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Syntheses without protection: a three-step synthesis of optically active clavicipitic acid by utilizing biomimetic synthesis of 4-bromotryptophan

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Abstract

The optically active clavicipitic acid (**4**), an ergot alkaloid, was synthesized by a three-step sequence from 4-bromoindole (**1**). The reaction of **1** with *dl*-serine (**2**) in the presence of Ac_2O followed by enzymatic kinetic resolution gave (*S*)-4-bromotryptophan (**3**). The Heck reaction of **3** with 1,1-dimethylallylalcohol in aqueous media gave clavicipitic acid in one-pot.

Keywords: aqueous media; amino acid derivatives; cyclization; Heck reactions.

Since amino acids are indispensable for synthetic use as inexpensive members of a chiral pool, numerous chemical transformations of amino acids have been reported.[1] However, most of those transformations have been performed with protected amino acids in order to avoid side reactions and to solubilize them into organic solvents.[2,3] We report here a biomimetic synthesis of (*S*)-4-bromotryptophan (**3**) from 4-bromoindole (**1**) and *dl*-serine (**2**) by a two-step sequence and one-pot transformation of **3** to optically active clavicipitic acid (**4**) (Scheme 1). This quite short synthesis was made possible by omission of the protection and deprotection steps in the synthetic route.

Although there have been several reports[4] for direct synthesis of tryptophan from indole and serine or its analogues mimicking the biosynthesis of tryptophan, the yields were far from satisfactory.[5] Snyder reported[6] that *N*-acetyltryptophan was obtained in practical yield by heating indole with *N*-acetyldehydroalanine (**5**) in the presence of Ac_2O in AcOH. This reaction seemed to be suitable for our present purpose, since, if the reaction of 4-bromoindole (**1**) with **5** proceeded, (*S*)-**3** would be easily obtained by enzymatic kinetic resolution of the resulted *N*-acetyl-4-bromotryptophan (**6**). Disappointingly, the attempted reaction of **1** with **5** did not proceed. However, the use of *dl*-serine (**2**) instead of **5** gave **6** in 58% yield under similar reaction conditions (Scheme 2). Those results surprised us,

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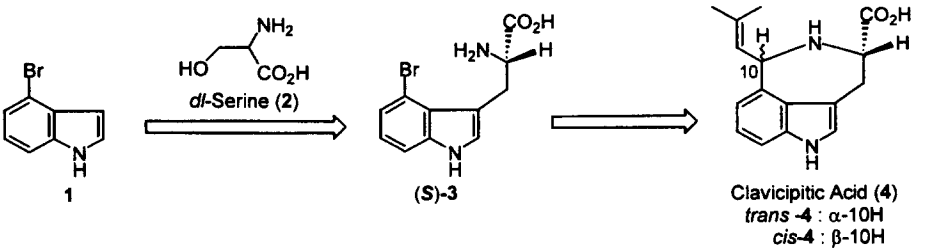
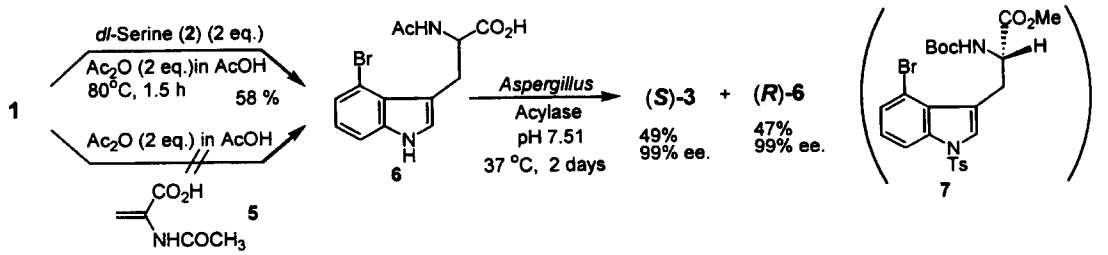


Scheme 1.

because **5** was supposed to be an intermediate[7] for the formation of **6**. The detailed reaction mechanism and extension of the procedure to other indoles are now under investigation.

