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A Concise and Scalable Strategy for the Total Synthesis of Dictyodendrin B Based on Sequential C–H Functionalization**

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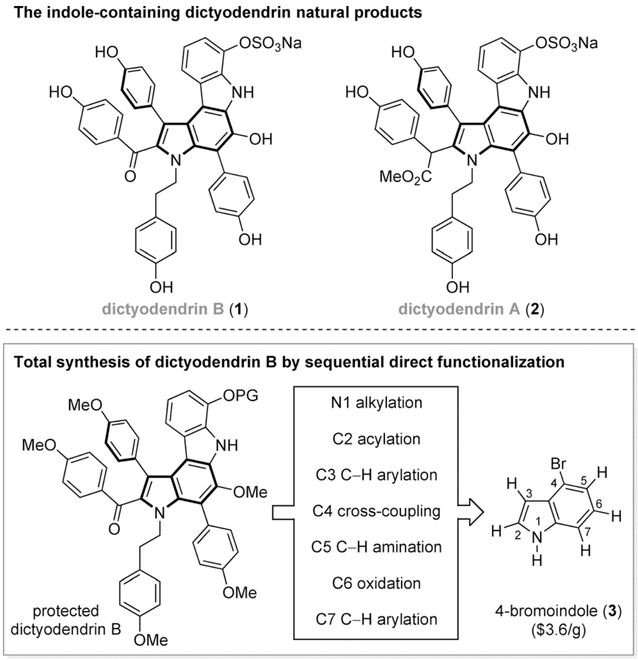
Abstract: *A sequential C–H functionalization strategy for the synthesis of the marine alkaloid dictyodendrin B is reported. Our synthesis begins from commercially available 4-bromoindole and involves six direct functionalizations around the heteroarene core as part of a gram-scale strategy towards the natural product.*

The dictyodendrins are a collection of pyrrolo[2,3-*c*]-carbazole-derived natural products, first isolated in 2003,[1] that display interesting inhibitory activities towards telomerases[2] and β-site APP cleaving enzyme 1 (BACE1; APP = amyloid precursor protein) and have received significant interest within the scientific community owing their potential as chemotherapy agents and neurodegenerative probes.[3] Furthermore, their complex poly(hetero)aromatic architecture has inspired a number of elegant total syntheses from the groups of Fürstner,[4a–c] Iwoa and Ishibashi,[4d–e] Tokuyama,[4f–g] and Jia.[4h–i] We envisaged a possible strategy to the dictyodendrins that involves sequential direct functionalizations of a simple, readily available heteroaromatic building block that would constitute the core of the natural product framework. Herein, we report a concise total synthesis of dictyodendrin B starting from a commercially available mono-substituted indole. Our strategy exploits selective reactions at each of the positions on the unfunctionalized heteroaromatic scaffold to consecutively add the architecture required for the natural product and enables the gram-scale synthesis of this biologically interesting natural product.

The development of new methods that enable the direct transformation of C–H bonds into useful functional groups remains an important goal for the continued advance of complex-molecule synthesis.[5,6] Our group has a long-standing interest in the metal-catalyzed C–H functionalization of aromatic heterocycles[7] and the deployment of these methods in the total synthesis of complex molecules.[8] A central theme in these strategies has been the exploitation of latent reactivity within simple, readily available, and relatively unfunctionalized heteroaromatic starting materials to streamline the assembly of the framework of the target natural products.



In considering a strategy for the synthesis of dictyodendrin B, we were attracted by a heptasubstituted indole embedded within the core of these complex aromatic molecules. We speculated that a simple indole building block could form the starting point for a strategy that would involve sequential direct functionalizations to append each of the seven substituents around the heteroaromatic framework. This strategy is distinct from all other approaches to this molecule as these elegant syntheses involved the construction of the central indole motif from elaborated fragments.[4] Such a sequential functionalization of a central heteroaromatic scaffold could have a number of advantages: A wide range of readily available and functionally simple hydrocarbon building blocks would be effective starting materials, syntheses would be streamlined, and the preparation of analogues for biological assessment would be greatly facilitated. We were, however, mindful of at least two major challenges that could arise from such a design plan: First, direct functionalization of

