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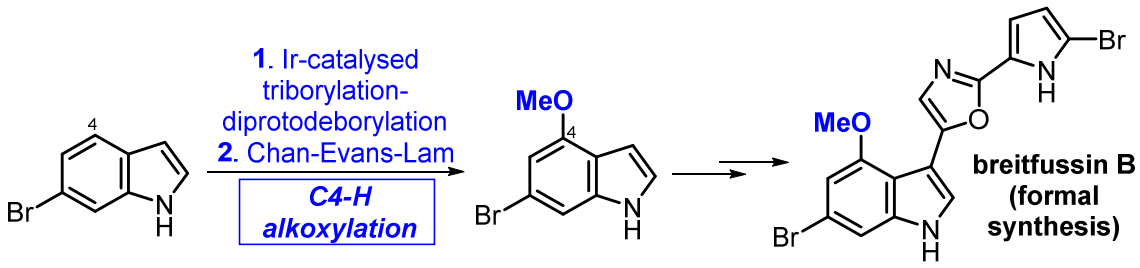

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C4−H Alkoxylation of 6-Bromoindole and its Application to the Synthesis of Breitfussin B

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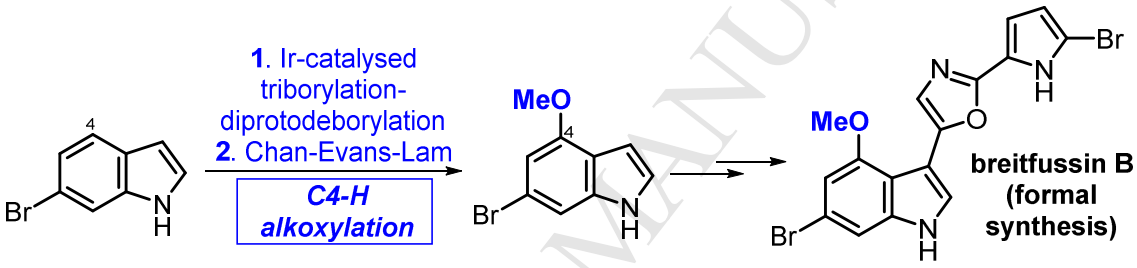

Subjecting 6-bromoindole to an iridium-catalysed triborylation-diprotodeborylation sequence followed by Chan-Evans-Lam coupling gives 6-bromo-4-methoxyindole in good overall yield. This indole C4−H alkoxylation process was used in a formal synthesis of the natural product breitfussin B.

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INTRODUCTION

Breitfussins A and B are modified dipeptide natural products isolated from the Arctic bryozoan *Thuiaria breitfussi*. The breitfussins are notable for their halogenated indole-oxazole-pyrrole scaffold, which was assigned with the aid of atomic-force microscopy.[1] Along with a unique heteroaromatic architecture, the breitfussins possess a 4,6-disubstituted indole, a substitution pattern rarely seen among indole alkaloids.[2]

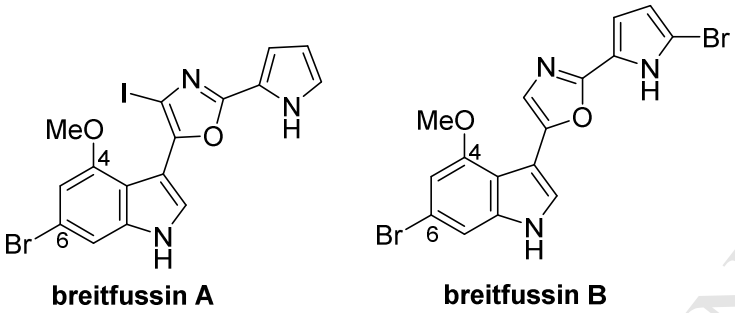

Figure 1. Breitfussins A and B

Synthetic studies towards the breitfussins has culminated in the synthesis of both members by Bayer and Hedberg,[3] followed by a synthesis of breitfussin B by Chen a short time later.[4] In both these reports, the syntheses began with 6-bromo-4-methoxyindole (**1**), which was prepared by Leimgruber-Batcho and Hemetsberger indolizations, respectively. (Scheme 1, **A** and **B**). Indeed, the synthesis of 4,6-disubstituted indoles is commonly achieved using (hetero)annulation reactions.[5,6] A conceptually different approach to this substitution pattern would be functionalisation of the C4−H site in commercially available 6-bromoindole (Scheme 1, **C**).

