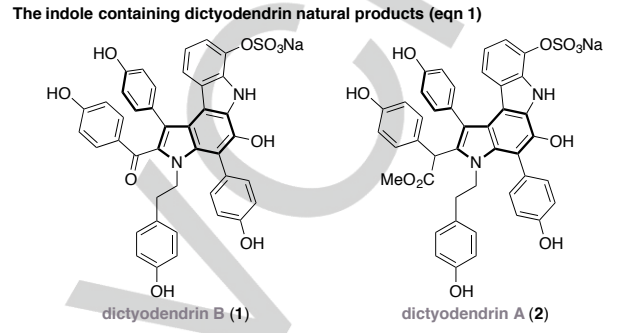
A concise and scalable strategy for the total synthesis of dictyodendrin B based on sequential C–H functionalization. **

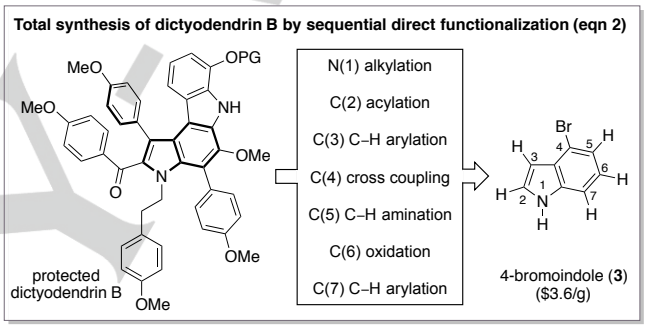
Andrew K. Pitts[†], Fionn O'Hara[†], Robert H. Snell and Matthew J. Gaunt*

ABSTRACT: We report a sequential C–H functionalization strategy for the synthesis of the marine alkaloid *dictyodendrin B*. Our synthesis begins from the 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 telomerase[2] and β-site amyloid-cleaving enzyme 1 (BACE) inhibition, and have created significant interest within the scientific community due 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 strategy to the dictyodendrins might be possible using sequential direct functionalizations upon a simple, readily available heteroaromatic building block that would constitute the core of the natural product framework (eqn 2). Herein, we report a concise total synthesis of dictyodendrin B starting from a commercially available mono-substituted indole. Our strategy exploits selective reaction at each of the positions on the unfunctionalized heteroaromatic scaffold to consecutively add the architecture required for the natural product and makes possible a gram-scale strategy to this biologically interesting natural product.

The development of new methods that enable the direct transformation of C–H bonds into useful functionality 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 electron 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 in order 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 hepta-substituted 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 functionalization to append each of the seven substituents around the heteroaromatic framework (eqn 2). This strategy is distinct from all other approaches to this molecule as these elegant syntheses involve 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 analogs for biological assessment would be greatly facilitated. We were, however, mindful of at least two major challenges arise from such a design plan: firstly, direct functionalization of the core heteroaromatic nucleus is likely to become increasingly difficult with every step due to the growing complexity of the molecule;[9] and secondly, how does one choose the correct route from the many hypothetical sequences of iterative direct functionalizations on the indole nucleus? By taking advantage of the broad range of distinct 'C–H functionalizations' (comprising of metal-catalyzed C–H activation, electrophilic aromatic substitution, radical addition and directed metalation) we reasoned 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

[*] A. K. Pitts,[+] Dr. F. O'Hara, [+] Dr. R. H. Snell & Prof. M. J. Gaunt
Department of Chemistry, University of Cambridge,
Lensfield Road, Cambridge, United Kingdom, CB2 1EW.
E-mail: mjg32@cam.ac.uk
Homepage: http://www-gaunt.ch.cam.ac.uk/
[†] These authors contributed equally to this work.
[**] We are grateful to AstraZeneca, Pfizer, and EPSRC (A.K.P., F.O. and R.H.S.) and the ERC and EPSRC for fellowships (M.J.G.). Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University. X-ray crystallography data was collected and solved by Mr Peter D. Matthews. We are grateful to Mr Phillip Murray and Professor Steven V. Ley for assistance and advice on flow chemistry. We also acknowledge Dr Johan Kajanus (AstraZeneca) and Dr Abid Massood (Pfizer) for useful discussion.

