Optically Active Total Synthesis of Clavicipitic Acid[1]

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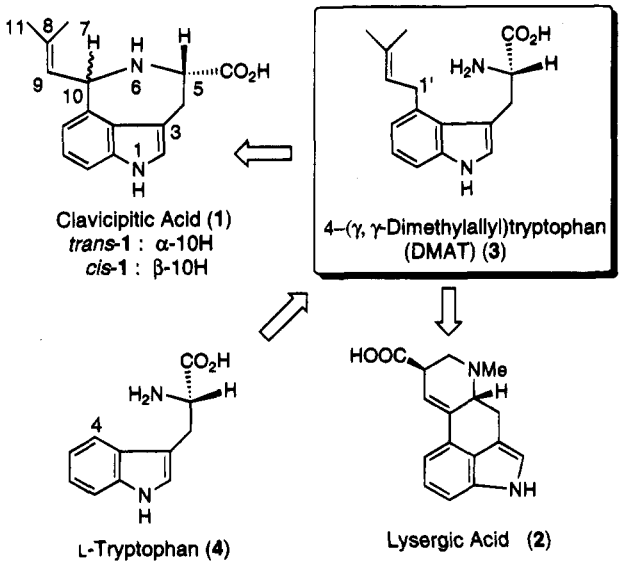
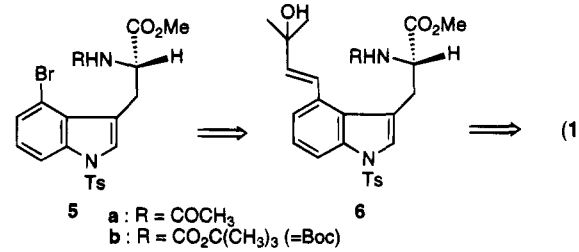
Clavicipitic acid (**1**) is an ergot alkaloid that has been isolated from the *Claviceps* strain SD58 and from *Claviceps fusiformis* as a mixture of diastereomers.[2] Although **1** has a unique tricyclic azepinoindole skeleton which is atypical of the ergot alkaloids such as lysergic acid (**2**), all of these alkaloids are biosynthesized from the same intermediate, 4-(γ,γ-dimethylallyl)tryptophan (**3**, DMAT).[3]



Since DMAT (**3**) is biosynthesized from L-tryptophan (**4**), commercially available L-tryptophan (**4**) might be a good starting material for the synthesis of optically active ergot alkaloids. Only limited success has been reported, however.[4] The chief obstacle has been the selective substitution at the C_4-position of the indole ring. We wish to report the first total syntheses of the optically-active clavicipitic acids (**1a** and **1b**).[5] The synthesis employs (*S*)-4-bromotryptophan (**5**) as a key intermediate and occurs *via* 4-(1′,1′-dimethyl-1′-hydroxy-2-propenyl-3-yl)-tryptophan (**6**), the synthetic equivalent of DMAT (**3**) (Scheme 1).

Scheme 1



Scheme 2

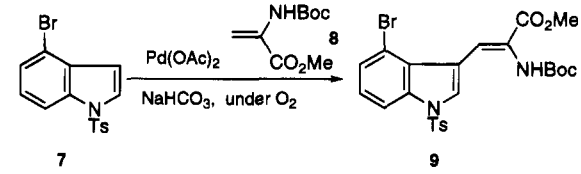


Table 1. Synthesis of 4-Bromodehydrotryptophan (9)

run	$Pd(OAc)_2$ (equiv)	chloranil (equiv)	time (h)	temp (°C)	solvent	yield (%)
1	1.0		7	70	CH_2ClCH_2Cl	31
2	1.0	0.25	7	70	CH_2ClCH_2Cl	74
3	1.0	1.0	8	83	CH_2ClCH_2Cl	87
4	1.0	1.0	4	90	TCB[a]	83
5	0.25	1.0	3	90	TCB	38

[a] TCB = 1,2,4-trichlorobenzene.

