Synthesis and Reactions of 3-(Bromomethyl)-1-carbethoxy-4-iodoindole: The Preparation of 3,4-Differentially Substituted Indoles

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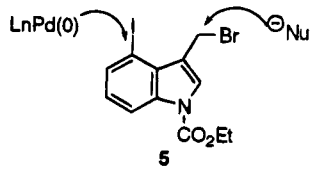
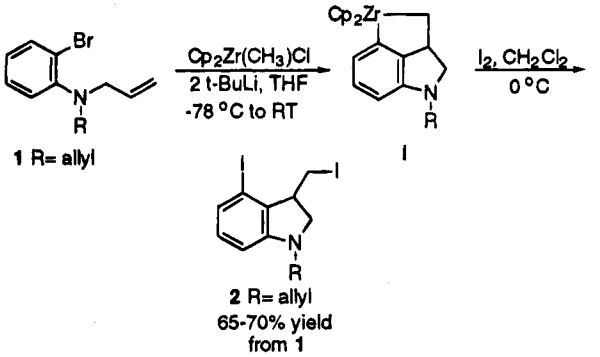
The synthesis of indoles bearing substituents at the 3 and 4 positions has been of interest to synthetic chemists for many years.[1] This is due to the large number of biologically active natural products having this substitution pattern. We recently reported the development of a method for the preparation of regiochemically pure, N-protected, 3,4-diiodoindolines using the intramolecular insertion reactions of zirconocene-stabilized benzyne complexes (Scheme 1).[2] We were interested in using compounds such as diiodide **2** as intermediates for the synthesis of more highly functionalized indoles and indolines. One avenue that we explored was nucleophilic displacement of the alkyl iodide. However, with most nucleophiles, we were unable to cleanly obtain the desired substitution product due to facile dehydrohalogenation reactions.[3] We reasoned, however, that this problem could be circumvented by converting the diiodoindoline into an indole so that dehydrohalogenation could not occur. In addition, we sought a general means for the synthesis of 3,4-differentially substituted indole derivatives. In this paper, we report a solution to this problem using 3-(bromomethyl)-1-carbethoxy-4-iodoindole (**5**).



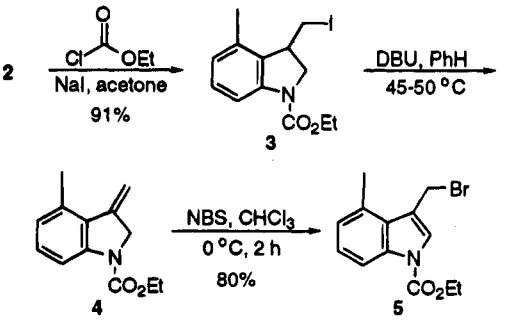
5

We anticipated that nucleophilic substitution reactions of **5** would proceed in good yields with a variety of nucleophiles, since 3-(halomethyl)indole derivatives are known to be excellent electrophiles.[4,5] The 4-iodo group could then be elaborated using a variety of Pd(0)-catalyzed transformations. Using this strategy, we have prepared a number of novel 3,4-disubstituted indoles, as well as an intermediate in Kozikowski's total synthesis of the clavicipitic acids.[6]

Scheme 1



Scheme 2



We envisioned two possible synthetic routes to compounds such as **5**. The first would involve the oxidation of an indoline such as **2** to an indole. The second would utilize the reaction of a 3-methyleneindoline derivative with an electrophilic halogen source. On the basis of our earlier success in the reactions of 3-methyleneindole derivatives with electrophilic iminium salts,[2a] we chose the latter route. Olefin **4** was prepared from 1-allyl-4-iodo-3-(iodomethyl)indoline (**2**) by a two-step process as shown in Scheme 2. Thus, the allyl group in indoline **2** was cleaved using ethyl chloroformate and NaI in acetone to provide ethyl carbamate **3** in 91% yield.[2b,7] Treatment of **3** with DBU in benzene affected quantitative dehydrohalogenation[2a] to give olefin **4**, which was then treated with NBS in $CHCl_3$ at 0 °C to give the desired 3-(bromomethyl)-1-carbethoxy-4-iodoindole (**5**) in 80% overall yield from **3**.[8]