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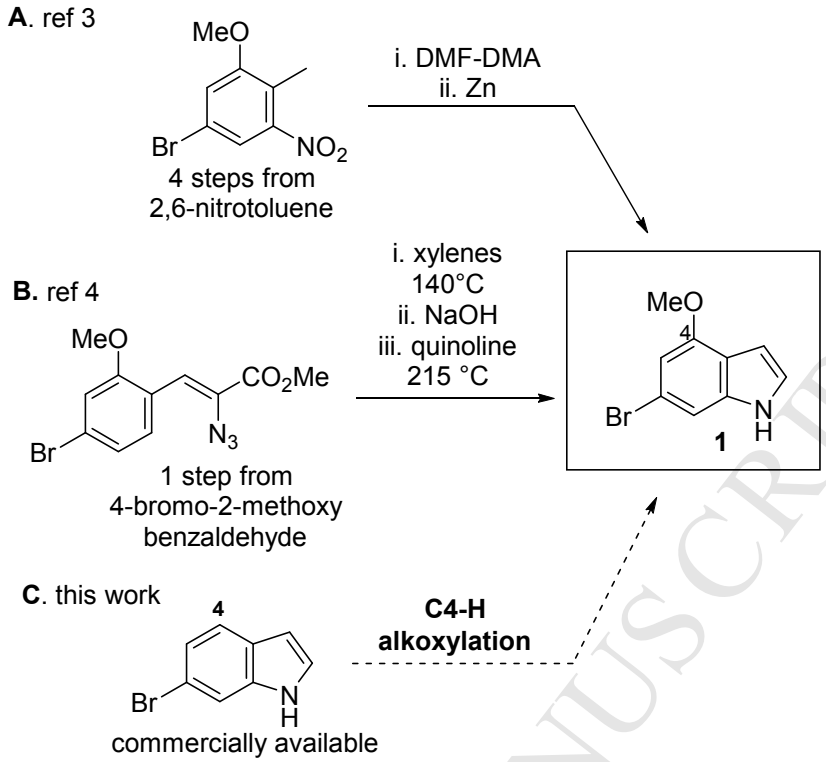

Scheme 1. Synthesis of 6-bromo-4-methoxyindole

Both the oxidation and alkoxylation of the indole C4-position can be achieved via directed metalation strategies that take advantage of an appropriately positioned directing group on the indole nucleus.[7] Transition metal mediated C−H functionalization of the indole C4-position relies on a directing group positioned at the C3 or C6 sites,[8,9] but we are not aware of any successful C4−H oxidations or alkoxylations emanating from this approach.[10] The tricarbonylchromium complexes of *N*-silylindoles undergo nucleophilic substitution at C4,[11] but oxidation or alkoxylation has not been achieved in this manner.

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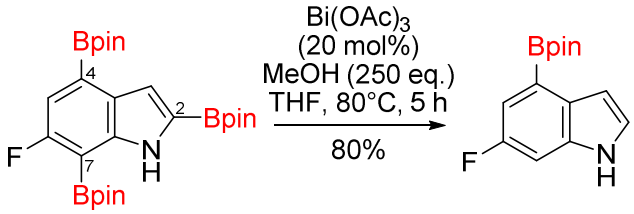
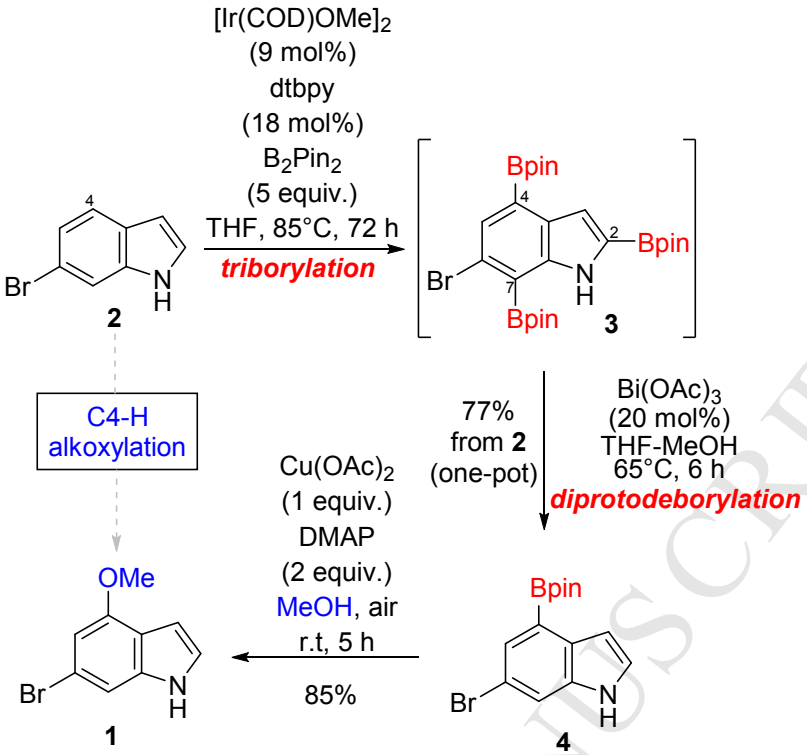
In alignment with ongoing interests in the iridium catalysed C−H borylation reaction,[12] our plan to develop an indole C4-alkoxylation process was shaped by a recent report describing the synthesis of a 6-fluoro-4-borylindole using a $Bi(OAc)_3$-catalyzed diprotodeborylation of the corresponding 2,4,7-triborylindole (Scheme 2).[13]