The vinylation of an aromatic bromide in the presence of a stoichiometric amount of Pd(II) chemoselectively occurs at the most electrophilic aromatic position without affecting the carbon–bromine bond.[6] This reaction provided our strategy for introduction of the first carbon side chain, and the regioselective introduction of the second carbon side chain to the position substituted with bromine would be accomplished using a transition-metal-catalyzed cross-coupling reaction. The preparation of 4-bromodehydrotryptophan (**9**) was achieved by the vinylation of 4-bromoindole (**7**) with the *N*-(*tert*-butoxycarbonyl)dehydroalanine methyl ester (**8**) in the presence of a stoichiometric amount of $Pd(OAc)_2$ (Scheme 2). The literature conditions [1.0 equiv of $Pd(OAc)_2$ in AcOH at 120 °C for 2 h][6,7] were not suitable for the preparation of **9**. However, compound **9** was obtained in 31% yield when the reaction was carried out in the presence of $NaHCO_3$ in the aprotic solvent, CH_2ClCH_2Cl (run 1 in Table 1). Furthermore, the addition of 0.25 equiv of chloranil was found to dramatically improve the yield (run 2). The use of 1.0 equiv of chloranil enhanced the yield even more (run 3), and higher temperature coupled with 1,2,4-trichlorbenzene as solvent shortened the reaction time (run 4). On the assumption that chloranil acts as an

(1) Synthetic Studies on Indoles and Related Compounds. 36. Part 35: Suzuki, H.; Tsukuda, A.; Kondo, M.; Aizawa, M.; Senoo, Y.; Makajima, M.; Watanabe, T.; Yokoyama, Y.; Murakami, Y. *Tetrahedron Lett.* in press.

(2) (a) Robbers, J. E.; Floss, H. G. *Tetrahedron Lett.* **1969**, 1857. (b) Robbers, J. E.; Otsuka, H.; Floss, H. G.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 1117. (c) King, G. S.; Mantle, P. G.; Szczyrbak, C. A.; Waight, E. S. *J. Chem. Soc.* **1977**, 2099.

(3) Floss, H. G. *Tetrahedron* **1976**, *32*, 873.

(4) (a) Nakatsuka, S.; Miyazaki, H.; Goto, T. *Chem. Lett.* **1981**, 407. (b) Rebek, J., Jr.; Tai, D. F.; Shue, Y.-K. *J. Am. Chem. Soc.* **1984**, *106*, 1813. (c) Nakatsuka, S.; Masuda, T.; Sakai, K.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 5735. (d) Kogan, T. P.; Somers, T. C.; Venuti, M. C. *Tetrahedron* **1990**, *46*, 6623. (e) Varie, D. L. *Tetrahedron Lett.* **1990**, *31*, 7583. (f) Mascal, M.; Moody; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 823. (f) Sommelhack, M. F.; Knochel, P.; Singleton, T. *Tetrahedron Lett.* **1993**, *32*, 5051.

(5) The total syntheses of racemic clavicipitic acids (**1**) have been reported by three groups; see: (a) Muratake, H.; Takahashi, T.; Natsume, M. *Heterocycles* **1983**, *20*, 1963. (b) Kozikowski, A. P.; Greco, M. N. *J. Org. Chem.* **1984**, *49*, 2310. (c) Matsumoto, M.; Kobayashi, H.; Watanabe, N. *Heterocycles* **1987**, *26*, 1197.

(6) (a) Yokoyama, Y.; Takahashi, M.; Kohno, Y.; Kataoka, K.; Fujikawa, Y.; Murakami, Y. *Heterocycles* **1990**, *31*, 803. (b) Yokoyama, Y.; Takashima, M.; Higaki, C.; Shidori, K.; Moriguti, M.; Ando, C.; Murakami, Y. *Heterocycles* **1993**, *36*, 1739. (c) Yokoyama, Y.; Takahashi, M.; Takashima, M.; Kohno, Y.; Kobayashi, H.; Kataoka, K.; Shidori, K.; Murakami, Y. *Chem. Pharm. Bull.* **1994**, *42*, 832.

