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Total Synthesis of (−)-Aspergilazine A

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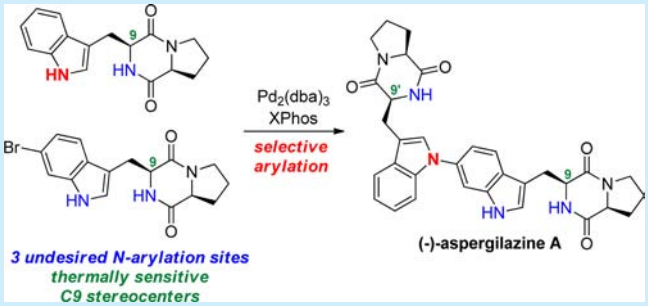
Supporting Information

ABSTRACT: The total synthesis of (−)-aspergilazine A, an alkaloid possessing a rare N1′ to C6 bisindole bond, is described. A palladium-catalyzed *N*-arylation was used to selectively install the N1′−C6 bond in the presence of three other possible arylation sites. The ligand XPhos displayed a unique capability to efficiently carry out the *N*-arylation while simultaneously suppressing epimerization of the sensitive C9 stereocenters. This total synthesis has confirmed that aspergilazine A is a dimer of brevianamide F.



Aspergilazine A (**1**) is a diketopiperazine dimer isolated from the marine-derived fungus *Aspergillus taichungensis* ZHN-7-707 in 2012 (Figure 1).[1] Aspergilazine A contains a rare N1′−C6 bisindole bond that, to the best of our knowledge, only exists in one other known natural product.[2] In continuation of our interest in bisindole alkaloids that possess uncommon dimerization sites,[3] we describe herein a total synthesis of **1** that employs a palladium-catalyzed *N*-arylation to forge the N1′−C6 bond.

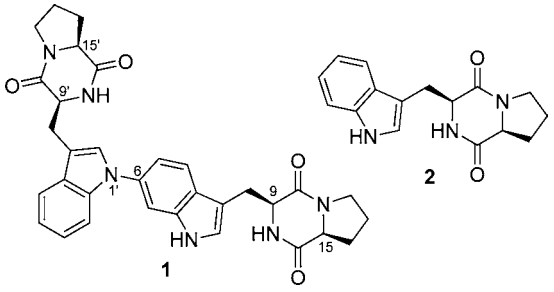
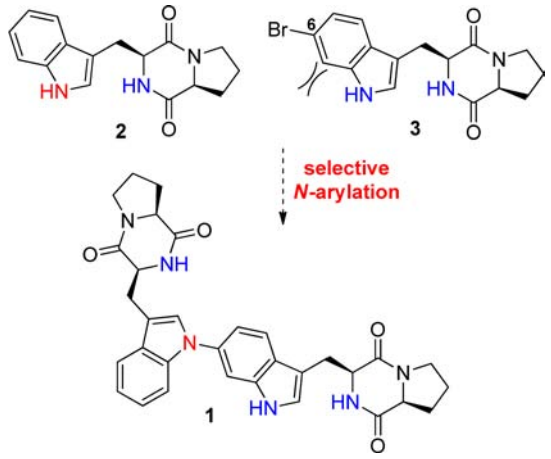


Figure 1. Aspergilazine A (**1**) and brevianamide F (**2**).

Marfey's analysis of **1** confirmed the presence of L-proline, and NOESY experiments showed a *cis*-relationship between H-9 and H-15 in both diketopiperazines. Aspergilazine A is thus proposed to be a dimer of cyclo-L-prolyl-L-tryptophyl, otherwise known as the natural product brevianamide F (**2**).[4] Our planned synthesis of **1** hinged on the selective indole *N*-arylation[5,6] of 6-bromobrevianamide F (**3**)[7] with brevianamide F (**2**), a challenging disconnection due to the presence of four possible *N*-arylation sites (2 × indole N−H and 2 × diketopiperazine N−H's, Scheme 1). However, we were confident of uncovering a catalytic system that would be selective for the indole and that the presence of the C6 bromide close to the indole N−H in **3** would restrict unwanted arylation at this site, favoring selective hetero-coupling between **2** and **3**.

Scheme 1. Proposed Synthetic Route to (−)-Aspergilazine A



The first task was the synthesis of the *N*-arylation partners **2** and **3**. Brevianamide F (**2**) is available by thermal deprotection−cyclization of *N*-Boc-L-Pro-L-Trp-OMe,[8] but substantial epimerization of the tryptophan stereocenter (C9) gave less than satisfactory results. Subjecting *N*-Fmoc-L-Pro-L-Trp-OMe[9] (**4**) to piperidine−DMF was the most reliable method for providing useful quantities of **2** without epimerization (Scheme 2).