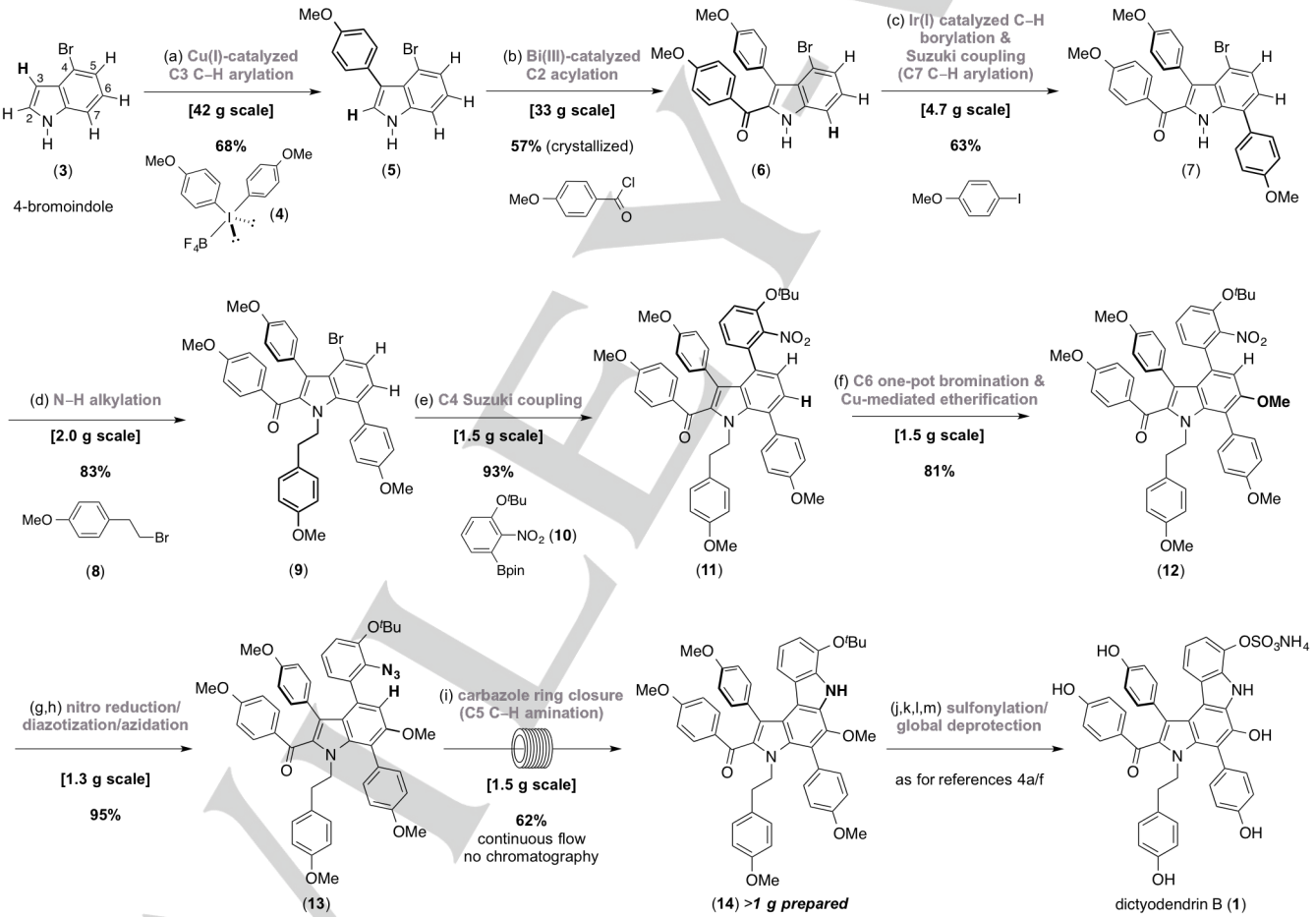
Supporting information for this article is given via a link at the end of the document.

