

Synthetic Methods

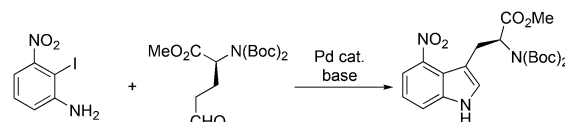
Total Synthesis of *cis*-Clavicipitic Acid from Asparagine via Ir-Catalyzed C–H bond Activation as a Key Step

Yu-ki Tahara,^[a] Mamoru Ito,^[a] Kyalo Stephen Kanyiva,^[b] and Takanori Shibata*^[a, c]

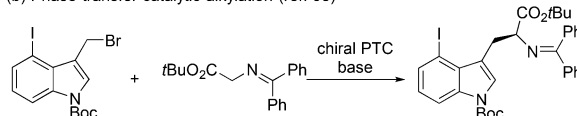
Abstract: 4-Substituted tryptophan derivatives and the total synthesis of *cis*-clavicipitic acid were achieved in reactions in which Ir-catalyzed C–H bond activation was a key step. The starting material for these reactions is asparagine, which is a cheap natural amino acid. The reductive amination step from the 4-substituted tryptophan derivative gave *cis*-clavicipitic acid with perfect diastereoselectivity.

Clavicipitic acid (**1**) is an ergot alkaloid that has been isolated from *Claviceps* strain SD-58 and *Claviceps fusiformis* as a mixture of *cis*- and *trans*-isomers.^[1] The unique tricyclic azepinoindole system has attracted synthetic chemists, and various strategies have been developed for its total syntheses.^[2,3] Clavicipitic acid (**1**) has a 4-substituted tryptophan skeleton, which was used as the key intermediate for the total synthesis of clavicipitic acid (**1**)^[3f] and other alkaloids,^[4,5] but the introduction of a substituent at the C-4 position is generally difficult compared with other positions on the indole ring of tryptophan derivatives. The three typical approaches to 4-substituted tryptophan derivatives are shown in Scheme 1: Pd-catalyzed indole synthesis by the coupling of *o*-haloanilines with aldehydes having an amino acid moiety (Scheme 1 a);^[5] amino acid synthesis by the enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with 3-(bromomethyl)indoles using a chiral phase-transfer catalyst (Scheme 1 b);^[3e] Pd-catalyzed C–H alkylation at the C-4 position of tryptophan using trifluoromethylsulfonamide as a directing group (Scheme 1 c).^[6] We envisioned that the indole skeleton of clavicipitic acid (**1**) could readily be obtained via intramolecular cyclodehydration initiated by the C–H bond activation of β -keto aniline, which can be derived from asparagine (Scheme 1 d).

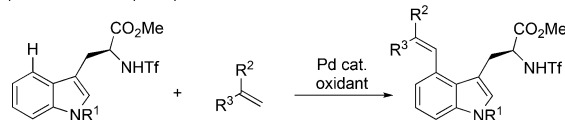
(a) Coupling of *o*-haloanilines with aldehydes (ref. 5)



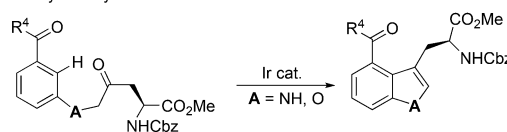
(b) Phase-transfer catalytic alkylation (ref. 3e)



(c) C–H olefination (ref. 6)



(d) This work: cyclodehydration via C–H activation



Scheme 1. Approaches to the synthesis to 4-substituted tryptophan derivatives.

Transition metal-catalyzed C–H bond activation has attracted much attention, because pre-activation of the substrate is unnecessary, thus realizing shorter and more atom-economical syntheses of complex molecules.^[7] To date, the direct C–H bond activation strategy has been used in key steps for the total synthesis of natural products and pharmaceuticals.^[7] Our group has focused on the Ir-catalyzed synthetic transformations initiated by C–H bond activation.^[8,9] For example, we reported intramolecular cyclodehydration via sp^2 C–H bond cleavage for the synthesis of 4-substituted benzoheteroles such as benzofuran and indole derivatives.^[10,11] Herein we report the use of this protocol for the synthesis of 4-substituted tryptophan derivatives (Scheme 1 d), and the conversion of one of the obtained derivatives into clavicipitic acid (**1**).

