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Iridium-Catalyzed C−H Borylation-Based Synthesis of Natural Indolequinones

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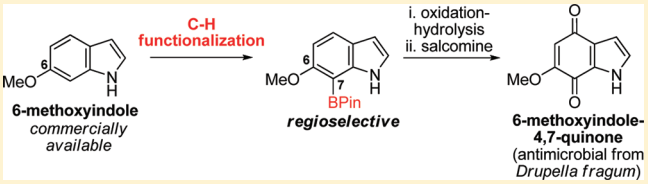
Supporting Information

ABSTRACT: An iridium-catalyzed C−H borylation provides the key step in a short synthesis of two indolequinone natural products. This regioselective C−H functionalization strategy delivers 7-borylindoles that undergo facile oxidation−hydrolysis to 7-hydroxyindoles and subsequent oxidation to the desired indolequinones, thereby demonstrating a powerful application of the iridium-catalyzed C−H borylation reaction. A significant result has arisen from the iridium-catalyzed borylation of *N*-diethylhydrosilyl-6-methoxyindole; even in the presence of a substituent at C6, the *N*-hydrosilyl group still directs borylation exclusively into the more sterically hindered C7 position in preference to C2.



The widespread interest in compounds bearing the indolequinone pharmacophore began with the discovery of the archetypal quinone bioreductive anticancer agent mitomycin C (MMC, **1**), a natural product in clinical practice since the 1970s for the treatment of breast, stomach, esophagus, and bladder tumors.[1−3] Another notable example is the MMC analogue apaziquone (E09, **2**), currently in the advanced stages of clinical trials for the treatment of superficial bladder cancer.[4] Other natural indolequinones with interesting biological activities include the topoisomerase II inhibitor BE-10988 **3**[5] and the antimicrobial indolequinones[6] **4** and **5** (Figure 1).

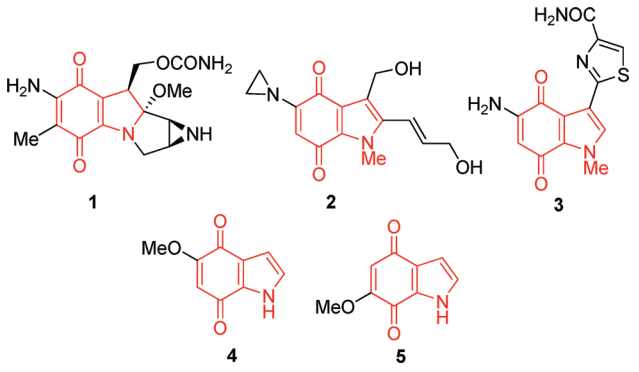


Figure 1. Biologically active indolequinones.

As part of an ongoing project aimed at the synthesis of natural indolequinones,[7] we desired a procedure that would provide indolequinones directly from the parent indole, thereby avoiding commonly employed fragment-based approaches to indolequinones that typically rely on the stepwise construction of an amino- or hydroxyindole followed by oxidation to the indolequinone[8] or the annulation of a substituted quinone.[9,10] These methods are often lengthy and sensitive to structural changes in the substrates, resulting in narrow scope that can inhibit the efficient production of structurally diverse analogues, a particularly important requirement in medicinal chemistry settings. The synthesis of indolequinones by a late-stage indole functionalization approach has the potential to circumvent these shortcomings but would require the selective manipulation of the benzo-fused aromatic ring of indole, a far from straightforward task when considering the greater reactivity of the azole ring.[11] Indeed, a review of the literature reveals that the majority of existing methods that functionalize the benzo-fused moiety of the indole ring in preparation for indolequinone synthesis require the azole ring to be substituted in order to avoid unwanted reactions at this site.[10,12−14] In the context of indolequinone synthesis, existing methods that can be used to selectively functionalize the benzo-fused moiety of indole in the presence of an unsubstituted azole ring are not ideal. The regioselective oxidation (C4) of the indole ring can be achieved but is highly substrate specific and requires the use of toxic thallium salts. The resulting 4-hydroxyindoles then undergo facile oxidation to the desired indolequinones.[15] The direct oxidation of indoles to indolequinones can be effected with Dess−Martin periodinane but is restricted to indoles bearing a benzylamide at C5 and the indole nitrogen must be alkylated.[16] Also, the direct electrochemical oxidation of 5-hydroxytryptamine leads directly to the corresponding indolequinone.[17] Because of the limited substrate scope of the methods outlined in the above, a novel procedure for the late-stage functionalization−oxidation of indole that would constitute a new approach to indolequinones was sought. Herein, we report our initial efforts toward this goal that has culminated in the efficient synthesis of two indolequinone natural products. A striking result obtained from the iridium-

