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Construction of Indole Structure on Pyrroloindolines via $AgNTf_2$-Mediated Amination/Cyclization Cascade: Application to Total Synthesis of (+)-Pestalazine B

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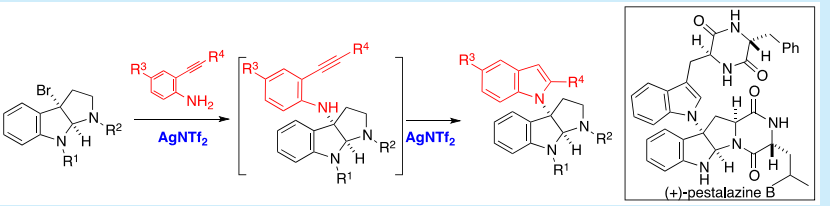
Supporting Information



ABSTRACT: An *N*-linked indole structure was constructed on the 3a-position of pyrroloindoline derivatives via a cascade process involving silver-mediated amination of bromopyrroloindolines with 2-ethynylanilines with subsequent 5-*endo*-*dig* cyclization. In this reaction, $AgNTf_2$ was used as a tandem reagent, which activated the bromo group as a σ-Lewis acid and the alkyne moiety as a π-Lewis acid. Switching from the initial step to the second step was conducted by controlling the temperature. This protocol was applied to the synthesis of various pyrroloindolines, α-carboline, and furoindolines and the total synthesis of a dimeric indole alkaloid, (+)-pestalazine B.

Alkaloids biosynthesized from tryptophan are ubiquitous in nature. Among these, bis-indole alkaloids comprising a pyrroloindoline skeleton and an indole segment with a C−N1′ linkage have attracted much attention because of their structural diversity and fascinating biological activity. Several of these compounds show potential as lead compounds in drug discovery (Figure 1).[1] For example, (+)-psychotriasine (**1**),

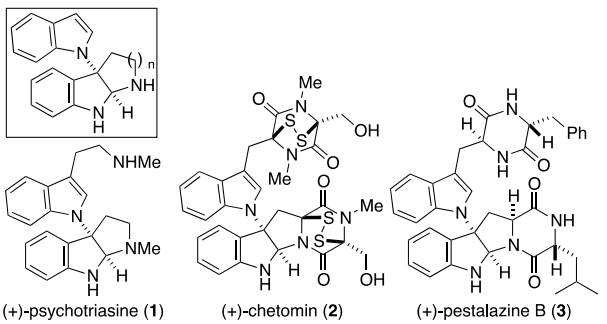
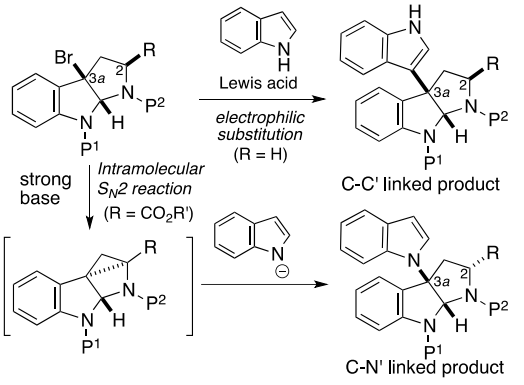


Figure 1. Bis-indole alkaloids containing a C−N1′ linkage.

isolated from plants of the genus *Psychotria*, was used in traditional medicines in China and Malaysia,[2] while (+)-chetomin (**2**), which is produced by several fungi of the genus *Chaetomium*, exhibited antitumor activity in multiple myeloma by blocking the HIF pathway.[3]

Because of their significant biological activity, enormous synthetic efforts have been devoted to synthesizing various bis-indole alkaloids.[4] However, constructing a pyrroloindoline-bearing indole segment with a C−N1′ linkage has remained challenging. Thus, electrophilic substitution of indole preferentially occurs at the C3-position (Scheme 1).[5] On the other

