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Convergent Total Syntheses of the Amaryllidaceae Alkaloids Lycoranine A, Lycoranine B, and 2-Methoxypratosine

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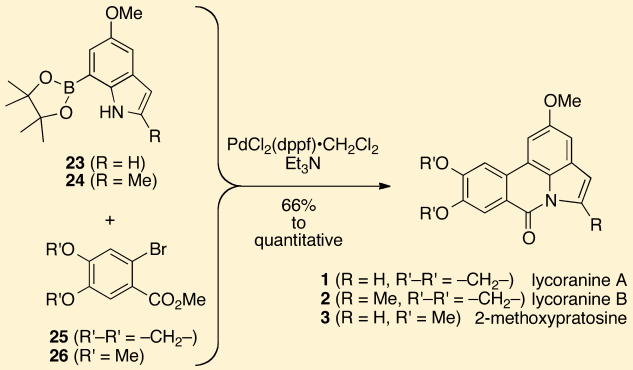
Supporting Information

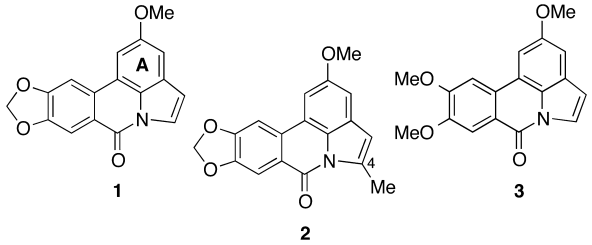
ABSTRACT: The title alkaloids, **1**, **2**, and **3** respectively, have been prepared in a convergent manner by two related routes. The superior one involves C−H functionalization of the relevant 5-methoxyindole at C-7 using Hartwig's protocol and thus forming the corresponding borolated indole that could be coupled with the requisite 2-bromobenzoate to deliver the title natural products. Single crystal X-ray analyses of the synthetically derived samples of compounds **1** and **2** are reported.



Lycoranine A (**1**) and lycoranine B (**2**) were isolated from the bulbs of *Lycoris radiata*, an Amaryllidaceae species collected in the Zhejiang Province of China and the crude extracts of which have been used as folk remedies for laryngeal problems as well as for the treatment of boils and carbuncles.[1] The structures of compounds **1** and **2** were proposed on the basis of extensive spectroscopic analyses, most particularly various 2D NMR studies. They represent the first examples of the pyrrolophenanthridinone class of natural product incorporating oxygenation (in this case in the form of a methoxy group) in the A-ring. The presence of the C4 methyl group in compound **2** is of biosynthetic interest because it suggests that the decarboxylation step that takes place during the *in vivo* production of all previously reported alkaloids of this type is not an obligatory event. The related 2-methoxypratosine (**3**, aka 2-MPT) was isolated from whole plants of *Narcissus serotinus L.*, an autumn flowering species collected in the Spanish region of Valencia, and its structure was established using the usual range of spectroscopic techniques.[2] Alkaloids of the genus *Narcissus* have been shown to possess, inter alia, cytotoxic, antiparasitic, and antifungal properties.[3]

Given the continued interest in the biological properties of the pyrrolophenanthridinone alkaloids generally,[4] the limited quantities of the title natural products available from their natural sources, and the lack of biological data on them, we sought to establish concise syntheses of these novel compounds. Details of the outcome of our studies in this area, which have culminated in total syntheses of the title alkaloids (**1**, **2**, and **3**, respectively),[5] are presented herein.

Our initial approach to compounds **1**, **2**, and **3** involved coupling the readily derived 2,6-dibromo-derivative, **5**,[6] of *p*-anisidine (**4**) (Scheme 1) with the known[7] acid chloride **6**, thereby generating the amide **7** in 55% yield. However,



compound **7** failed to participate in the desired intramolecular Ullmann cross-coupling reaction[8] to deliver phenanthridinone **8**. Rather, upon exposure to copper powder in DMSO, acetanilide **7** afforded, probably via dimerization of intermediate benzoxazole **9**, the novel polycyclic compound **10** (7%). While all of the spectroscopic data obtained on this last compound were in accord with the assigned structure, final confirmation of this followed from a single-crystal X-ray analysis.[9] The conversion **7** → **9** is not without precedent. Thus, for example, Glorius, Batey, and Sekar[10] have each shown that various amides derived from *o*-bromoanilines are converted, via C−O bonding forming processes, into the corresponding benzoxazoles upon treatment of the former compounds with certain copper species.

The lack of success associated with the above-mentioned approach to the title alkaloids prompted consideration of one of a number introduced by Tønder et al.[5r] and wherein Suzuki−Miyaura cross-coupling of a C-7 halogenated indole with an *o*-borolated benzoate is followed by an in situ lactamization reaction that delivers the pyrrolophenanthridinone framework. A related approach has been delineated by Snieckus[5l] wherein a

