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Total Synthesis of (+)-Decursivine

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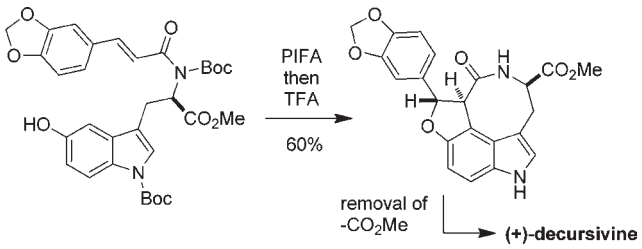
ABSTRACT



The first asymmetric synthesis of natural indole alkaloid (+)-decursivine was accomplished. The key step involves the PIFA-mediated intramolecular [3 + 2] cycloaddition of 5-hydroxytryptophan with a substituted cinnamamide in a highly diastereoselective manner.

Decursivine (**1**) is an optically active natural indole alkaloid originally isolated from the leaves and stems of *Rhaphidophora decursiva* Schott (Araceae) by Fong and co-workers in 2002.[1] Decursivine is structurally related to serotobenine (**2**),[2] both having a unique tetracyclic skeleton including an indole, dihydrobenzofuran, and eight-membered lactam. (+)-Decursivine exhibits antimalarial activity against D6 and W2 clones of *Plasmodium falciparum*. However, the natural (±)-serotobenine is not active against *Plasmodium falciparum*.[1] This difference clearly necessitates the asymmetric total synthesis of (+)-decursivine. However, the complex structure makes it a challenging target. Kerr and Leduc reported the first synthesis of (±)-decursivine starting from a quinone monoamine.[3] Very recently, the Mascal group and Jia group independently introduced the expedient synthesis of (±)-decursivine via the Witkop photocyclization.[4] The Jia group also extended this methodology to the synthesis of (±)-serotobenine.[4b] In the meantime, Fukuyama and co-workers reported the first synthesis of (−)-serotobenine in 24 steps starting from 3-methyl-4-nitrophenol.[5] We were lured to this project due to our interest in the construction of eight-membered lactams.[6] Herein we report the first asymmetric synthesis of (+)-decursivine.

Our approach originated from the study of the bioorigin of serotobenine by Sato et al.[2] They observed the generation of serotobenine in the enzymatic (peroxidase, horse radish) or nonenzymatic ($K_3Fe(CN)_6$) oxidation of *N*-feruloylserotonin (**3**),[7] an ingredient also isolated along with serotobenine,[2] suggesting that **3** could be the biosynthetic precursor for **2**. Because of the structural similarity between **1** and **2**, it might be possible that decursivine can be generated by the oxidation of *N*-[3,4-(methylenedioxy)]cinnamoylserotonin (**4**), the analog of **3**. However, it is also worth mentioning that, contrary to Sato's

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(4) (a) Mascal, M.; Modes, K. V.; Durmus, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 4445–4446. (b) Qin, H.; Xu, Z.; Cui, Y.; Jia, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 4447–4449.

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(7) (a) Sakamura, S.; Terayama, Y.; Kawakatsu, S.; Ichihara, A.; Saito, H. *Agric. Biol. Chem.* **1978**, *42*, 1805–1806. (b) Sakamura, S.; Terayama, Y.; Kawakatsu, S.; Ichihara, A.; Saito, H. *Agric. Biol. Chem.* **1980**, *44*, 2951–2954.

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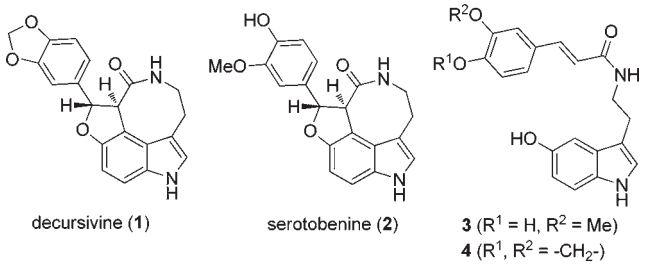
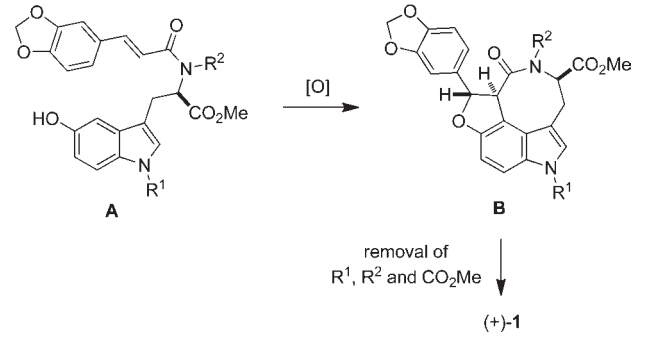
observation, the oxidation of **3** to **2** under a variety of oxidation conditions was unsuccessful as reported by the Jia group.[4b]



