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Total Syntheses of Tardioxopiperazine A, Isoechinulin A, and Variecolorin C

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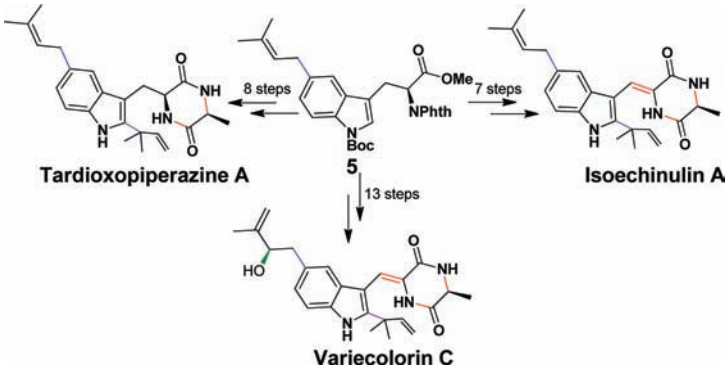
ABSTRACT



First total syntheses of the isoechinulin-type alkaloids: Tardioxopiperazine A, Isoechinulin A, and Variecolorin C have been achieved from a common key intermediate 5, which was derived from a regiocontrolled Stille cross-coupling reaction of an allylindium reagent.

The structurally fascinating and biologically active metabolites Tardioxopiperazine A (**1**), Isoechinulin A (**2**), and Variecolorin C (**3**), isolated from the *Aspergillus* species by Zhu and co-workers in 2007,[1] are three new members of isoechinulin-type alkaloids (Figure 1). These 2,3,5-trisubstituted indole alkaloids contain three structural units: an indole, a 2-methyl-3-buten-2-yl, and a diketopiperazine. A bioactivity test shows that compounds **1**–**3** display radical scavenging activity, ultraviolet-A protecting activity, immunosuppressive activity, and antibacterial activity.[1] Herein, we report the first total syntheses of **1**–**3** starting from a common key intermediate **5**, which was derived

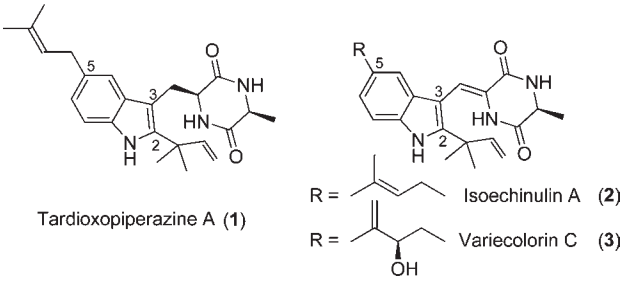


Figure 1. Structures of Tardioxopiperazine A (**1**), Isoechinulin A (**2**), and Variecolorin C (**3**).

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(1) (a) Wang, W.-L.; Lu, Z.-Y.; Tao, H.-W.; Zhu, T.-J.; Fang, Y.-C.; Gu, Q.-Q.; Zhu, W.-M. *J. Nat. Prod.* **2007**, *70*, 1558–1564. (b) Fujimoto, H.; Fujimaki, T.; Okuyama, E.; Yamazaki, M. *Chem. Pharm. Bull.* **1999**, *47*, 1426–1432. (c) Nagasawa, H.; Isogai, A.; Suzuki, A.; Tamura, S. *Tetrahedron Lett.* **1976**, *19*, 1601–1604. (d) He, J.; Wijeratne, E. M. K.; Bashyal, B. P.; Zhan, J.; Seliga, C. J.; Liu, M. X.; Pierson, E. E.; Pierson, L. S.; VanEtten, H. D.; Gunatilaka, A. A. L. *J. Nat. Prod.* **2004**, *67*, 1985–1991. (e) Chu, Y.-S.; Niu, X.-M.; Wang, Y.-L.; Guo, J.-P.; Pan, W.-Z.; Huang, X.-W.; Zhang, K.-Q. *Org. Lett.* **2010**, *12*, 4356–4359. (f) Gugnani, H. C. *Frontiers Biosci.* **2003**, *8*, 346–357. (g) Li, Y.; Li, X.; Kim, S. K.; Kang, J. S.; Choi, H. D.; Rho, J. R.; Son, B. W. *Chem. Pharm. Bull.* **2004**, *52*, 375–376. (h) Li, Y.; Li, X.; Kang, J. S.; Choi, H. D.; Son, B. W. *J. Antibiot.* **2004**, *57*, 337–340. (i) Ravikanth, V.; Niranjan Reddy, V. L.; Ramesh, P.; Prabhakar Raoa, T.; Diwan, P. V.; Khar, A.; Venkateswarlu, Y. *Phytochemistry* **2001**, *58*, 1263–1266. (j) Naik, C. G.; Devi, P.; Rodrigues, E. U.S. Patent 2,005,143,392, 2005.