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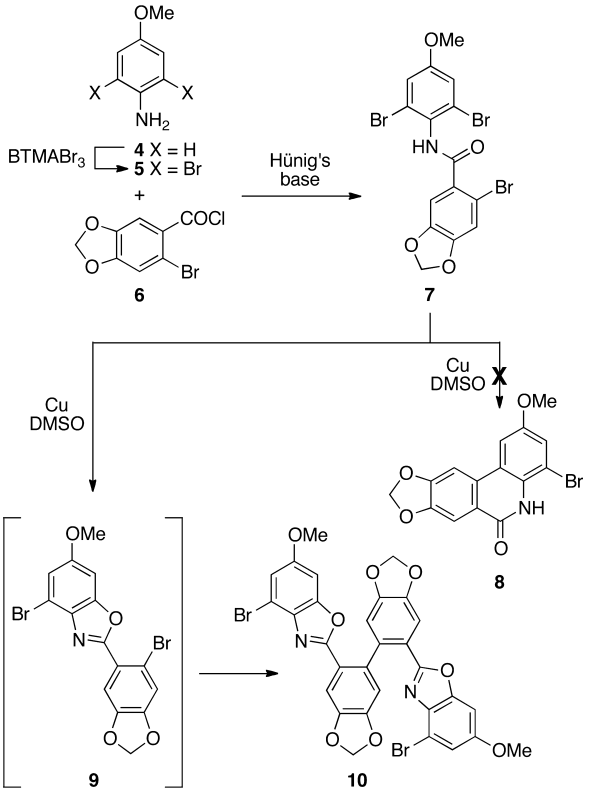
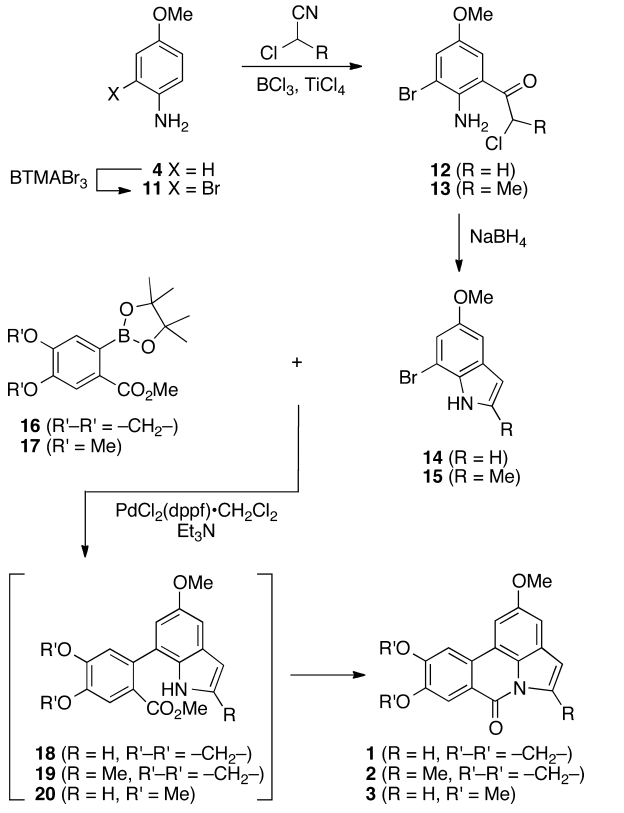
Scheme 1



Scheme 2



C-7 borolated indole is cross-coupled with an *o*-halogenated benzoic acid ester. Pursuit of either one of these variants requires construction of the relevant C-7 substituted indole, a nontrivial task. While the Bartoli reaction[11] failed[12] to provide a means for converting 2-bromo-4-methoxynitrobenzene into 7-bromo-5-methoxyindole and its C-2 methylated derivative (as required for the assembly of targets **1**–**3** via Tønder's approach), these heterocycles could be prepared using modifications to an underutilized protocol reported some time ago by Sugasawa et al.[13] In particular, and as shown in Scheme 2, reaction of *p*-anisidine (**4**) with benzyltrimethylammonium tribromide ($BTMABr_3$)[14] afforded the monobromo-derivative **11**[6,15] (40%) that upon reaction with either *α*-chloroacetonitrile or *α*-chloropropionitrile in the presence of boron trichloride and titanium tetrachloride gave the 2-amino-*α*-chloroacetophenone **12** or the corresponding propiophenone **13** in 45% and 51% yields, respectively. Independent treatment of these aryl ketones with sodium borohydride resulted in sequential reductive cyclization and elimination reactions to afford the required indole **14**[16] (81%) or **15** (93%). In the final step, compound **14** was engaged in a Suzuki–Miyaura cross-coupling reaction with the readily available arylboronate ester **16**[17] or its dimethoxy-analogue **17**[18] to afford, presumably via either intermediate **18** or **20**, target compounds **1**[1] (81%) and **3**[2] (89%), respectively. In an analogous manner, indole **15** was coupled with arylboronate ester **16** and thereby affording, via intermediate **19**, lycoranine B (**2**)[1] in 65% yield. The NMR spectroscopic properties of the synthetically derived samples of compounds **1**–**3** were in complete accord with the assigned structures and matched those reported for the natural products (see Tables 1 and 2). Final confirmation of the structures of targets **1** and **2** followed from single-crystal X-ray analyses.[9] The derived ORTEPs are shown in the Supporting Information.