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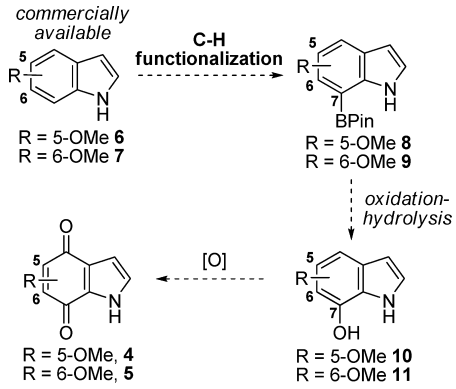
catalyzed C−H borylation of a 6-substituted indole is also discussed.

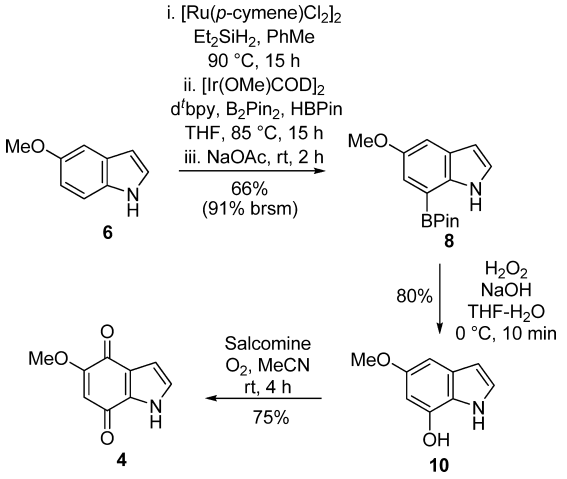
A particularly fascinating area of C−H functionalization is the recently discovered iridium-catalyzed C−H borylation of indole,[18] a reaction that was initially only selective for C7 when a substituent at C2 was present to block reactivity at this site.[19] In a landmark recent development, Hartwig and co-workers demonstrated that *N*-hydrosilylindoles undergo borylation exclusively at C7 even in the absence of a substituent at C2, vastly increasing the scope of this process.[20] Inspired by these recent advances, we set out to apply this C−H borylation methodology as the basis for a novel approach to indolequinones and chose to target the relatively simple natural products **4** and **5** to gauge the viability of this proposal (Scheme 1). It was envisaged commercially available methoxyindoles **6** and **7** would undergo iridium-catalyzed C−H borylation to their respective 7-borylindoles **8** and **9** that upon oxidation−hydrolysis would furnish 7-hydroxyindoles **10** and **11**; 7-hydroxyindoles are themselves highly useful and sought after synthetic intermediates that often require lengthy and/or poor yielding routes for their preparation.[21,22] The oxidation of 7-hydroxyindoles **10**/**11** would then provide the natural indolequinones **4** and **5**. At the outset of this project it was evident that there were no literature examples reporting the iridium-catalyzed borylation of a 6-substituted indole;[18−20] therefore, obtaining the desired regioisomer (**9**) from the borylation of 6-methoxyindole **7** was not guaranteed.

