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Metal-Free and Versatile Synthetic Routes to Natural and Synthetic Prodiginines from Boron Dipyrrin

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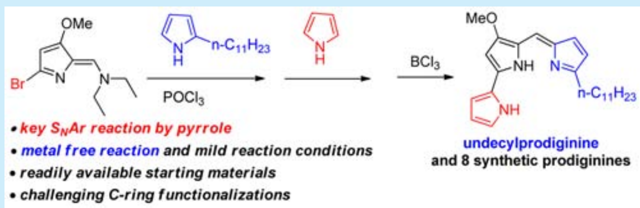
Supporting Information

ABSTRACT: Prodiginines, as a family of bacterial alkaloids, possess a number of interesting biological activities. New, concise synthetic routes for the facile preparation of both synthetic and natural prodiginines in good yields have been developed, which use BODIPY functionalization reactions, such as condensation, nucleophilic substitution, and BF_2 deprotection. This new metal-free synthetic method opens the door toward a wide variety of C-ring functionalized prodiginines, including those that are not possible to obtain through current synthetic methods, for their advanced biological activities.



Prodiginines are tripyrrolic, red-pigmented alkaloids produced by microorganisms such as *Streptomyces* and *Serratiaare.*[1] The natural and synthetic prodiginines have attracted widespread attention in the medicinal chemistry because of their wide range of biological activities, including antibacterial,[2] antimicrobial,[3] anticancer,[4] and immunosuppressive properties.[5] Prodiginines are also found to promote the cotransport of H^+/Cl^- across bilayer membranes,[4a,f,6] and certain prodiginines have also been observed to bind duplex DNA and can cleave this biomolecule in the presence of Cu(II) and O_2.[6d,7] However, a limited variety of prodiginines were used for the evaluation of their biological properties, and most are naturally occurring prodiginines (Figure 1). However, synthetic prodiginines may show improved *in vivo* efficiency or reduced toxicity. Specifically, Obatoclax (Figure 1), a rather simple monoindole analogue of prodigiosin, has recently entered into phase II clinical trials for the treatment of refractory chronic lymphoid leukemia and small cell lung cancer.[8] Another example, PNU-156804 (Figure 1), a simple analogue of undecylprodiginine, can act synergistically with the standard drugs for the prevention of allograft rejection in organ transplanted mammals.[9] Although the rational bioengineering via cloning of the gene cluster and decoding of the biosynthesis pathway might be able to provide novel prodiginines in the future,[10] our present knowledge of the structure−activity relationship (SAR) of these alkaloids is solely derived from chemical synthesis.[2−5] Total synthesis also played an important role in the structural elucidation and structural revision of some prodiginines.[1a,11]

Currently, several synthetic strategies are available for the preparation of prodiginines (**I**), and most rely on the two synthetic routes shown in Figure 1.[2−9] The core pyrrolyldipyrrin scaffold was prepared either by mimicking the final stages of the proposed biosynthesis of this chromophore via the acid-promoted condensation between bipyrrole aldehyde **II** or