Scheme 1. Reactive Site of Indole Ring



hand, nucleophilic substitution of indole with alkyl halides is difficult owing to the low nucleophilicity of the indole nitrogen, whose lone-pair electrons delocalize over the aromatic system. In Rainier's pioneering work, the C−N1′-linked indolylpyrroloindoline motif was constructed by reacting the indole *N*-anion with a cyclopropane intermediate generated from bromopyrroloindoline (Scheme 1).[6] The substrate scope of this protocol, however, was limited due to

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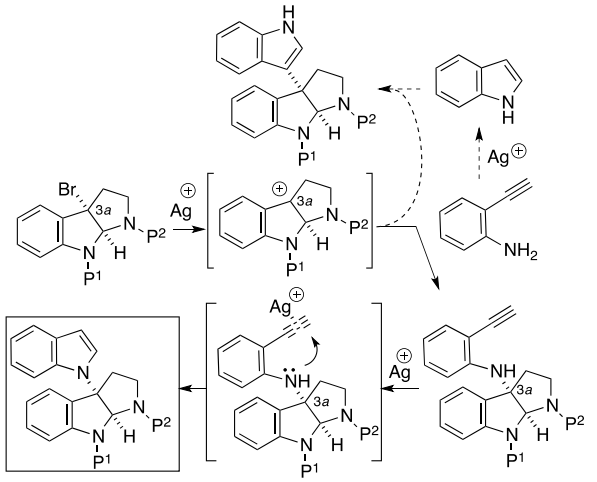
the strongly basic conditions and requirement for an electron-withdrawing group at the C2-position to form a cyclopropane intermediate.[7] Several other indirect strategies, for example, stepwise construction of an indole skeleton via coupling of an *o*-halo aniline derivative and subsequent indole formation,[8] or introduction of an indole precursor,[9] have been reported. However, these methods require additional steps after introducing the indole segment by C−N bond formation. In this paper, we describe a novel construction of a C−N1′-linked indolylpyrroloindoline structure by $AgNTf_2$-mediated one-pot amination[10] and an indole formation sequence. Furthermore, the utility of this protocol was fully demonstrated by total synthesis of a dimeric indole alkaloid, (+)-pestalazine B (**3**).

Our working hypothesis is shown in Scheme 2. During synthetic studies on indole alkaloids, (+)-haplophytine,[10a]

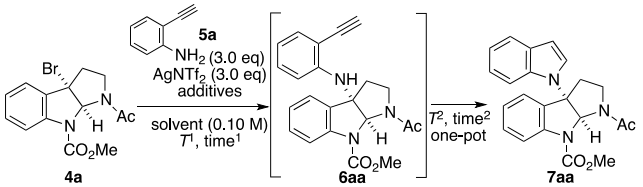
Scheme 2. Working Hypothesis for C−N1′-Linked Indolylpyrroloindoline



T988s,[10b] and amauromines,[10c] we established $AgNTf_2$-promoted Friedel−Crafts-type arylation of iodoindolenines or bromoindolines and allylation of bromoindolines using electron-rich aromatic compounds and allylsilanes, respectively. In addition to these C−C bond formations, we observed C−N bond formation of aniline derivatives. With this observation and two properties of $AgNTf_2$, i.e., high halogenophilicity and mild π-Lewis acidity, we envisioned the following sequential reaction. Treating a mixture of bromopyrroloindoline and 2-ethynylaniline with $AgNTf_2$ would promote C−N′ bond formation between aniline and the carbocation generated from bromopyrroloindoline, and subsequent 5-*endo*-*dig* cyclization of the 2-ethynylaniline moiety with alkyne activation by $AgNTf_2$ would afford the desired C−N1′-linked indolylpyrroloindoline. If 5-*endo*-*dig* cyclization of 2-ethynylaniline occurs faster than intermolecular C−N bond formation, Friedel−Crafts-type reaction of the indole proceeds to give the undesired byproduct, C3a−C3′-linked indolylpyrroloindoline. Therefore, control of the relative reaction rates of the two processes should be crucial to the success of the sequential formation of the *N*-linked indole on pyrroloindoline.