Scheme 2. Selective protodeborylation at C2 and C7[13]

We envisioned that upon applying this procedure[13] to 6-bromoindole, it should then be possible to convert the resulting 4-borylindole into the desired 6-bromo-4-methoxyindole (**1**) by Chan-Evans-Lam coupling[14] and we initiated a study to examine this proposal (Scheme 3). Upon subjecting 6-bromoindole (**2**) to an iridium-catalysed-borylation using an excess of B_2Pin_2, the 2,4,7-triborylindole **3** was isolated in good yield. In contrast to our previous work on iridium-catalyzed triborylations that required the ligand 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4Phen),[12a,c] in this case the ligand 4,4-di-*tert*-butyl bipyridine (dtbpy) was pivotal for the success of this reaction. The use of bismuth triacetate to effect diprotodeborylation[13] at C2 and C7 in **3** worked very well, affording the desired 6-bromo-4-borylindole **4**. The entire sequence from **2**→**4** is easily performed in one-pot in good overall yield. Based on our previous experience[12c] using the Chan-Lam Evans coupling to access methoxyindoles, it was found that the addition of DMAP[15] was essential to obtain good yields of 6-bromo-4-methoxyindole **1**. The conversion of 6-bromoindole (**2**) to 6-bromo-4-methoxyindole (**1**) represents a net C4−H alkoxylation process. Unfortunately, attempts to perform the whole sequence (**2**→**1**) in one-pot were not successful.



Scheme 3. C4−H alkoxylation of 6-bromoindole

With the C4−H alkoxylation of 6-bromoindole successful, this methodology was applied to a formal synthesis of breitfussin B (Scheme 4). Reductive alkylation[16] of **4** gave the protected tryptamine **5**. Hydrolysis gave tryptamine **6** which underwent amide coupling with 2-(chloroacetyl)pyrrole (**7**) to give amide **8**, an intermediate in Chen's synthesis of breitfussin B,[4] thus completing a formal synthesis of the natural product. The synthesis of **8** (six steps, four column purifications) compares well with Chen's route to the same compound (nine steps, three column purifications).

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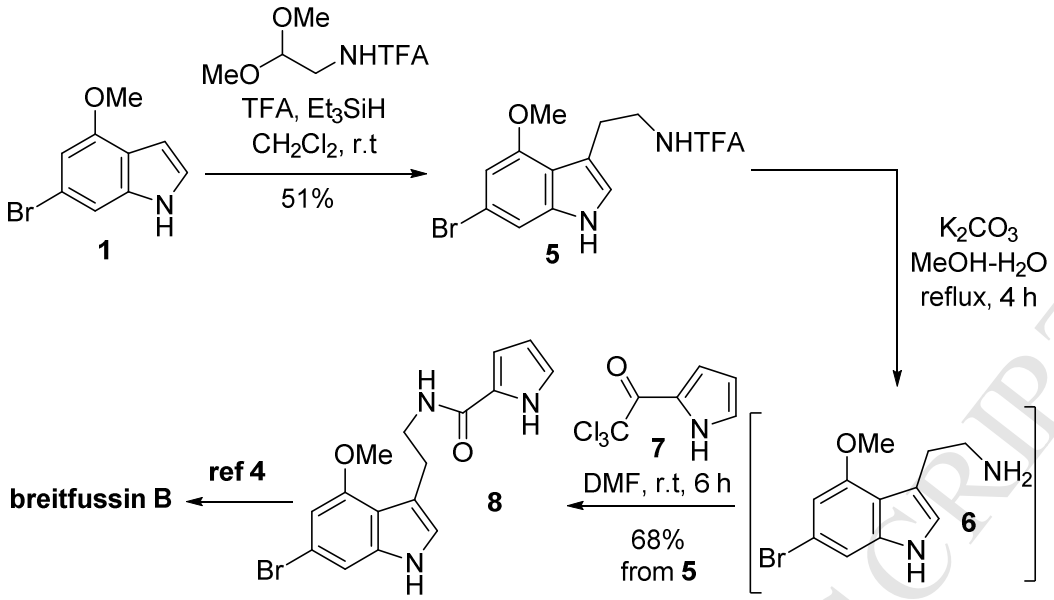

