ORGANIC LETTERS
2013
Vol. 15, No. 17
4528–4531

Direct Olefination at the C-4 Position of Tryptophan via C−H Activation: Application to Biomimetic Synthesis of Clavicipitic Acid

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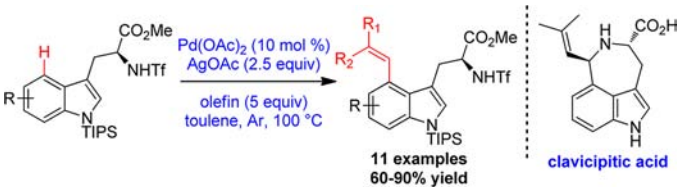
Received July 24, 2013

ABSTRACT



The first Pd-catalyzed method for direct olefination at the C4 position of tryptophan derivatives has been developed via C−H activation to prepare 4-substituted tryptophans, which could be used for the synthesis of many hemiterpenoid indole alkaloids. This reaction proceeds under mild reaction conditions and with exceptional tolerance to a variety of functional groups. Furthermore, the efficiency of this method is demonstrated by the rapid and biomimetic synthesis of clavicipitic acid.

Tryptophan-derived hemiterpenoid indole alkaloids, represented by the ergot alkaloids, have been considered attractive synthetic targets because of their unique structures and potent biological activities.[1] Indeed, several ergot alkaloids and their synthetic analogues are useful therapeutics for human diseases.[2] One of these compounds, the lysergic acid diethylamide (LSD), is strongly and notoriously psychoactive. The commonly accepted biosynthesis pathway for the ergot alkaloids is initiated by prenylation of tryptophan with dimethylallyl pyrophosphate (**1**) (DMAPP) to yield 4-dimethylallyltryptophane (**2**) (DMAT).[3] Subsequent transformations led to different classes of ergot alkaloids (Scheme 1). The prenylation step is believed to be the rate-limiting step catalyzed by an enzyme.[4]

Optically pure 4-substituted tryptophan derivatives have been widely used as critical intermediates for the synthesis of the ergot alkaloids and 3,4-fused indole alkaloids.[5−11] Classic approaches to the synthesis of these skeletons mainly involve three general strategies (Scheme 2): (1) palladium-catalyzed indole synthesis of *o*- haloanilines **5** and aldehydes or alkynes (path a);[5b−e,9] (2) direct functionalization at the reactive C3 position of an existing

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(1) (a) *The Merck Index*, 12th ed.; Merck and Co., Inc.: Whitehouse Station, NY, 1996; p 231. (b) Somei, M.; Yokoyama, Y.; Murakami, Y.; Ninomiya, I.; Kiguchi, T.; Naito, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 2000; Vol. 54, pp 191−257.

(2) Mukherjee, J.; Menge, M. *Adv. Biochem. Eng. Biotechnol.* **2000**, *68*, 1–20.

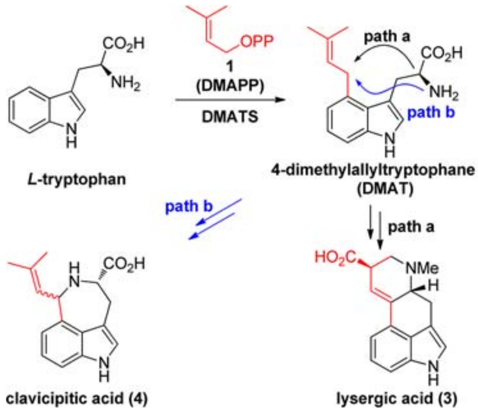
(3) (a) Floss, H. G. *Tetrahedron* **1976**, *32*, 873–912. (b) Floss, H. G.; Anderson, J. A. In *The Biosynthesis of Mycotoxins*; Steyn, P. S., Ed.; Academic Press: New York, 1980; pp 17−67.

(4) (a) Lee, S.-L.; Floss, H. G.; Heinstein, P. *Arch. Biochem. Biophys.* **1976**, *177*, 84–94. (b) Cress, W. A.; Chayet, L. T.; Rilling, H. C. *J. Biol. Chem.* **1981**, *256*, 10917–10923. (c) Gebler, J. C.; Woodside, A. B.; Poulter, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 7354–7360. (d) Luk, L. Y. P.; Tanner, M. E. *J. Am. Chem. Soc.* **2009**, *131*, 13932–13933.