The route in Scheme 2 was used as a guide for the synthesis of 6-bromobrevianamide F (**3**). Accordingly, 6-bromo-L-tryptophan was required and a reported biocatalytic route[10] seemed attractive (Scheme 3). Enzymatic resolution of N^{α}-acetyl-(±)-tryptophan (**5**) followed by esterification gave

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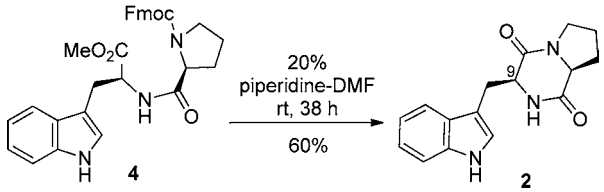
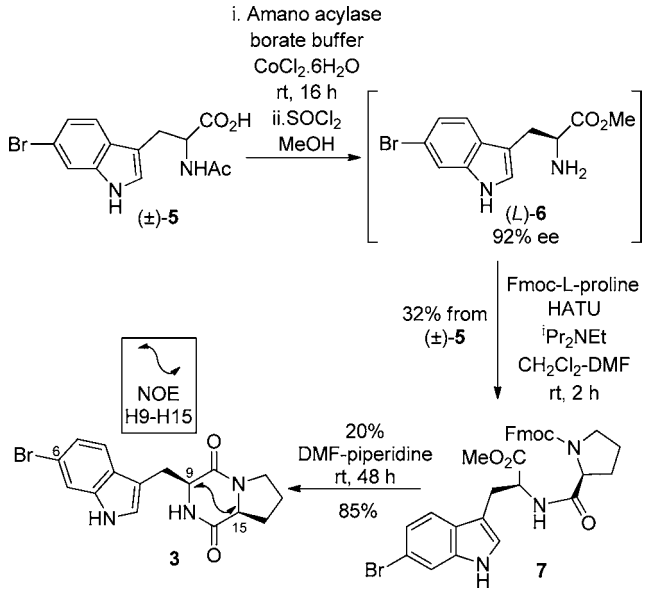
Scheme 2. Synthesis of Brevianamide F (2)



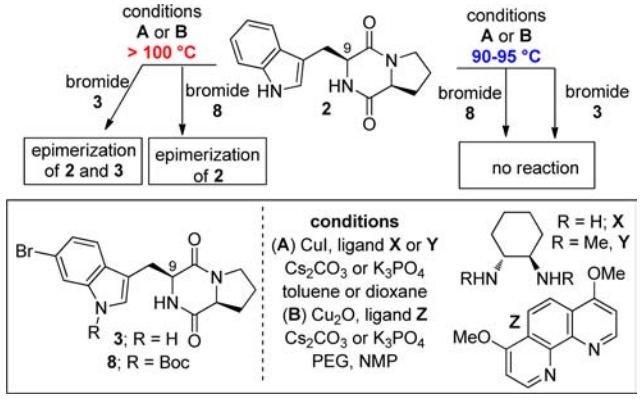
Scheme 3. Synthesis of (−)-6-Bromobrevianamide F (3)



6-bromo-L-tryptophan methyl ester (**6**) with a 92% enantiomeric excess.[11] Subsequent amide coupling with *N*-Fmoc-L-proline gave dipeptide **7** as a rotameric mixture[9] that upon exposure to piperidine−DMF underwent concomitant deprotection−cyclization to give 6-bromobrevianamide F (**3**) as a single diastereomer.[12,13] A strong NOE correlation between H-9 and H-15 confirmed the desired *cis*-relationship.[7,11]

With the coupling partners **2** and **3** in hand, the *N*-arylation was considered. Due to the low abundance of *N*-arylindoles in nature, intermolecular indole *N*-arylations are uncommon in total synthesis and hence the utility of this reaction in the assembly of complex molecules is somewhat unexplored.[6] Notable exceptions are the total syntheses of psychotrimine[14] that used Buchwald's[5d,e] copper-diamine conditions to install the *N*-arylindole subunit. This previous work was used as a starting point for the attempted arylation of brevianamide **F** (**2**) with 6-bromobrevianamide **F** (**3**) but was found unsuccessful. Various copper-diamine[5d,e] and copper-phenanthroline[15] catalytic systems resulted in the epimerization of **2** and **3** (C9) at temperatures above 100 °C (Scheme 4). Conducting the reactions at 90−95 °C suppressed epimerization, but no arylation products were observed. The poor recovery of bromide **3** from all the reactions suggested it was degrading, and as a result, the *N*-Boc bromide **8** was prepared.[11] However, the attempted *N*-arylation of **8** with **2** under a similar array of copper-catalyzed conditions led to comparable results: no reaction at 90−95 °C and epimerization of **2** at 100 °C (Scheme 4). We were now faced with the conundrum that not only did the *N*-arylation fail under copper catalysis, substrates **2** and **3** were prone to thermally