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 reaction 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, established in our laboratory (Scheme 1).[10] Using conditions modified from our original work, we found that 5 mol% of inexpensive Cu(I)Cl functioned effectively as a catalyst to combine 4-bromoindole with 1.2 equivalents of bis(4-methoxylphenyl)iodonium tetrafluoroborate **4** in 68% yield on a 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 1.1 equivalents of 4-methoxylbenzoyl chloride 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 resultant crude mixture without the need for further chromatographic purification.

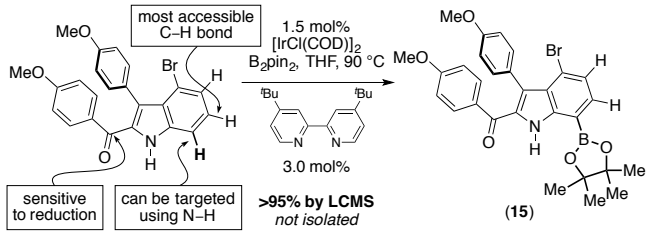
We next turned our attention to the installation of the C7 substituent with the intention of utilizing the indole N–H motif to direct an Ir-catalyzed C–H borylation, previously described by Maleczka and Smith,[12] that could be linked directly to a Suzuki-Miyuara coupling to complete the C–H arylation in a one-pot process. The C–H borylation of the C7 position of indole **6** was successfully implemented using 1.5 mol% of $[IrCl(COD)]_2$ as catalyst with 1.5 equivalents of B_2pin_2 in THF at 90 °C in a sealed tube, to afford boronic ester **15** on a gram scale (see also, Scheme 2). Addition of 5 mol% $PdCl_2$(dppf), 3 equivalents of 4-iodoanisole, an aqueous solution of 3 M KOH directly to the reaction mixture and stirring at 80 °C for 30 minutes afforded **7** in 63% yield. We were able to scale this reaction to 4.7 gram batches, enabling effective throughput of material. With the



[a]Reagents and conditions: (a) 1.2 equiv bis(4-methoxyphenyl) iodonium tetrafluoroborate **4**, 1.2 equiv 2,6-di-*tert*-butylpyridine, Cu(I)Cl (5 mol%), CH_2Cl_2 (0.2 M), 35 °C, 48 h, 68%. (b) 1.1 equiv 4-methoxybenzoyl chloride, $Bi(OTf)_3$ (5 mol%), $MeNO_2$ (0.5 M), rt, 24 h, 57%. (c) 1.5 equiv $(Bpin)_2$, $[IrCl(COD)]_2$ (1.5 mol%, 3.0 mol% Ir), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (3.0 mol%), THF (0.2 M), 90 °C, 1.5 h; 3 equiv 4-iodoanisole, $PdCl_2$(dppf) (5.0 mol%), 5 equiv 3 M $KOH_{(aq)}$, 80 °C, 30 min, 63%. (d) 5 equiv 4-methoxylphenethyl bromide, 7 equiv K_2CO_3, DMF (0.2 M), 100 °C, 16 h, 83%. (e) 1.5 equiv 2-(3-(*tert*-butoxy)-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **10** (dropwise), $PdCl_2$(dppf) (5.0 mol%), 5.0 equiv 2 M $K_2CO_{3(aq)}$, dioxane (0.2 M), 90°C, 20 h, 91%. (f) 1.15 equiv NBS, DMF (0.1 M), rt, 24 h; 30 equiv NaOMe, 3 equiv Cu(I)I, 80 °C, 18.5 h, 81%. (g) $Pd(OH)_2$ (10 mol%), 10 bar H_2, MeCN (0.2 M), 24 h; (h) 30 equiv AcOH, 1.5 equiv ^{t}BuONO, 1.2 equiv $TMSN_3$, rt, 20 min, 95%. (i) dioxane (0.1 M), 180 °C, 30 min residence time, 0.333 mL/min, Vapourtec R2+/R4 system, 62%. (j-m) see references 4a/f.