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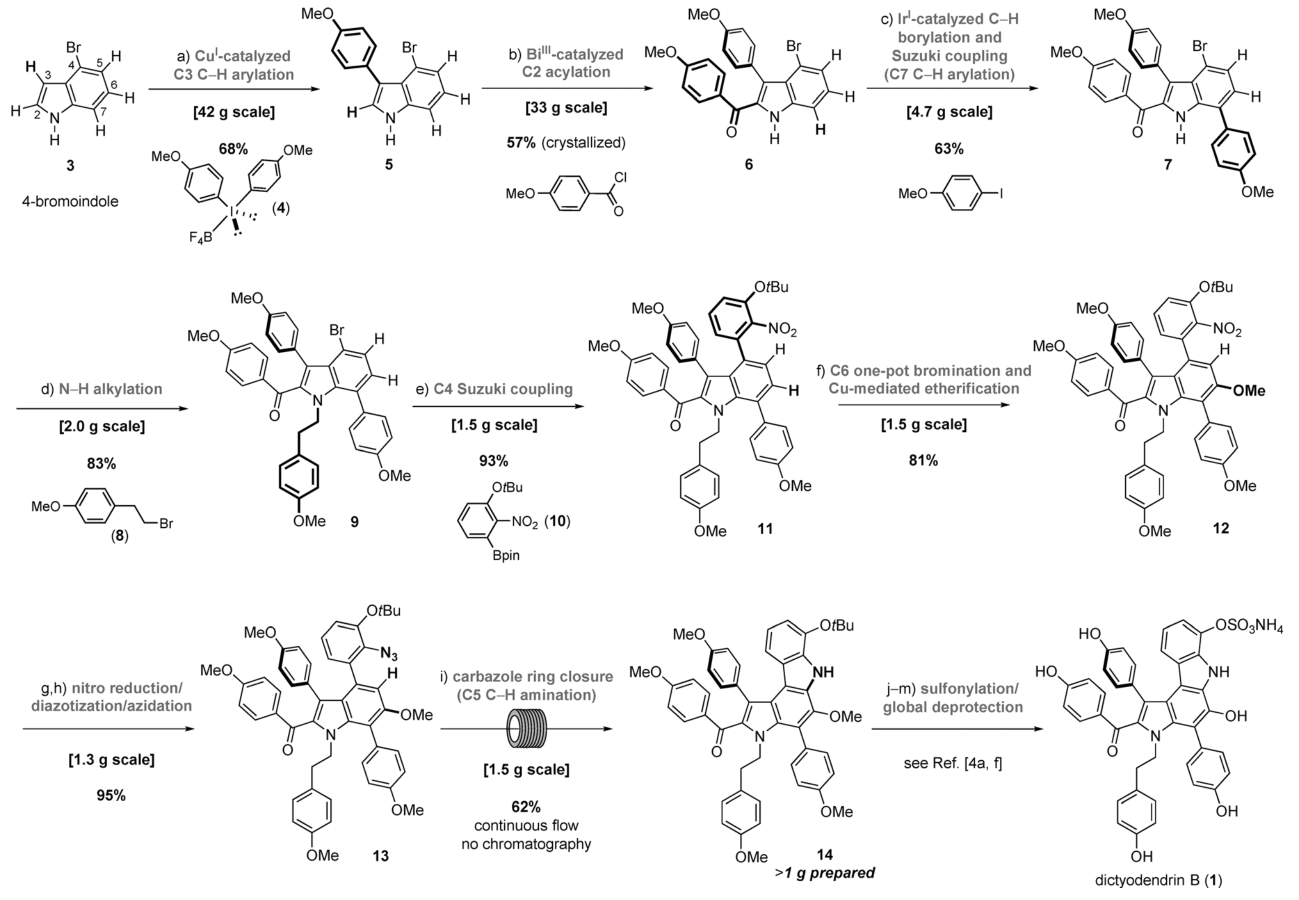
the heteroaromatic core is likely to become increasingly difficult with every step owing to the growing complexity of the molecule,[9] and second, how does one choose the correct route from the many hypothetical sequences of iterative direct functionalizations on the indole core? By taking advantage of the broad range of distinct C–H functionalization processes that are available to us (metal-catalyzed C–H activation, electrophilic aromatic substitution, radical addition, and directed metalation), we reasoned that we would be well equipped to meet the ever-changing demands of the evolving molecule as the synthesis progressed. We elected to begin the synthesis of dictyodendrin B from commercially available 4-bromoindole and follow a strategy that would ultimately elaborate each position on the framework of this heteroaromatic starting material.