As noted above, the reversal of the polarity of the cross-coupling process used by Tønder[5r] in his approach to pyrrolophenanthridinones has been introduced by Snieckus and co-workers.[5l] The C-7 borolated indoles required in applying such an approach can be prepared in various ways including via directed-metalation techniques. In a recent refinement of these, Hartwig et al.[5t] have established an iridium-catalyzed method for the direct borolation of indoles at C-7 and exploited this in a one-pot synthesis of the natural product hippadine (the demethoxy-analogue of lycoranine A). Accordingly, we sought to explore the utility of such methodology in allowing access to the title natural products. To such ends, each of the commercially available indoles **21** and **22** was subjected, in a one-pot operation, to treatment with $[Ru(p\text{-cymene})Cl_2]_2$ and diethylsilane (so as to form the corresponding *N*-hydrosilylindole) and then/or $[Ir(OMe)\text{-}COD]_2$ in the presence of 4,4′-di-*tert*-butyl-2,2′-bipyridine (di-*t*-bpy), bis(pinacolato)diboron (B_2Pin_2), and pinacolborane (HBPin) followed by a "workup" using aqueous sodium acetate (Scheme 3). By such means the requisite C-7 borolated indole, **23**[5t,19] (36%) and **24**[20] (66%) respectively, was obtained. Pleasingly, Suzuki–Miyaura cross-coupling of compound **23** with the readily available 2-bromobenzoate **25**[17] afforded lycoranine A (**1**) in 88% yield while analogous coupling of the same indole with bromobenzoate **26**[19] yielded 2-MPT (**3**) in near-quantitative yield. Similarly, coupling of compounds **24** and **25** led directly to lycoranine B (**2**) which was obtained in 66% yield. The spectral data recorded on each of compounds **1**–**3** obtained via the Snieckus/Hartwig route matched those derived from the materials secured using Tønder's approach.

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Table 1. Comparison of the ^{13}C NMR Data (δ_C) Recorded for the Synthetically Derived Samples of Compounds 1−3 with Those Reported for Lycoranines A and B and 2-MPT

compd 1[a]	lycoranine A[b]	compd 2[a]	lycoranine B[b]	compd 3[a]	2-MPT[c]
157.9	157.9	159.6	159.6	158.1	158.3
157.6	157.6	157.4	157.4	157.6	157.7
152.5	152.5	152.4	152.4	153.6	153.7
148.7	148.7	148.5	148.5	149.8	149.9
131.3	131.3	140.1	140.1	129.1	129.3
128.9	128.9	131.3	131.3	128.9	129.1
126.3	126.3	128.2	128.2	126.4	126.6
124.1	124.1	127.0	126.9	124.0	124.2
122.8	122.9	123.5	123.5	121.0	121.2
116.9	116.9	116.5	116.5	116.9	117.1
110.7	110.7	109.1	109.1	110.5	110.7
108.2	108.2	108.0	108.0	110.3	110.4
107.3	107.4	106.1	106.1	106.7	106.9
106.0	106.0	103.9	103.9	106.0	106.2
102.3	102.3	102.2	102.2	103.9	104.1
101.8	101.8	101.5	101.5	56.4	56.5
56.3	56.4	56.3	56.3	56.3	56.4
–	–	16.0	15.9	56.2	56.4

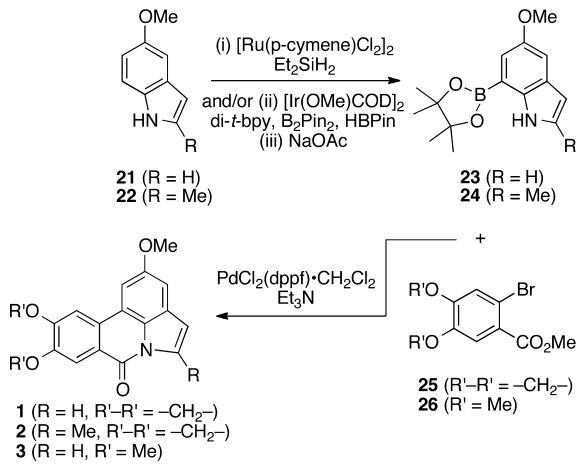
[a]Recorded in $CDCl_3$ at 200 MHz on a sample obtained by route described above. [b]Obtained from ref 1; recorded in $CDCl_3$ at 100 MHz. [c]Obtained from ref 2; recorded in $CDCl_3$ at 125 MHz.

Table 2. Comparison of the ^{1}H NMR Data (δ_H) Recorded for the Synthetically Derived Samples of Compounds 1−3 with Those Reported for Lycoranines A and B and 2-MPT

compd 1[a]	lycoranine A[b]	compd 2[a]	lycoranine B[b]	compd 3[a]	2-MPT[c]
8.01 (1H, d, *J* = 3.2 Hz)	8.01 (1H, d, *J* = 3.6 Hz)	7.97 (1H, s)	7.96 (1H, s)	8.01 (1H, d, *J* = 3.6 Hz)	8.03 (1H, d, *J* = 3.5 Hz)
7.98 (1H, s)	7.98 (1H, s)	7.57 (1H, s)	7.56 (1H, s)	7.98 (1H, s)	8.01 (1H, s)
7.59 (1H, s)	7.59 (1H, s)	7.39 (1H, d, *J* = 1.9 Hz)	7.38 (1H, d, *J* = 1.9 Hz)	7.55 (1H, s)	7.59 (1H, s)
7.50 (1H, d, *J* = 1.6 Hz)	7.49 (1H, d, *J* = 1.9 Hz)	7.18 (1H, d, *J* = 1.9 Hz)	7.17 (1H, d, *J* = 1.9 Hz)	7.51 (1H, d, *J* = 1.6 Hz)	7.55 (1H, d, *J* = 2.0 Hz)
7.30 (1H, d, *J* = 1.6 Hz)	7.30 (1H, d, *J* = 1.9 Hz)	6.48 (1H, q, *J* = 1.2 Hz)	6.47 (1H, s)	7.28 (1H, d, *J* = 1.6 Hz)	7.30 (1H, d, *J* = 2.0 Hz)
6.83 (1H, d, *J* = 3.2 Hz)	6.82 (1H, d, *J* = 3.6 Hz)	6.16 (2H, s)	6.16 (2H, s)	6.82 (1H, d, *J* = 3.6 Hz)	6.84 (1H, d, *J* = 3.5 Hz)
6.17 (2H, s)	6.17 (2H, s)	3.95 (3H, s)	3.95 (3H, s)	4.11 (3H, s)	4.12 (3H, s)
3.97 (3H, s)	3.96 (3H, s)	2.88 (3H, d, *J* = 1.2 Hz)	2.87 (3H, s)	4.06 (3H, s)	4.07 (3H, s)
–	–	–	–	3.97 (3H, s)	3.98 (3H, s)