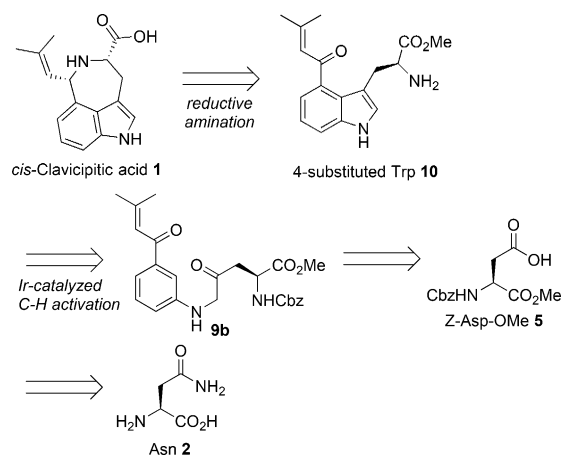
Our retro-synthetic strategy is shown in Scheme 2. *cis*-Clavicipitic acid (**1**) would be accessible from the 4-substituted tryptophan derivative **10** by intramolecular reductive amination. Compound **10** would be converted from β -keto aniline derivative **9b** by our originally developed intramolecular cyclodehydration. We considered that substrate **9b** could be readily prepared from commercially available Cbz-L-aspartic acid α -

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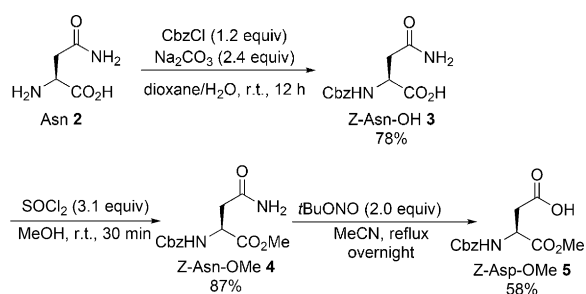


Scheme 2. Retrosynthetic analysis of *cis*-clavicipitic acid.

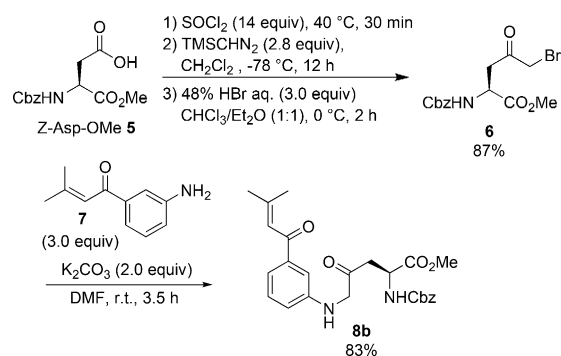
methyl ester (**5**; Z-Asp-OMe), or cheaper asparagine (**2**; Asn), which is a natural amino acid.

We initiated our synthesis by the transformation of commercially available Asn (**2**) to Z-Asp-OMe **5** (Scheme 3). The carbobenzoxylation of **2** with benzyl chloroformate (CbzCl) and sodium carbonate gave Z-Asn-OH **3**.^[12a] Subsequent methyl esterification proceeded in the presence of thionyl chloride in methanol.^[12b] Transformation from amide to carboxylic acid using *tert*-butyl nitrite afforded **5**.^[12c,d]

The synthesis of β -keto aniline **8b**, which is a substrate of the key reaction, is depicted in Scheme 4. α -Keto bromide **6** was prepared by Arndt-Eistert synthesis from **5** using thionyl



Scheme 3. Synthesis of Z-Asp-OMe **5** from Asn (**2**).



Scheme 4. Synthesis of β -keto aniline **8b**.

chloride, trimethylsilyldiazomethane, and aqueous hydrobromic acid in 87% yield. Subsequent nucleophilic substitution of α -keto bromide **6** with 1-(3-aminophenyl)-3-methylbut-2-en-1-one (**7**)^[13] in the presence of potassium carbonate gave β -keto aniline **8b** in 83% yield.