Our synthetic design is illustrated in Scheme 1. Upon oxidation, compound **A** might undergo stereoselective intramolecular [3 + 2] cycloaddition in a biomimetic manner to give compound **B**. The methyl ester group may help direct the stereochemistry of the α-carbamoyl carbon when forming the eight-membered lactam.[6a] As a result, the chirality of tryptophan can be transferred to the two newly formed chiral centers.[8] The subsequent removal of R^1, R^2, and the ester group will lead to the optically active decursivine.

Scheme 1. Synthetic Design of (+)-Decursivine



Compared to the hypervalent iodine-mediated[9] phenol dearomatization,[10] the formation of dihydrobenzofurans via the formal [3 + 2] cycloaddition of phenols with alkenes has received much less attention. Nevertheless, they can be found in the oxidative[11] or enzymatic[12] dimerization of substituted *p*-hydroxystyrenes. A number of oxidants have been employed for these coupling reactions with variable efficiencies.[11] Other than the dimerization, the cycloaddition requires the use of electron-rich alkenes and is typically mediated by hypervalent iodine reagents such as [bis(trifluoroacetoxy)iodo]benzene (PIFA) or (diacetoxy)-iodobenzene (DIB),[13] or under enzymatic[14] conditions.[15] These reactions are intermolecular. The only intramolecular [3 + 2] cycloaddition was reported by Harran et al. in their elegant total synthesis of (−)-diazonamide A.[16]

In order to develop the intramolecular [3 + 2] cycloaddition depicted in Scheme 1, substrates **5a**–**5f** (similar to **A**) with different R^1 and R^2 substituents were prepared from L-tryptophan (see the Supporting Information and also vide infra). Their oxidation reactions were carried out, and the results are summarized in Table 1. The PIFA-mediated oxidation of **5a** (R^1 = R^2 = H) in 2,2,2-trifluoroethanol (TFE) at room temperature led only to the decomposition of **5a** while no expected cycloaddition product could be detected (entry 1, Table 1). When the indolic nitrogen was protected with an ester group (**5b**), no desired [3 + 2] cycloaddition product **6b** could be observed either (entry 2, Table 1). With the idea that the cycloaddition might require the amide in an s-*cis* conformation, a benzyl group was then attached to the amide nitrogen to facilitate the s-*trans* to s-*cis* interconversion of the amide bond. Substrates **5c** (R^1 = H) and **5d** (R^1 = Bn) again failed to give the corresponding cycloaddition products on treatment with PIFA (entries 3 and 4, Table 1). However, the oxidation of **5e** (R^1 = Ts) afforded the corresponding cycloaddition product **6e** in 20% yield (entry 5, Table 1), whose structure was unambiguously established by the X-ray diffractional experiments (see the Supporting Information). In a similar fashion, the oxidation of **5f** (R^1 = CO_2Bn) also gave the cyclized product **6f** (entry 6, Table 1). Although the yields were low, the reactions were highly diastereoselective as expected. In order to improve the efficiency of cycloaddition, **5f** was chosen for the optimization of reaction conditions. Changing the oxidant to DIB led to the decrease of product yield. Raising or lowering the reaction temperature did not help. Switching

(8) For a similar example, see:Chen, P.; Cao, L.; Tian, W.; Wang, X.; Li, C. *Chem. Commun.* **2010**, *46*, 8436–8438.

(9) For reviews on the chemistry of hypervalent iodine compounds, see: (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358.

(10) For a recent review, see: Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235–2261.