Scheme 4. Formal synthesis of breitfussin B

CONCLUSIONS

In conclusion, we have developed a simple indole C4−alkoxylation process involving an iridium-catalysed triborylation-diprotodeborylation sequence followed by Chan-Evans-Lam coupling. This indole-functionalization procedure enabled a formal synthesis of the natural product breitfussin B to be accomplished. Given the wide range of transformations that are possible with (hetero)arylboronates,[14d,17] this methodology should find utility in the functionalization of the indole C4-position.

Experimental Section

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using 0.2 mm silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Melting points were recorded on a melting point apparatus and are uncorrected. Infrared (IR) spectra were

recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a diamond ATR sampling accessory and absorption maxima are expressed in wavenumbers (cm^{-1}). NMR spectra were recorded as indicated on an NMR spectrometer operating at 500, 400 and 300 MHz for ^{1}H nuclei and 125, 100 and 75 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/ TMS solvent, or the residual acetone (δ 2.05 ppm), chloroform (δ 7.24 ppm), DMSO (δ 2.50 ppm) or methanol (δ 3.31 ppm) peaks. The ^{13}C NMR values were referenced to the residual acetone (δ 29.9 ppm) chloroform (δ 77.1 ppm), DMSO (δ 39.5 ppm) or methanol (δ 49.0 ppm) peaks. ^{13}C NMR values are reported as chemical shift δ and assignment. ^{1}H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (*J* in Hz) and assignment. Assignments are made with the aid of DEPT 90, DEPT 135, COSY, NOESY and HSQC experiments. High resolution mass spectra were obtained by electrospray ionization in positive ion mode at a nominal accelerating voltage of 70 eV on a microTOF mass spectrometer.

6-Bromo-2,4,7-tri (4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2 yl) indole (3)

In a sealed tube, a solution of 6-bromoindole (**2**, 200 mg, 1.02 mmol), bis(pinacolato)diboron (B_2Pin_2) (907 mg, 3.57 mmol, 3.5 equiv), $[Ir(OMe)cod]_2$ (61 mg, 0.092 mmol, 9 mol %) and 4,4-di-*tert*-butyl bipyridine (dtbpy) (49 mg, 0.18 mmol, 18 mol %) in THF (5 mL) was heated to 85 °C for 72 h. After cooling to room temperature, a few drops of methanol were added and the reaction mixture was concentrated *in vacuo.* The crude material was purified by column chromatography on silica gel eluting with petroleum ether-ethyl acetate (9:1) to afford the *title compound* (501 mg, 0.87 mmol, 86 %) as a colourless solid, M.p. 289.3−294.5 °C; HRMS [ESI, $(M + Na)^+$] found 596.2119; $[C_{26}H_{39}B_3{}^{79}BrNO_6 + Na]^+$ requires 596.2151;

ν_{max} (neat)/cm^{-1} 3440, 3300, 2979, 1650, 1537, 1371, 1265, 1129, 973, 855, 698; δ_H (400 MHz, $CDCl_3$) 9.62 (1 H, br s, NH), 7.74 (1 H, s, CH), 7.48 (1 H, d, *J* 2.2, CH), 1.43 (12 H, s, 4 x Me), 1.35 (24 H, s, 8 x Me) ; δ_C (125 MHz, $CDCl_3$) 144.0 (C), 132.3 (CH), 130.5 (C), 124.7 (C), 115.0 (C), 84.1 (4 x C of BPin), 83.8 (2 x C of BPin), 25.1 (4 x Me of BPin), 25.0 (4 x Me of BPin), 24.9 (4 x Me of BPin), 3 x C not observed.