With this idea in mind, we tested the hypothesis using tricyclic bromopyrroloindoline **4a** as a model substrate. On the basis of our procedure for arylation of bromopyrroloindolines,[10d] a mixture of **4a** and 2-ethynylaniline **5a** was treated with $AgNTf_2$ in CH_2Cl_2 at 0 °C. After **4a** was converted to **6aa** at 0 °C, the reaction temperature was raised to ambient temperature to promote subsequent 5-*endo*-*dig* cyclization. As expected, desired product **7aa** was obtained, but the yield was low (Table 1, entry 1). Considering the stabilization of the

Table 1. Optimization of Reaction Conditions



entry	solvent	additive	T^1 (°C)	time^1 (h)	T^2 (°C)	time^2 (h)	yield[a] (%)
1	CH_2Cl_2		0	0.5	rt	1.0	<9[b]
2	MeCN		0 to rt	3.5	50	1.0	<24[b]
3	MeCN	DTBP	0 to rt	4.0	50	4.0	48
4	MeCN	DTBP MS4 Å	0 to rt	5.0	50	16	65
5	MeCN	DTBP MS4 Å	0 to rt	5.0	70	3.0	74
6[c]	MeCN	DTBP MS4 Å	0 to 45	4.0	70	15	73

[a]Isolated yield. [b]Including a small amount of inseparable byproduct. [c]1.5 equiv of $AgNTf_2$ was used.

carbocation intermediate derived from bromopyrroloindoline **4a**, we changed the solvent to acetonitrile. Although the reactivity of each step decreased, the yield of indole **7aa** improved slightly (Table 1, entry 2). After extensive optimization, we found that addition of 2,6-di-*tert*-butylpyridine (DTBP) as a proton scavenger was effective in suppressing the proto-decomposition of intermediate **6aa**, and the yield of **7aa** increased to 48% (Table 1, entry 3). Eventually, conducting the reaction with a combination of DTBP and MS4A at 70 °C was most effective, affording **7aa** in 74% yield (Table 1, entry 5). Finally, the amount of $AgNTf_2$ could be decreased to 1.5 equiv without reducing the yield (Table 1, entry 6).

Having optimized the conditions for the $AgNTf_2$-mediated one-pot sequential process involving intermolecular C−N bond formation and 5-*endo*-*dig* cyclization, we investigated the substrate scope of bromopyrroloindolines (Figure 2). Regarding protecting groups on two nitrogen atoms, various combinations of electron-withdrawing protecting groups provided the corresponding products in good to high yields (Figure 2, **7aa**−**ga**). This protocol was also applicable to the reactions of various functionalized substrates. The reactions of substrates **4ha** and **4ia** prepared from tryptophan derivatives proceeded smoothly to give corresponding products **7ha** and **7ia**, respectively. Notably, this protocol complements Rainier's reaction[6a] since the former **4ha** would give a mixture of diastereomers due to epimerization of the α-position of the ester, and the latter **4ia** should not undergo introduction of an indole nucleus since formation of the cyclopropane intermediate is impossible. A substrate with a sterically demanding methyl group on the aminal carbon uneventfully afforded desired product **7ja**. Additionally, this protocol was applied to a highly elaborate substrate possessing a dioxopiperazine ring to furnish **7ka** in 64% yield. Furthermore, C−N1′-linked furoindoline **7la**, furoindolinone **7ma**, and tetrahydro-α-