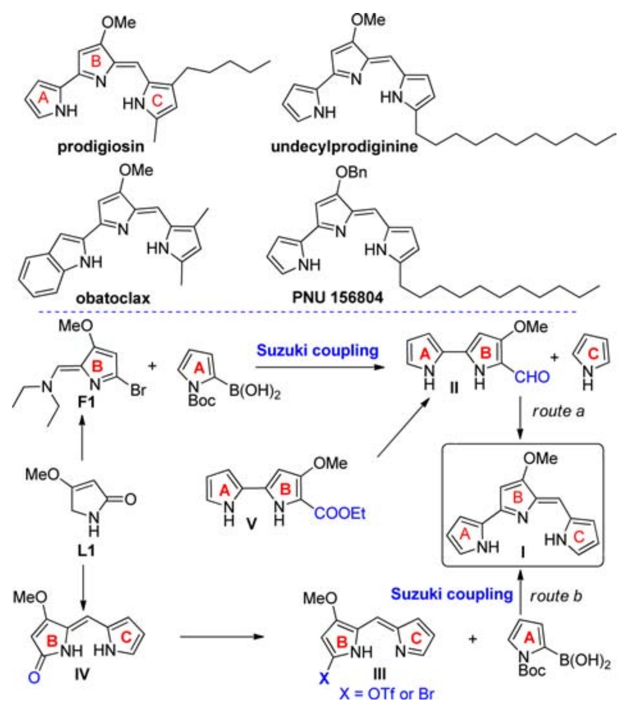


Figure 1. Naturally occurring prodiginines (prodigiosin and undecylprodiginine) and their corresponding synthetic analogues (Obatoclax and PNU-156804), and two most widely used synthetic strategies for prodiginines.

analogues thereof and a suitable third substituted pyrrole unit (*route a*);[12−16] or via the Suzuki coupling between Boc-

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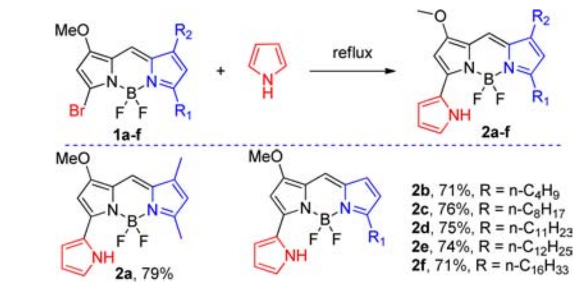
protected pyrrole 2-boronic acid and 9-triflate-[17a] (by D'Alessio) or bromo-[17b] (by Thompson) dipyrrin **III** (*route b*) generated from dipyrrinone **IV**.[11b,17] The 2–2′-bipyrrole unit **V** was synthesized using McFayen–Stevens reduction in low yields.[12] Later, the improved synthesis of bipyrrole aldehyde has been developed, including (1) an inverse-electron-demand Diels–Alder reaction of 1,2,4,5-tetrazine with 1,1-dimethoxyethene and subsequent reductive ring contraction by Boger and Patel,[13] (2) the cyclization of the vicinal tricarbonyl intermediate by Wasserman and Lombardo,[14a] (3) the oxidation of pyrrole-carboxylic acid ester with singlet oxygen by Wasserman,[14b] and (4) the Suzuki coupling between bromo pyrrole enamine **F1** and Boc-protected pyrrole 2-boronic acid by Lavallée.[11a,15,16]

These syntheses of prodiginines published so far, although elegant, involve several steps, often requiring the use of expensive catalyst, and provide prodiginines with an overall yield far from optimal. This prompted us to elaborate a new synthetic route for prodiginines. Recently, we have developed efficient direct nucleophilic aromatic substitution (S_NAr) reactions of halogenated, benzofused dipyrrins or boron dipyrrins (BODIPYs) with pyrroles.[18] This method provides a facile entry to oligopyrroles with direct 2,2′-bipyrrole linkages. In addition to being used as a useful chromophore, BODIPYs are stable, easy to synthesize and purify, and exhibit rich functionalization chemistry.[19] These properties render the BF_2 group to be used as a useful protecting group for various functionalized dipyrrins, which are often unstable and hard to purify.[20] Recently developed methods for efficiently removing the BF_2 group further facilitate this method.[21] Herein, we report a new synthetic route to prodiginines by using BODIPY functionalization chemistry. Various natural and synthetic prodiginines were synthesized in three steps from formyl pyrrole **P1** or enamine **F1**, which are the key B ring precursors of prodiginines.

