Total synthesis of PDE-II by copper-mediated double amination†

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A concise total synthesis of PDE-II featuring copper-mediated double aryl amination with the combination of CuI, CsOAc, and Cs_2CO_3 is described. The highly substituted pyrroloindole skeleton was constructed by a one-pot five-step sequence including double aryl amination, β-elimination, deprotection of a Cbz group, and removal of an Ns group followed by rearomatization.

PDE-I (**1**) and PDE-II (**2**) (Fig. 1), isolated from *Streptomyces* MD769-C6 by Umezawa and co-workers, exhibit inhibitory activity towards cyclic adenosine-3′,5′-monophosphate phosphodiesterase.[1] The structures were initially identified by NMR spectroscopy and later confirmed by X-ray crystallography[2] and total synthesis.[3] Since PDEs are the partial structure of potent sequence-selective DNA alkylating agents, such as CC-1065[4] and yatakemycin,[5] construction of the highly functionalized 1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole has attracted considerable attention from the synthetic community.[6] Although tremendous effort has been devoted to the synthesis of this class of compounds, no efficient and straightforward route has been reported except Martin's synthesis.[6i] As an application of our original mild copper-mediated aryl amination reaction (Scheme 1),[7] we also developed a method for synthesis of PDE analogs, which are key segments for the synthesis of duocarmycins[8] and yatakemycin.[5b,d] However, there is still room for improvement with regard to efficiency. Herein, we describe an efficient synthesis of PDE-II (**2**) utilizing copper-mediated double aryl amination.

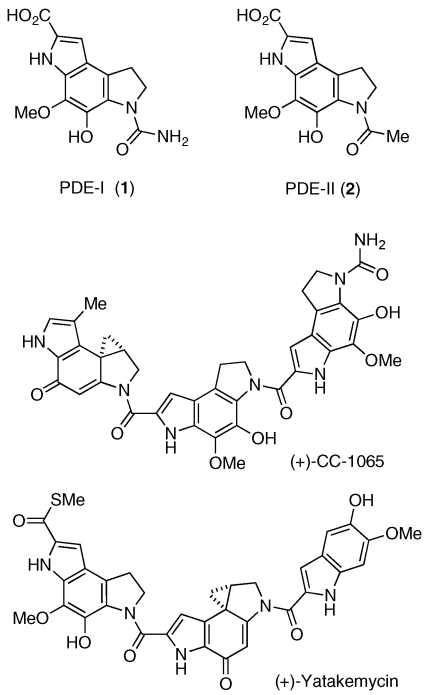
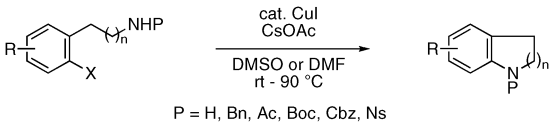


Fig. 1 Structure of PDEs, CC-1065, and yatakemycin.

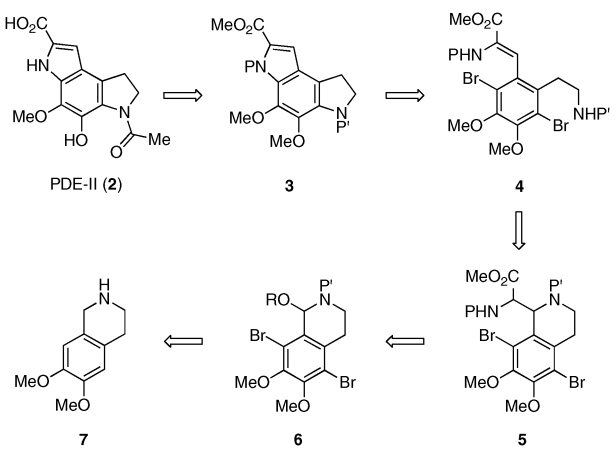


Scheme 1 Mild aryl amination with CuI and CsOAc.

Our retrosynthetic analysis is outlined in Scheme 2. We planned to synthesize dihydropyrroloindole **3**, a possible precursor of PDE-II (**2**), directly from **5** through **4**, by generation of the primary amine side-chain by β-elimination and copper-mediated intramolecular double amination in one pot. Tetrahydroisoquinoline **5** would be prepared by Mannich-type addition of a glycine unit to hemiaminal **6**, which should be derived from commercially available tetrahydroisoquinoline **7**.