(7) The direct activation of the aromatic carbon–hydrogen bond by the palladium salt has been extensively investigated by Fujiwara and co-workers. AcOH was used as a solvent or cosolvent in most of these reactions; for example: (a) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. (b) Moritani, I.; Fujiwara, Y. *Synthesis* **1973**, 524. (c) Nakata, K.; Miyata, T.; Jintoku, T.; Kitani, A.; Taniguti, Y.; Takaki, K.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3755.

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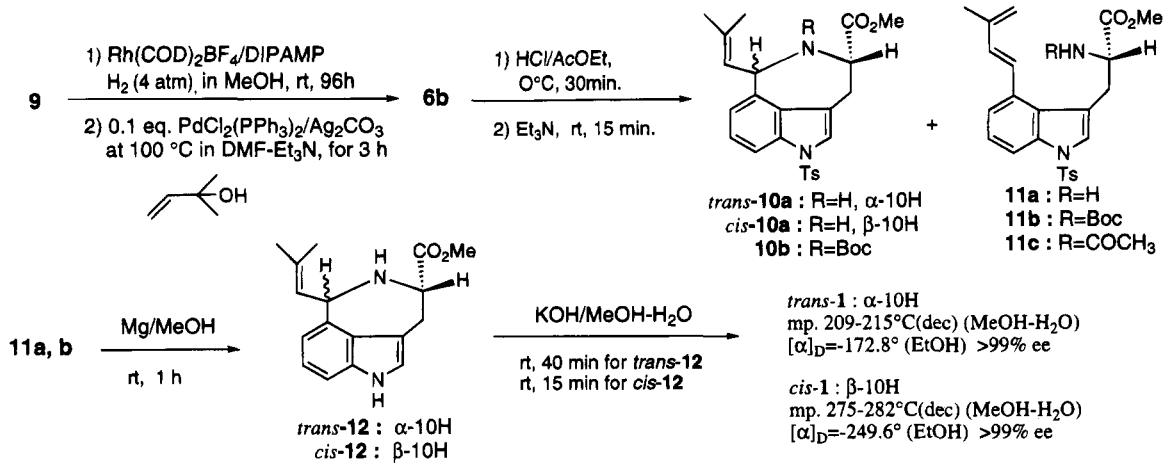
Scheme 3



oxidizing reagent to recycle Pd(0) to Pd(II),[8] a catalytic amount of Pd(II) was employed in run 5; however, the yield of **9** was only 38% under these conditions.[9]

The asymmetric reduction of **9** was attempted using various chiral phosphine ligands. Among these, only DIPAMP, developed by the Monsanto group, gave a satisfactory optical yield (94% ee).[10,11] The absolute configuration of **5b** was determined to be S by conversion to *N*-Boc-tryptophan methyl ester, which proved to be identical to a sample synthesized from L-tryptophan (**4**). Vinylation of **5b** under Heck conditions in the presence of Ag_2CO_3 smoothly proceeded to give the C_4-vinylated product (**6b**) without racemization (83%). In the absence of Ag_2CO_3, a higher reaction temperature (120 °C) was required and significant racemization was observed (82% yield, 71% ee).

Hegedus reported[12] that the attempted cyclization of **6a** gave the diene (**11c**) as the sole product. However, the cyclization of **6b** occurred simultaneously with the loss of the Boc group under acidic conditions.[13] Optimum conditions involved treatment of **6b** with HCl–AcOEt (0 °C, 30 min) and subsequent neutralization with Et_3N (rt, 15 min) (Scheme 3). A mixture of *cis* and *trans* isomers (**10**) was obtained in 62% yield, accompanied by the diene (**11a**, 29%). Separation of *trans*-**10a** (38%) and *cis*-**10a** (24%) was achieved by silica gel chromatography. When the reaction was carried out in MeOH, the yield of **10** decreased to 13%, while the yield of the diene (**11a**) increased to 52%. Upon changing the acid to CF_3COOH, a mixture of the diene (**11b**, 30%) and cyclized product (**10b**, 30%) was obtained when AcOEt was used as solvent. The detosylation of *trans*-**10a** (*cis*-**10a**) with Mg/MeOH was carried out to give *trans*-**12** (*cis*-**12**) in 72% yield (64%). The optical purity of each isomer was determined to be 91% ee. However, one recrystallization from benzene–hexane provided optically pure samples (>99%).[14,15] Alkaline hydrolysis of the esters (**12**) gave the clavicipitic acids (**1**), in 79% yield for *trans*-**1** and 80% yield for *cis*-**1**, respectively. Their NMR spectra were identical to those reported for the synthetic *dl*-clavicipitic acids.[5c,16]