Scheme 1. Synthesis of dictyodendrin B by sequential C–H functionalization[a]

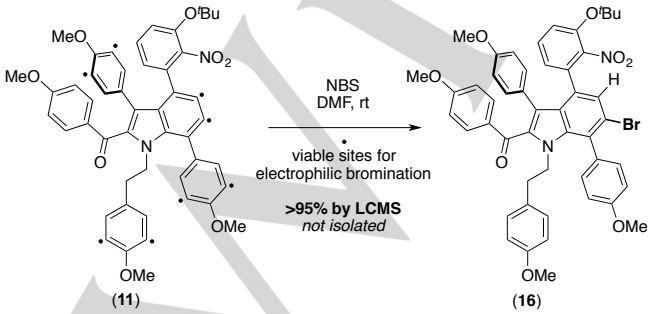
indole N–H having served its purpose for directing the C–H arylation, we next performed the *N*-alkylation, which also served to prevent this nucleophilic motif from interfering with any subsequent metal-catalyzed processes. Treatment with commercial 4-methoxylphenethyl bromide **8** and K_2CO_3 afforded the desired product **9** in 83% yield and could be conducted in batches of 2 grams.



Scheme 2. Ir-catalyzed C–H borylation at C7.

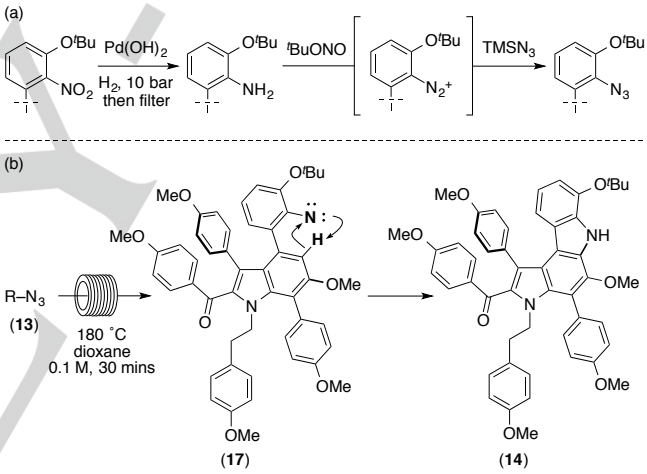
Suzuki-Miyuara coupling of the C4 bromide was next investigated to incorporate in the final aryl component to the structure of dictyodendrin B (Scheme 1). The nitrophenol derived boronic ester **10** could be assembled in 2 steps from a commercial building block and subsequent cross coupling was performed using relatively standard conditions. These involved dropwise addition of the arylboronic ester[13] to a mixture of 5 mol% $PdCl_2$(dppf) and a 2 M aqueous solution of K_2CO_3 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 in order to avoid competing the deleterious protodeboronation that we observed when the arylboronic ester was present in the reaction mixture from the outset.

The nitro group on the C4 arene 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 functions) resulted in bromination on the C4 aryl substituent. After 24 h, direct addition of a 4 M sodium methoxide in methanol and copper(I) iodide to the bromination reaction mixture formed 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 C6

The choice of the nitro group was also important to provide maximum flexibility in the carbazole ring closure process that we hoped to achieved via a C–H amination. Despite considerable efforts, we were unable to affect 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 transformation of the nitro group to the azide via 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 methods 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 high boiling solvents are often required to reach the azide decomposition temperature, which can make isolation difficult.



Scheme 4. C–H amination for carbazole

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 the nitrene intermediate **17** (Scheme 4b), in super-heated dioxane at 180 °C in continuous flow, processing over a gram of azide **13** in 30 min. The synthesis to this point produced one gram of protected dictyodendrin B. From here the known four-step deprotection and sulfonylation sequence was applied on a small scale to reach 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 functionalizationing all positions of a commercially available mono-substituted 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 multi-gram 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 via disconnection strategies based on the logic of such C–H functionalizations.

Keywords: total synthesis • C–H functionalization • metal catalysis • flow chemistry

(1) K. Warabi, S. Matsunaga, R. W. M. van Soest, N. Fusetani. *J. Org. Chem.* **2003**, 68, 2765.