(11) For examples, see: (a) Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 519–521. (b) Antus, S.; Gottsegen, A.; Kolonits, P.; Wagner, H. *Liebigs Ann. Chem.* **1989**, 593–594. (c) Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull.* **1994**, *42*, 2500–2505. (d) Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull.* **1994**, *42*, 2536–2545. (e) Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull.* **1995**, *43*, 84–90. (f) Shimamura, T.; Arakawa, Y.; Hikita, K.; Niwa, M. *Heterocycles* **1996**, *43*, 2223–2227. (g) Bolzacchini, E.; Brunow, G.; Meinardi, S.; Orlandi, M.; Rindone, B.; Rummakko, P.; Setala, H. *Tetrahedron Lett.* **1998**, *39*, 3291–3294. (h) Wang, E.-C.; Wein, Y.-S.; Kuo, Y.-H. *Tetrahedron Lett.* **2006**, *47*, 9195–9197.

(12) Langcake, P.; Pryce, R. J. *J. Chem. Soc., Chem. Commun.* **1977**, 208–210.

(13) For examples of DIB- or PIFA-mediated intermolecular formal [3 + 2] cycloaddition of phenols with electron-rich alkenes, see: (a) Wang, S.; Gates, B. D.; Swenton, J. S. *J. Org. Chem.* **1991**, *56*, 1979–1981. (b) Chan, C.; Li, C.; Zhang, F.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 4839–4841. (c) Bérard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett.* **2007**, *48*, 8238–8241. (d) Nicolaou, K. C.; Majumder, U.; Roche, S. P.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4715–4718. (e) Bérard, D.; Racicot, L.; Sabot, C.; Canesi, S. *Synlett* **2008**, 1076–1080. (f) Bérard, D.; Giroux, M.-A.; Racicot, L.; Sabot, C.; Canesi, S. *Tetrahedron* **2008**, *64*, 7537–7544.

(14) For an example, see: He, S.; Wu, B.; Pan, Y.; Jiang, L. *J. Org. Chem.* **2008**, *73*, 5233–5241.

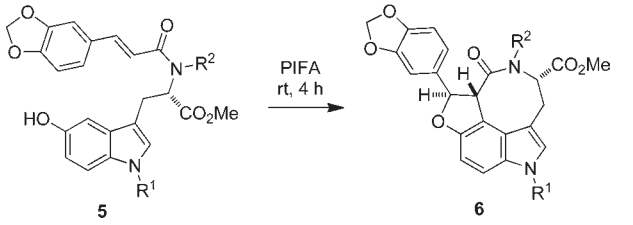
(15) The synthesis of dihydrobenzofurans via gold-catalyzed annulation of phenols with dienes was recently reported. See: Nguyen, R.-V.; Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 2397–2399.

(16) Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961–4966.

(17) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775–5785.

the solvent to 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)[17] resulted in the increase of product yield from 24% to 41% (entry 7, Table 1). When the substrate concentration was lowered from 0.05 to 0.01 M, we were delighted to find that the cyclized product **6f** was obtained in 66% yield (entry 8, Table 1). The addition of a base such as K_2CO_3 or *n*-BuLi did not show a further improvement.[18] Thus, the substitution of electron-withdrawing group R^1 and bulky group R^2 is essential for the successful intramolecular cycloaddition of **5**.