[a]Recorded in $CDCl_3$ at 800 MHz on sample obtained by route described above. [b]Obtained from ref 1; recorded in $CDCl_3$ at 400 MHz. [c]Obtained from ref 2; recorded in $CDCl_3$ at 500 MHz.

Scheme 3



The two approaches to the title natural products reported herein only differ in the nature of the polarity of the pivotal Suzuki−Miyaura cross-coupling reactions. The second approach is superior because of the ready ease of access to C-7 borolated indoles using Hartwig chemistry[5t] and the removal of any need, therefore, to convert 2-bromobenzoates into the corresponding 2-borolated congeners. The present studies not only serve to confirm the structures assigned to the title natural products but also provide a means by which sufficient quantities can be generated so as to undertake appropriate biological evaluations, a worthwhile endeavor given the generally significant cytotoxic, antifungal, and/or other biological properties of many pyrrolophenanthridinones.

EXPERIMENTAL SECTION

General Experimental Procedures. These have been detailed elsewhere.[21] Certain NMR spectra were recorded on an 800 MHz instrument.

Compound 5. A magnetically stirred solution of compound **4** (1.00 g, 8.12 mmol) in dichloromethane/methanol (100 mL of a 3:1 v/v mixture) was treated with calcium carbonate (3.02 g, 30.2 mmol) and benzyltrimethylammonium tribromide (6.49 g, 16.6 mmol). The ensuing mixture was stirred at 18 °C for 2 h and then filtered through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure and then treated with HCl (80 mL of a 1 M aqueous solution) before being extracted with dichloromethane (3 × 80 mL). The combined organic extracts were washed with brine (1 × 100 mL),

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then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a dark-purple oil. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.35) then gave the title compound **5**[6] (1.69 g, 74%) as a white, crystalline solid, mp 81−82 °C (lit.[6] mp 79−80 °C) (Found: $M^{+\bullet}$, 278.8896. Calcd for $C_7H_7{}^{79}Br_2NO$: $M^{+\bullet}$, 278.8894). ^1H NMR ($CDCl_3$, 400 MHz) 7.01 (s, 2H), 4.19 (broad s, 2H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 152.0, 136.2, 118.0, 109.1, 56.1; IR ν_{max} (KBr) 3401, 3281, 2950, 2928, 2829, 1591, 1551, 1480, 1435, 1313, 1234, 1207, 1045, 836 cm^{-1}; Mass spectrum (EI) *m*/*z* 283, 281, and 279 ($M^{+\bullet}$, 43, 75, and 45%), 268, 266, and 264 (58, 100, and 61), 240, 238, and 236 (16, 27, and 16), 78 (35).

Compound 7. A magnetically stirred suspension of the carboxylic acid precursor to compound **6** (261 mg, 1.07 mmol) in dichloromethane (10 mL) maintained at 0 °C was treated with oxalyl chloride (0.12 mL, 1.40 mmol) and DMF (3 drops). The ensuing mixture was stirred at 0 °C for 0.08 h, then allowed to warm to 18 °C, and stirred at this temperature for 0.5 h before being cooled back to 0 °C and then treated, dropwise, with a solution of compound **5** (360 mg, 1.28 mmol) and triethylamine (0.37 mL, 2.65 mmol) in dichloromethane (5 mL). The resulting solution was stirred at 0 °C for 0.5 h, then allowed to warm to 18 °C, and stirred at this temperature for 3.5 h before being poured into ice-cold $NaHCO_3$ (20 mL of a saturated aqueous solution) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with HCl (1 × 30 mL of a 1 M aqueous solution) and brine (1 × 30 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow oil. Trituration of this material with ice-cold dichloromethane then gave the *title compound* **7** (295 mg, 55%) as a white, crystalline solid, mp 233−235 °C [Found: $(M + H)^+$, 505.8238. Calcd for $C_{15}H_{10}{}^{79}Br_3NO_4$: $(M + H)^+$, 505.8238]. ^1H NMR (DMSO-d_6, 400 MHz) 10.13 (s, 1H), 7.35 (s, 2H), 7.32 (s, 1H), 7.14 (s, 1H), 6.16 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) 165.3, 159.0, 149.2, 146.7, 131.1, 127.8, 124.7, 117.7, 113.1, 110.6, 108.7, 102.5, 56.2; IR ν_{max} (KBr) 3216, 3182, 3008, 2960, 2896, 1671, 1594, 1514, 1496, 1475, 1258, 1227, 1038, 935 cm^{-1}; MS (ESI) *m*/*z* 532 and 530 [$(M + Na)^+$, 96 and 100%], 510 and 508 [$(M + H)^+$, both 34], 350 and 348 (27 and 30), 339, 337, and 335 (18, 35, and 18), 229 and 227 (36 and 35).