Scheme 4. Failed Copper-Catalyzed Arylations of 2 with 3 and 8



induced epimerization. As a result, the focus shifted to palladium-catalyzed *N*-arylations.[5a,b]

We chose to employ the more robust *N*-Boc bromide **8** in the subsequent palladium-catalyzed *N*-arylation, as it did not appear to undergo epimerization or degradation as readily as bromide **3** (Scheme 4). Early attempts using Hartwig's[5a,b] conditions only epimerized **2** and **8** (Table 1, entries 1 and 2), and therefore, Buchwald's dialkylbiaryl phosphine ligands[5c] were trialled. While the *N*-arylation with DavePhos was unsuccessful (entry 3), ^{t}Bu-XPhos[16] gave the desired product **9** in 6% yield (entry 4) that rose to 33% by increasing the catalyst and ligand loadings (entries 5−6). Interestingly, epimerization was only evident at the higher loading (entry 6) and subsequent efforts focused on eliminating this process. In particular, a publication detailing that SPhos suppresses racemization in the Suzuki coupling of α-amino acids appeared promising.[17] Indeed, SPhos completely suppressed epimerization in our system (even at 100 °C) but with no benefit to the overall yield (entry 7). Further ligand screening showed that Me$_4$^{t}BuXPhos[16] performed poorly on both fronts (epimerization and yield; entry 8) and RuPhos[18] suppressed epimerization but gave a poor yield of **9** (entry 9). In a pivotal experiment, XPhos doubled the previous best yield (entry 10) with no evidence of epimerization and increasing the catalyst and ligand loadings did not induce epimerization (as in the case of ^{t}BuXPhos, entries 4−6), affording **9** in 79% yield (entry 11). We examined the behavior of the bidentate ligand XantPhos in the *N*-arylation, obtaining a yield of 24% with accompanying epimerization (entry 12).

Encouraged by the successful *N*-arylation of **2** with **8**, we were eager to attempt the protecting-group-free *N*-arylation (Scheme 5). Upon subjecting 6-bromobrevianamide F (**3**) and brevianamide F (**2**) to the optimized conditions from Table 1, the *N*-arylated product **1** was obtained in 9% yield along with an 80% recovery of **2**. The yield of this reaction is limited by instability of bromide **3** under the reaction conditions, and various attempts at adding bromide **3** portionwise over the course of the reaction did not increase the yield of **1**. Even so, a selective indole *N*-arylation in the presence of four possible arylation sites had been accomplished, with no epimerization apparent. The product **1** was spectroscopically identical to the material obtained by removing the Boc group from dimer **9** (Scheme 5).

The NMR data of synthetic **1** were in full agreement with the natural product.[1,11] However, the optical rotation of synthetic **1** {$[\alpha]_D^{22}$ −70.0 (c = 0.10, CH_2Cl_2/MeOH 1:1)} was

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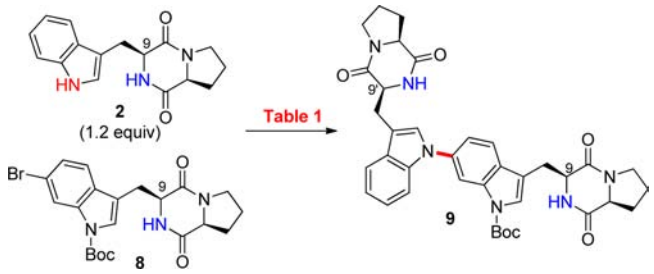
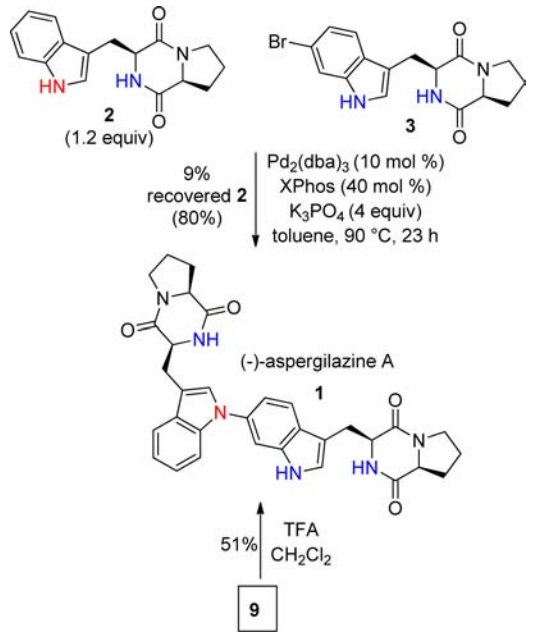
Table 1. Palladium-Catalyzed *N*-Arylation of 8 with 2[a]