Next, we examined the Ir-catalyzed cyclodehydration of β -keto aniline **8a** as a model substrate, which has an acetyl group as a directing group (DG), and submitted it to an intramolecular reaction in the presence of an Ir catalyst prepared from [Ir(cod)₂]BARF and *rac*-BINAP at 135 °C in chlorobenzene (PhCl).^[10a] The desired 4-substituted tryptophan **9a** was obtained in moderate yield (entry 1). When β -keto aniline **8b**, which has a 3,3-dimethyl acryloyl group as a directing group, was used, the corresponding 4-substituted tryptophan **9b** was obtained in 79% yield (entry 2).^[14] The high yield was also achieved even by using a smaller amount of the catalyst, albeit with a longer reaction time. The reaction of β -keto aniline **8c** derived from the *R*-form of the amino acid also proceeded smoothly to give the 4-substituted *R*-tryptophan derivative **9c**, which is the opposite enantiomer of **9b** (entry 3). β -Keto phenol ether could be also used in the present transformation,

Table 1. Cyclodehydration via Ir-catalyzed C–H bond activation for the synthesis of 4-substituted tryptophan derivatives **9**.

Entry	A	DG	Substrate	Time, Yield
1	NH	Acetyl	8a	9a 20 h, 54%
2	NH	3,3-Dimethyl acryloyl	8b	9b 15 h, 79% 54 h, 74% ^a
3	NH	3,3-Dimethyl acryloyl	8c	9c 6 h, 69%
4	O	Acetyl	8d	9d 24 h, 84%

[a] Catalyst (5 mol%) was used.

and the reaction of **8d** afforded 4-substituted (3-benzofuranyl) alanine derivative **9d** in 84% (entry 4). These results indicate that Ir-catalyzed cyclodehydration is a versatile protocol for the synthesis of 4-functionalized tryptophan derivatives including its oxygen analogue.

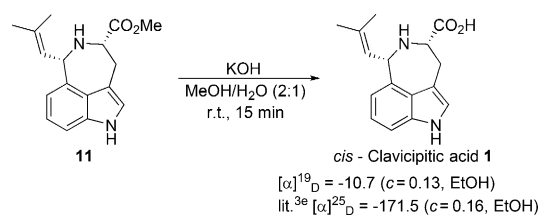
We next turned our attention to the construction of the tricyclic azepinoindole skeleton by an intramolecular reductive amination, where ketimine would be formed between the carbonyl moiety of the 3,3-dimethyl acryloyl group and the amino moiety of the amino acid (Table 2).^[2g] We first deprotected the

Table 2. Intramolecular reductive amination for the synthesis of *cis*-clavicipitic acid methyl ester **11**.^[a]

Entry	Reductant	X [equiv]	Additive	Yield [%]
1	NaBH(OAc) ₃	1.4	none	N. D.
2	NaBH(OAc) ₃	1.4	Et ₃ N	21
3	NaBH ₃ CN	1.4	Et ₃ N	N. D.
4	NaBH(OAc) ₃	2.8	Et ₃ N	46
5	NaBH(OAc) ₃	4.2	Et ₃ N	53

[a] N.D. = not determined.

Cbz group in **9b** by using hydrogen bromide in acetic acid and then submitted the free amine **10** to a variety of conditions for the intramolecular reductive amination without isolation (Table 2). When sodium triacetoxyborohydride was used as a reductant in dichloromethane, the desired cyclic amine **11** could not be detected at all (entry 1). In contrast, amine **11** was obtained by the addition of a stoichiometric amount of triethylamine, albeit in low yield because of the low conversion of the ketimine (entry 2). However, it is noteworthy that the reductive amination proceeded with perfect diastereoselectivity and that the configuration was the desired *cis*-form. We next used sodium cyanoborohydride as a stronger reductant in the presence of triethylamine, and could ascertain the formation of the tricyclic azepinoindole, but the alkene reduction of 2-methyl-1-propene moiety also proceeded and the desired product **11** was not detected (entry 3). We next investigated the amount of sodium triacetoxyborohydride, and achieved a moderate yield of 53% by the addition of 4.2 equivalents of the reductant (entries 4 and 5). However, a significant decrease of the *ee* of compound **11** was observed (13% *ee*).^[15,16] In the final step, we examined the hydrolysis of **11** using potassium hydroxide in a mixed solvent of methanol and water (2:1),^[6] and we obtained *cis*-clavicipitic acid (**1**) (Scheme 5).



Scheme 5. Synthesis of *cis*-clavicipitic acid.