The key B ring precursor, 5-bromo-3-methoxy-1*H*-pyrrole-2-carbaldehyde **P1**, was synthesized in 90% yield by basic hydrolysis of **F1** (Scheme S1, Supporting Information (SI)). $POCl_3$-promoted condensation between **P1** and a variety of pyrroles **P2-7** (Figure S1, SI) in dichloromethane at room temperature gave BODIPYs **1a–f** in above 40% yields after BF_2 complexation (Scheme 1a). BODIPYs **1** are much more stable than the corresponding dipyrrins. They were efficiently separated by silica gel column chromatography due to their hydrophobic nature. During the synthesis of **1a**, a minor product 1,3,5,7-tetramethyl BODIPY was isolated, and the amount of this BODIPY was increased when mixing formyl pyrrole **P1**, pyrrole **P2**, and $POCl_3$ at high temperature. We then decided to condense **F1** and pyrroles **P2–7** directly in the presence of $POCl_3$ (Scheme 1b). This reaction was efficient and gave BODIPYs **1a–f** in 53–61% yields. The yields were higher than those in the above method, and the symmetrical BODIPYs were not found in this reaction.

Next, simply refluxing BODIPY **1a** with neat pyrrole (Scheme 2), a new reddish spot (later identified as **2a**) was smoothly generated and isolated in 79% yield. Subsequently, this efficient S_NAr reaction was extended for the condensation BODIPYs **1b–f** with pyrrole, from which the corresponding pyrrolyl-BODIPYs **2b–f**, as BF_2 complexed prodiginines, were obtained in 71–76% yields.

Scheme 2. Synthesis of Pyrrolyl-BODIPYs 2 from BODIPYs 1



The single crystal X-ray structure of **2e** is shown in Figure 2. The BF_2-complexed tripyrromethene framework is extremely flat. The average and maximum deviations of the 16 atoms from the mean plane of tripyrromethene core are 0.0438 and 0.0795 Å, respectively. The dihedral angle between the idealized, uncoordinated pyrrole ring (A ring) and the BODIPY core (B and C rings) in **2e** is 5.35°. B–N bond lengths are around 1.56 and 1.53 Å, respectively. The crystal packing diagram of **2e** (Figure S1, SI) showed that two neighboring molecules form slipped π-stacked dimer structures in a head-to-head arrangement with an intermolecular distance of 3.63 Å between the π-conjugated planes of the neighboring molecules.

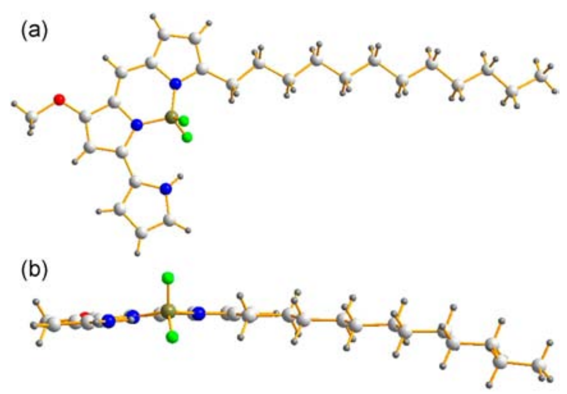
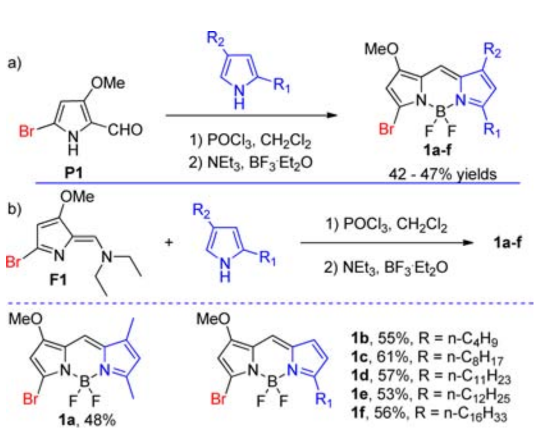


Figure 2. Top (a) and front (b) views of X-ray crystal structure of **2e**. C, light gray; N, blue; O, red; B, dark yellow; F, green.