entry[b]	catalyst[c] (mol %)	ligand (mol %)	temp (°C)	time (h)	yield **9** (%)	epimerization[d]
1	$Pd(dba)_2$ (10)	$P(^tBu)_3{\cdot}HBF_4$ (8)	90	40	0	*epi*-**2**/*epi*-**8**
2	$Pd(OAc)_2$ (30)	dppf (40)	95	64	0	*epi*-**2**/*epi*-**8**
3	$Pd_2(dba)_3$ (15)	DavePhos (60)	90	64	0	*epi*-**2**/*epi*-**8**
4	$Pd_2(dba)_3$ (5)	^{t}BuXPhos (20)	90	46	6	no
5	$Pd_2(dba)_3$ (10)	^{t}BuXPhos (40)	90	17	25	no
6	$Pd_2(dba)_3$ (15)	^{t}BuXPhos (60)	90	39	33	*epi*-**2**/*epi*-**8** /epimeric dimers[e]
7	$Pd_2(dba)_3$ (15)	SPhos (60)	100	45	28	no
8	$Pd_2(dba)_3$ (10)	$Me_4{}^tBu$XPhos (40)	90	72	8	*epi*-**2**/*epi*-**8**/epimeric dimers[f]
9	$Pd_2(dba)_3$ (15)	RuPhos (60)	90	39	14	no
10	$Pd_2(dba)_3$ (10)	XPhos (40)	100	29	62	no
11	$Pd_2(dba)_3$ (15)	XPhos (60)	100	39	79	no
12[h]	$Pd_2(dba)_3$ (1.7)	XantPhos (5)	95	39	24	*epi*-**2**/*epi*-**8** /epimeric dimers[g]

[a]All reactions carried out on a 0.02 mmol scale using toluene as solvent. [b]Entries 1 and 2 used Cs_2CO_3 (1.5 equiv) as the base. Entries 3−12 used K_3PO_4 (4 equiv). [c]$Pd_2(dba)_3$ was superior to $Pd(OAc)_2$ in entries 3−12 (ref 5b). [d]Epimerization occurs at C9. Epimeric dimers refer to the presumed formation (by ^1H NMR) of the three compounds 9-*epi*-**9**, 9′-*epi*-**9**, and 9,9′-di-*epi*-**9**, of which only 9-*epi*-**9** could be completely characterized. [e]~2% combined yield of the three epimeric dimers. [f]~9% yield. [g]~20% yield. [h]Catalyst and ligand loadings were taken from ref 19.

Scheme 5. Total Synthesis of (−)-Aspergilazine A (1)



of opposite sign to the literature value {$[\alpha]_D^{25}$ +72 (c = 0.10, CH_2Cl_2/MeOH, 1:1)}.[1] After some initial concern, communication with the authors of the isolation paper confirmed the optical rotation had been reported incorrectly and should have been quoted as negative.[1b] Hence, the absolute configuration of (−)-aspergilazine A (**1**) is as shown and is indeed a dimer of brevianamide F. Unfortunately, we were unable to obtain a sample of natural (−)-**1** for direct comparison to the synthetic material.

To conclude, a selective palladium-catalyzed indole *N*-arylation has been used to complete the total synthesis of the natural product (−)-aspergilazine A (**1**). Although the arylation between **2** and **3** gave a poor yield of (−)-aspergilazine A (**1**), it represents a selective indole *N*-arylation in the presence of four possible arylation sites. Using the protected bromide **8** in the *N*-arylation gave an excellent yield of the product **9**, which upon facile deprotection gave (−)-aspergilazine A (**1**). The XPhos ligand demonstrated a unique capability to bring about *N*-arylation while simultaneously suppressing epimerization during the coupling. As previous examples of intermolecular indole *N*-arylations in natural products synthesis have relied on copper catalysis,[14] the use of palladium catalysis herein represents an important advance in this area.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, 1D and 2D NMR spectra along with tabulated spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) See Supporting Information for full details.
(12) The minor diastereomer (<5%; originating from small quantities of the D-tryptophan and/or epimerization during the cyclization) is advantageously removed by flash column chromatography to give diastereomerically pure diketopiperazine **3**.
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