Scheme 1. Synthetic Plan



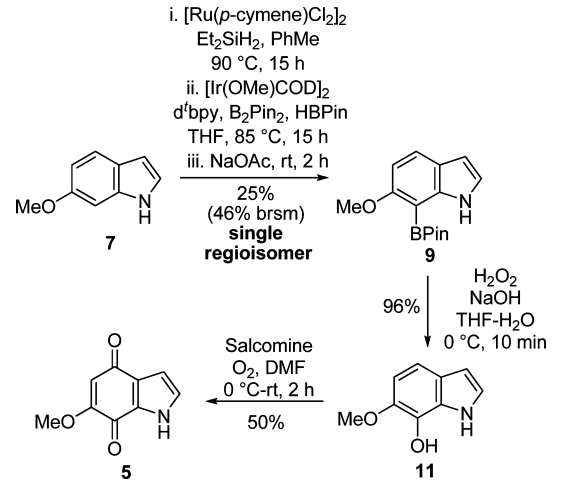
The natural product **4** was the initial target which could be traced back to commercially available 5-methoxyindole. Thus, indole **6** was subjected to an uneventful one-pot hydrosilylation, iridium-catalyzed borylation, and desilylation according to the reported procedure,[20] affording 5-methoxy-7-borylindole **8**,[20] whereupon the boronate oxidation−hydrolysis was considered. Examples reporting the oxidation−hydrolysis of borylindoles to hydroxyindoles in the literature are scarce,[23] but it was found that treatment of **8** with hydrogen peroxide and sodium hydroxide in THF at 0 °C gratifyingly gave 5-methoxyindol-7-ol **10** after 10 min in excellent yield. Finally, salcomine-catalyzed oxidation of **10** gave the indolequinone **4** which was identical in all aspects to the natural product[6,24] (Scheme 2). The synthesis of the natural product **4** described herein required three steps from commercially available 5-methoxyindole, compared to the single literature synthesis that required seven steps.[6] More importantly, the successful synthesis of **4** from 5-methoxyindole **6** constitutes a novel approach to indolequinones based on a late-stage indole functionalization.

Scheme 2. Synthesis of Indolequinone Natural Product 4



With the synthesis of the natural product **4** successful, we set out to extend this methodology to the synthesis of the indolequinone natural product **5** (Scheme 3). Upon subjecting 6-methoxyindole **7** to the same C−H borylation conditions described for the preparation of regioisomer **8**, TLC and ^{1}H NMR analysis of the reaction mixture indicated the formation of single borylindole regioisomer. We were confident from 2D NMR experiments[24] that the regioisomer was indeed the desired 7-borylindole **9**, but this was pleasingly confirmed upon its oxidation-hydrolysis to the known 6-methoxyindol-7-ol **11**.[6] Although it is well-established that *N*-hydrosilylindoles undergo iridium-catalyzed borylation exclusively at C7 even in the absence of a substituent at C2,[20] this example demonstrates that the remarkable regiochemical outcome is still observed even in the presence of a substituent at C6. The moderate yield observed in the borylation of **7** to **9** was not due to incomplete borylation, but attributed to protodeborylation during the cleavage of the hydrosilyl group, a phenomenon previously reported.[20] Oxidation of **10** with salcomine then delivered the indolequinone **5**, the spectroscopic data of which was in full agreement with the natural product[24] (Scheme 3). The

Scheme 3. Synthesis of Indolequinone Natural Product 5



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synthesis of **5** described herein is significantly shorter than the existing methods.[6,10,25]

In conclusion, we have reported the short synthesis of two indolequinone natural products that was enabled by an iridium-catalyzed C−H borylation. It has also been discovered that even in the presence of a substituent at C6, the C−H borylation of *N*-diethylhydrosilyl-6-methoxyindole still occurs regioselectively at the more sterically hindered C7 position in preference to C2. This late-stage functionalization approach to indolequinones should allow for the modular introduction of different substituents and functional groups onto the indole substrates, facilitating the production of a diverse series of indolequinone analogues. This approach also describes a potentially useful synthesis of 7-hydroxyindoles. The scope and utility of this methodology with a variety of indoles, related heterocycles and in natural product synthesis, together with its application in large scale settings, is currently under investigation.