(2) E. K. Parkinson *Ann. Med.* **2003**, 35, 466.

(3) H. Zhang, M. M. Conte, Z. Khalil, X.-C. Huang, R. J. Capon *RSC Adv.* **2012**, 2, 4209

(4) Total synthesis of dictyodendrins B, C, E and F: (a) A. Fürstner, M. M. Domostoj, B. Scheiper *J. Am. Chem. Soc.* **2005**, 127, 11620; (b) A. Fürstner, M. M. Domostoj, B. Scheiper. *J. Am. Chem. Soc.* **2006**, 128, 8087; (c) P. Buchgraber, M. M. Domostoj, B. Scheiper, B., C. Wirtz, R. Mynott, J. Rust, A. Fürstner *Tetrahedron* **2009**, 65, 6519. Total synthesis of dictyodendrin B: (d) S. Hirao, Y. Sugiyama, M. Iwao, F. Ishibashi *Biosci. Biotechnol. Biochem.* **2009**, 73, 1764; (e) S. Hirao, Y. Sugiyama, M. Iwao, F. Ishibashi *Tetrahedron Lett.*, **2010**, 51, 533. Total synthesis of dictyodendrins A–E: (f) K. Okano, H. Fujiwara, T. Noji, T, Fukuyama, H. Tokuyama *Angew. Chem., Int. Ed.* **2010**, 49, 5925; (g) K. Okano, H. Fujiwara, T. Noji, T, Fukuyama, H. Tokuyama *Chem. - Asian J.* **2011**, 6, 560. Total synthesis of dictyodendrins B and E: (h) J. Liang, W. Hu, P. Tao, Y. Jia *J. Org. Chem*. **2013**, 78, 5810; (i) P. Tao, J. Liang, Y. Jia *Eur. J. Org. Chem.* **2014**, 5735.

(5) For selected reviews on C–H functionalization in natural product synthesis see: (a) L. McMurray, F. O'Hara, M. J. Gaunt *Chem. Soc. Rev.* **2011**, 40, 1885; (b) W. R. Gutekunst, P. S. Baran *Chem. Soc. Rev.* **2011**, 40, 1976; (c) D. Y.-K Chen, S. W. Youn *Chem. Eur. J.* **2012**, 18, 9452; (d) J. Yamaguchi, A. D. Yamaguchi, K. Itami, K. *Angew. Chem., Int. Ed.* **2012**, 51, 8960.

(6) For recent natural product syntheses that utilize C–H functionalization as part of their strategy see: (a) D. Wang, J.-Q. Yu *J. Am. Chem. Soc.* **2011**, 133, 5767; (b) W. R. Gutekunst, P. S. Baran *J. Am. Chem. Soc.* **2011**, 133, 19076; (c) D. Mandal, A. D. Yamaguchi, J. Yamaguchi, K. Itami *J. Am. Chem. Soc.* **2011**, 133, 19660; (d) L. Zhao, C. Tsukano, E. Kwon, Y. Takemoto, M. Hirama *Angew. Chem., Int. Ed.* **2012**, 52, 1722; (e) K. Amaike, K. Muto, J. Yamaguchi, Itami, K. *J. Am. Chem Soc.* **2012**, 134, 13573; (f) H. Wang, G. Li, K. M. Engle, J.-Q. Yu, H. M. L. Davies *J. Am. Chem. Soc.* **2013**, 135, 6774.; (g) B. R. Rosen, L. R. Simke, P. S. Thuy-Boun, D. D. Dixon, J.-Q. Yu, P. S. Baran *Angew. Chem., Int. Ed.* **2013**, 52, 7317; (h) P. Lu, Z. Gu, A. Zakarian *J. Am. Chem. Soc.* **2013**, 135, 14552; (i) E. C. Cherney, J. M. Lopchuk, J. C. Green, P. S. Baran *J. Am. Chem. Soc.* **2014**, 136, 12592.

(7) (a) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt *Angew. Chem., Int. Ed.* **2005**, 44, 3125. (b) E. M. Beck, N. P. Grimster, R. Hatley, M. J. Gaunt *J. Am. Chem. Soc.* **2006**, 128, 2528.