Further removal of the BF_2 protecting groups of pyrrolyl-BODIPYs **2** to give the desired prodiginines were studied using a variety of recently developed conditions. Under the basic condition (potassium *tert*-butoxide in ethylene glycol),[21a,b] pyrrolyl-BODIPY **2a** was successfully deprotected to give prodiginine **3a** in 37% yield after column separation (Scheme

Scheme 1. Synthesis of BODIPYs 1 from Pyrrole P1 or F1



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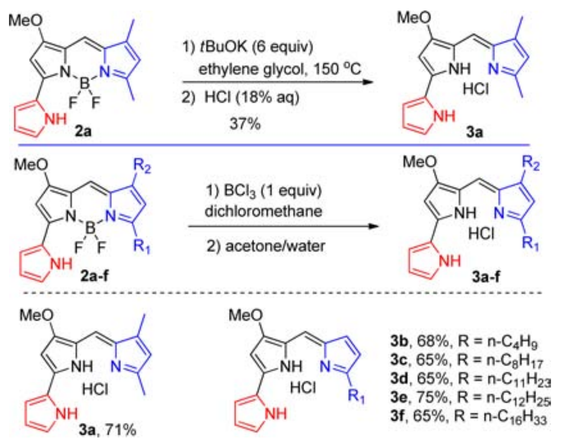
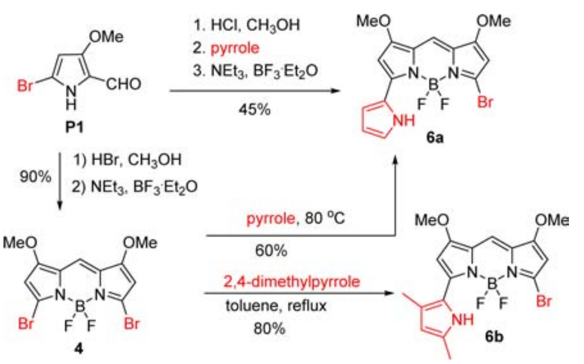
3). Similar yields for the synthesis of **3b–f** were obtained using this condition. By using the modified condition developed by Thompson,[21c] we found BCl_3 was able to remove the BF_2 protecting groups at room temperature in high yields. More importantly, this method did not require the use of column separation. The target prodiginines **3a–f** were obtained in 65–75% yields as HCl salts by recrystallization from dichloromethane. Thus, through this new synthetic method, various C-ring derivatized prodiginines **3** were efficiently synthesized in three steps from common precursor **F1**. For example, naturally occurring undecylprodiginine **3d** was synthesized in three steps with an overall yield of 28% from bromo pyrrole enamine **F1**.

Scheme 3. Synthesis of Prodiginines 3 by Removing BF_2 Groups of Pyrrolyl-BODIPYs 2



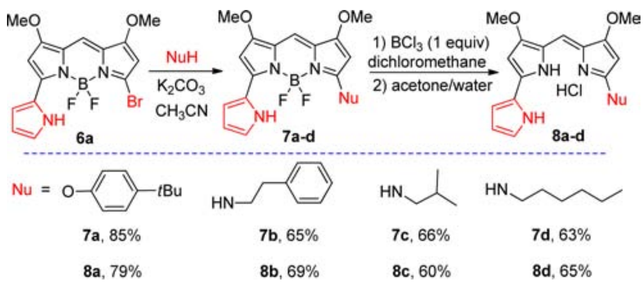
To demonstrate further the versatility of this new synthetic method, we designed key pyrrolyl-BODIPYs **6** through similar S_NAr reaction of bromo-BODIPYs or bromodipyrrins. By taking advantage of BODIPY chemistry, we studied the application of pyrrolyl-BODIPY **6a** to introduce functional groups onto the C-ring of the pyrrolyldipyrrin chromophore through well-known nucleophilic substitution reactions.[22] Initially, we carried out the self-condensation of formyl pyrrole **P1** in the presence of HBr in methanol at room temperature (Scheme 4), from which bromo-BODIPY **4** was isolated after BF_2 complexation. The single crystal X-ray structure of **4** is shown in Figure S2 (SI). The S_NAr reaction between bromo-BODIPY **4** and neat pyrrole gave pyrrolyl-BODIPY **6a** in 60% yield (Scheme 4). Similarly, the condensation between bromo-BODIPY **4** and 2,4-dimethylpyrrole in refluxing toluene smoothly generated the corresponding pyrrolyl-BODIPY **6b** in 80% yield. Interestingly, pyrrolyl-BODIPY **6a** was also synthesized in one pot reaction in 45% yield from formyl pyrrole **P1** through S_NAr reaction of bromodipyrrins followed by BF_2 complexation (Scheme 4).