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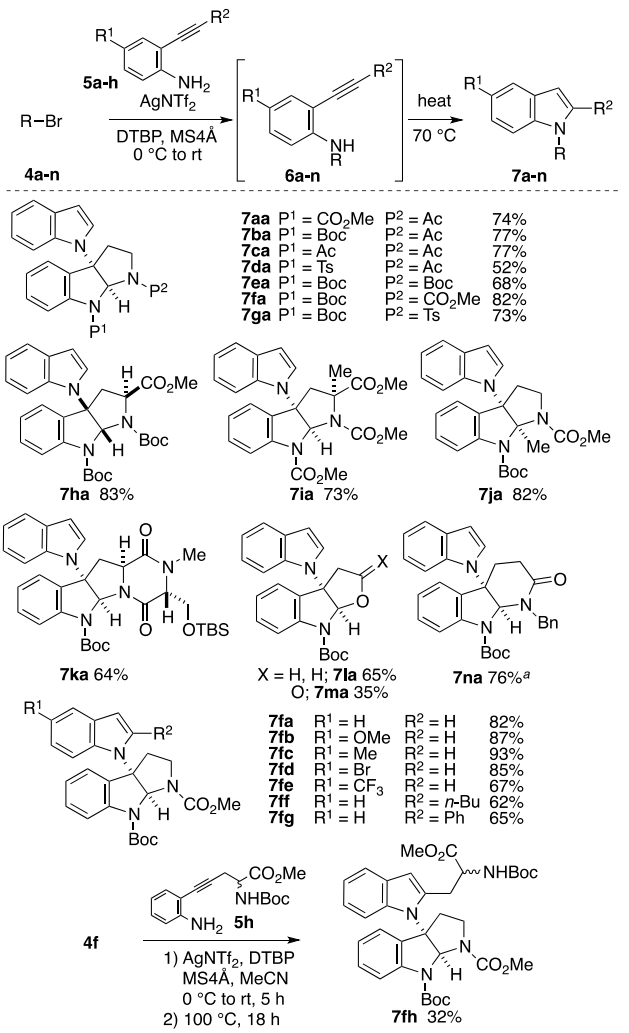


Figure 2. Scope of bromopyrroloindoline, its related substrates, and 2-alkynylanilines. (a) The initial step was conducted at −15 °C.

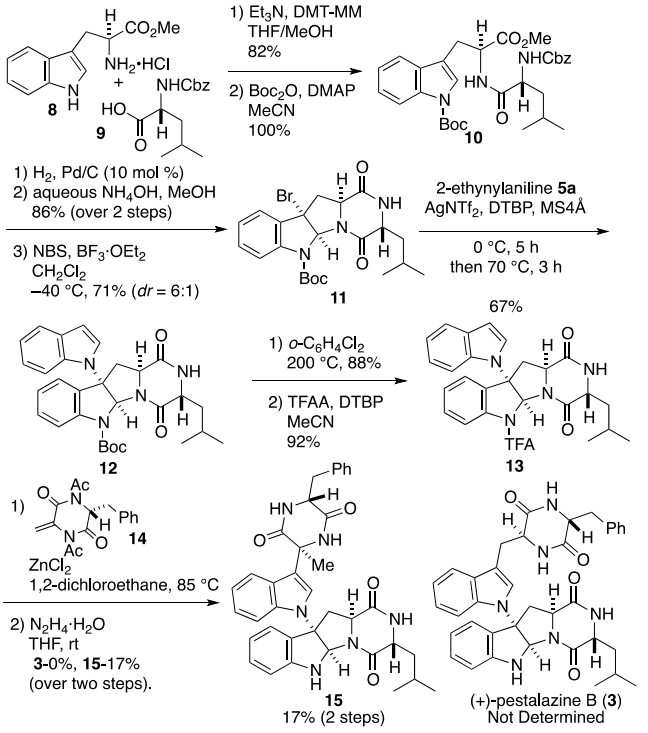
carbolin-2-one derivative **7na**, which possesses the main framework of kapakahine family,[11] were constructed using this protocol.

Next, the scope of the aniline fragment was investigated using bromopyrroloindoline **4fa** (Figure 2). Anilines **5b**−**e** having various substituents such as methoxy, methyl, bromo, and trifluoromethyl groups at the *para*-position gave corresponding products **7fb**−**fe** in good to excellent yields. We found that even internal alkynes underwent the second cyclization to furnish 2-substituted indoles. Thus, the reaction using 2-alkynylanilines bearing *n*-butyl or phenyl groups at the alkynyl terminus gave **7ff** or **7fg**, respectively. In particular, 2-alkynylaniline **5h** bearing an *α*-amino-ester unit gave an isotryptophan derivative **7fh**.[12]

The establishment of a novel protocol for constructing C−N1′-linked indolylpyrroloindoline prompted us to conduct synthetic studies on (+)-pestalazine B (**3**). This was isolated from *Pestalotiopsis theae* by Che and co-workers in 2008.[13] Because of its fascinating structure, this compound has attracted considerable attention as a synthetic target, and three total syntheses have been achieved.[14] We envisioned that (+)-pestalazine B (**3**) should be easily accessed by introducing a dioxopiperazinyl methyl unit to the C−N1′-linked indolylpyrroloindoline, e.g., **7ka** (Figure 2), either by Michael addition or aldol/deoxygenation.