The chemistry of **5** was first explored by examining its reaction with a variety of nucleophilic reagents (Scheme 3). For example, reaction of **5** with water or benzylamine gave alcohol **6** or amine **7**, respectively, in good yields. The displacement reaction was also conducted with carbon nucleophiles. For example, reaction of **5** with KCN gave the corresponding 3-indoleacetonitrile derivative **8** in 76% yield. Soft carbon nucleophiles, such as malonate anions, gave substituted malonate derivatives in good yield. For instance, reaction of **5** with dimethyl

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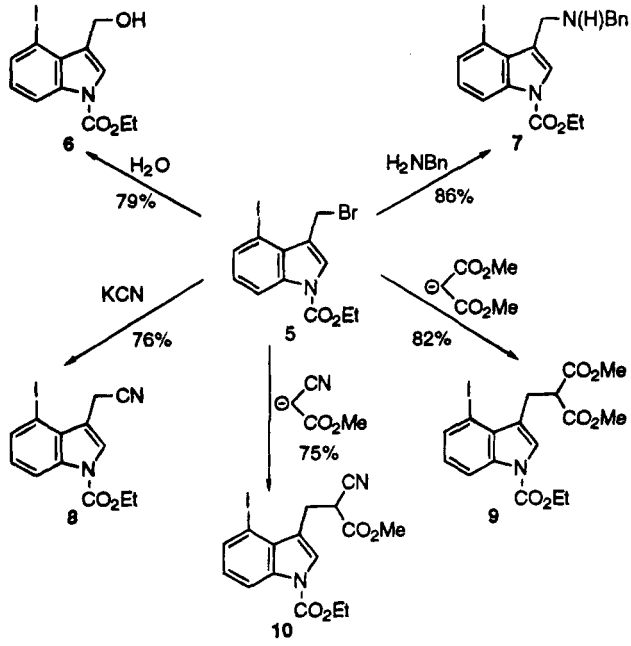
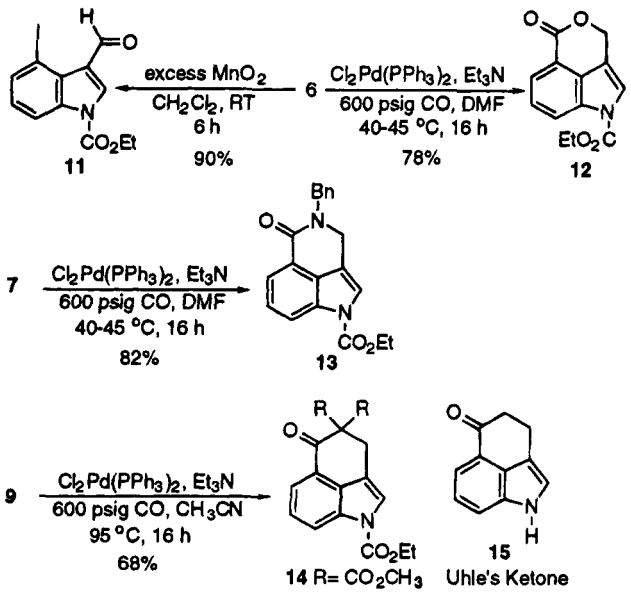
Scheme 3