The substrate for the amination reaction was synthesized from hemiaminal **8**, which was readily prepared from commercially available tetrahydroisoquinoline **7** using a five-step sequence established in our synthetic studies on yatakemycin (Scheme 3).[5b,d] After transacetalization to **9** with trimethyl orthoformate and PPTS, a glycine moiety was introduced by reaction of ketene silyl acetal **10** in the presence of $BF_3{\cdot}OEt_2$ to give **11**.[9,10]

To test the proposed elimination and double amination sequence, we first subjected **11** to the standard amination conditions with a combination of CuI and CsOAc (Table 1,



Scheme 2 Retrosynthetic analysis.

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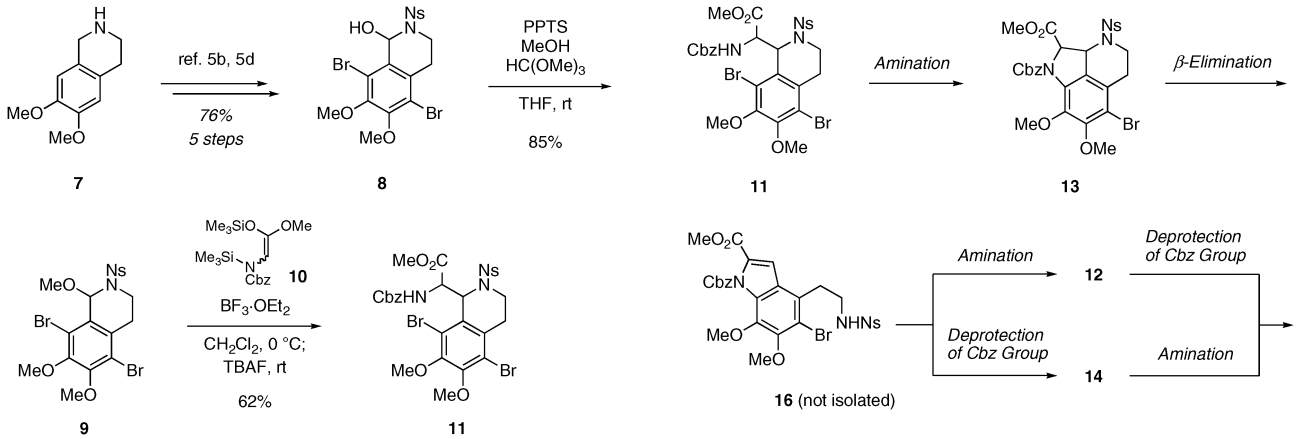
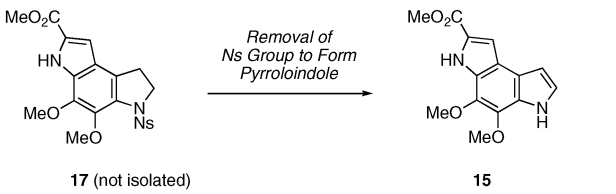


Scheme 3 Preparation of the precursor for the key amination.



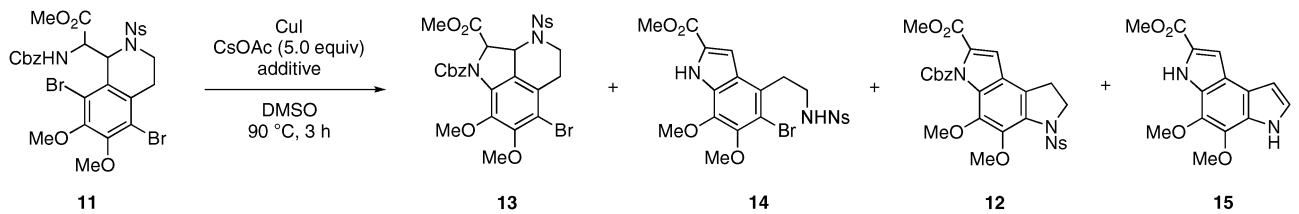
Scheme 4 Outline of pyrroloindole formation.

entry 1). As expected, we observed formation of the double amination product, dihydropyrroloindole **12**, although the yield was only 12%. A careful analysis of the crude material revealed formation of a series of byproducts, including tricyclic compound **13**[11] (14% yield), indole **14** (22%), and pyrroloindole **15** (11%). Based on these results, we speculated that the reaction should be initiated by amination of the Cbz carbamate to provide tricyclic compound **13**, which would undergo β-elimination to give **16** (not isolated) (Scheme 4). Then, the second amination or removal of the Cbz group provided **12** or **14**, respectively. Finally, conversion to **17** (not isolated) and the subsequent removal of the Ns group with concomitant aromatization furnished pyrroloindole **15**.