Table 1. Synthesis of **6** via the Oxidation of **5** with PIFA



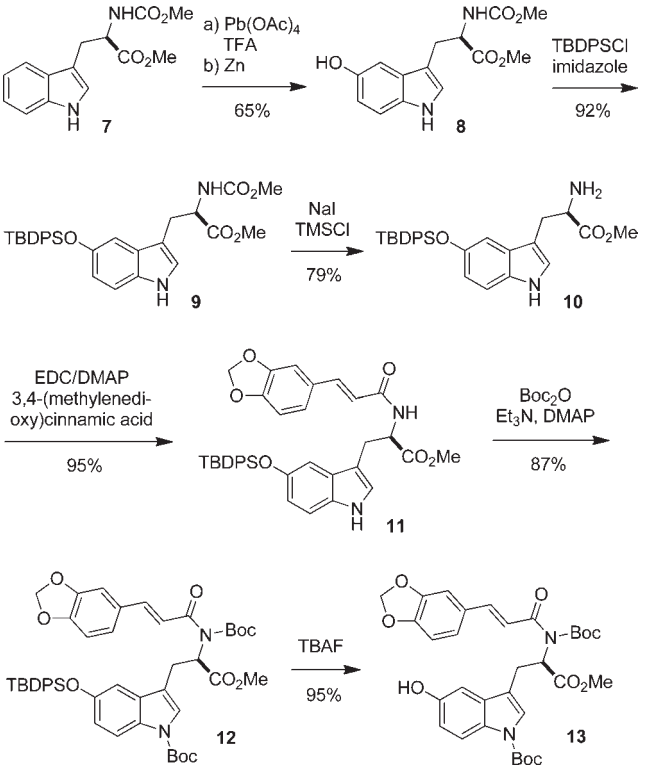
5 6

entry[a]	5	R^1	R^2	solvent	6	yield (%)[b]
1	**5a**	H	H	TFE	**6a**	0
2	**5b**	CO_2Bn	H	TFE	**6b**	0
3	**5c**	H	Bn	TFE	**6c**	0
4	**5d**	Bn	Bn	TFE	**6d**	0
5	**5e**	Ts	Bn	TFE	**6e**	20
6	**5f**	CO_2Bn	Bn	TFE	**6f**	24
7	**5f**	CO_2Bn	Bn	HFIP	**6f**	41
8[c]	**5f**	CO_2Bn	Bn	HFIP	**6f**	66

[a] Reaction conditions: **5** (0.05 mmol), PIFA (0.06 mmol), TFE or HFIP (1 mL), rt, 4 h. [b] Isolated yield based on **5**. [c] 5 mL of HFIP were used.

In light of the above results and with the assumption that (+)-decursivine has the same absolute configuration as (+)-serotobenine,[5] we designed the following strategy toward the synthesis of (+)-decursivine starting from D-tryptophan derivative **7** (Scheme 2). The oxidation of **7** with $Pb(OAc)_4$ in trifluoroacetic acid (TFA) followed by reduction with zinc according to the literature method afforded the 5-hydroxylated product **8** in a one-pot procedure.[19] The hydroxyl of phenol **8** was then protected by reaction with *tert*-butyldiphenylchlorosilane (TBDPSCl)/imidazole to give silyl ether **9**. The *N*-ester moiety of **9** was then chemoselectively removed by treatment with trimethylchlorosilane (TMSCl)/NaI to give amine **10**.[20] The condensation of **10** with 3,4-(methylenedioxy)cinnamic acid with the aid of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide (EDC)[21] and 4-(dimethylamino)pyridine (DMAP) afforded the corresponding amide **11** in 95% yield. For the ease of protection and deprotection, we chose the *N*-Boc-protection for both of the nitrogen atoms in **11**. This can be easily done by reaction of **11** with Boc_2O/Et_3N/DMAP in a single step, and the expected product **12** was secured in 87% yield. The subsequent removal of the silyl group by tetrabutylammonium fluoride (TBAF) furnished compound **13** as the precursor for [3 + 2] cycloaddition.