EXPERIMENTAL SECTION

General Experimental Details. Commercially available reagents were used throughout without purification unless otherwise stated. Anhydrous solvents were used as supplied. Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen atmosphere. Dichloromethane was distilled from calcium hydride under a nitrogen atmosphere. Ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen or argon atmosphere. Analytical thin-layer chromatography was carried out on aluminum backed plates coated with silica gel and visualized under UV light at 254 and/or 360 nm and/or potassium permanganate or ethanolic vanillin dip. Chromatography was carried out on silica gel. Fully characterized compounds were chromatographically homogeneous. Infrared spectra were recorded on an FT-IR spectrometer in the range 4000−600 cm^{-1}. NMR spectra were recorded on a 400 MHz (^1H frequency) spectrometer. Chemical shifts are quoted in ppm and *J* values in Hz. Chemical shift values are referenced against residual proton in the deuterated solvents. Assignments were made with the aid of DEPT 135, COSY, NOESY, HSQC and HMBC experiments. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 are assigned from DEPT-90 and -135 spectra; all others are quaternary C. Mass spectra were recorded on a time-of-flight mass spectrometer using electrospray ionization (ESI).

Procedure for C−H Borylation. In a Pyrex sealed tube with a stirring bar and Teflon-lined screwcap were added [Ru(*p*-cymene)Cl_2]$_2$ (3 mg, 0.005 mmol, 1 mol %), methoxyindole **6** or **7** (74 mg, 0.5 mmol), diethylsilane (0.14 mL, 1 mmol), and degassed toluene (0.5 mL), and the resulting mixture was heated to 90 °C for 15 h under a blanket of argon. After being cooled to room temperature, the mixture was transferred to a round bottomed flask, and volatile materials were removed under reduced pressure to give the *N*-hydrosilylindole (0.5 mmol). A catalyst solution was prepared by adding [Ir(OMe)COD]$_2$ (10 mg, 0.015 mmol, 6 mol %) and 4,4′-di-*tert*-butylbipyridine (8 mg, 0.03 mmol, 12 mol %) in THF (0.5 mL) followed by the addition of bis(pinacolato)diboron (190 mg, 0.75 mmol) and pinacolborane (0.01 mL, 0.07 mmol, 14 mol %) with stirring for 1 min. The resulting deep-red solution was transferred to the round bottomed flask containing the *N*-hydrosilylindole (0.5 mmol) in THF (1 mL) and the whole reaction mixture immediately transferred to a sealed tube and heated to 85 °C for 15 h under a blanket of argon. Upon cooling to room temperature, sodium acetate (3 M, 0.25 mL) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ether (20 mL) and water (20 mL). The aqueous layer was separated and washed with ether (2 × 15 mL), and the combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification gave the borylindole product **8** or **9**.

*5-Methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole (**8**).* From 5-methoxyindole **6**: Purification by flash-column chromatography on silica gel eluting with *n*-hexanes−ethyl acetate (3:1) gave the title compound as an orange oil [90 mg, 0.33 mmol, 66%, (91% brsm)]: δ_H (400 MHz, $CDCl_3$) 9.14 (1 H, br s, NH), 7.36 (1 H, d, *J* 2.8, Ar-H), 7.31 (1 H, d, *J* 2.0, Ar-H), 7.27 (1 H, t, *J* 2.0, H-2), 6.51 (1 H, dd, *J* 2.0, 2.8, H-3), 3.90 (3 H, s, Me), 1.42 (12 H, s, 4 × Me); δ_C (100 MHz, $CDCl_3$) 154.1 (C), 136.8 (C), 127.9 (C), 125.2 (CH), 118.1 (CH), 107.9 (CH), 101.8 (CH), 84.2 (2 × C), 56.5 (Me), 25.3 (4 × Me), 1 × C not observed. Spectroscopic data consistent with literature values.[20]