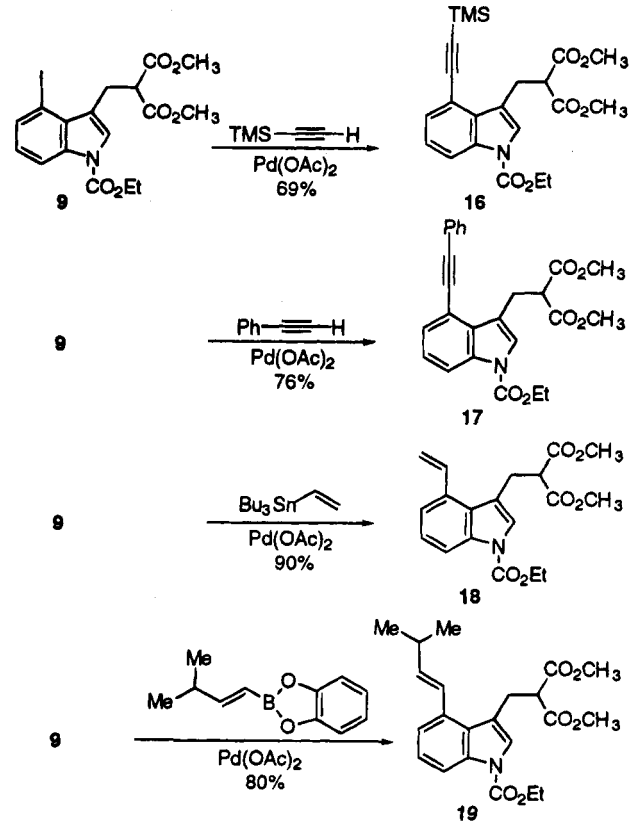
Scheme 4



malonate, K_2CO_3, and a catalytic amount of 18-crown-6 gave malonate product **9** in 82% yield.

While products **6**–**10** are interesting in their own right, they also serve as convenient precursors to other novel and structurally interesting indoles. For example, alcohol **6** could be oxidized to the corresponding carboxaldehyde derivative **11** in 90% yield using an excess of MnO_2 in CH_2Cl_2 (Scheme 4).[9,10] Alcohol **6** could also be carbonylated using a catalytic amount of $Cl_2Pd(PPh_3)_2$ to give tricyclic lactone **12** in 78% yield (Scheme 4).[11] Under similar conditions, amine **7** could be converted to tricyclic

Scheme 5



lactam **13** in 82% yield. Similarly, the malonate derivative **9** was carbonylated using an anion capture process[12] to give tricyclic ketone **14** in 68% yield. Ketone **14** is closely related to Uhle's ketone[13] **15** which is an important intermediate in the synthesis of ergot alkaloids. The reactivity of the aryl iodide moiety in **9** was also exploited in the preparation of a variety of indole derivatives (Scheme 5). Treatment of **9** with (trimethylsilyl)acetylene under standard Castro–Stephens conditions[14] afforded the desired alkyne **16** in 69% yield. When phenylacetylene was employed, alkyne **17** was obtained in 76% yield. Stille coupling[15] of **9** with vinyltributyltin gave the corresponding styrene derivative **18** in 90% isolated yield. Finally, treatment of **9** with the boronate ester prepared from the hydroboration reaction[16] of 3-methyl-1-butyne with catechol borane, under Suzuki-type reaction conditions,[17] gave the desired *E*-olefin **19** in 80% yield. The conversion of compound **19** to the clavicipitic acids was previously described by Kozikowski and co-workers.[6] Therefore, the preparation of **19** represents a formal synthesis of the clavicipitic acids.

In summary, we have shown that readily available **5** serves as a vehicle for the preparation of a variety of differentially substituted 3,4-disubstituted indoles. Further exploration of the chemistry of **5** and its application

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to the synthesis of several natural products is currently underway in our laboratories and will be reported in due time.