Compound 10. A magnetically stirred solution of compound **7** (200 mg, 0.394 mmol) in DMSO (5 mL) was treated with Cu powder (125 mg, 1.97 mmol), and the ensuing mixture was stirred at 100 °C for 48 h. The cooled reaction mixture was diluted with dichloromethane (20 mL), and the resulting solution was washed with NH_4OH (2 × 10 mL of a 4% aqueous solution) and then water (1 × 10 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a brown oil. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.15) then gave the *title compound* ***10*** (18 mg, 7%) as a white, crystalline solid, mp 266−270 °C [Found: $(M + Na)^+$, 714.9328. Calcd for $C_{30}H_{18}{}^{79}Br_2N_2O_8$: $(M + Na)^+$, 714.9328]. ^1H NMR ($CDCl_3$, 400 MHz) 7.72 (s, 2H), 7.03 (d, *J* = 2.0 Hz, 2H), 6.77 (s, 2H), 6.67 (d, *J* = 2.0 Hz, 2H), 6.10 (broad s, 4H), 3.78 (s, 6H); ^{13}C NMR ($CDCl_3$, 200 MHz) 162.3, 158.1, 151.1, 149.7, 147.4, 136.2, 135.1, 120.1, 115.6, 112.2, 111.2, 109.5, 102.0, 94.9, 56.2; IR ν_{max} (KBr) 3105, 2965, 2909, 2838, 1615, 1598, 1475, 1441, 1307, 1260, 1236, 1202, 1119, 1030, 974, 826 cm^{-1}; MS (ESI) *m*/*z* 719, 717, and 715 [$(M + Na)^+$, 47, 85, and 40%], 697, 695, and 693 [$(M + H)^+$, 48, 78, and 43], 617 and 615 (41 and 40), 169 (100).

Compound 11. A magnetically stirred solution of compound **4** (1.98 g, 16.08 mmol) in dichloromethane/methanol (150 mL of a 2:1 v/v mixture) was treated with benzyltrimethylammonium tribromide (6.58 g, 16.87 mmol). The ensuing mixture was stirred at 20 °C for 2 h and then treated with Na_2SO_3 (100 mL of a saturated aqueous solution) before being extracted with diethyl ether (1 × 150 mL). The separated organic extract was washed with water (1 × 100 mL) and brine (1 × 100 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a dark-red oil. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.15) gave the title compound **11**[6,15] (1.31 g, 40%) as a light-brown oil (Found: $M^{+\bullet}$, 200.9790. Calcd for $C_7H_8{}^{79}BrNO$: $M^{+\bullet}$, 200.9789). ^1H NMR ($CDCl_3$, 400 MHz) 7.01 (d, *J* = 2.4 Hz, 1H), 6.71 (m, 2H), 3.83 (broad s, 2H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 152.5, 137.8, 117.4, 116.5, 114.9, 109.4, 55.8; IR ν_{max} (KBr) 3442, 3359, 3203, 2999, 2947, 2832, 1623, 1600, 1574, 1499, 1440, 1274, 1230, 1212, 1037, 865, 808 cm^{-1}; MS (EI) *m*/*z* 203 and 201 ($M^{+\bullet}$, 74 and 75%), 188 and 186 (99 and 100), 160 and 158 (17 and 18), 86 (29), 84 (45).

Compound 12. A magnetically stirred solution of compound **11** (336 mg, 1.66 mmol) in dichloromethane (15 mL) maintained at 0 °C was treated, dropwise, with boron trichloride (2.5 mL of a 1 M solution in dichloromethane, 2.50 mmol), α-chloroacetonitrile (0.2 mL, 3.16 mmol), and then titanium tetrachloride (2.5 mL of a 1 M solution in dichloromethane, 2.50 mmol). The ensuing mixture was heated at reflux for 72 h before being cooled to 18 °C and poured into a mixture of ice and HCl (10 mL of a 20% aqueous solution). The volatile organic component of the resulting biphasic system was removed by distillation, and the aqueous residue was heated at reflux for 0.5 h. The cooled reaction mixture was then treated, dropwise at 0 °C, with NaOH (40 mL of a saturated aqueous solution) until pH 4 was attained, and then it was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with brine (1 × 100 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown solid. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.25) gave the *title compound* ***12*** (209 mg, 45%) as a yellow, crystalline solid, mp 80−81 °C (Found: $M^{+\bullet}$, 276.9506. Calcd for $C_9H_9{}^{79}Br^{35}ClNO_2$: $M^{+\bullet}$, 276.9505). ^1H NMR ($CDCl_3$, 400 MHz) 7.36 (d, *J* = 3.2 Hz, 1H), 7.15 (d, *J* = 3.2 Hz, 1H), 4.66 (s, 2H), 3.78 (s, 3H) (signals due to NH_2 group protons obscured/not observed); ^{13}C NMR ($CDCl_3$, 100 MHz) 191.7, 149.3, 143.1, 126.7, 115.3, 113.9, 112.0, 56.3, 46.5; IR ν_{max} (KBr) 3478, 3342, 2988, 2938, 1664, 1568, 1535, 1455, 1231, 1048, 834 cm^{-1}; MS (EI) *m*/*z* 281, 279, and 277 ($M^{+\bullet}$, 24, 93, and 73%), 230 and 228 (94 and 100), 202 and 200 (30 and 32), 86 (30), 84 (45), 78 (29).