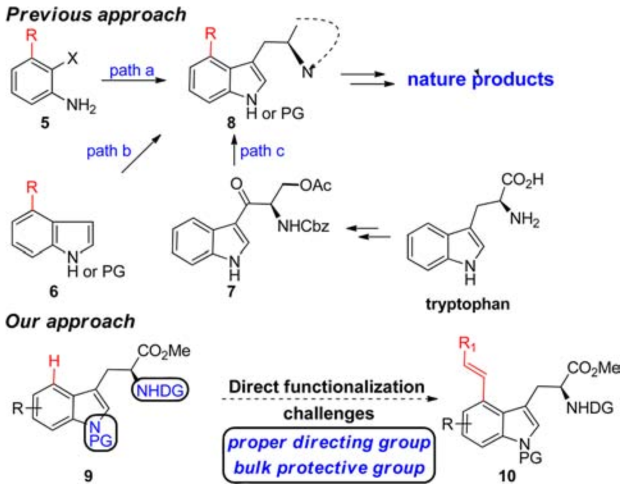
(5) For selected applications of optically pure 4-substituted tryptophan derivatives in the total synthesis of nature products, see: (a) Inoue, T.; Yokoshima, S.; Fukuyama, T. *Heterocycles* **2009**, *79*, 373–378. (b) Liu, Q.; Jia, Y. *Org. Lett.* **2011**, *13*, 4810–4813. (c) Xu, Z.; Li, Q.; Zhang, L.; Jia, Y. *J. Org. Chem.* **2009**, *74*, 6859–6862. (d) Xu, Z.; Hu, W.; Liu, Q.; Zhang, L.; Jia, Y. *J. Org. Chem.* **2010**, *75*, 7626–7635. (e) Xu, Z.; Zhang, F.; Zhang, L.; Jia, Y. *Org. Biomol. Chem.* **2011**, *9*, 2512–2517. (f) Zhang, Y.; Liu, Q.; Wang, C.; Jia, Y. *Org. Lett.* **2013**, *15*, 3662–3665.

10.1021/ol4020877

Scheme 1. Ergot Alkaloid Biosynthesis Pathway



Scheme 2. Synthesis of Optically Pure C4-Substituted Tryptophan Derivatives



4-substituted indole nucleus **6** (path b);[10] (3) nitration of the C4 position of tryptophan derivatives **7** containing the carbonyl group at the C3 position (path c).[11] However, the preparation of the special substrates such as aldehydes, alkynes, 4-substituted indoles **6**, and functionalized tryptophans **7** normally require a multistep synthesis. Thus, the development of a general synthetic method for the rapid synthesis of these skeletons in a single operation remains an important challenge for organic chemists. In fact, the direct functionalization of the C4 position of the tryptophan derivatives **9** by using the naturally abundant tryptophan as starting material is an ideal route (Scheme 2). However, the selective functionalization of the less reactive C4 position of tryptophan is extremely difficult since most electrophiles prefer attacking the C2 position. *Therefore, although the direct introduction of such a substituent at the C4 position of tryptophan has been studied for a long time, no successful method except the Witkop photocyclization was reported.*[12]

Transition-metal-catalyzed direct C−H activation presents a powerful and economical way to construct C−C bonds without prior functionalization, and some successful applications of C−H activation for the total synthesis of complex natural products are emerging.[13] With our ongoing study on the efficient synthesis of indole alkaloids, and inspired by Yu's work,[14a] we took the challenge to functionalize directly the less reactive C4 position of tryptophan **9**. We faced two challenges to achieve this transformation (Scheme 2): (1) Selection of a proper directing group on the amino group to enhance reactivity and direct metalation to the C4 position of tryptophan; (2) protecting the nitrogen of indole with a bulky protective group to improve the site selectivity at the C4 position. Herein, we describe the development of a $Pd(OAc)_2$-catalyzed method for the regioselective and direct olefination of tryptophan via C−H activation to access the 4-substituted tryptophan derivatives and application of this method to the biomimetic synthesis of clavicipitic acid.