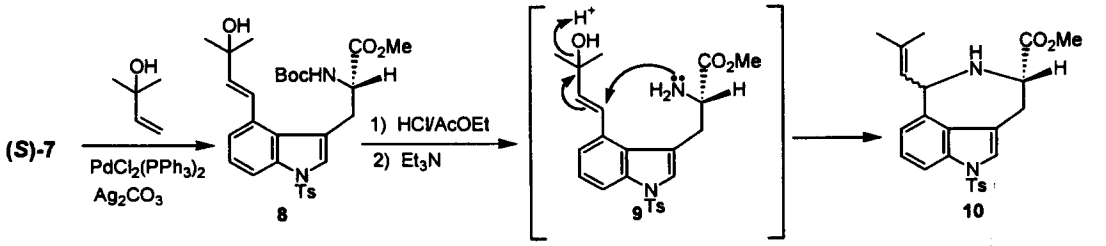


Scheme 2.

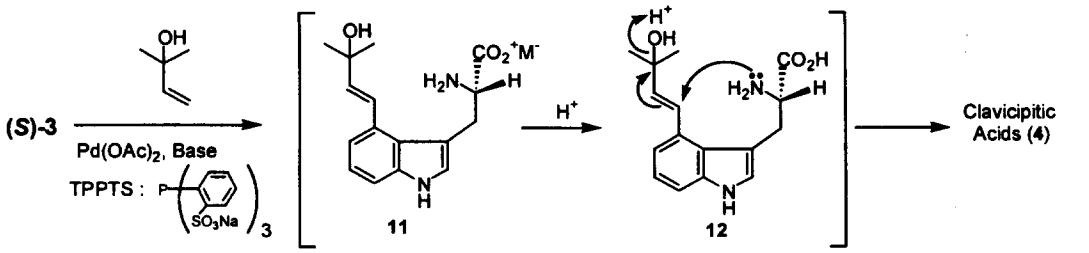
The kinetic resolution of the racemate (**6**) was achieved by incubation with inexpensive acylase from *Aspergillus* in a phosphate buffer. The resolution worked perfectly to give (*S*)-**3** (>99% ee) and the acid[8] (*R*)-**6** (>99% ee) in 49% and 47% yield, respectively. The present two-step synthesis of (*S*)-**3** from **1** is more convenient and economical than the alternative method, which is a five-step synthesis from the same starting material **1** via a fully protected (*S*)-4-bromotryptophan (**7**) prepared[9] by us with expensive reagents such as a stoichiometric amount of $Pd(OAc)_2$ and an optically active phosphine ligand. Also, it is noteworthy that this is the first successful example of a practical biomimetic synthesis of a tryptophan derivative.

The next step was a one-step conversion of the free amino acid **3** to clavicipitic acid (**4**). We have already found[9] that deprotection of the Boc group of **8**, which was prepared by Heck reaction of (*S*)-**7** with 1,1-dimethylalcohol, caused spontaneous cyclization of the resulted **9** to give protected clavicipitic acid (**10**) in one-pot (Scheme 3). From this result, we considered that, if Heck reaction of free amino acid **3** with 1,1-dimethylallylalcohol had been attempted, the resulting intermediate **11** would be cyclized spontaneously under weakly acidic condition to give **4** in one-pot (Scheme 4). At first, we attempted the Heck reaction in an organic solvent (dioxane or DMF), but the reaction gave the complex mixture. We considered that the reason for this failure was due to the insolubility of the amino acid in the organic solvent. So the reaction was carried out in alkaline aqueous media[10] by using a water-soluble phosphine ligand, TPPTS.[11] A mixture of **3** and 1,1-dimethylallylalcohol was heated at 130°C for 8 h in the presence of $Pd(OAc)_2$ (0.1 equiv.), TPPTS (0.2 equiv.), and base (3 equiv.), and the results are shown in Table 1. When AcONa was used, only *N*-allylated product **13** was isolated[12] (run 1) and a complex mixture was formed in the presence of $NaHCO_3$ (run 2). However, by the use of a stronger base, such as Na_2CO_3, 4-vinylated product **11** (M^+=Na^+) was obtained in moderate yield accompanied with the starting material (run 3). The yield of **11** was increased by increasing the basicity of the alkaline salt; K_2CO_3 and NaOH gave **11** in good yield (runs 4, 5). The carboxylate salt (**11**) was unexpectedly stable under basic conditions and could be isolated after ODS column chromatography. An organic base such

as Et_3N decreased the yield (run 6). It is very interesting that the basicity affected the chemoselectivity of this reaction, but the reason for this is not understood at present.