6-Bromo-4- (4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2 yl) indole (4)

In a sealed tube, a solution of 6-bromoindole (**2**, 400 mg, 2.04 mmol), bis(pinacolato)diboron (B_2Pin_2) (1814 mg, 7.14 mmol, 3.5 equiv), $[Ir(OMe)cod]_2$ (122 mg, 0.184 mmol, 9 mol %) and 4,4-di-*tert*-butyl bipyridine (dtbpy) (98 mg, 0.36 mmol, 18 mol %) in THF (5 mL) was heated to 85 °C for 72 h. After cooling to room temperature, a few drops of methanol were added and the reaction mixture was concentrated *in vacuo* to give the crude triborylindole **3** that is used directly in the next step.

For characterization purposes, an analytical sample was purified by column chromatography on silica gel eluting with petroleum ether-ethyl acetate (9:1) to afford pure **3** as a colourless solid, M.p. 289.3−294.5 °C; HRMS [ESI, $(M + Na)^+$] found 596.2119; $[C_{26}H_{39}B_3{}^{79}BrNO_6 + Na]^+$ requires 596.2151; ν_{max} (neat)/cm^{-1} 3440, 3300, 2979, 1650, 1537, 1371, 1265, 1129, 973, 855, 698; δ_H (400 MHz, $CDCl_3$) 9.62 (1 H, br s, NH), 7.74 (1 H, s, CH), 7.48 (1 H, d, *J* 2.2, CH), 1.43 (12 H, s, 4 x Me), 1.35 (24 H, s, 8 x Me); δ_C (125 MHz, $CDCl_3$) 144.0 (C), 132.3 (CH), 130.5 (C), 124.7 (C), 115.0 (C), 84.1 (4 x C of BPin), 83.8 (2 x C of BPin), 25.1 (4 x Me of BPin), 25.0 (4 x Me of BPin), 24.9 (4 x Me of BPin), 3 x C not observed.

Bismuth triacetate (135 mg, 0.35 mmol, 20 mol%) was added to a solution of the unpurified triborylindole **3** in THF (6 mL) and methanol (15 mL).The reaction mixture was stirred at 65

°C for 15 h in a sealed tube and then cooled to room temperature. The reaction mixture was concentrated *in vacuo* and purified by column chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:9) to afford the *title compound* (510 mg, 1.58 mmol, 77 % over 2 steps) as a colourless solid, M.p. 141.1−143.7 °C; HRMS [ESI, $(M + Na^+)$] found 344.0422; $[C_{14}H_{17}B^{79}BrNO_2 + Na]^+$ requires 344.0431; ν_{max} (neat)/cm^{-1} 3440, 3300, 2979, 1650, 1379, 1265, 1129, 973, 855, 698; δ_H (400 MHz, $CDCl_3$) 8.13 (1 H, br s, NH), 7.70 (1 H, d, *J* 1.8, CH), 7.62 (1 H, dd, *J* 1.8, 1.0, CH), 7.21 (1 H, dd, *J* 3.2, 2.4, CH), 6.99 (1 H, m, CH), 1.37 (12 H, s, 4 x Me); δ_C (125 MHz, $CDCl_3$) 136.1 (C), 131.4 (C), 130.5 (CH), 125.2 (CH), 116.6 (CH), 115.3 (C), 105.0 (CH) 83.9 (2 x C of BPin), 25.0 (4 x Me of BPin), 1 x C not observed.

6-Bromo-4-methoxyindole (1)[3,4]