We initiated our studies by examining different directing groups and protecting groups under Yu's conditions

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(6) For the synthesis of 4-substituted tryptophan derivatives by rearrangement, see: (a) Schwarzer, D. D.; Gritsch, P. J.; Gaich, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 11514–11516. (b) Bailey, P. D.; Cochrane, P. J.; Irvine, F.; Morgan, K. M.; Pearson, D. P. J.; Veal, K. T. *Tetrahedron Lett.* **1999**, *40*, 4593–4596. (c) Nyong, A. M.; Rainier, J. D. *J. Org. Chem.* **2005**, *70*, 746–748.

(7) For the synthesis of 4-substituted tryptophan derivatives by enzymatic resolution, see: (a) Meseguer, B.; Alonso-Díaz, D.; Griebenow, N.; Herget, T.; Waldmann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2902–2906. (b) Meseguer, B.; Alonso-Díaz, D.; Griebenow, N.; Herget, T.; Waldmann, H. *Chem.—Eur. J.* **2000**, *6*, 3943–3957.

(8) Other examples for the synthesis of 3,4-disubstituted tryptophan derivatives, see: (a) Shan, D.; Gao, Y.; Jia, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4902–4905. (b) Fisher, E. L.; Wilkerson-Hill, S. M.; Sarpong, R. *J. Am. Chem. Soc.* **2012**, *134*, 9946–9949. (c) Davies, H. M. L.; Manning, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 1060–1061. (d) Kalinin, A. V.; Chauder, B. A.; Rakhit, S.; Snieckus, V. *Org. Lett.* **2003**, *5*, 3519–3521. (e) Koizumi, Y.; Kobayashi, H.; Wakimoto, T.; Furuta, T.; Fukuyama, T.; Kan, T. *J. Am. Chem. Soc.* **2008**, *130*, 16854–16855. (f) Lim, H. J.; Gallucci, J. C.; RajanBabu, T. V. *Org. Lett.* **2010**, *12*, 2162–2165. (g) Shan, D.; Jia, Y. *Chin. J. Org. Chem.* **2013**, *33*, 1144–1156.

(9) (a) Jia, Y.; Zhu, J. *Synlett* **2005**, 2469–2472. (b) Jia, Y.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826–7834. (c) Ma, J.; Yin, W.; Zhou, H.; Cook, J. M. *Org. Lett.* **2007**, *9*, 3491–3494. (d) Ma, J.; Yin, W.; Zhou, H.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2009**, *74*, 264–273.

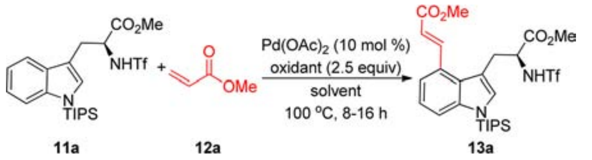
(10) (a) Kieffer, M. E.; Repka, L. M.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 5131–5137. (b) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 3832–3835. (c) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *Synlett.* **2011**, 2599–2604. (d) Arai, T.; Awata, A.; Wasai, M.; Yokoyama, N.; Masu, H. *J. Org. Chem.* **2011**, *76*, 5450–5456. (e) Goss, R. J. M.; Newill, P. L. A. *Chem. Commun.* **2006**, 4924–4925. (f) Sui, Y.; Liu, L.; Zhao, J.-L.; Wang, D.; Chen, Y.-J. *Tetrahedron* **2007**, *63*, 5173–5183. (g) Yokoyama, Y.; Osanai, K.; Mitsuhashi, M.; Kondo, K.; Murakami, Y. *Heterocycles* **2001**, *55*, 653–659. (h) Sato, K.; Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073–4076. (i) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1395–1398. (j) Shinohara, H.; Fukuda, T.; Iwao, M. *Tetrahedron* **1999**, *55*, 10989–11000.

(11) (a) Nakatsuka, S.; Masuda, T.; Sakai, K.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 5735–5738. (b) Kogan, T. P.; Somers, T. C.; Venuti, M. C. *Tetrahedron* **1990**, *46*, 6623–6632.