Scheme 4. Synthesis of Pyrrolyl-BODIPYs 6 from Pyrrole P1



Pyrrolyl-BODIPY **6a** was then reacted with various nucleophiles in acetonitrile under mild conditions (Scheme 5). This efficient nucleophilic substitution reaction gave pyrrolyl-BODIPYs **7a–d** in 63–85% yields. Further removal of the BF_2 protecting groups of pyrrolyl-BODIPYs **7** using the above optimized condition gave the desired prodiginines **8a–d** in 60–79% yields as HCl salts (Scheme 5). Thus, through this method, various C-ring derivatized prodiginines **8** were efficiently synthesized in three steps (condensation, nucleophilic substitution reaction, and BF_2 deprotection) from formyl pyrrole **P1** by using unique BODIPY chemistry. Notably, these types of synthetic prodiginines were not possible to obtain through current synthetic methods.

Scheme 5. Synthesis of Pyrrolyl-BODIPYs 7 from 6 though Nucleophilic Substitution and Prodiginines 8 by Removing BF_2 Groups of Pyrrolyl-BODIPYs 7



BODIPYs **1** show typical narrow absorption bands with maxima around 500 nm and strong fluorescence maxima around 515 nm with excellent quantum yields close to unity in dichloromethane (Table S3 and Figure S3, SI). After installation of a pyrrole ring in the 3-position, pyrrolyl-BODIPYs **2** and **6a** give red-shifted absorption and emission spectra with maxima around 550 and 570 nm in dichloromethane, respectively (Table S3 and Figure S4, SI). Pyrrolyl-BODIPYs **2**, **6a**, and **7a** also have good fluorescence quantum yields (from 0.66 to 0.99) in dichloromethane. In contrast, amine-substituted pyrrolyl-BODIPYs **7b–d** show broad absorption bands with maxima around 500 nm and also strong fluorescence maxima around 560–570 nm with good quantum yields (from 0.57 to 0.67) in dichloromethane (Table S3, Figures S6 and S7, SI). After removal of the BF_2 group, prodiginines **3** and **8** (as HCl salts) both give around 25 nm blue-shifted absorptions in dichloromethane compared with those of pyrrolyl-BODIPYs **2** and **7**. In the neutral form of prodiginines **3** by adding NEt_3, these absorption bands further blue-shifted to around 460 nm (Figures S5 and S7, SI).

In conclusion, we have developed new, concise synthetic routes for the facile preparation of both synthetic and natural prodiginines in good yields using recently developed BODIPY functionalization chemistry (condensation, nucleophilic substitution, and BF_2 deprotection). This new, metal-free synthetic method is suited for the generation of a library of C-ring functionalized prodiginines for their advanced biological activities and SAR studies, and also provides various C-ring derivatized prodiginines that are not possible to obtain though current synthetic methods. The biological activities of these compounds and the comparison with natural product

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(undecylprodiginine **3d**) will be reported elsewhere in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02924.

Experimental details, tables, and additional spectra (PDF)
Compound **2e** (CIF)
Compound **4** (CIF)

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Notes

The authors declare no competing financial interest.

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