in the presence of the electron-rich and bulky phosphine ligands,[7] only a limited number of these catalytic processes have been applied to the coupling of highly deactivated (electron-rich) aryl chlorides with deactivated (electron-rich) alkenes.[13] A wide variety of reaction conditions (ligands, bases, and solvents) were examined, and some of the representative results are shown in Table 1. Of the ligands examined (entries 1−5), Cy_3P was the most efficient. Among the bases tested, K_2CO_3 was the best one, although *t*-BuOK was also capable of promoting the reaction (entry 6). Dioxane could promote the reaction greatly in comparison with other solvents used (entries 8−11). In all cases, the major side product frequently observed is the dechlorinated starting material, resulting from a reductive process. It was noteworthy that 50 equiv of alkenol and relatively dilute reaction concentration (0.06 M) were also critical.

Subsequent selective cleavage of mono-Boc from di-Boc in **2** was proven to be challenging due to the electron-rich indole ring. In addition, the desired product **2** was only achieved in 48% yield in the aforementioned Heck reaction. We envisioned that the coordination of the lone pair electrons on the indole nitrogen to palladium at some point of the catalytic cycle would influence the efficiency of this reaction. Taking

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into consideration the two problematic reactions, an electron-withdrawing group was next planned to be introduced at the indole nitrogen to reduce these effects.

Treatment of **3** with Boc_2O in the presence of DMAP gave **7** in 98% yield. As anticipated, a Heck reaction of **7** under the aforementioned optimized conditions provided **8** in 75% yield. Selective cleavage of mono-Boc in **8** was easily successful using $Mg(ClO_4)_2$ in CH_3CN at room temperature.[14] Unexpectedly, during the deprotection using $Mg(ClO_4)_2$, a small amount of the cyclization product **9** was isolated. This result indicated that a cascade one-pot version of $Mg(ClO_4)_2$-promoted deprotection/cyclization could be achieved, thus streamlining the synthesis.[15] After several attempts, the one-pot process could be performed with a catalytic amount of $Mg(ClO_4)_2$ in CH_3CN at reflux for 2 h, affording the *cis*-**9a** and *trans*-**9b** in 98% overall yield in a ratio of 5:1, respectively. The diastereomeric product of *cis*-**9a** and *trans*-**9b**, both of which appear as a pair of distinct rotamers, could be separated by careful flash column chromatography, and their relative conformations were deduced by the NOESY spectrum. The yield is higher and the diastereoselectivity is similar to those reported using $PdCl_2(CH_3CN)_2$ in a similar substrate.[5e]

Although, we cannot rationalize the exact mechanism of $Mg(ClO_4)_2$-mediated cyclization, it is reasonable to postulate that the magnesium cation, acting as a mild Lewis acid, first coordinates to the alcohol oxygen and activates the allylic alcohol, thus facilitating the intramolecular S_N2' substitution reaction. To the best of our knowledge, this is the first example that $Mg(ClO_4)_2$ is used in such a carbon−nitrogen bond-formation process.[16] Its diastereoselectivity may be due to the steric interactions between the allylic methyl groups and the methyl ester group in the transition state, similar to that of Park's explanations.[5e]

The final deprotection of the two Boc groups in **9** proved to be especially challenging. Under normal conditions, either a partial epimerization at the C(6)-position occurred or a complex mixture was obtained. After extensive trials, the problem was finally overcome by first deprotection of N(5)-Boc in **9a** with TMSOTf in the presence of 2,6-lutidine (95% yield),[17] followed by deprotection of the Boc group at the indole nitrogen and saponification of methyl ester with K_2CO_3 in MeOH/H_2O (3:1) to provide the target molecule **1a** in 95% yield and without any epimerization.[18,19] Meanwhile, **9b** could be converted to **1b** following the same synthetic scheme as described for **9a**. Spectroscopic data for the synthetic materials were identical in all respects to those reported for the natural products.

In conclusion, an efficient total synthesis of (−)-*cis*-clavicipitic acid was achieved in seven linear steps from the known compound **6**. The 42% overall yield represents the highest one. It was also discovered that the intramolecular aminocyclization could be mediated by $Mg(ClO_4)_2$, leading to the azepinoindole nucleus. Key elements include a palladium-catalyzed method for the synthesis of the optically pure 4-chlorotryptophan derivative, a Heck reaction using aryl chloride as partner, and a one-pot $Mg(ClO_4)_2$-mediated tandem deprotection/aminocyclization reaction. To the best of our knowledge, this is the first example that aryl chloride was used as the Heck reaction partner in natural product total synthesis.