To a solution of **4** (140 mg, 0.435 mmol) in methanol (5.0 mL) was added $Cu(OAc)_2.H_2O$ (87 mg, 0.435 mmol, 1 equiv), 4-dimethylaminopyridine (4-DMAP) (106 mg, 0.87 mmol, 2.0 equiv) and 4Å molecular sieves (~1 g). The reaction mixture was stirred in an open flask at room temperature for 5 h. The reaction mixture was filtered through Celite, washed with dichloromethane (~ 20 mL) and the filtrate concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel eluting with toluene-petroleum ether (1:1) to give the *title compound* (83 mg, 0.37 mmol, 85%) as a colourless solid, M.p. 85.3−87.1 °C (lit[3] 69−70 °C); HRMS [ESI, $(M - H)^-$] found 223.9709; $[C_9H_8{}^{79}BrNO - H]^-$ requires 223.9716; ν_{max} (neat)/cm^{-1} 3387, 2941, 2839, 1615, 1580, 1497, 966, 854, 760; δ_H (400 MHz, $CDCl_3$) 8.11 (1 H, br s, NH), 7.17 (1 H, t, *J* 1.2, CH), 7.06 (1 H, dd, *J* 3.2, 2.4, CH), 6.63 (1 H, d, *J* 1.4, CH), 6.60 (1 H, m, CH), 3.92 (3 H, s, Me); δ_C (100 MHz, $CDCl_3$) 137.6 (C), 123.1 (CH), 117.8 (C), 115.9 (C), 107.7 (CH), 104.1 (CH), 100.4 (CH), 55.7 (Me), 1 x C not observed; spectroscopic data consistent with literature data.[3,4]

***N*-(2-(6-Bromo-4-methoxyindol-3-yl)ethyl)-2,2,2-trifluoroacetamide (5)**

A solution of 6-bromo-4-methoxyindole (**1**, 100 mg, 0.44 mmol) and *N*-(2,2-dimethoxyethyl)-trifluoroacetamide[15] (178 mg, 0.88 mmol, 2.0 equiv) in dichloromethane (3.0 mL) was added to a solution of triethylsilane (0.43 mL, 2.64 mmol, 6 equiv) and TFA (0.17 mL, 2.21 mmol, 5 equiv) in dichloromethane (2.0 mL). The reaction mixture was stirred at room temperature for 3 h, cooled down to 0 °C and then neutralized with a saturated solution of sodium bicarbonate (~ 75 mL). The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic phases washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:3) gave the *title compound* (83 mg, 0.23 mmol, 51%) as light yellow solid, M.p. 111.3−113.1 °C; HRMS [ESI, $(M + Na)^+$] found 386.9925; $[C_{13}H_{12}{}^{79}BrF_3N_2O_2 + Na]^+$ requires 386.9926; ν_{max} (neat)/cm^{-1} 3434, 3343, 2938, 2885, 1690, 1615, 1175, 978, 795; δ_H (500 MHz, $CDCl_3$) 8.07 (1 H, br s, NH), 7.17 (1 H, d, *J* 1.4, CH), 6.96 (1 H, br s, NH), 6.89 (1 H, d, *J* 2.3, CH), 6.65 (1 H, d, *J* 1.4, CH), 3.94 (3 H, s, Me), 3.62 (2 H, dd, *J* 12.0, 5.7, CH_2), 3.12 (2 H, dd, *J* 9.3, 3.4, CH_2); δ_C (100 MHz, $CDCl_3$) 154.2 (C=O), 138.5 (C), 122.0 (CH), 116.12 (C), 116.10 (C), 113.1 (C), 108.3 (CH), 104.3 (CH), 55.7 (Me), 42.2 (CH_2), 25.4 (CH_2), 2 x C not observed.

_N_-(2-(6-Bromo-4-methoxyindol-3-yl)ethyl)pyrrole-2-carboxamide (8)

A suspension of tryptamine **5** (70 mg, 0.19 mmol) and potassium carbonate (106 mg, 0.77 mmol, 4.0 equiv) in methanol (18.5 mL) and water (1.5 mL) was heated at reflux for 4 hr. The reaction mixture was concentrated *in vacuo* and water (50 mL) was added. The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic phases washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude tryptamine **6** that was used directly in the next step without further purification.