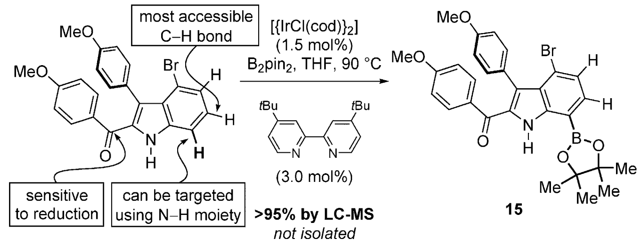
The inherent nucleophilicity of indole makes reactions through the C3 position an ideal starting point from which to execute our conceptually distinct approach to the synthesis of dictyodendrin B. Accordingly, our synthesis began with a copper-catalyzed C–H arylation using diaryliodonium salts, which was established in our laboratory (Scheme 1).[10] Using conditions modified from our original work, we found that inexpensive Cu^{I}Cl (5 mol %) functioned effectively as the catalyst to combine 4-bromoindole with bis(4-methoxyphenyl)iodonium tetrafluoroborate **4** (1.2 equiv) in 68 % yield on 42 gram scale. Importantly, the 2,6-di-*tert*-butylpyridine base can be easily recovered from these large-scale reactions for reuse.

We were able to further exploit the intrinsic reactivity of indole for the C2 acylation. After significant experimentation, we found that a bismuth(III) triflate catalyzed Friedel–Crafts-type acylation of **5** with 4-methoxybenzoyl chloride (1.1 equiv) gave the 2,3-disubstituted indole product as a single isomer in 57 % yield.[11] The reaction could be performed at high concentration and at room temperature, allowing for large amounts of material to be processed with ease (40 gram batches). After aqueous workup, the product could be directly crystallized from the resulting crude mixture without the need for further chromatographic purification.



Scheme 1. Synthesis of dictyodendrin B by sequential C–H functionalization. Reagents and conditions: a) **4** (1.2 equiv), 2,6-di-*tert*-butylpyridine (1.2 equiv), Cu^{I}Cl (5 mol %), CH$_2$Cl$_2$ (0.2 M), 35 °C, 48 h, 68 %; b) 4-methoxybenzoyl chloride (1.1 equiv), Bi(OTf)$_3$ (5 mol %), MeNO$_2$ (0.5 M), RT, 24 h, 57 %; c) (Bpin)$_2$ (1.5 equiv), [{IrCl(cod)}$_2$] (1.5 mol %), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (3.0 mol %), THF (0.2 M), 90 °C, 1.5 h; 4-iodoanisole (3 equiv), [PdCl$_2$(dppf)] (5.0 mol %), 3 M KOH (aq, 5 equiv), 80 °C, 30 min, 63 %; d) 4-methoxyphenethyl bromide (5 equiv), K$_2$CO$_3$ (7 equiv), DMF (0.2 M), 100 °C, 16 h, 83 %; e) **10** (1.5 equiv, dropwise), [PdCl$_2$(dppf)] (5.0 mol %), 2 M K$_2$CO$_3$ (aq, 5 equiv), dioxane (0.2 M), 90 °C, 20 h, 93 %; f) NBS (1.15 equiv), DMF (0.1 M), RT, 24 h; NaOMe (30 equiv), Cu^{I}I (3 equiv), 80 °C, 18.5 h, 81 %; g) Pd(OH)$_2$ (10 mol %), 10 bar H$_2$, MeCN (0.2 M), 24 h; h) AcOH (30 equiv), *t*BuONO (1.5 equiv), TMSN$_3$ (1.2 equiv), RT, 20 min, 95 %; i) dioxane (0.1 M), 180 °C, 30 min residence time, 0.333 mL min^{-1}, Vapourtec R2+/R4 system, 62 %; j–m) see Ref. [4a, f]. cod = 1,5-cyclooctadiene, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, NBS = *N*-bromosuccinimide, pin = pinacolato, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