(12) (a) Yonemitsu, O.; Cerutti, P.; Witkop, B. *J. Am. Chem. Soc.* **1966**, *88*, 3941–3945. (b) Kobayashi, T.; Spande, T. F.; Aoyagi, H.; Witkop, B. *J. Med. Chem.* **1969**, *12*, 636–638. (c) Mascal, M.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 823–830. (d) For a recent application of Witkop photocyclization, see: Hu, W.; Qin, H.; Cui, Y.; Jia, Y. *Chem.—Eur. J.* **2013**, *19*, 3139–3147and references therein.

(13) (a) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885–1898. (b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991. (c) Chen, D. Y.-K.; Youn, S. W. *Chem.—Eur. J.* **2012**, *18*, 9452–9474. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960–9009. (e) Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 5767–5769. (f) Wang, H.; Li, G.; Engle, K. M.; Yu, J.-Q.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6774–6777.

Table 1. Optimization of Reaction Conditions[a]



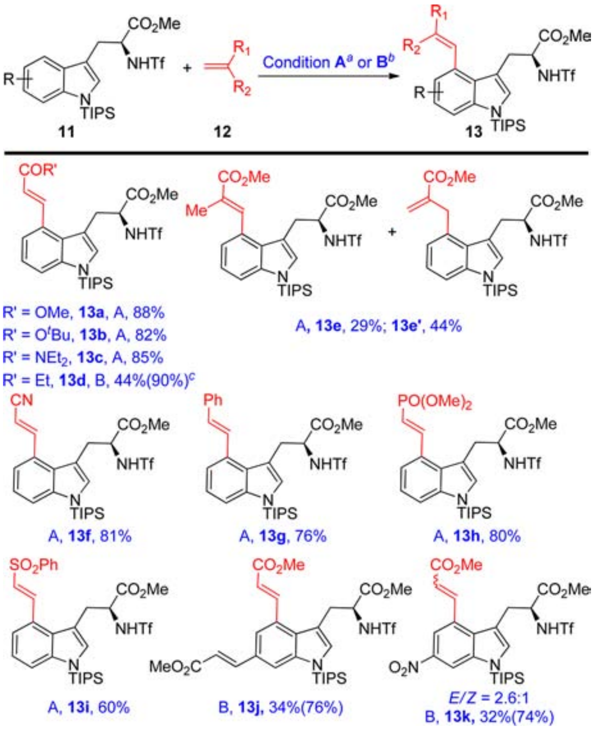
entry	oxidant	solvent	yield [%][b]
1	Ag_2CO_3	$ClCH_2CH_2Cl$	28
2	$Cu(OAc)_2 \cdot H_2O$	$ClCH_2CH_2Cl$	9
3	AgOAc	$ClCH_2CH_2Cl$	42
4	$PhI(OAc)_2$	$ClCH_2CH_2Cl$	0
5	BQ	$ClCH_2CH_2Cl$	4
6	AgOAc	DMF	0
7	AgOAc	CH_3CN	21
8	AgOAc	HOAc	0
9	AgOAc	toluene	48
10[c]	**AgOAc**	**toluene**	**91 (88)**
11[d]	AgOAc	toluene	40
12[e]	AgOAc	toluene	78

[a] General reaction conditions: **11a** (0.1 mmol, 0.1 M in solvent), **12a** (0.5 mmol), $Pd(OAc)_2$ (0.01 mmol), oxidant (0.25 mmol), 100 °C for 8−16 h. [b] Yields determined by 400 MHz NMR using 1,3,5-trimethoxybenzene as the internal standard; isolated yield in parentheses. [c] Reaction works under Ar. [d] 5 mol % $Pd(OAc)_2$ was employed. [e] Reaction works at 80 °C under Ar.

(20 mol % $Pd(OAc)_2$, 2.5 equiv of AgOAc, 4 equiv of methyl acrylate, DMF/DCE = 1:10, 130 °C). BocNH−, CF_3CONH−, and TrocNH− as directing groups to assist C−H activation did not give satisfactory yields of the desired products. However, the TfNH− directing group was found to give complete conversion with an acceptable yield.[14] The protection of the indole nitrogen with the bulky TIPS group enhanced the site selectivity at the C4 position more efficiently than the Piv and Boc protecting groups.[15] Consequently, TIPS for the protection of the indole nitrogen and TfNH− as the directing group were used for the regioselective olefination of tryptophan at the C4 position.