To a solution of crude tryptamine **6** in DMF (2 mL) was added 2-(trichloroacetyl) pyrrole (41 mg, 0.193 mmol). The reaction mixture was stirred at room temperature for 6 h and then diluted with dichloromethane (15 mL). The organic layer was washed with water, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:1) gave the *title compound* (47 mg, 0.13 mmol, 68 % over two steps) as a light brown solid, M.p. 206.4−210.9 °C (lit.[4] mp not given); HRMS [ESI, $(M + Na)^+$] found 384.0312; $[C_{16}H_{16}{}^{79}BrN_3O_2 + Na]^+$ requires 384.0318; ν_{max} (neat)/cm^{-1} 3372, 3278, 2998, 2836, 1607, 1607, 1557, 740; δ_H (400 MHz, $(CD_3)_2SO$) 11.36 (1 H, br s, NH), 10.91 (1 H, br s, NH), 7.95 (1 H, t, *J* 5.7, NH), 7.11 (1 H, d, *J* 1.5, CH), 7.01 (1 H, d, *J* 2.3, CH), 6.82 (1 H, td, *J* 2.7, 1.5, CH), 6.72 (1 H, ddd, *J* 3.8, 2.5, 1.5, CH), 6.57 (1 H, d, *J* 1.5, CH), 6.05 (1 H, dt, *J* 3.6, 2.4, CH), 3.86 (3 H, s, Me), 3.48 (2 H, dd, *J* 13.2, 7.2, CH_2), 2.99 (2 H, t, *J* 7.3, CH_2); δ_C (100 MHz, $(CD_3)_2SO$) 160.5 (C), 154.6 (C), 138.1 (C), 126.5 (C), 122.0 (CH), 120.9 (CH), 116.0 (C), 113.8 (C), 112.5 (C), 110.5 (CH), 109.5 (CH), 108.3 (CH), 107.5 (CH), 102.4 (CH), 55.4 (Me), 26.8 (CH_2). Spectroscopic data consistent with literature.[4]

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Supplementary Data Available. ^1H / ^{13}C NMR spectra for all novel compounds.

REFERENCES

1. Hanssen, K. Ø.; Schuler, B.; Williams, A. J.; Demissie, T. B.; Hansen, E.; Andersen, J. H.; Svenson, J.; Blinov, K.; Repisky, M.; Mohn, F.; Meyer, G.; Svendsen, J.-S.; Ruud, K.;

Elyashberg, M.; Gross, L.; Jaspars, M.; Isaksson, J. *Angew. Chem., Int. Ed*. **2012**, *51*, 12238−12241.

2. For natural products harbouring a 4,6-disubstituted indole, see: (a) Franco, L. H; de Kier Joffé, E. B.; Puricelli, L.; Tatian, M.; Seldes, A. M.; Palermo, J. A. *J. Nat. Prod*. **1998**, *61*, 1130−1132; (b) Motohashi, K.; Takagi, M.; Shin-ya, K. *J. Nat. Prod* **2010**, *73*, 226−228; (c) Fu, P.; Jamison, M.; La, S.; MacMillan, J. B. *Org. Lett*. **2014**, *16*, 5656−5659; (d) Patiño C, L. P.; Muniain, C.; Knott, M. E.; Puricelli, L.; Palermo, J. A. *J. Nat. Prod*. **2014**, *77*, 1170−1178; (e) Izumikawa, M.; Kawahara, T.; Kagaya, N.; Yamamura, H.; Hayakawa, M.; Takagi, M.; Yoshida, M.; Doi, T.; Shin-ya, K. *Tetrahedron Lett*. **2015**, *56*, 5333−5336.

3. Pandey, S. K.; Guttormsen, Y.; Haug, B. E.; Hedberg, C.; Bayer, A. *Org. Lett*. **2015**, *17*, 122−125.

4. Khan, A. H.; Chen, J. S. *Org. Lett*. **2015**, *17*, 3718−3721.

5. For the synthesis of 4,6-disubstituted indoles using (hetero)annulation reactions (a) Sofiyev, V.; Lumb, J.-P.; Volgraf, M.; Trauner, D. *Chem. Eur. J*. **2012**, *18*, 4999−5005; (b) Chernyak, N.; Buchwald, S. L. *J. Am. Chem. Soc.*, **2012**, *134*, 12466–12469; (c) Lam, T. Y.; Wang, Y.-P.; Danheiser, R. L. *J. Org. Chem.* **2013**, *78*, 9396−9414; (d) Hayashi, K.; Yoshida, K.; Yanagisawa, A. *J. Org. Chem.* **2013**, *78*, 3464–3469; (e) Reddy, C. R.; Dilipkumar, U.; Reddy, M. D. *Org. Lett*. **2014**, *16*, 3792−3795; (f) Guo, T.; Jiang, Q.; Yu, Z. *Org. Chem. Front.* **2015**, *2*, 1361−1365; (g) Li, Y.; Waser, J. *Angew. Chem., Int. Ed*. **2015**, *54*, 5438−5442; (h) Bhusal, R. P.; Sperry, J. *Green Chem*. **2016**, *18*, 2453−2459; (i) Li, X.; Xie, H.; Fu, X.; Liu, J.-t.; Wang, H.-y.; Xi, B.-m.; Liu, P.; Xu, X.; Tang, W. *Chem. Eur. J*. **2016**, *22*, 10410−10414.