*6-Methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole (**9**).* From 6-methoxyindole **7**: Purification by flash-column chromatography on silica gel eluting with *n*-hexanes−ethyl acetate (9:1) gave the title compound as an orange solid [34 mg, 0.12 mmol, 25%, (46% brsm)]; mp 91.5−96.6 °C; ν_{max} (neat)/cm^{-1} 3406, 2978, 2929, 1859, 1601, 1585, 1537, 1507, 1497, 1459, 1430, 1380, 1338, 1299, 1238, 1202, 1168, 1135, 979, 878, 856; δ_H (400 MHz, $CDCl_3$) 9.39 (1 H, br s, NH), 7.68 (1 H, d, *J* 8.4, Ar-H), 7.16 (1 H, dd, *J* 5.3, 2.4, H-2), 6.80 (1 H, d, *J* 8.4, Ar-H), 6.46 (1 H, dd, *J* 5.3, 2.0, H-3), 3.91 (3 H, s, Me), 1.41 (12 H, s, 4 × Me); δ_C (100 MHz, $CDCl_3$) 162.5 (C), 142.4 (C), 124.9 (CH), 123.4 (CH), 122.0 (C), 106.2 (CH), 101.6 (CH), 83.2 (2 × C), 57.6 (Me), 25.0 (4 × Me), 1 × C not observed; *m*/*z* (ESI) 296 [100, $(M + Na)^+$], 226 (4), 134 (5); HRMS [ESI, $(M + Na)^+$] found 296.1440, $[C_{15}H_{20}BNO_3 + Na]^+$ requires 296.1431.

Procedure for Boronate Oxidation-Hydrolysis. A solution of indole **8** or **9** (30 mg, 0.11 mmol) in THF (3 mL) was cooled to 0 °C. Hydrogen peroxide (30% in H_2O, 0.1 mL) and sodium hydroxide (1 M, 0.1 mL) were added, and the reaction mixture was stirred at 0 °C for 10 min. Ether (20 mL) was added, and the organic layer was removed, washed with water (8 mL) and brine (8 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash-column chromatography gave the 7-hydroxyindole product **10** or **11**.

*5-Methoxyindol-7-ol (**10**).* From borylindole **8**: Purification by flash-column chromatography on silica gel using *n*-hexanes−ethyl acetate (1:1) as eluent gave the title compound (14.4 mg, 0.087 mmol, 80%) as an orange oil: ν_{max} (neat)/cm^{-1} 3410, 3292, 2965, 1714, 1649, 1589, 1530, 1426, 1289, 1240, 1135, 1032, 821, 757; δ_H (400 MHz, DMSO-d_6) 10.68 (1 H, br s, NH), 9.56 (1 H, s, OH), 7.14 (1 H, t, *J* 2.8, H-2), 6.48 (1 H, d, *J* 2.0, Ar-H), 6.25 (1 H, t, *J* 2.8, H-3), 6.16 (1 H, d, *J* 2.0, Ar-H), 3.68 (3 H, s, Me); δ_C (100 MHz, DMSO-d_6) 153.9 (C), 143.8 (C), 129.0 (C), 124.8 (CH), 121.4 (C), 101.3 (CH), 96.3 (CH), 92.4 (CH), 55.1 (Me); *m*/*z* (ESI) 186 [100, $(M + Na)^+$]; HRMS [ESI, $(M + Na)^+$] found 186.0519, $[C_9H_9NO_2 + Na]^+$ requires 186.0525.

*6-Methoxyindol-7-ol (**11**).* From borylindole **9**: Purification by flash-column chromatography on silica gel using *n*-hexanes−ethyl acetate (1:1) as eluent gave the title compound (15.7 mg, 0.096 mmol, 96%) as an orange oil; δ_H (400 MHz, $CDCl_3$) 8.21 (1 H, br s, NH), 7.13 (2 H, m, Ar-H, H-2), 6.84 (1 H, d, *J* 8.5, Ar-H), 6.19 (1 H, dd, *J* 5.3, 2.3, H-3), 5.65 (1 H, br s, OH), 3.93 (3 H, s, Me); ^1H NMR data consistent with that reported in the literature[6] but due to incomplete literature characterization, full spectroscopic data was obtained; ν_{max} (neat)/cm^{-1} 3188, 2921, 2852, 1728, 1610, 1557, 1422, 1384, 1199, 1052, 894, 789; δ_H (400 MHz, DMSO-d_6) 10.72 (1 H, br s, NH), 8.78 (1 H, s, OH), 7.13 (1 H, t, *J* 2.6, H-2), 6.91 (1 H, d, *J* 8.6, Ar-H), 6.75 (1 H, d, *J* 8.6, Ar-H), 6.27 (1 H, dd, *J* 3.2, 2.6, H-3), 3.78 (3 H, s, Me); δ_C (100 MHz, DMSO-d_6) 141.2 (C), 132.5 (C), 127.2 (C), 124.6 (C), 124.5 (CH), 110.1 (CH), 108.6 (CH), 101.0 (CH), 57.9 (Me); *m*/*z* (ESI) 186 [100, $(M + Na)^+$]; HRMS [ESI, $(M + Na)^+$] found 186.0529, $[C_9H_9NO_2 + Na]^+$ requires 186.0525.