After determining the optimal combination of the directing group and protecting group, we turned our attention to optimization of the reaction conditions. *N*-Triisopropylsilyl-*N*-trifluoromethylsulfonamide tryptophan methyl ester **11a** and methyl acrylate **12a** were employed as model substrates. A wide variety of reaction conditions (oxidants, solvents) were examined, and some of the representative results are shown in Table 1. AgOAc was the best oxidant (entry 3), albeit Ag_2CO_3, $Cu(OAc)_2 \cdot H_2O$, and BQ (1,4-benzoquinone) were also capable of promoting the reaction but with lower yields (entries 1−2 and 4−5). The solvent also played an important role. The use of toluene afforded a higher yield (entry 9). Degassing would dramatically improve the transformation yield (entry 10). When the reaction was conducted at a lower temperature (80 °C) or the catalyst loading was reduced to 5 mol %, a significant decrease of the yield was observed (entries 11−12).

Scheme 3. Summary of the Substrate Scope



[a] *Condition A*: olefin (5.0 equiv), $Pd(OAc)_2$ (10 mol %), AgOAc (2.5 equiv), toluene, Ar, 100 °C, 16−72 h, 0.1 M. [b] *Condition B*: olefi1n (5.0 equiv), $Pd(OAc)_2$ (20 mol %), AgOAc (2.5 equiv), toluene, Ar, 100 °C, 72−140 h, 0.1 M. [c] Yield based on recovered starting material in parentheses.

With the optimized conditions in hand, we next investigated the substrate scope of this reaction (Scheme 3). We found that unsubstituted tryptophan substrates gave moderate to high yields with a broad scope of olefins (Scheme 3, **13a**−**13i**). Both aliphatic and aromatic olefins (Scheme 3, **13g**) reacted smoothly. The presence of functional group1s on the olefins including ester, ketone, amide, nitrile, benzenesulfonyl, and dimethoxy phosphoryl groups did not affect the transformation (Scheme 3, **13a**−**13i**). The electron-withdrawing groups on tryptophan slowed the reaction, but products were still isolated in moderate yields based on the recovered starting materials (Scheme 3, **13j** and **13k**).

Having established the methodology for the direct functionalization at the C4 position of tryptophan derivatives, we began to explore the feasibility of our original goal of biomimetic synthesis of tryptophan-derived hemiterpene indole alkaloids. Clavicipitic acid was selected as the target (Scheme 4).[5c,d,16] The synthesis commenced with **11a**. According to the biosynthesis of clavicipitic acid, a five carbon unit should be used for cyclization to afford an azepinoindole intermediate. Under our standard reaction conditions, compound **11a** and 2-methyl-3-buten-2-ol (**14**) reacted smoothly, generating the allyl alcohol **15** in 17%

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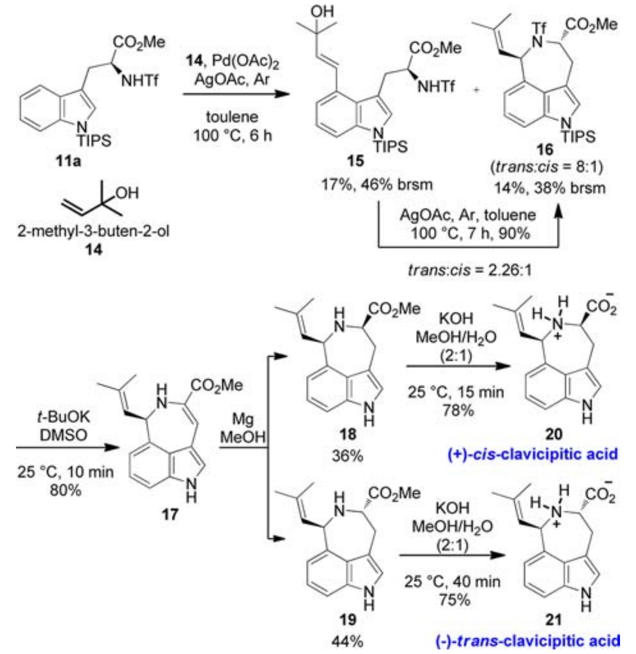
(14) (a) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452–6455. (b) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511–2513. (c) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806–10807.