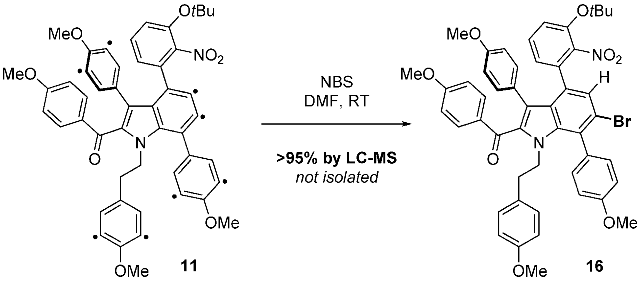
We next turned our attention to the installation of the C7 substituent with the intention of utilizing the indole N–H motif to direct an iridium-catalyzed C–H borylation, as previously described by Maleczka, Smith and co-workers,[12] that could be directly combined with a Suzuki–Miyaura coupling to complete the C–H arylation in a one-pot process. The C–H borylation at the C7 position of indole **6** was successfully implemented using [$\{IrCl(cod)\}_2$] (1.5 mol%) as the catalyst with B_2pin_2 (1.5 equiv) in THF at 90 °C in a sealed tube and afforded boronic ester **15** on a gram scale (see also Scheme 2). Adding [$PdCl_2(dppf)$] (5 mol%), 4-iodoanisole (3 equiv), and an aqueous solution of KOH (3 M) directly to the reaction mixture and stirring at 80 °C for 30 minutes afforded **7** in 63% yield. We were able to scale up this reaction to 4.7 gram batches, enabling effective material throughput. With the indole N–H moiety having served its purpose for directing the C–H arylation, we next performed the N-alkylation, which also served to prevent this nucleophilic motif from interfering with any subsequent metal-catalyzed processes. Treatment of compound **7** with commercial 4-methoxyphenethyl bromide (**8**) and K_2CO_3 afforded the desired product **9** in 83% yield; this process could be conducted in batches of two grams.



Scheme 2. Iridium-catalyzed C–H borylation at the C7 position.

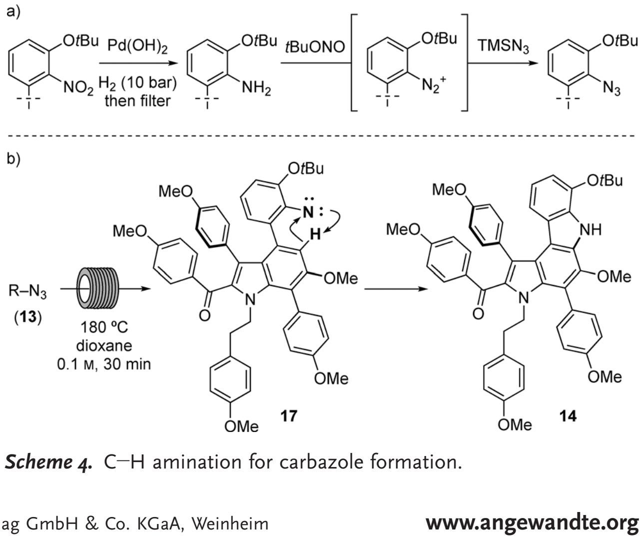
Suzuki–Miyaura coupling of the C4 bromide was next investigated to incorporate the final aryl component into the structure of dictyodendrin B (Scheme 1). The nitrophenol-derived boronic ester **10** could be assembled in two steps from a commercial building block, and subsequent cross-coupling was performed using relatively standard conditions. These involved the dropwise addition of the aryl boronic ester[13] to a mixture of [$PdCl_2(dppf)$] (5 mol%) and an aqueous solution of K_2CO_3 (2 M) in dioxane at 90 °C to furnish the C4-arylated product **11** in 93% yield on a 1.5 gram scale. The dropwise addition was important to avoid the competing deleterious protodeboronation process that we observed when the aryl boronic ester was present in the reaction mixture from the outset.