Experimental Section

Compound 8. A mixture of **7** (300 mg, 0.54 mmol), 2-methyl-3-buten-2-ol (2.33 g, 27.12 mmol), and K_2CO_3 (89 mg, 0.65 mmol) in dry dioxane (9.0 mL, 0.06 M) was degassed for 20 min. $Pd(OAc)_2$ (12.1 mg, 0.054 mmol) and PCy_3 (30.2 mg, 0.108 mmol) were added to the reaction, and the resulting reaction mixture was heated at 120 °C under argon atmosphere for 12 h. After cooling, the solvent was evaporated under reduced pressure and purified by FCC (PE−EtOAc, 3:1) to give **8** (243 mg, 75%) as white foam: $[\alpha]^{23}_D$ −21.4 (*c* 1.00, $CHCl_3$); IR (KBr) 3433, 2979, 1738, 1424, 1370, 1283, 1255, 1141, 1094, 966, 853, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.5 Hz, 1H), 7.15−7.28 (m, 4H), 6.19 (d, J = 15.3 Hz, 1H), 5.13 (dd, J = 2.7, 10.8 Hz, 1H), 3.83 (dd, J = 2.7, 15.0 Hz, 1H), 3.75 (s, 3H), 3.30 (dd, J = 10.8, 15.0 Hz, 1H), 2.42 (br s, 1H), 1.62 (s, 9H), 1.41 (s, 3H), 1.36 (s, 3H), 1.25 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 151.6, 149.4, 141.7, 136.3, 131.9, 127.2, 125.3, 124.5, 123.8, 121.4, 116.7, 114.3, 83.5, 82.9, 70.8, 58.6, 52.4, 29.6, 29.5, 28.0, 27.6, 27.4; HRMS (ESI) m/z calcd for $C_{32}H_{46}N_2O_9Na$ $(M + Na)^+$ 625.3096, found 625.3088.

Compounds 9a (*cis*) and 9b (*trans*). A stirred solution of **8** (500 mg, 0.83 mmol) and $Mg(ClO_4)_2$ (111 mg, 0.50 mmol) in CH_3CN (12.0 mL) was heated to reflux for 2 h. The reaction was allowed to cool and evaporated to dryness. Careful purification by FCC (PE−EtOAc, 10:1) afforded the *cis*-form **9a** (328.5 mg, 82%) and *trans*-form **9b** (65.4 mg, 16%). ***cis*-Form 9a:** white foam, $[\alpha]^{23}_D$ −157.3 (*c* 1.00, $CHCl_3$); IR (KBr) 3435, 2977, 2931, 1740, 1698, 1425, 1383, 1369, 1349, 1287, 1251, 1161, 1106, 971, 916, 867, 784, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) showed the presence of two conformers in a ratio of 1/2.2, δ 8.06−8.11 (m, 1H, both), 7.45 (br s, 1H, both), 7.22−7.27 (m, 1H, both), 7.02 (d, J = 7.5 Hz, 1H, major), 6.96 (d, J = 7.5 Hz, 1H, minor), 6.41 (d, J = 6.9 Hz, 1H, major), 6.15 (d, J = 6.0 Hz, 1H, minor), 5.25 (br s, 1H, minor), 5.17 (d, J = 6.3 Hz, 1H, major), 4.36 (dd, J = 3.6, 11.4 Hz, 1H, both), 3.75 (s, 3H, major), 3.74 (s, 3H, minor), 3.40−3.63 (m, 2H, both), 1.88 (s, 3H, both), 1.77 (s, 3H, minor), 1.75 (s, 3H, major), 1.66 (s, 9H, both), 1.40 (s, 9H, major), 1.37 (s, 9H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) major conformer shown δ 171.6, 153.5, 149.5, 139.8, 137.5, 136.5, 126.7, 124.3, 124.0, 123.3, 121.4, 116.5, 113.4, 83.4, 80.7, 57.0, 55.6, 51.8, 28.1, 28.0, 27.2, 25.5, 18.6; HRMS (ESI) m/z calcd for $C_{27}H_{37}N_2O_6$ $(M + H)^+$ 485.2646, found 485.2650. ***trans*-Form 9b:** white foam; $[\alpha]^{23}_D$ 105.0 (*c* 0.85, $CHCl_3$); IR (KBr) 3436, 2974, 2928, 1736, 1695, 1439, 1389, 1317, 1303, 1284, 1167, 1106, 1049, 967, 952, 864, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) showed the presence of two conformers in a ratio of 1/1, δ 7.92−7.98 (m, 1H × 2), 7.43 (s, 1H), 7.41 (s, 1H), 7.16−7.24 (m, 1H × 2), 7.08 (d, J = 7.2 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 6.42 (d, J = 8.1 Hz, 1H), 6.03 (d, J = 8.1 Hz, 1H), 5.39 (d, J = 8.1 Hz, 1H), 5.36 (d, J = 8.1 Hz, 1H), 5.16 (dd, J = 6.9, 12.3 Hz, 1H), 4.74 (dd, J = 5.1, 12.9 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.50−3.60 (m, 1H × 2), 3.35 (dd, J = 6.6, 15.6 Hz, 1H), 3.25 (dd, J = 4.8, 15.6 Hz, 1H), 1.86 (s, 3H × 2), 1.71 (s, 3H × 2), 1.65 (s, 9H × 2), 1.34 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) both conformers

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(19) No diastereomers of the final products were detected in the NMR spectrum in *cis*-**10a** or *trans*-**10b** cases under such basic conditions.

shown δ 173.2, 172.9, 155.6, 154.9, 149.74, 149.68, 139.7, 139.2, 137.7, 137.2, 136.1, 135.9, 128.5, 128.4, 124.7, 124.6, 124.2, 123.3, 122.5, 122.0, 121.0, 120.4, 117.1, 116.7, 114.14, 114.07, 83.6, 83.5, 80.5, 80.4, 60.2, 57.5, 55.8, 52.1, 51.9, 28.1, 27.1, 26.8, 25.6, 25.5, 18.8, 18.5; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{37}N_2O_6$ $(M + H)^+$ 485.2646, found 485.2640.

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Supporting Information Available: Experimental procedures and physical data for compounds **1a**,**b**, **2**−**4**, **7**, and **10a**,**b** and copies of spectra for compounds **1a**,**b**, **2**−**4**, **7**, **8**, **9a**,**b**, and **10a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.