Our synthesis began with condensation between L-tryptophan methyl ester **8** and D-leucine derivative **9** (Scheme 3). After the indole nitrogen was protected with Boc_2O, a

Scheme 3. Attempt To Construct the Upper Dioxopiperazine Unit Based on Conjugated Addition Strategy



dioxopiperazine ring was formed by removing the Cbz group under hydrogenation to give **10**. Diastereoselective bromocyclization proceeded smoothly under modified Movassaghi conditions using NBS and $BF_3{\cdot}OEt_2$ to give tetracyclicbromopyrroloindoline **11**,[15] which underwent a $AgNTf_2$-mediated amination/cyclization sequence with 2-ethynylaniline **5a** under the optimal conditions to afford the desired C−N1′-linked indolylpyrroloindoline **12** on a gram scale. After the Boc group on indoline was switched with a trifluoroacetyl group, we attempted the proposed Michael addition to enamide **14** with zinc chloride,[16] subsequently removing the protecting groups using hydrazine. Unexpectedly, however, the detailed spectral data, including ^{1}H NMR analysis, indicated that the product structure was not pestalazine B (**3**) but product **15**, which was possibly generated by addition of the indole unit to an acyliminium ion generated from enamide **14** and zinc chloride.

The failure of the Michael addition strategy led us to investigate an aldol/deoxygenation strategy using imidate **16**[17] (Scheme 4). Since formylation of indole **12** under conventional Vilsmeier−Haack conditions was also ineffective, giving a side product due to elimination of the Boc group and performylation on the dioxopiperazine ring, we tested a modified formylation developed by Doi using dichloromethyl methyl ether. Consequently, the side reactions were suppressed to give the desired product **17** in 85% yield.[18] The crucial aldol reaction was then examined. An anionic species of imidate **16** generated by treatment with LHMDS was reacted

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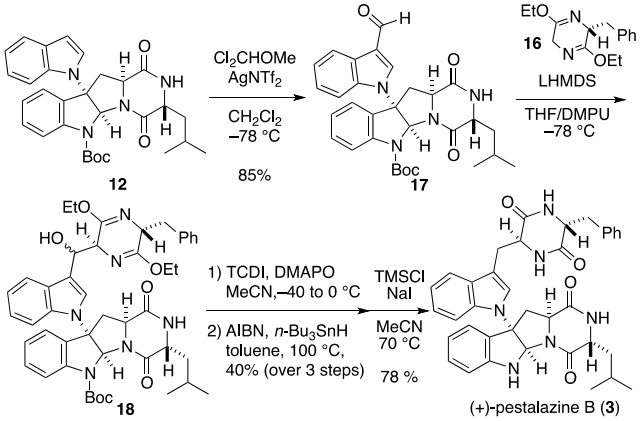
Scheme 4. Total Synthesis of (+)-Pestalazine B (3) via an Aldol Reaction−Deoxygenation Strategy



with aldehyde **17** in the presence of DMPU. The desired aldol was obtained as a mixture of diastereomers, which was subjected to the Barton−McCombie protocol to furnish deoxygenated product. Finally, a Boc and two ethyl groups were removed under Lewis acidic conditions to achieve the total synthesis of (+)-pestalazine B (**3**). All of the spectral data were identical with those reported in de Lera's total synthesis, unambiguous supporting de Lera's structural revision.[14a]