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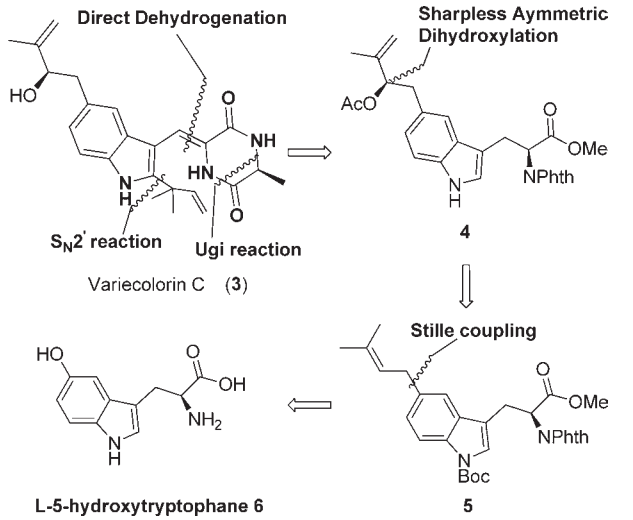
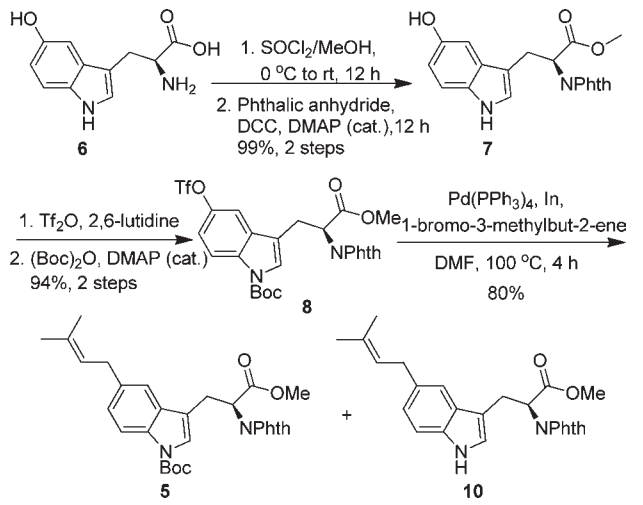
Scheme 1. Retrosynthetic Analysis



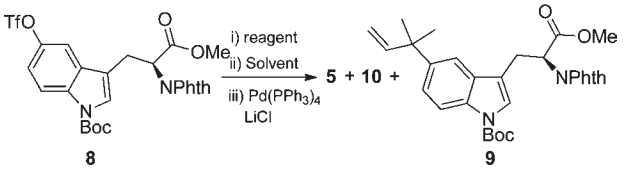
Scheme 2. Synthesis of Key Intermediate **5**



from a regiocontrolled Stille cross-coupling reaction of an allylindium reagent.

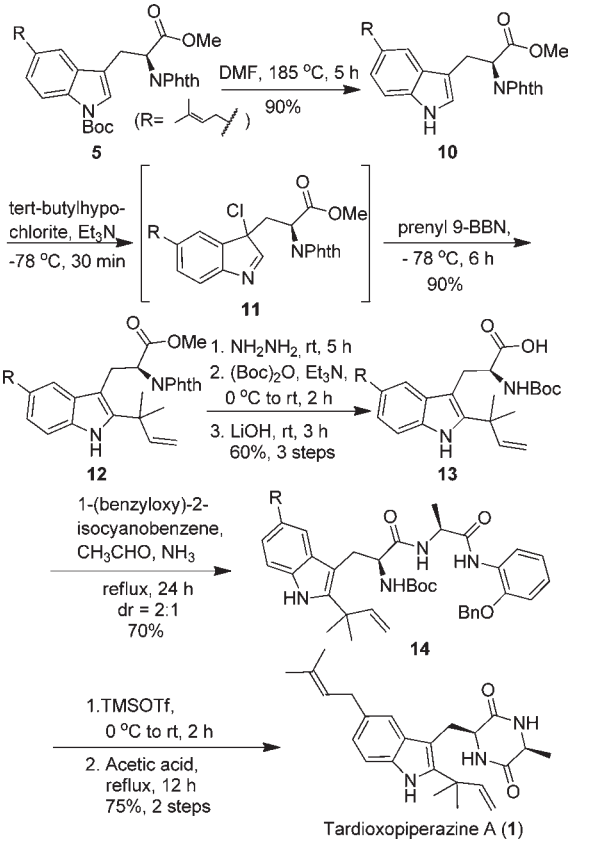
We envisioned that these 2,3,5-trisubstituted indole alkaloids could be synthesized by an efficient regioselective strategy due to the common subunit they shared. Variecolorin C (**3**) was chosen as a representive example, and its retrosynthetic analysis is outlined in Scheme 1. We planned to construct Variecolorin C (**3**) by a direct dehydrogenation reaction,[2] a multicomponent Ugi reaction,[3] and an S_N2' reaction[4] from **4**. The chiral secondary hydroxyl group of **4**