Compound 13. A magnetically stirred solution of compound **11** (570 mg, 2.82 mmol) in 1,2-dichloroethane (13 mL) maintained at 0 °C was treated, dropwise, with boron trichloride (3.4 mL of a 1 M solution in dichloromethane, 3.40 mmol), α-chloropropionitrile (0.37 mL, 4.18 mmol), and titanium tetrachloride (3.4 mL of a 1 M solution in dichloromethane, 3.40 mmol). The ensuing mixture was heated at reflux for 24 h before being cooled to 18 °C and then poured into a mixture of ice and HCl (10 mL of a 20% aqueous solution). The volatile organic component of the resulting biphasic system was removed by distillation, and the aqueous residue was heated at reflux for 0.5 h. The cooled reaction mixture was treated, dropwise at 0 °C, with NaOH (40 mL of a saturated aqueous solution) until pH 4 was attained and then extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with brine (1 × 100 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown solid. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.30) then gave the *title compound* ***13*** (420 mg, 51%) as a yellow, crystalline solid, mp 107−108 °C (Found: $M^{+\bullet}$, 292.9646. Calcd for $C_{10}H_{11}{}^{81}Br^{35}ClNO_2$: $M^{+\bullet}$, 292.9641). ^1H NMR ($CDCl_3$, 400 MHz) 7.35 (d, *J* = 3.2 Hz, 1H), 7.30 (d, *J* = 3.2 Hz, 1H), 5.24 (q, *J* = 6.8 Hz, 1 H), 3.78 (s, 3H), 1.73 (d, *J* = 6.8 Hz, 3H) (signal due to NH_2 protons obscured/not observed); ^{13}C NMR ($CDCl_3$, 100 MHz) 194.4, 149.3, 143.5, 126.7, 115.1, 114.2, 111.9, 56.3, 53.0, 20.3; IR ν_{max} (KBr) 3427, 3314, 2960, 1647, 1568, 1533, 1454, 1363, 1249, 1219, 1049, 896, 844, 784 cm^{-1}; MS (EI) *m*/*z* 295, 293, and 291 ($M^{+\bullet}$, 15, 58, and 46%), 230 and 228 (98 and 100), 202 and 200 (30 and 31), 78 (28).

Compound 14. A magnetically stirred solution of compound **12** (209 mg, 0.750 mmol) in 1,4-dioxane/water (10 mL of a 9:1 v/v mixture) was treated with sodium borohydride (29 mg, 0.767 mmol).

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The ensuing mixture was heated at reflux for 17 h, then cooled, poured into HCl (10 mL of a 0.1 M aqueous solution), and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.25) then gave the title compound **14**[16] (137 mg, 81%) as a pale-yellow, crystalline solid, mp 66−68 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 8.18 (broad s, 1H), 7.24 (t, J = 2.6 Hz, 1H), 7.06 (s, 2H), 6.55 (dd, J = 2.8 and 2.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 154.6, 130.1, 128.8, 125.4, 114.6, 104.5, 103.6, 102.2, 56.2; IR ν_{max} (KBr) 3423, 3123, 2998, 2934, 2830, 1620, 1563, 1479, 1313, 1295, 1222, 1133, 1033, 965 cm^{-1}.

Compound 15. Compound **13** (213 mg, 0.728 mmol) was subjected to the same procedure as employed for the conversion **12** → **14**, and a brown oil was thereby obtained. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) then gave the *title compound* ***15*** (163 mg, 93%) as a white, crystalline solid, mp 68−69 °C (Found: M$^{+\bullet}$, 240.9928. $C_{10}H_{10}{}^{81}BrNO$ requires M$^{+\bullet}$, 240.9925). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.88 (broad s, 1H), 6.95 (t, J = 2.4 Hz, 2H), 6.21 (m, 1H), 3.82 (s, 3H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 154.4, 136.7, 130.1, 130.0, 112.8, 103.6, 101.7, 101.5, 56.2, 13.8; IR ν_{max} (KBr) 3425, 2937, 1578, 1486, 1396, 1223, 1204, 1125, 1037, 834 cm^{-1}; MS (EI) m/z 241 and 239 (M$^{+\bullet}$, 98 and 100%), 226 and 224 (45 and 46), 198 and 196 (41 and 42), 117 (30).