6. For the synthesis of 4,6-disubstituted indoles by indolyne insertion, see: (a) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc*. **2011**, *133*, 3832−3835; (b) Fine Nathel, N. F.; Shah, T. K.; Bronner, S. M.; Garg, N. K. *Chem. Sci*. **2016**, *5*, 2184−2190; (c) Yang, Y.; Li,

R.; Zhao, D.; Shi, Z. *J. Am. Chem. Soc.* **2016**, *138*, 8734−8737; C−H diamination: (d) Dong, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 18350−18353.

7. (a) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett*. **2002**, *4*, 815−817; For directed thallation, see: (b) Yamada, F.; Tamura, M.; Somei, M. *Heterocycles* **1998**, *49*, 451−457; (c) Carr, Gavin; Chung, Marco K. W.; Mauk, A. Grant; Andersen, Raymond J. *J. Med. Chem.* **2008**, *51*, 2634−2637; (d) Pedras, M. Soledade C. Hossain, S. *Phytochemistry*, **2011**, *72*, 2308−2316.

8. (a) Leitch, J. A.; Bhonoah, Y.; Frost, C. G. *ACS Catal.* **2017**, *7*, 5618–5627; (b) For a recent report describing the radical functionalization of indoles at C4 with cycloalkanes, see: Xiu, J.; Yi, W. *Catal. Sci. Technol*. **2016**, *6*, 998−1002.

9. (a) Wang, P.; Farmer, M. E.; Huo, X.; Jain, P.; Shen, P.-X.; Ishoey, M.; Bradner, J. E.; Wisniewski, S. R.; Eastgate, M. E.; Yu, J.-Q. *J. Am. Chem. Soc*. **2016**, *138*, 9269−9276; (b) Wang, P.; Li, G-C.; Jain, P.; Farmer, M. E.; He, J.; Shen, P.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 14092–14099; (c) Shi, H.; Wang, P.; Suzuki, S.; Farmer, M. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 14876–14879.

10. For the synthesis of a 4-trifluoromethoxyindole by OCF_3 migration, see: Hojczyk, K. N.; Feng, P.; Zhan, C.; Ngai, M.-Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 14559–14563.

11. (a) Beswick, P. J.; Greenwood, C. S.; Mowlem, T. J.; Nechvatal, G.; Widdowson, D. A. *Tetrahedron* **1988**, *44*, 7325−7334; (b) Dickens, M. J.; Gilday, J. P.; Mowlem, T. J.; Widdowson, D. A. *Tetrahedron* **1991**, *47*, 8621−8634; (c) Semmelhack, M. F.; Knochel, P.; Singleton, T. *Tetrahedron Lett.* **1993**, *34*, 5051–5054.

12. (a) Eastabrook, A. S.; Sperry. J. *Aus. J. Chem.* **2015**, *68*, 1810−1814; (b) Eastabrook, A. S.; Wang, C.; Davison, E. K. Sperry. J. *J. Org. Chem*. **2015**, *80*, 1006−1017; (c) Eastabrook, A. S.; Sperry. J. *Synthesis*, **2017**, *49*, 4731−4737.

13. Shen, F.; Tyagarajan, S.; Perera, D.; Krska, S. W.; Maligres, P. E.; Smith III, M. R.; Maleczka Jr, R. E. *Org. Lett*. **2016**, *18*, 1554−1557.

14. (a) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett*. **1998**, *39*, 2933–2936; (b) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett*. **1998**, *39*, 2937–2940; (c) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett*. **1998**, *39*, 2941–2944; Review: (d) Qiao, J.; Lam, P. Y. S. *Synthesis*, **2011**, 829−856.

15. Quach, T. D.; Batey, R. A. *Org. Lett*. **2003**, *5*, 1381−1384.

16. Righi, M.; Topi, F.; Bartolucci, S.; Bedini, A.; Piersanti, G.; Spadoni, G. *J. Org. Chem.* **2012**, *77*, 6351–6357.

17. (a) Lee, A.-L. *Org. Biomol. Chem.*, **2016**, *14*, 5357–5366; (b) *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, 2005

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