Table 1. Regioselective of Intermediate **5**



Entry	Solvent	(i)	Reaction temperature/time	Yield **5**	Yield **10**	Yield **9**
1	DMF	In	100°C, 4h	60%	20%	0%
2	DMF	In	65°C, 24h	50%	5%	0%
3	THF	In	reflux, 24h	40%	5%	0%
4	DMF	$SnBu_3$	65°C, 24h	60%	0%	25%
5	DMF	9-BBN	65°C, 24h	0%	0%	80%

Scheme 3. Completion of the Synthesis of Tardioxopiperazine A



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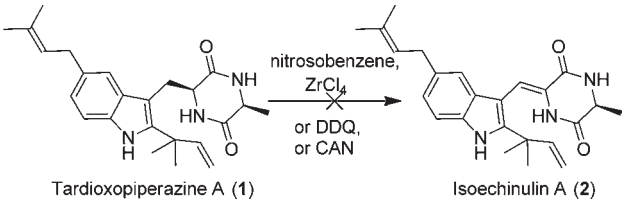
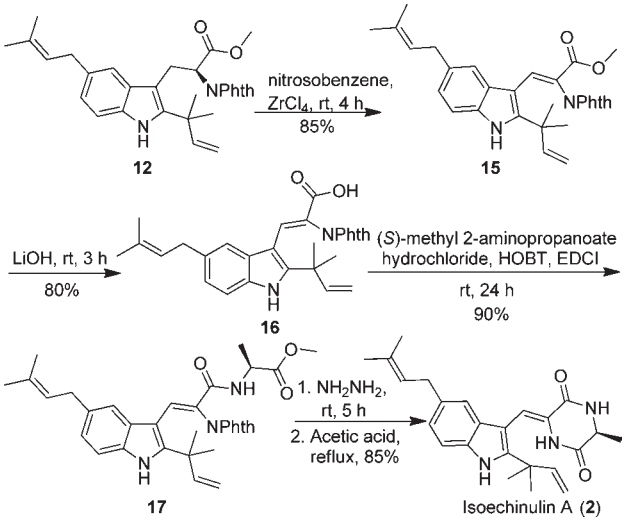
Scheme 4. Unsuccessful Route towards Isoechinulin A



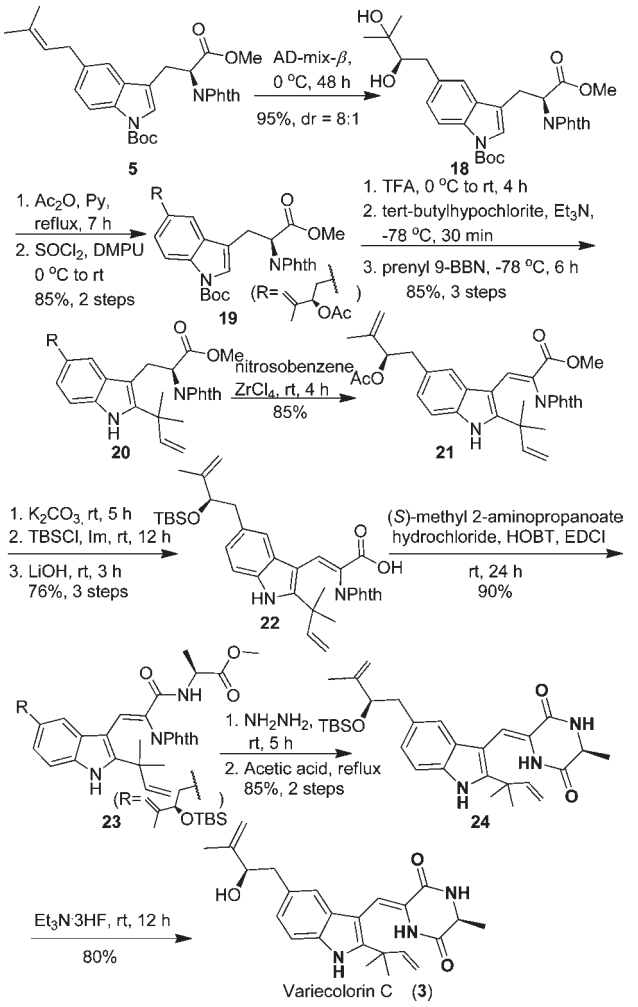
Scheme 5. Completion of the Synthesis of Isoechinulin A