Compound 23. While being maintained in a drybox, a dry borosilicate glass tube containing a stirring bar and capable of being fitted with a PTFE-lined screwcap was charged with indole **21** (148 mg, 1.01 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (6 mg, 0.01 mmol, 1 mol %), diethylsilane (0.194 mL, 1.50 mmol), and degassed toluene (0.5 mL). The ensuing mixture was sealed in the tube and stirred at 20 °C for 18 h before being concentrated under reduced pressure to afford a brown oil. [Ir(OMe)COD]$_2$ (10 mg, 0.015 mmol, 3 mol %), di-*tert*-butylbipyridine (8 mg, 0.03 mmol, 3 mol %), bis(pinacolato)diboron (383 mg, 1.51 mmol), pinacolborane (0.02 mL, 0.138 mmol), and degassed THF (1 mL) were then added to this oil, and the ensuing mixture was stirred at 80 °C for 22 h. After the mixture had cooled to 20 °C, the volatile components of the reaction mixture were removed under high vacuum at 40 °C. The resulting brown oil was dissolved in THF (2 mL), and the solution thus obtained treated with sodium acetate (0.5 mL of 3 M aqueous solution). The ensuing mixture was stirred at 20 °C for 4 h before being diluted with diethyl ether (20 mL) and water (20 mL). The separated aqueous layer was extracted with diethyl ether (2 × 20 mL), and the combined organic extracts were washed with brine (1 × 20 mL), then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a brown oil. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.25) then gave the title compound **23**[St,19] (97 mg, 36%) as a white, crystalline solid, mp 106−109 °C (Found: M$^{+\bullet}$, 273.1537. $C_{15}H_{20}{}^{11}BNO_3$ requires M$^{+\bullet}$, 273.1536). ^{1}H NMR ($CDCl_3$, 400 MHz) 9.08 (broad s, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 7.23 (broad t, J = 2.8 Hz, 1H), 6.46 (dd, J = 2.8 and 2.0 Hz, 1H), 3.86 (s, 3H), 1.38 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 153.8, 136.4, 127.6, 124.8, 117.8, 107.6, 101.5, 83.9 (2C), 56.2, 25.0 (4C) (signal due to one carbon obscured or overlapping); IR ν_{max} (KBr) 3454, 2978, 2935, 1598, 1477, 1426, 1371, 1315, 1218, 1137, 1039, 985 cm^{-1}; MS (EI) m/z 274 [(M+H)$^+$, 30%], 273 and 272 (M$^{+\bullet}$, 100 and 40), 258 and 257 (13 and 4), 216 and 215 (34 and 11), 191 (16), 173 (61), 158 (31), 130 (17).

Compound 24. While being maintained in a drybox, a Schlenk flask containing a magnetic stirring bar was charged with indole **22** (161 mg, 1.00 mmol). Two separate test tubes within the same drybox were charged with [Ir(OMe)COD]$_2$ (10 mg, 0.015 mmol, 3 mol %) and di-*tert*-butylbipyridine (8 mg, 0.03 mmol, 3 mol %), respectively. Pinacolborane (0.22 mL, 1.52 mmol) was added to the [Ir(OMe)-COD]$_2$-containing test tube, and the di-*tert*-butylbipyridine in the second test tube was dissolved in degassed hexane (1 mL) and the resulting solution was added to the mixture of [Ir(OMe)COD]$_2$ and pinacolborane; after 0.02 h this was transferred to the Schlenk flask containing compound **22**. Additional hexane (2 × 1 mL) was used to wash the test tubes, and the washings were transferred to the Schlenk flask that was then removed from the drybox and attached to a Schlenk line. The reaction mixture was heated, under N_2, at 60 °C for 4 h before being cooled and concentrated under reduced pressure to afford a brown oil. This oil was dissolved in dichloromethane, and the mixture thus obtained was filtered through a pad of TLC-grade silica gel and diatomaceous earth. The filtrate was concentrated under reduced pressure to afford a clear, colorless oil. Trituration of this material (hexane) at −10 °C then gave the title compound **24**[20] (190 mg, 66%) as a white, crystalline solid, mp 73−74 °C (lit.[20] mp 72−74 °C) (Found: M$^{+\bullet}$, 287.1694. $C_{16}H_{22}{}^{11}BNO_3$ requires M$^{+\bullet}$, 287.1693). ^{1}H NMR ($CDCl_3$, 400 MHz) 8.72 (broad s, 1H), 7.22 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.14 (broad s, 1H), 3.86 (s, 3H), 2.48 (s, 3H), 1.41 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 153.6, 136.8, 136.0, 128.9, 115.8, 107.2, 99.5, 83.8 (2C), 56.2, 24.9 (4C), 13.9 (signal due to one carbon obscured or overlapping); IR ν_{max} (KBr) 3454, 2978, 1482, 1372, 1335, 1283, 1215, 1142, 1126, 1041, 851, 751 cm^{-1}; MS (EI) m/z 288 [(M + H)$^+$, 31%], 287 and 286 (M$^{+\bullet}$, 100 and 41), 272 (11), 230 (13), 214 (11), 205 (14), 187 and 186 (63 and 28), 172 and 171 (31 and 10), 144 and 143 (16 and 10).

Compound 1. *Method A.* A magnetically stirred solution of compound **14** (25 mg, 0.11 mmol), boronate ester **16** (48 mg, 0.164 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (9 mg, 0.01 mmol), and triethylamine (0.15 mL, 1.08 mmol) in THF/water (6 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.25 h and then heated at reflux for 72 h before being cooled and then diluted with ethyl acetate (10 mL) and water (10 mL). The separated aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were passed through a pad of TLC-grade silica gel. The resulting filtrate was concentrated under reduced pressure to give a brown solid. Recrystallization (9:1 v/v mixture of chloroform/methanol) of this material then gave the title compound **1**[1] (26 mg, 81%) as a white, crystalline solid, mp 260−261 °C (lit.[1] mp 230−232 °C) (Found: M$^{+\bullet}$, 293.0688. $C_{17}H_{11}NO_4$ requires M$^{+\bullet}$, 293.0688). ^{1}H NMR ($CDCl_3$, 800 MHz) see Table 2; ^{13}C NMR ($CDCl_3$, 200 MHz) see Table 1; IR ν_{max} (KBr) 2949, 2929, 1682, 1624, 1494, 1369, 1343, 1307, 1252, 1133, 1026, 921 cm^{-1}; MS (EI) m/z 294 [(M + H)$^+$, 20%], 293 (M$^{+\bullet}$, 100), 278 (36), 250 (43), 164 (14).