In conclusion, we have developed a new approach to the synthesis of 4-substituted tryptophan derivatives **9** by cyclodehydration via Ir-catalyzed C–H bond activation. We further achieved the total synthesis of the *cis*-clavicipitic acid (**1**) from asparagine (**2**) via this original Ir-catalyzed reaction and intramolecular reductive amination in a few steps. Our synthesis started from a commercially available and cheap compound, and realized higher atom-efficiency through the minimum use of protecting groups. Further studies for the use of our originally developed C–H bond activation in natural product syntheses are underway in our laboratory.

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- [1] a) J. Robbers, H. Floss, *Tetrahedron Lett.* **1969**, 10, 1857–1858; b) G. King, P. Mantle, C. Szczyrbak, E. Waight, *Tetrahedron Lett.* **1973**, 14, 215–218; c) G. S. King, E. Waight, P. Mantle, C. Szczyrbak, *J. Chem. Soc. Perkin Trans. 1* **1977**, 2099–2103; d) J. Robbers, H. Otsuka, H. Floss, E. Arnold, J. Clardy, *J. Org. Chem.* **1980**, 45, 1117–1121.
- [2] Total synthesis of racemic clavicipitic acid, see: a) A. P. Kozikowski, M. N. Greco, *Heterocycles* **1982**, 19, 2269–2273; b) H. Murakami, T. Takahashi, M. Natsume, *Heterocycles* **1983**, 20, 1963–1968; c) A. P. Kozikowski, M. N. Greco, *J. Org. Chem.* **1984**, 49, 2310–2314; d) S. Nakatsuka, T. Masuda, K. Yamada, T. Goto, *Heterocycles* **1984**, 21, 407; e) A. P. Kozikowski, M. Okita, *Tetrahedron Lett.* **1985**, 26, 4043–4046; f) P. J. Harrington, L. S. Hegedus, K. F. McDaniel, *J. Am. Chem. Soc.* **1987**, 109, 4335–4338; g) M. Matsumoto, H. Kobayashi, N. Watanabe, *Heterocycles* **1987**, 26, 1197–1202; h) M. Iwao, F. Ishibashi, *Tetrahedron* **1997**, 53, 51–58; i) F. Bartocini, M. Casoli, M. Mari, G. Piersanti, *J. Org. Chem.* **2014**, 79, 3255–3259.
- [3] Total synthesis of optically active clavicipitic acid, see: a) Y. Yokoyama, T. Matsumoto, Y. Murakami, *J. Org. Chem.* **1995**, 60, 1486–1487; b) Y. Yokoyama, H. Hikawa, M. Mitsuhashi, A. Uyama, Y. Murakami, *Tetrahedron Lett.* **1999**, 40, 7803–7806; c) H. Shinohara, T. Fukuda, M. Iwao, *Tetrahedron* **1999**, 55, 10989–11000; d) Y. Yokoyama, H. Hikawa, M. Mitsuhashi, A. Uyama, Y. Hiroki, Y. Murakami, *Eur. J. Org. Chem.* **2004**, 1244–1253; e) J. Ku, B. Jeong, S. Jew, H. Park, *J. Org. Chem.* **2007**, 72, 8115–8118; f) Z. Xu, Q. Li, L. Zhang, Y. Jia, *J. Org. Chem.* **2009**, 74, 6859–6862; g) Z. Xu, Q. Li, L. Zhang, Y. Jia, *J. Org. Chem.* **2010**, 75, 6316.
- [4] a) Q. Liu, Y. Jia, *Org. Lett.* **2011**, 13, 4810–4813; b) Z. Xu, F. Zhang, L. Zhang, Y. Jia, *Org. Biomol. Chem.* **2011**, 9, 2512–2517; c) Y. Zhang, Q. Liu, C. Wang, Y. Jia, *Org. Lett.* **2013**, 15, 3662–3665.
- [5] Z. Xu, W. Hu, Q. Liu, L. Zhang, Y. Jia, *J. Org. Chem.* **2010**, 75, 7626–7635.