Indolequinone Oxidation. *5-Methoxyindole-4,7-quinone (**4**).* To a solution of indole **10** (10 mg, 0.061 mmol) in acetonitrile (3 mL) was added salcomine (2.38 mg, 0.007 mmol, 12 mol %), and the reaction mixture was stirred at room temperature under an atmosphere of oxygen for 4 h. Silica gel (∼30 mg) was added and the solvent concentrated in vacuo. The dry silica gel residue which was purified by flash chromatography on silica gel using *n*-hexanes−ethyl acetate (1:1) as eluent to give the title compound (8.1 mg, 0.045 mmol, 75%) as a bright yellow solid: mp 198−200 °C (lit.[6] mp 198−200 °C); ν_{max} (neat)/cm^{-1} 3363, 3230, 2850, 1673, 1589, 1496, 1402, 1247, 1124, 1084, 927, 807, 748; δ_H (400 MHz, DMSO-d_6) 12.63 (1 H, br

s, NH), 7.15 (1 H, d, *J* 2.6, H-2), 6.52 (1 H, d, *J* 2.6, H-3), 5.82 (1 H, s, H-6), 3.78 (3 H, s, Me); δ_C (100 MHz, DMSO-d_6) 177.9 (C═O), 176.7 (C═O), 160.6 (C), 131.4 (C), 125.6 (CH), 122.9 (C), 107.3 (CH), 106.1 (CH), 56.6 (Me); *m*/*z* (ESI) 200 [100, $(M + Na)^+$], 176 (35), 167 (40), 156 (23); HRMS [ESI, $(M + Na)^+$] found 200.0323. $[C_9H_7NO_3 + Na]^+$ requires 200.0318. Spectroscopic data consistent with literature values.[6]