In summary, we have developed a novel $AgNTf_2$-mediated amination/cyclization cascade for constructing an *N*-linked indole segment at the 3a-position of pyrroloindolines. This cascade process is a novel entry of a Ag salt mediated tandem reaction, in which $AgNTf_2$ plays a dual role: activation of a bromo group and an alkyne moiety. Owing to the mildness of the Ag salt mediated activation, the established reaction conditions displayed high functional group compatibility. The utility of our process for synthesizing bis-indole alkaloids was fully demonstrated by the total synthesis of (+)-pestalazine B. In view of the general applicability of this protocol to constructing a broad range of scaffolds such as pyrroloindolines, furoindolines, and tetrahydro-α-carboline, this modular synthetic strategy integrating three building blocks, involving bromopyrroloindoline, alkynylanilines, and an imidate unit, should pave the way to accessing various natural and synthetic dimeric indole compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01399.

Experimental details and procedures, compound characterization data, and copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Álvarez, M. *Chem. - Eur. J.* **2011**, *17*, 1388−1408. (b) Tadano, S.; Ishikawa, H. *Synlett* **2014**, *25*, 157−162. (c) Kim, J.; Movassaghi, M. *Acc. Chem. Res.* **2015**, *48*, 1159−1171.

(2) Zhou, H.; He, H.-P.; Wang, Y.-H.; Hao, X.-J. *Helv. Chim. Acta* **2010**, *93*, 1650−1652.

(3) Kung, A. L.; Zabludoff, S. D.; France, D. S.; Freedman, S. J.; Tanner, E. A.; Vieira, A.; Cornell-Kennon, S.; Lee, J.; Wang, B.; Wang, J. M.; Memmert, K.; Naegeli, H. U.; Peterson, F.; Eck, M. J.; Bair, K. W.; Wood, A. W.; Livingston, D. M. *Cancer Cell* **2004**, *6*, 33−43.

(4) For representative total syntheses of the bis-indole alkaloid vinblastine, see: (a) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137−2139. (b) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 4904−4916.

(5) For selected examples of syntheses of C−C-linked pyrroloindolines with indoles, see: (a) Yamada, F.; Goto, A.; Somei, M. *Heterocycles* **2000**, *53*, 1255−1258. (b) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9655−9659. (c) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 14940−14943. (d) Boyer, N.; Movassaghi, M. *Chem. Sci.* **2012**, *3*, 1798−1803. (e) Tayu, M.; Higuchi, K.; Ishizaki, T.; Kawasaki, T. *Org. Lett.* **2014**, *16*, 3613−3615. (f) Lei, H.; Wang, L.; Xu, Z.; Ye, T. *Org. Lett.* **2017**, *19*, 5134−5137. (g) Tayu, M.; Hui, Y.; Takeda, S.; Higuchi, K.; Saito, N.; Kawasaki, T. *Org. Lett.* **2017**, *19*, 6582−6585. (h) Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H. *J. Am. Chem. Soc.* **2018**, *140*, 14490−14497.

(6) (a) Espejo, V. R.; Rainier, J. D. *J. Am. Chem. Soc.* **2008**, *130*, 12894−12895. (b) Espejo, V. R.; Rainier, J. D. *Org. Lett.* **2010**, *12*, 2154−2157.

(7) (a) Villanueva-Margalef, I.; Thurston, D. E.; Zinzalla, G. *Org. Biomol. Chem.* **2010**, *8*, 5294−5303. (b) Welch, T. R. Dissertation, Colorado State University, 2012. (c) Welch, T. R.; Williams, R. M. *Tetrahedron* **2013**, *69*, 770−773.

(8) (a) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886−10887. (b) Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2716−2719. (c) Liu, C.; Yi, J.-C.; Zheng, Z.-B.; Tang, Y.; Dai, L.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2016**, *55*, 751−754. (d) Adhikari, A. A.; Chisholm, J. D. *Org. Lett.* **2016**, *18*, 4100−4103. (e) Dai, J.; Xiong, D.; Yuan, T.; Liu, J.; Chen, T.; Shao, Z. *Angew. Chem., Int. Ed.* **2017**, *56*, 12697−12701. (f) Gentry, E. C.; Rono, L. J.; Hale, M. E.; Matsuura, R.; Knowles, R. R. *J. Am. Chem. Soc.* **2018**, *140*, 3394−3402.