could be installed by Sharpless asymmetric dihydroxylation,[5] and the C5 branch chain could be constructed from the commercially available L-5-hydroxytryptophane (**6**) via a Stille cross-coupling reaction.[6]

A concise synthesis of Tardioxopiperazine A (**1**) was outlined in Scheme 2. According to the retrosynthetic analysis, our synthesis started from the commercially available L-5-hydroxy-tryptophane (**6**). Esterification of **6** followed by protection of the primary amino group gave **7**. Sequential treatment of **7** with triflic anhydride followed by protection of indole's amino group with $(Boc)_2O$ afforded **8**, which was subjected to the Stille coupling reaction; however, two isomers **5** and **9** were obtained under the classic Stille coupling reaction conditions (Scheme 2), and the separation was very difficult. To solve this problem, many coupling partners were

Scheme 6. Completion of the Synthesis of Variecolorin C



tested such as organomagnesium,[7] organozinc,[8] organolithium,[9] and organoboron;[10] however the same results were obtained (Tables 1). Fortunately, when the allylindium reagent generated in situ was utilized in this reaction, we found that **5** and Boc-deprotected product **10** with heat in DMF were obtained in 60% and 20% yields respectively.

With key intermediate **5** in hand, removal of the Boc group with heat in DMF gave **10** in 90% yield (Scheme 3). Treatment of **10** with *tert*-butyl-hypochlorite[4] led to the formation of an unstable 3-chloroindolenine intermediate **11** which was directly coupled with freshly prepared prenyl-9-BBN[11] to give 2,3-disubstituted indole **12** in 90% yield. Changing the protecting group at *N*-Phth and followed by hydrolysis of methyl ester gave the Ugi

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reaction precursor **13**, which underwent a four-component reaction with NH_3/MeOH, CH_3CHO, and 1-(benzyloxy)-2-isocyanobenzene to afford **14** in 70% yield (dr 2:1). After deprotection and acid-promoted cyclization, we successfully obtained Tardioxopiperazine A (**1**).

As the structure of Isoechinulin A (**2**) was close to Tardioxopiperazine A (**1**), we proposed **2** could be derived from the direct dehydrogenation[2] of **1**; however, that was proven to be unsuccessful (Scheme 4). Therefore, we modified the synthetic sequence and conducted the direct dehydrogenation of **12** first to provide the corresponding product **15** in 85% yield as a single isomer (Scheme 5). Then hydrolysis of **15** provided **16** that was coupled with (*S*)-methyl 2-aminopropanoate hydrochloride in the presence of HOBT and EDCI to afford **17**.[12] Deprotection and acid-promoted cyclization[12] afforded Isoechinulin A (**2**) in 85% yield.

The total synthesis of Variecolorin C (**3**) was shown in Scheme 6. Asymmetric dihydroxylation of the olefin **5** with AD-mix-β afforded the diol **18** in 95% yield (dr 8:1). Selective protection of the secondary hydroxyl group followed by dehydration gave ester **19**. Using the same synthetic schemes employed before, Variecolorin C (**3**) was obtained in high yield.

In conclusion, the concise total syntheses of Tardioxopiperazine A (**1**), Isoechinulin A (**2**), and Variecolorin C (**3**) were achieved. Our synthetic route features three highlights: (1) application of a key intermediate for three molecules; (2) application of allylindium reagents; (3) construction of the diketopiperazine core with the reagent 1-(benzyloxy)-2-isocyanobenzene. The application of this route paves the way for the total syntheses of other isoechinulin-type alkaloids which are underway in our laboratory and will be reported in due course.

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

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