(15) (a) Beswick, P. J.; Greenwood, C. S.; Mowlem, T. J.; Nechvatal, G.; Widdowson, D. A. *Tetrahedron* **1988**, *44*, 7325–7334. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528–2529.

Scheme 4. Total Synthesis of Clavicipitic Acid



yield and 46% yield based on recovered starting material, along with cyclized product **16** (*trans*/*cis* = 8:1) in 14% yield and 38% yield based on recovered starting material. *It was noteworthy that a tandem olefination/aminocyclization sequence was found in this reaction, which was similar to the biosynthetic process*. Surprisingly, Pd-mediated cyclization conditions could not convert alcohol **15** to cyclized product **16**.[16c,17] AgOAc was shown to be an effective catalyst in this cyclization. To the best of our knowledge, this was the first report that AgOAc catalyzed an intramolecular amination reaction of allylic alcohol. Treatment of compound *trans*-**16** with *tert*-BuOK in DMSO at room temperature resulted in the simultaneous elimination of trifluoromethanesulfonic acid and deprotection of triisopropylsilyl to afford enamine **17** in 80% yield.[18] The reduction of an inert conjugated double bond in **17** presented a considerable challenge.[17a,19] After many conditions were screened, enamine **17** was reduced with Mg in dry methanol to give *cis*-ester **18** in 36% yield and *trans*-ester **19** in 44% yield. Alkaline hydrolysis of *cis*-**18** and *trans*-**19** furnished (+)-*cis*-clavicipitic acid **20** and (−)-*trans*-clavicipitic acid **21**, respectively, according to the literature procedure.[5c,d,16a]

In summary, we have developed the first site-selective Pd-catalyzed method for the direct olefination of tryptophan via C−H bond activation, which allows access to 3,4-disubstituted indole derivatives directly. A broad range of terminal olefins and tryptophan derivatives can be coupled in good yields. Based on this transformation, the rapid biomimetic total synthesis of (+)-*cis*- and (−)-*trans*-clavicipitic acid was achieved. This methodology could provide a facile means for accessing 3,4-disubstituted indole alkaloids.

Acknowledgment. This research was supported by the National Natural Science Foundation of China (Nos. 21290180, 20972007), the National Basic Research Program of China (973 Program, No. 2010CB833200), and the State Key Laboratory of Drug Research.

Supporting Information Available. Experimental procedures and analytical data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For a recent total synthesis of optical active clavicipitic acids, see: (a) Yokoyama, Y.; Matsumoto, T.; Murakami, Y. *J. Org. Chem.* **1995**, *60*, 1486–1487. (b) Yokoyama, Y.; Hikawa, H.; Mitsuhashi, M.; Uyama, A.; Hiroki, Y.; Murakami, Y. *Eur. J. Org. Chem.* **2004**, 1244–1253. (c) Ku, J.-M.; Jeong, B.-S.; Jew, S.-s.; Park, H.-g. *J. Org. Chem.* **2007**, *72*, 8115–8118.

(17) (a) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335–4338. (b) Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Org. Lett.* **2000**, *2*, 2427–2429. (c) Makabe, H.; Kong, L. K.; Hirota, M. *Org. Lett.* **2003**, *5*, 27–29. (d) Hande, S. M.; Kawai, N.; Uenishi, J. *J. Org. Chem.* **2009**, *74*, 244–253.

(18) Shoji, T.; Yokoyama, R.; Ito, S.; Watanabe, M.; Toyota, K.; Yasunami, M.; Morita, N. *Tetrahedron Lett.* **2007**, *48*, 1099–1103.

(19) Muratake, H.; Takahashi, T.; Natsume, M. *Heterocycles* **1983**, *20*, 1963–1968.

The authors declare no competing financial interest.