(9) (a) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125−128. (b) Araki, T.; Ozawa, T.; Yokoe, H.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Org. Lett.* **2013**, *15*, 200−203. (c) Zhang, H.; Kang, H.; Hong, L.; Dong, W.; Li, G.; Zheng, X.; Wang, R. *Org. Lett.* **2014**, *16*, 2394−2397. (d) Tayu, M.; Ishizaki, T.; Higuchi, K.; Kawasaki, T. *Org. Biomol. Chem.* **2015**, *13*, 3863−3865. (e) Lian, X.-L.; Meng, J.; Han, Z.-Y. *Org. Lett.* **2016**, *18*, 4270−4273.

(10) (a) Satoh, H.; Ojima, K.; Ueda, H.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 15157−15161. (b) Sato, S.; Hirayama, A.; Ueda, H.; Tokuyama, H. *Asian J. Org. Chem.* **2017**, *6*, 54−58. (c) Hakamata, H.; Sato, S.; Ueda, H.; Tokuyama, H. *Org. Lett.* **2017**, *19*, 5308−5311. (d) Sato, S.; Hirayama, A.; Adachi, T.; Kawauchi, D.; Ueda, H.; Tokuyama, H. *Heterocycles* **2017**, *94*, 1940−1957.

DOI: 10.1021/acs.orglett.9b01399
Org. Lett. XXXX, XXX, XXX−XXX

(11) (a) Nakao, Y.; Yeung, B. K. S.; Yoshida, W. Y.; Scheuer, P. J.; Kelly- Borges, M. *J. Am. Chem. Soc.* **1995**, *117*, 8271. (b) Yeung, B. K. S.; Nakao, Y.; Kinnel, R. B.; Carney, J. R.; Yoshida, W. Y.; Scheuer, P. J.; Kelly- Borges, M. *J. Org. Chem.* **1996**, *61*, 7168. (c) Nakao, Y.; Kuo, J.; Yoshida, W. Y.; Kelly-Borges, M.; Scheuer, P. *Org. Lett.* **2003**, *5*, 1387.

(12) For a silver-catalyzed isotryptophan synthesis, see: van Esseveldt, B. C. J.; van Delft, F. L.; Smits, J. M. M.; de Gelder, R.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2004**, *346*, 823−834.

(13) Ding, G.; Jiang, L.; Guo, L.; Chen, X.; Zhang, H.; Che, Y. *J. Nat. Prod.* **2008**, *71*, 1861−1865.

(14) For a total synthesis of (+)-pestalazine B, see: (a) Pérez-Balado, C.; de Lera, Á. R. *Org. Biomol. Chem.* **2010**, *8*, 5179−5286. (b) Li, Q.; Xia, T.; Yao, L.; Deng, H.; Liao, X. *Chem. Sci.* **2015**, *6*, 3599−3605. (c) Nelson, B. M.; Loach, R. P.; Schiesser, S.; Movassaghi, M. *Org. Biomol. Chem.* **2018**, *16*, 202−207.

(15) Loach, R. P.; Fenton, O. S.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 1057−1064.

(16) For $ZnCl_2$-promoted Michael addition of indole, see: An, Y.-L.; Shao, Z.-Y.; Cheng, J.; Zhao, S.-Y. *Synthesis* **2013**, *45*, 2719−2726.

(17) For anionic introductions of imidate unit, see: (a) Zhao, S.; Gan, T.; Yu, P.; Cook, J. *Tetrahedron Lett.* **1998**, *39*, 7009−7012. (b) DeLorbe, J. E.; Jabri, S. Y.; Mennen, S. M.; Overman, L. E.; Zhang, F.-L. *J. Am. Chem. Soc.* **2011**, *133*, 6549−6552.

(18) Ohsawa, K.; Yoshida, M.; Doi, T. *J. Org. Chem.* **2013**, *78*, 3438−3444.

DOI: 10.1021/acs.orglett.9b01399
Org. Lett. XXXX, XXX, XXX−XXX