Scheme 2. Synthesis of Precursor **13**

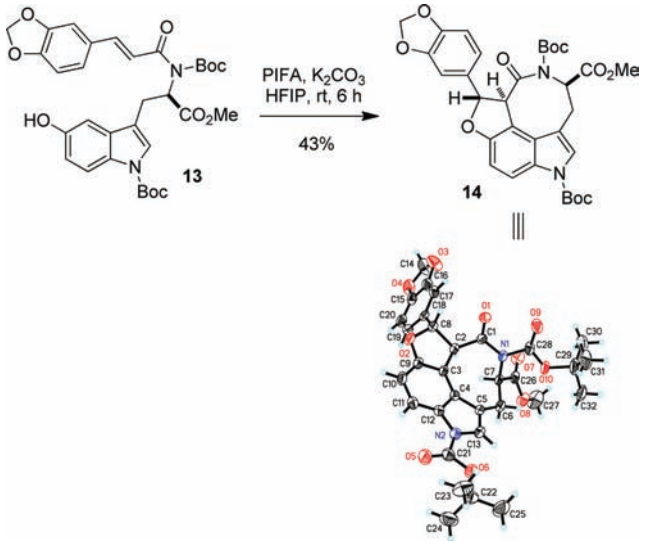


The PIFA-mediated intramolecular [3 + 2] cycloaddition of precursor **13** was then carried out in the presence of excess (300 mol %) K_2CO_3. The role of K_2CO_3 was to quench the TFA generated in order to keep the Boc group safe. Indeed, the cycloaddition product **14** was secured in 43% yield, whose configuration was also confirmed by the X-ray diffractional experiments (Scheme 3). Careful examination of the reaction revealed that the product **14** (rather than the substrate **13**) still underwent partial decomposition under the experimental conditions, implying that the cycloaddition took place piror to the deprotection of the Boc group(s). Switching the base to *n*-BuLi or ^{t}BuOK did not show any improvement.

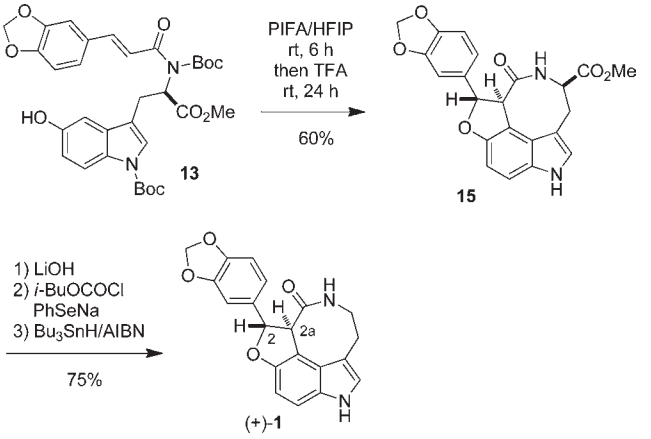
On the basis of the above observations, we performed the cycloaddition reaction without the presence of a base. After the precursor **13** was all consumed, TFA (500 mol %) was then added directly into the reaction mixture for the *N*-Boc-deprotection. The cycloaddition−deprotection product **15** was thus obtained in 60% yield in a single step

(18) Shigehisa, H.; Takayama, J.; Honda, T. *Tetrahedron Lett.* **2006**, *47*, 7301–7306.
(19) Taniguchi, M.; Anjiki, T.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull.* **1984**, *32*, 2544–2554.
(20) Zembower, D. E.; Ames, M. M. *Synthesis* **1994**, 1433–1436.
(21) Yoya, G. K.; Bedos-Belval, F.; Constant, P.; Duran, H.; Daffé, M.; Baltas, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 341–343.
(22) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541–4550.

Scheme 3. Oxidation of **13** with PIFA in the Presence of K_2CO_3



Scheme 4. Completion of the Synthesis of (+)-**1**



(Scheme 4). The methyl ester **15** was then hydrolyzed with aqueous LiOH to give the free acid, which was converted to the corresponding phenylseleno ester in about 75% yield by reaction with *i*-BuOCOCl/PhSeNa.[22] Further treatment of the ester with Bu_3SnH/AIBN cleanly afforded the target molecule (+)-**1** in almost quantitative yield (Scheme 4), whose spectra were identical with those reported in the literature.[4b] The $[\alpha]^{23}_D$ value was measured to be +283.4 (*c* 0.02, MeOH), in good agreement with the literature value[1] ($[\alpha]^{20}_D$ = +299.0 (*c* 0.02, MeOH)). On the basis of the above synthesis (Schemes 2–4), the absolute configuration of (+)-**1** was unambiguously assigned as (2*S*, 2a*S*), although it might be inferred from Fukuyama and Kan's synthesis of (−)-serotobenine.[5]

In conclusion, the first asymmetric total synthesis of natural indole alkaloid (+)-decursivine has been successfully accomplished in 10 steps and a 16.7% overall yield starting from the D-tryptophan derivative **7**. Our synthesis features the oxidative intramolecular [3 + 2] cycloaddition of 5-hydroxytryptophans with substituted cinnamamides in a highly diastereoselective manner. The chirality of tryptophan is transferred into the target molecule tracelessly. In view of the abundance of the dihydrobenzofuran skeleton in biologically active natural products and medicinal agents, the successful implementation of the above [3 + 2] cycloaddition should encourage further applications of this versatile methodology.

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Supporting Information Available. Full experimental procedures, compound characterizations, copies of ^1H and ^{13}C NMR spectra, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.