Since pyrroloindole **15** is known to be a synthetic intermediate of PDEs,[6c] the next step was to optimize the reaction conditions to improve the yield of **12** or **15**. First, we examined the effect of additional base on the product distribution. Although the yields of tricyclic compound **15** were substantially improved, products **12**, **13**, and **14** still remained (entries 2 to 4). We then increased the amount of CuI in the presence of an additional base to converge all products to **15**. We found that using 1.5 equiv. of CuI and 3.0 equiv. of Cs_2CO_3 was effective to improve the yield of **15** to 57% (entry 6) while the reaction using K_3PO_4 resulted in a diminished yield of **15** and isolation of **13** (entry 5).

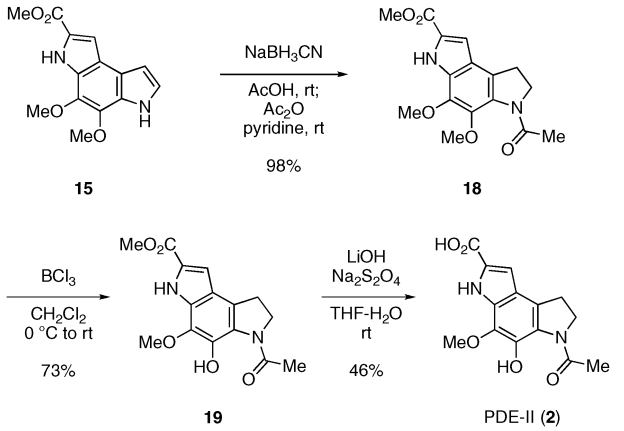
Having established improved conditions to execute the double amination reaction to construct the tricyclic framework of PDEs, we then manipulated the functionalities of **15** to complete the total synthesis of PDE-II (**2**) (Scheme 5). According to the reported procedure,[6a] selective reduction of the indole moiety followed by introduction of an acetyl group provided **18** in one pot. We carried out the next demethylation reaction using BCl_3 by modification of Cava's conditions.[6c] In addition, we found that high dilution conditions (1 mM) were required for complete consumption of the starting material **18**. For the final hydrolysis step, we employed Boger's conditions utilizing $Na_2S_2O_4$ as a mild reductant.[12] Thus, treatment of **19** under the hydrolysis conditions provided PDE-II (**2**), whose physical properties were identical in all aspects to those reported for the natural product.[1]

Table 1 Effect of bases on the double amination cascade



Entry	CuI (equiv.)	Additive (equiv.)	**13** (%)[a]	**14** (%)[a]	**12** (%)[a]	**15** (%)[a]
1	1.0	none	14	22	12	11
2	1.0	KO*t*-Bu (1)	8.7	15	5.1	41
3	1.0	K_3PO_4 (3)	4.5	13	8.9	50
4	1.0	Cs_2CO_3 (3)	6.1	26	3.1	38
5[b]	1.5	K_3PO_4 (3)	13	—	—	18
6	1.5	Cs_2CO_3 (3)	—	—	—	57

[a] Isolated yield. [b] Reaction time: 5 h.



Scheme 5 Total synthesis of PDE-II (**2**).

In summary, we have accomplished a highly efficient method for the total synthesis of PDE-II (**2**) utilizing one-pot copper-mediated intramolecular double amination. The methodology enabled us to synthesize PDE-II (**2**) in 7.5% yield over 11 steps from tetrahydroisoquinoline **7**. Because of the high utility of the aryl amination reaction,[5b,d,7,8] we believe that the synthetic strategy should be generally applicable to a wide variety of nitrogen-containing heterocycles.

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9 Mannich reaction of **8** with **10** did not proceed at all.
10 Preparation of ketene silyl acetal **10** was carried out according to Corey's internal quench method: E. J. Corey and A. W. Gross, *Tetrahedron Lett.*, 1984, **25**, 495. Additional TBAF was found to be necessary for smooth removal of a trimethylsilyl group on nitrogen.
11 Compound **11** was isolated as a mixture of diastereomers. The relative stereochemistry was not determined due to the presence of the rotamers.
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