(8) For natural product syntheses from our group that utilize C–H functionalization as part of their strategy see: (a) E. M. Beck, R. Hatley, M. J. Gaunt. *Angew. Chem., Int. Ed.* **2008**, 47, 3004; (b) L. McMurray, E. M. Beck, M. J. Gaunt *Angew. Chem., Int. Ed.* **2012** 51, 9288.

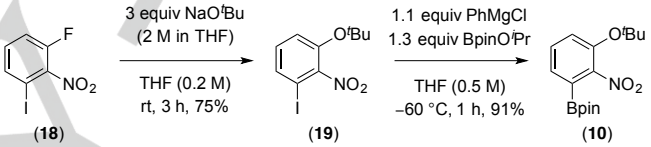
(9) C. Schneider, E. David, A. Toutov, V. Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, 51, 2722.

(10) R. J. Phipps, N. P. Grimster, M. J. Gaunt *J. Am. Chem. Soc.* **2008**, 130, 8172.

(11) (a) I. Komoto, J. Matsuo, S. Kobayashi *Top. Catal.* **2002**, 19, 43. (b) The mass balance in this reaction is the dimer of **5** coupled through the C2 position.

(12) S. Paul, G. A. Chotana, D. Holmes, R. C. Reichle, R. E. Maleczka, M. R. Smith *J. Am. Chem. Soc.* **2006**, 128, 15552.

(13) (a) S. E. Collibee, J. Yu *Tetrahedron Lett.* **2005**, 46, 4453. (b) The synthesis of the tri-substituted aryl boronic ester is easily achieved on gram-scale from the commercially available 1-fluoro-3-iodo-2-nitrobenzene.



(14) (a) H. L. Aalten, G. van Koten, D, M, Grove, T. Kuilman, O. Piekstra, L. A. Hulshof, R. A. Sheldon *Tetrahedron* **1989**, 45, 5565; (b) Y. Kikugawa, Y. Aoki, T. Sakamoto *J. Org. Chem* **2001**, 66, 8612; (c) S, M. Bhosale, A. A. Momin, R. S. Kusurkar *Tetrahedron* **2012**, 68, 6420.

(15) (a) G. I. J. Cadogan, M. Carmen-Wood *Proc. Chem. Soc.* **1962**, 361; (b) J. H. Smitrovich, I. W. Davies *Org. Lett.* **2004**, 6, 533; (c) W. C. P Tsang, N. Zheng, S. L. Buchwald *J. Am. Chem. Soc.* **2005**, 127, 14560; (d) J. A. Jordan-Hore, C. C. C. Johansson, M. G. Costa, E. M. Beck, M. J. Gaunt *J. Am. Chem. Soc.* **2008**, 130, 16184.

(16) B. J. Stokes, B. Jovanović, H. Dong, K. J. Richert, R. D. Riell, T. G. Driver *J. Org. Chem.* **2009**, 74, 3225.

(17) (a) P. A. S. Smith, B. B. Brown *J. Am. Chem. Soc.* **1951**, 73, 2435; (b) M. Pudlo, D. Csányi, F. Moreau, G. Hajós, Z. Riedl, J. Sapi *Tetrahedron* **2007**, 63, 10320.

(18) J. C. Pastre, D. L. Browne, S. V. Ley *Chem. Soc. Rev.* **2013**, 42, 8849.

(19) See supporting information for details.

(20) During the course of our work we because aware of a related study by the Itami and Davies laboratories. We are grateful to them for their collegiality and support. A. D. Yamaguchi, K. M. Chepiga, J. Yamaguchi, K. Itami, and H. M L. Davies *J. Am. Chem. Soc.* **2015**, *137*, 644.

Entry for the Table of Contents

COMMUNICATION

*Andrew K. Pitts†, Fionn O'Hara†, Robert H. Snell and Matthew J. Gaunt**

Page No. – Page No.

A concise and scalable strategy for the total synthesis of dictyodendrin B based on sequential C–H functionalization

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