Method B. A magnetically stirred solution of compound **25** (15 mg, 0.058 mmol), borylindole **23** (24 mg, 0.088 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (5 mg, 0.006 mmol), and triethylamine (0.08 mL, 0.577 mmol) in THF/water (5 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.25 h and then heated at reflux for 72 h before being cooled and then diluted with ethyl acetate (10 mL) and water (10 mL). The separated aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were passed through a pad of TLC-grade silica gel and diatomaceous earth; the resulting filtrate was concentrated under reduced pressure to give a brown solid. Recrystallization of this material (9:1 v/v chloroform/methanol) afforded compound **1** (15 mg, 88%) as a white, crystalline solid. This material was identical, in all respects, with that obtained by Method A.

Compound 2. *Method A.* A magnetically stirred solution of compound **15** (41 mg, 0.17 mmol), boronate ester **16** (74 mg, 0.254 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (14 mg, 0.02 mmol), and triethylamine (0.23 mL, 1.67 mmol) in THF/water (9.2 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.25 h and then heated at reflux for 120 h before being cooled and then diluted with ethyl acetate (15 mL) and water (15 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were passed through a pad of TLC-grade silica gel. The resulting filtrate was concentrated under reduced pressure to give a brown solid. Recrystallization (9:1 v/v mixture of chloroform/methanol) of this material gave the title compound **2**[1] (34 mg, 65%) as a white, crystalline solid, mp 257 °C (lit.[1] mp 220−222 °C) (Found: M$^{+\bullet}$, 307.0847. $C_{18}H_{13}NO_4$ requires M$^{+\bullet}$, 307.0845). ^{1}H NMR ($CDCl_3$, 800 MHz) see Table 2; ^{13}C NMR

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($CDCl_3$, 200 MHz) see Table 1; IR ν_{max} (KBr) 2962, 2918, 1677, 1621, 1483, 1365, 1329, 1299, 1252, 1193, 1104, 1039, 931 cm^{-1}; MS (EI) m/z 308 [$(M + H)^+$, 20%], 307 ($M^{+\bullet}$, 100), 292 (17), 264 (27), 160 (22).

Method B. A magnetically stirred solution of compound **25** (18 mg, 0.069 mmol), borylindole **24** (30 mg, 0.104 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (6 mg, 0.007 mmol), and triethylamine (0.096 mL, 0.693 mmol) in THF/water (6 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.25 h and then heated at reflux for 120 h before being cooled and diluted with ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were passed through a pad of TLC-grade silica gel and diatomaceous earth. The resulting filtrate was concentrated under reduced pressure to give a brown solid. Recrystallization of this material (9:1 v/v chloroform/methanol) gave compound **2** (14 mg, 66%) as a white, crystalline solid. This material was identical, in all respects, with that obtained by Method A.

Compound 3. *Method A.* A magnetically stirred solution of compound **14** (36 mg, 0.159 mmol), boronate ester **17** (77 mg, 0.239 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (13 mg, 0.016 mmol), and triethylamine (0.22 mL, 1.59 mmol) in THF/water (6 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.25 h, heated at reflux for 48 h, and then cooled before being diluted with ethyl acetate (10 mL) and water (10 mL). The separated aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were passed through a pad of TLC-grade silica gel; the filtrate thus obtained was concentrated under reduced pressure to give a brown solid. Recrystallization (4:1 v/v dichloromethane/methanol) gave the title compound **3**[2] (44 mg, 89%) as a white, crystalline solid, mp 218−220 °C (Found: $M^{+\bullet}$, 309.1000. $C_{18}H_{15}NO_4$ requires $M^{+\bullet}$, 309.1001). ^1H NMR ($CDCl_3$, 800 MHz) see Table 2; ^{13}C NMR ($CDCl_3$, 200 MHz) see Table 1; IR ν_{max} (KBr) 2939, 2833, 1668, 1603, 1507, 1467, 1365, 1310, 1267, 1143, 1100 cm^{-1}; MS (EI) m/z 310 [$(M + H)^+$, 21%], 309 ($M^{+\bullet}$, 100), 294 (17), 266 (21).

Method B. A magnetically stirred solution of compound **26** (9 mg, 0.033 mmol), borylindole **23** (14 mg, 0.051 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (3 mg, 0.004 mmol), and triethylamine (0.05 mL, 0.361 mmol) in THF/water (3 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.25 h, heated at reflux for 48 h, then cooled, and diluted with ethyl acetate (5 mL) and water (5 mL). The separated aqueous layer was extracted with ethyl acetate (2 × 5 mL), and the combined organic extracts were passed through a short pad of TLC-grade silica gel and diatomaceous earth; the filtrate thus obtained was concentrated under reduced pressure to give a brown solid. Recrystallization (4:1 v/v chloroform/methanol) of this material gave compound **3** (10 mg, quantitative) as a white, crystalline solid. This material was identical, in all respects, with that obtained by Method A.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data (CIFs), anisotropic displacement ellipsoid plots, and unit cell packing diagrams derived from the single-crystal analyses of compounds **1**, **2**, and **10**; ^1H and ^{13}C NMR spectra for compounds **1**−**3**, **7**, **10**, **12**−**15**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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