Scheme 3.



Scheme 4.

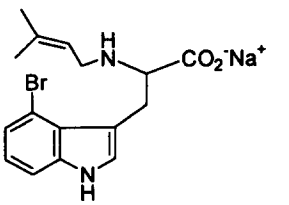
Next, we attempted a one-pot synthesis of clavicipitic acid (**4**) in optically active form. Thus, after the Heck reaction of (*S*)-**3** with 1,1-dimethylallylalcohol under the same reaction condition with run 4 in Table 1, 60% AcOH aq. was added to the resulting solution of **11**, and the mixture was warmed to 60°C for 2 h. This reaction proceeded smoothly to give a diastereomixture (1:1) of clavicipitic acids (**4**) in 61% overall yield from (*S*)-**3**. Surprisingly, this one-pot process did not cause any racemization[13] in spite of the strong basic condition during the Heck reaction (K_2CO_3 in H_2O at 130°C for 2 h), although the reason is not clear at this stage.

The present three-step synthesis clearly shows that protection of the free amino acid is not always necessary in organic synthesis, and that such methodology not requiring protection would not only remarkably decrease the number of reaction steps needed, but also improve the likelihood of discovering new reaction and selectivity in aqueous media.[14]

Table 1
Results of Heck reaction of 4-bromotryptophan (**3**) with dimethylallylalcohol

Run	Base	Product (%) 11	13	Other Product (%)
1	AcONa*	-	34	SM (35)
2	$NaHCO_3$	-	-	Many Products
3	Na_2CO_3	51	-	SM (38)
4	K_2CO_3	91	-	
5	NaOH	91	-	
6	Et_3N	55	-	SM (8) + Tryptophan (38)

* Reaction Condition; 120 °C, 4.5 h SM : starting material



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5. For example, Murakami reported[4c] that a tryptophan–synthetase biomimetic reaction conducted in the presence of an *N*-alkylated pyridoxal quaternary salt and an optically active bilayer membrane consisting of synthetic peptide lipids gave quite unsatisfactory yields of tryptophan for synthetic purposes (3% yield, 35% ee).
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7. We observed the formation of **5** by heating of serine (**2**) with Ac_2O in AcOH followed by direct evaporation of the solvent and Ac_2O. A similar reaction has been also reported: Nakagawa, M.; Torisawa, Y.; Hosoka, T.; Tanabe, K.; Tavet, F.; Aikawa, M.; Hino, T. *Heterocycles* **1993**, *35*, 1167–1170.
8. The yields and optical purities were determined after esterification with Me_3SiCHN_2.
9. Yokoyama, Y.; Matsumoto, T.; Murakami, Y. *J. Org. Chem.* **1995**, *60*, 1486–1487.
10. For a comprehensive review of Heck reaction in aqueous media, see: Beletskaya, I. P.; Cheprakow, A. V. In *Organic Synthesis in Water*; Grieco P. A., Ed.; Blackie Academic and Professional: London, 1998; Chap. 6, pp. 141–213.
11. Merola, J. S.; Stelzer, H. In *Aqueous-Phase Organometallic Catalysis: Concepts and Application*; Cornnils, B.; Herrmann, W. A., Eds.; Wiley–VCH: Wienheim, 1998; pp. 59–89.
12. Since this reaction did not proceed without the palladium catalyst, a SN2′ type reaction mechanism was excluded in the formation of *N*-allyl derivative **13**. Recently, Magari et al. reported the palladium catalyzed direct amination of 1,1-dimethylallyl alcohol with diethylamine: Magari, K.; Ishimura, Y.; Ooe, T.; Nagato, N. *Nippon Kagakukaishi* **1996**, 250–255.
13. The optical purities of *cis* and *trans* clavicipitic acid (**4**) were determined by HPLC after isolation of each isomer as methyl ester prepared by the reaction with diazomethane [Chiralpak AS (Daicel) hexane:*iso*-Pro-OH=50:1].
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