- [6] a) J. Li, T. Mei, J. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 6452–6455; *Angew. Chem.* **2008**, *120*, 6552–6555; b) Q. Liu, Q. Li, Y. Ma, Y. Jia, *Org. Lett.* **2013**, *15*, 4528–4531.
- [7] For selected reviews, see: a) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1769; b) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; c) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72; d) H. Davies, J. Manning, *Nature* **2008**, *451*, 417–424; e) X. Chen, K. Engle, D. Wang, J. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; *Angew. Chem.* **2009**, *121*, 5196–5217; f) T. Lyons, M. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; g) C. Sun, B. Li, Z. Shi, *Chem. Commun.* **2010**, *46*, 677–685; h) C. Yeung, V. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; i) S. Cho, J. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068–5083; j) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 128–131; *Angew. Chem.* **2012**, *124*, 132–135.
- [8] Ir-catalyzed sp^2 C–H bond activation reaction, see: a) K. Tsuchikama, M. Kasagawa, Y. Hashimoto, K. Endo, T. Shibata, *J. Organomet. Chem.* **2008**, *693*, 3939–3942; b) K. Tsuchikama, M. Kasagawa, K. Endo, T. Shibata, *Synlett* **2010**, 97–100; c) S. Takebayashi, T. Shibata, *Organometallics* **2012**, *31*, 4114–4117; d) S. Pan, N. Ryu, T. Shibata, *J. Am. Chem. Soc.* **2012**, *134*, 17474–17477; e) S. Pan, N. Ryu, T. Shibata, *Adv. Synth. Catal.* **2014**, *356*, 929–933; f) S. Pan, T. Wakaki, N. Ryu, T. Shibata, *Chem. Asian J.* **2014**, *9*, 1257–1260; g) T. Shibata, T. Shizuno, *Angew. Chem. Int. Ed.* **2014**, *53*, 5410–5413; h) T. Shibata, Y. Matsuo, *Adv. Synth. Catal.* **2014**, *356*, 1516–1520.
- [9] Ir-catalyzed sp^3 C–H bond activation reaction, see: a) K. Tsuchikama, M. Kasagawa, K. Endo, T. Shibata, *Org. Lett.* **2009**, *11*, 1821–1823; b) S. Pan, K. Endo, T. Shibata, *Org. Lett.* **2011**, *13*, 4692–4695; c) T. Shibata, H. Hirashima, M. Kasagawa, K. Tsuchikama, K. Endo, *Synlett* **2011**, 2171–2176; d) S. Pan, Y. Matsuo, K. Endo, T. Shibata, *Tetrahedron* **2012**, *68*, 9009–9015.
- [10] a) K. Tsuchikama, Y. Hashimoto, K. Endo, T. Shibata, *Adv. Synth. Catal.* **2009**, *351*, 2850–2854; b) T. Shibata, Y. Hashimoto, M. Otsuka, K. Tsuchikama, K. Endo, *Synlett* **2011**, 2075–2079.
- [11] For a highly enantioselective reaction using original bidentate phosphoramidite ligands, see: T. Shirai, H. Ito, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2014**, *53*, 2658–2661.
- [12] a) Z. Zhang, A. Aerschot, C. Hendrix, R. Busson, F. David, P. Sandra, P. Herdewijn, *Tetrahedron* **2000**, *56*, 2513–2522; b) J. Maddaluno, A. Corruble, V. Leroux, G. Plé, P. Duhamel, *Tetrahedron: Asymmetry* **1992**, *3*, 1239–1242; c) D. Adams, P. Bailey, I. Collier, J. Heffernan, S. Stokes, *Chem. Commun.* **1996**, 349–350; d) P. Ottersbach, J. Schmitz, G. Schnakenburg, M. Gütschow, *Org. Lett.* **2013**, *15*, 448–451.
- [13] A. Kluge, R. Petter, R. W. Tester, L. Qiao, D. Niu, W. F. Westlin, J. Singh, H. Mazdiyasn, *PCT Int. Appl.* 2009158571A1, **2009**.
- [14] 4-Substituted tryptophane derivative **9b** did not racemize under the Ir-catalyzed reaction conditions.
- [15] When the reduction was conducted at 0 °C, the *ee* of **11** was slightly improved to 29% *ee*, but the yield decreased to 29%.
- [16] The racemization proceeded even with other organic and inorganic bases, such as *N,N*-diisopropylethylamine, NaHCO_3 , K_2CO_3 , and Cs_2CO_3 . In the absence of the bases, the formation of the cyclic imine could not be observed.

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