6-Methoxyindole-4,7-quinone (**5**). To a solution of indole **11** (8 mg, 0.049 mmol) in dimethylformamide (3 mL) at 0 °C was added salcomine (2 mg, 0.006 mmol, 12 mol %), and the reaction mixture was stirred at room temperature under an atmosphere of oxygen for 2 h. The reaction mixture was diluted with ethyl acetate (20 mL) and water (10 mL), the organic phase removed, and the aqueous layer extracted with ethyl acetate (15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel eluting with *n*-hexanes−ethyl acetate (1:1) gave the title compound (4.2 mg, 0.024 mmol, 50%) as a bright orange solid: mp 186−189 °C (lit.[6] mp 188−190 °C); ν_{max} (neat)/cm^{-1} 3184, 2924, 2854, 1726, 1667, 1634, 1586, 1539, 1494, 1403, 1331, 1283, 1193, 1093, 922, 887, 797; δ_H (400 MHz, DMSO-d_6) 12.74 (1 H, br s, NH), 7.25 (1 H, d, *J* 2.4, H-2), 6.47 (1 H, d, *J* 2.4, H-3), 5.80 (1 H, s, H-5), 3.76 (3 H, s, Me); δ_C (100 MHz, DMSO-d_6) 182.9 (C═O), 170.7 (C═O), 159.7 (C), 129.1 (C), 127.5 (CH), 126.0 (C), 107.1 (CH), 106.9 (CH), 56.3 (Me). *m*/*z* (ESI) 200 [100%, $(M + Na)^+$]; HRMS [ESI, $(M + Na)^+$] found 200.0318, $[C_9H_7NO_3 + Na]^+$ requires 200.0318. Spectroscopic data consistent with literature values.[6,25]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of all compounds and 2D NMR spectra of **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) Carter, S. K.; Crooke, S. T. *Mitomycin C: Current Status and New Developments*; Academic Press: New York, 1979.
(2) Seow, H.; Penketh, P. G.; Baumann, R. P.; Sartorelli, A. C. *Methods Enzymol.* **2004**, *382*, 221−233.
(3) Alcain, F. J.; Villalba, J. M. *Expert Opin. Ther. Pat.* **2007**, *17*, 649−665.
(4) Jain, A.; Phillips, R. M.; Scally, A. J.; Lenaz, G.; Beer, M.; Puri, R. *Urology* **2009**, *73*, 1083−1086.
(5) Oka, H.; Yoshinari, T.; Murai, T.; Kuwamura, K.; Satoh, F.; Funaishi, K.; Okura, A.; Suda, H.; Okanishi, M.; Shizuri, Y. *J. Antibiot.* **1991**, *44*, 486−491.
(6) Fukuyama, Y.; Iwatsuki, C.; Kodama, M.; Ochi, M.; Kataoka, K.; Shibata, K. *Tetrahedron* **1998**, *54*, 10007−10016.
(7) Wang, C.; Sperry, J. *Org. Lett.* **2011**, *13*, 6444−6447.
(8) For a representative example, see: Nobuhiro, J.; Hirayama, M.; Choshi, T.; Kamoshita, K.; Maruyama, S.; Sukenaga, Y.; Ishizu, T.; Fujioka, H.; Hibino, S. *Heterocycles* **2006**, *70*, 491−499.
(9) For a representative example, see: Inman, M.; Moody, C. J. *J. Org. Chem.* **2010**, *75*, 6023−6026 and references therein..
(10) For complementary fragment based approaches, see: Saá, J. M.; Marti, C.; Raso-García, A. *J. Org. Chem.* **1992**, *57*, 589−594 and references therein.
(11) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608−9644.
(12) Nitration−reduction: Natasuka, S.-I.; Ueda, K.; Asano, O.; Goto, T. *Heterocycles* **1987**, *26*, 65−68.
(13) Hydroxyindole oxidation then Thiele−Winter acetoxylation or reductive alkylation: Allen, G. R. Jr.; Poletto, J. F.; Weiss, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 3877−3878.
(14) Dakin oxidation: Alamgir, M.; Mitchell, P. S. R.; Bowyer, P. K.; Kumar, N.; Black, D. StC. *Tetrahedron* **2008**, *64*, 7136−7142.
(15) Carr, G.; Chung, M. K. W.; Mauk, A. G.; Andersen, R. J. *J. Med. Chem.* **2008**, *51*, 2634−2637.
(16) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *10*, 2221−2232.
(17) Wrona, M. Z.; Lemordant, D.; Lin, L.; Blank, C. L.; Dryhurst, G. *J. Med. Chem.* **1986**, *29*, 499−505.
(18) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056−3058.
(19) Sulanga, P.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E. Jr.; Smith, M. R. III *J. Am. Chem. Soc.* **2006**, *128*, 15552−15553.
(20) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068−4069 The directed C−H borylation reaction was only conducted on indoles with substituents at the 3-, 4-, and 5-positions..
(21) Dalpozzo, R.; Bartoli, G. *Curr. Org. Chem.* **2005**, *9*, 163−178.
(22) Charrier, N.; Demont, E.; Dunsdon, R.; Maile, G.; Naylor, A.; O'Brien, A.; Redshaw, S.; Theobald, P.; Vesey, D.; Walter, D. *Synlett* **2005**, 3071−3074 and references therein..
(23) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899−1902.
(24) See Supporting Information for relevant spectra.
(25) Jackson, Y. A.; Billimoria, A. D.; Sadanandan, E. V.; Cava, M. P. *J. Org. Chem.* **1995**, *60*, 3543−3545.