This short synthesis of **1** (six steps from 4-bromoindole) is the first successful example that employs optically-active tryptophan derivatives. This strategy provides easy access to many optically-active indole alkaloids having a tryptophan skeleton, especially to the ergot alkaloids, which are of synthetic and biosynthetic importance.

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Supplementary Material Available: Experimental procedures and characterization data as well as NMR spectral data for compounds **9**, **5b**, **6b**, **10**, **13**, and **1** (18 pages).

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(8) Other oxidizing reagents such as DDQ, MnO_2, Ag_2CO_3, $Co(salen)_2$ + O_2, and $Cu(OAc)_2$ were not as effective as chloranil. It has been reported that many oxidizing reagents, including the above reagents, were tried in palladium-assisted vinylations, arylations, carbonylations and hydroxylation; see ref 7a,b and the following: (a) Maruyama, O.; Yoshidomi, M.; Fujiwara, Y.; Taniguchi, H. *Chem. Lett.* **1979**, 1229. (b) Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguti, H. *J. Org. Chem.* **1981**, *46*, 851. (c) Itahara, T. *Chem. Lett.* **1982**, 1151. (d) Itahara, T.; Ikeda, M.; Sakakibara, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1361. (e) Backvall, J.-E.; Hopkins, R. B.; Grennberg, H.; Mader, M. M.; Awasthi, A. K. *J. Am. Chem. Soc.* **1990**, *112*, 5160.

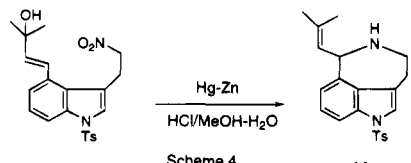
(9) A longer reaction time (7 h) lowered the yield (28%).

(10) Schmidt reported that high optical yield (95% ee) was obtained by the asymmetric reduction of (*tert*-butoxycarbonyl)dehydroamino acid using rhodium–DIPAMP complex; see: Schmidt, U.; Wild, J. *Angew. Chem., Int. Ed. Engl.* **1984**, 991; *Liebigs Ann. Chem.* **1985**, 1882.

(11) Other phosphine ligands gave the following results: NORPHOS, 72% ee; BPPM, 60% ee; BINAP, 28% ee.

(12) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335.

(13) Somei reported that the cyclized product (**14**) was obtained from a one-pot reaction by reduction of the nitro group of **15** under acidic conditions; see: Yamada, F.; Makita, Y.; Suzuki, T.; Somei, M. *Chem. Pharm. Bull.* **1985**, *33*, 2162.



13 Scheme 4 14

(14) *trans*-**12**: mp 158–160 °C, $[\alpha]_D = -129.1°$ (EtOH). *cis*-**12**: mp 144.0–145.5 °C, $[\alpha]_D = -195.3°$ (EtOH).

(15) *dl*-Clavicipitic acid methyl esters (**12**), which were alternatively synthesized by our route, showed the same melting point as the reported value:[5a] *dl-trans*-**12**, mp 134.0–135.0 °C (lit.[5a] 129.0–129.5 °C); *dl-cis*-**12**, mp 140.0–141.5 °C (lit.[5a] 146.0–147.5 °C).

(16) Although the optical rotations of natural clavicipitic acids have not been reported,[2] the absolute configurations of these compounds were unequivocally determined as the *S*-configuration using the biosynthetic technique of Floss.[2b]