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Graphical Abstract

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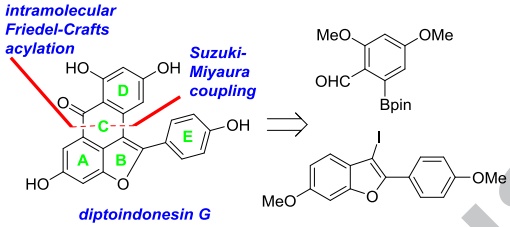

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Convergent Synthesis of Diptoindonesin G

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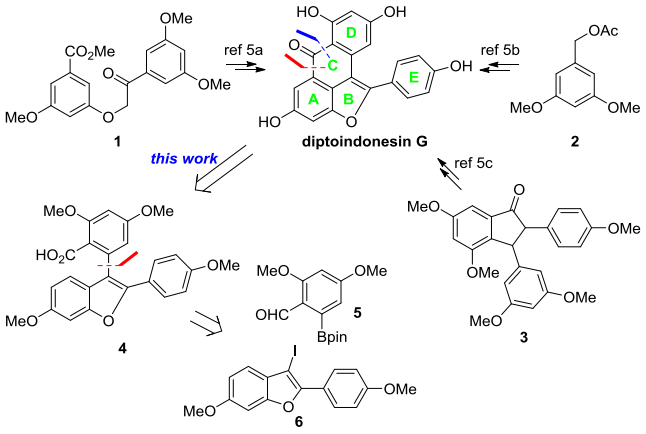
ABSTRACT

A convergent and scalable synthetic route to a tetracyclic oligostilbenoid natural product, diptoindonesin G, is described where Suzuki-Miyaura cross-coupling and intramolecular Friedel-Crafts acylation were employed to construct the central C ring of diptoindonesin G. Two fragments for cross-coupling reaction were readily synthesized with similar efficiency.

Biologically active natural products have been a source of a number of inspirations and creativities on total synthesis over the last decades.[1] Diptoindonesin G, a tetracyclic oligostilbenoid natural product first isolated from the tree bark of *Hopea mengarawan* in 2009,[2] has been such a case in our laboratory. Although it is relatively small, its intriguing biological activity[3] as well as our interest on benzofurans[4] guided us to pursue several synthetic approaches to diptoindonesin G from three different starting materials, **1**-**3** (Scheme 1).[5,6]

Notably, all these approaches took advantage of intramolecular Friedel-Crafts type acylation[7] as a means to form the C ring as noted in blue line due to high reactivity of the electron-rich D ring toward the neighboring acid moiety attached to the A ring. Disconnection of the central C ring in a distinctive way (indicated in red line) provided us an opportunity to devise a new convergent route to this natural product as retrosynthetically analyzed in Scheme 1. Thus, we envisioned that construction of the target skeleton would be achieved via intramolecular Friedel-Crafts acylation of **4**, which in turn could be assembled by Suzuki-Miyaura cross-coupling reaction of **5** and **6**.

With this idea in mind, we began the synthesis by making two fragments, **5** and **6**, respectively. Boronate **5** was prepared from commercially available starting material in two steps (Scheme 2).[8] Vilsmeier-Haack formylation[9] of 1-bromo-3,5-dimethoxybenzene afforded aldehyde **7** which was transformed to boronate **5** under Miyaura borylation conditions.[10] 3-Iodobenzofuran **6** was easily synthesized from 1,3-dimethoxybenzene as shown in Scheme 3. Mono-iodination of



Scheme 1. Our Synthetic Plans to Diptoindonesin G

1,3-dimethoxybenzene in the presence of iodine and (diacetoxyiodo)benzene[11] took place to give **8** which was coupled with 4-ethynylanisole under Sonogashira cross-coupling conditions to furnish **9** in 95% yield.Subsequent iodine-mediated cyclization[12,13] of **9** led to 3-iodobenzofuran **6**.Suzuki-Miyaura coupling[14] of **5** and **6** proceeded smoothly to afford **10** in good yield (Scheme 4). Aldehyde **10** was oxidized to acid **4** under Lindgren-Kraus-Pinnick conditions.[15] Intramolecular Friedel-Crafts type cyclization of **4** occurred upon exposure to trifluoroacetic anhydride to give tetramethyl ether of diptoindonesin G **(11)**, a known intermediate, whose spectral data were in good agreement with those from the literature.[5a]

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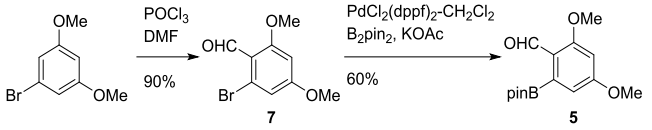
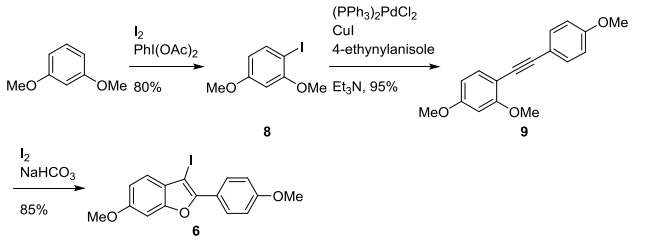
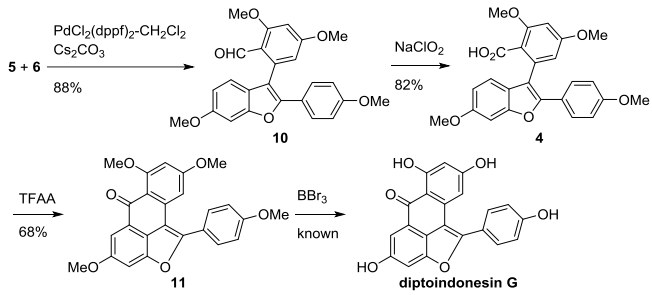
Conversion of **11** to diptoindonesin G by excess BBr_3 treatment was known in the literature.[5a]



Scheme 2. Synthesis of **5**



Scheme 3. Synthesis of **6**



Scheme 4. Assembly of **5** and **6**

In conclusion, we have established a new convergent synthetic approach to biologically active diptoindonesin G by relying on Suzuki-Miyaura coupling and intramolecular Friedel-Crafts cyclization to construct the central C ring. Ease of synthetic manipulations, flexibility, and high overall yields of this route should be useful for large-scale synthesis of diptoindonesin G and its derivatives for further biological evaluation.

Acknowledgments

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Supplementary Material

Experimental procedures, compound characterization data, and ^1H and ^{13}C NMR spectra of synthesized compounds can be found, in the online version at…

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Highlights

- A convergent and scalable synthetic approach to diptoindonesin G is decribed.
- Suzuki-Miyaura coupling and intramolecular Friedel-Crafts acylation as key steps
- This route should be useful for synthesis of diptoindonesin G and its derivatives.