The nitro group of the arena at the C4 position was critical to successful oxygenation at the C6 position (Scheme 1). Unfortunately, all attempts to secure a direct C–H oxygenation at this position failed. However, with the nitro group deactivating the C4 aryl moiety, we found that electrophilic bromination at the C6 position of the indole occurred with exclusive selectivity at room temperature using a slight excess of *N*-bromosuccinimide (see Scheme 3). All other nitrogen-based substituents (azide, amide, and amine moieties) resulted in bromination on the C4 aryl substituent. After 24 hours, direct addition of a sodium methoxide solution in methanol (4 M) and copper(I) iodide to the bromination reaction mixture led to the formation of the methyl ether,[14] completing a two-step one-pot etherification process from **11** and affording **12** in 81% yield on a 1.5 gram scale.



Scheme 3. Selective electrophilic bromination at the C6 position. Viable sites for electrophilic bromination are indicated (●).

The choice of the nitro group was also important to provide maximum flexibility in the carbazole ring-closure process that we hoped to achieved by a C–H amination process. Despite considerable efforts, we were unable to effect a phosphite-mediated Cadogen cyclization[15a] or Merck's reductive palladium-catalyzed process directly from the nitro group.[15b] Attempts to use Buchwald's catalytic C–H carbazole synthesis (from a corresponding acetamide)[15c] as well as our own palladium-catalyzed method (from a corresponding benzylamine) also failed.[15d] Finally, we found that the transformation of the nitro group into the azide by a two-step reduction/diazotization/azidation process provided **13** in 95% yield on 1.5 gram scale (Scheme 1 and Scheme 4a).[16] Although we investigated metal-catalyzed C–H insertion processes using the azide, none of these reactions resulted in the desired heterocycle.[17] Carbazole **14** could be isolated using Tokuyama's batch conditions for the thermal decomposition of the azide;[4f–g] however, this approach is not without issues, and we sought to address some of the problems associated with this procedure that may preclude a larger scale reaction. For instance, the sudden and exothermic production of nitrogen gas on scale can be very dangerous, and solvents with high boiling points are often required to



Scheme 4. C–H amination for carbazole formation.

reach the azide decomposition temperature, which can make isolation difficult.

We speculated that a flow process could provide the ideal platform with which to perform this reaction without any of these disadvantages.[18] Pleasingly, we were able to execute the C–H amination, presumably via the formation of nitrene intermediate **17** (Scheme 4b), in super-heated dioxane at 180 °C in a continuous-flow process, processing over one gram of azide **13** in 30 minutes. To this point, the synthesis has produced one gram of protected dictyodendrin B. From here, the known four-step deprotection and sulfonylation sequence was applied on a small scale to obtain the natural product. Selective removal of the *tert*-butyl ether and subsequent sulfonylation afforded crystalline material suitable for X-ray diffraction, confirming the regioselectivity of all direct functionalization reactions.[19] Global demethylation and zinc-mediated cleavage of the sulfonyl protecting group afforded dictyodendrin B, which matched authentic material in every respect.[1,4]

In summary, we have successfully executed a synthesis of dictyodendrin B by functionalizing all positions of a commercially available monosubstituted indole building block. Novel aspects of our synthesis include the deployment of a number of catalytic C–H functionalization processes, highly selective electrophilic aromatic substitutions performed in complex environments, and a late-stage application of a carbazole ring closure using flow chemistry. Moreover, the synthesis was performed on multigram scale to produce over one gram of the protected natural product. Our work clearly demonstrates the utility of sequential C–H functionalizations in the rapid and modular construction of complex molecules from minimally functionalized and widely available aromatic precursors. This overall approach is streamlined and will allow for the diversification and testing of complex analogues towards the identification of more potent variants of this interesting natural product. We see this as a highly complementary and competitive strategy to existing synthetic approaches, and current studies are focused on the synthesis of other natural products by disconnection strategies based on the logic of such C–H functionalization processes.

Keywords: C–H functionalization · flow chemistry · metal catalysis · natural products · total synthesis

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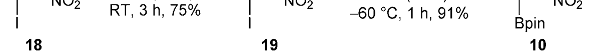

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[20] During the course of our studies, we became aware of a related study by the Itami and Davies laboratories. We are grateful to them for their collegiality and support; see: A. D. Yamaguchi, K. M. Chepiga, J. Yamaguchi, K. Itami, H. M. L. Davies, *J. Am. Chem. Soc.* **2015**, *137*, 644.

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