Experimental Section

All reactions involving organometallic reagents were conducted under an atmosphere of purified argon using standard Schlenk techniques or under nitrogen in a Vacuum Atmospheres Co. drybox. The argon was purified and deoxygenated by passage through a column of activated R3-11 catalyst obtained from Schweizer-Hall, Plainfield, NJ. It was then dried by passage through a column of activated 3 Å molecular sieves. All organic reactions were performed under an atmosphere of argon or nitrogen. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, VXR-500, or a Bruker AC250 FT spectrometer. Infrared (IR) spectra were recorded on either a Mattson Cygnus Starlab 100 or Perkin-Elmer Series 1600 FT spectrometer. Gas chromatography analyses were performed on a Hewlett-Packard Model 5890 GC with a 3392A integrator and FID detector using a 25 m capillary column with crosslinked SE-30 as a stationary phase. Liquid chromatography analyses were performed on a Hewlett-Packard Model 1050 HPLC equipped with a Hewlett-Packard Model 1040A diode array detector using an Alltech 250 mm × 4.6 mm silica 5 μm column. Electron impact mass spectra and high-resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Tetrahydrofuran, benzene, and diethyl ether were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Hexane was deolefinated by stirring over H_2SO_4, from which it was decanted and then stored over CaH_2. The deolefinated hexane thus obtained was dried and deoxygenated by refluxing over sodium/benzophenone ketyl followed by distillation. Alternatively, HPLC grade hexane was dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Methylene chloride was dried by refluxing over CaH_2, followed by distillation. Acetonitrile was stored over activated 3 Å molecular sieves prior to use. Anhydrous, N,N-dimethyl formamide (DMF) was purchased from Aldrich Chemical Co. and was used without further purification. Cp_2ZrCl_2 was purchased from Boulder Scientific Inc., Mead, CO. All other reagents were either prepared according to published procedures or were available from commercial sources and used without further purification. Unless otherwise stated, preparative flash chromatography was performed on E.M. Science Kieselgel 60 (230–400 mesh). Yields refer to isolated yields of compounds estimated to be ≥95% pure (unless otherwise noted) as determined by ^{1}H NMR, and either capillary GC, HPLC analysis, or combustion analysis. All reported yields are representative. Elemental analyses were performed by Onieda Research Services, Whitesboro, NY.

3-(Bromomethyl)-1-carbethoxy-4-iodoindole (5). Into a flask were placed 1-carbethoxy-4-iodo-3-(iodomethyl)indoline (**3**) (980 mg, 2.14 mmol), DBU (0.35 mL, 356 mg, 2.34 mmol), and benzene (5 mL). The mixture was heated to 50 °C for 1 h and then filtered, and the benzene was removed via rotary evaporation leaving a brownish solid. The solid was dissolved in $CHCl_3$ (5 mL), the solution was cooled to 0 °C, and NBS (402 mg, 2.26 mmol) was added as a solid in one portion. The resulting mixture was allowed to stir at 0 °C for 2 h, and then it was poured into a separatory funnel containing $CHCl_3$ (15 mL) and water (15 mL). The organic layer was collected and washed with water (2 × 15 mL) and brine (15 mL), dried over $MgSO_4$, and filtered through a plug of silica (15 cm), and the solvents were removed via rotary evaporation to leave 700 mg (80%) of a white solid, mp = 109–110 °C. An analytical sample was prepared by recrystallization from CH_3CN: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, J = 8.40 Hz, 1H), 7.79 (d, J = 8.10 Hz, 1H), 7.00 (t, J = 8.10 Hz, 1H), 4.90 (s, 2H), 4.46 (q, J = 7.05 Hz, 2H), 1.45 (t, J = 7.05 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.7, 136.3, 135.0, 129.1, 127.8, 126.2, 118.7, 115.3, 84.2, 63.8, 25.1, 14.5. IR (film, cm^{-1}) 1734, 1425. Anal. Calcd for $C_{12}H_{11}BrNO_2I$: C, 35.32; H, 2.72; N, 3.43. Found: C, 35.41; H, 2.68; N, 3.64.

1-Carbethoxy-3-(hydroxymethyl)-4-iodoindole (6). Into a flask were placed 3-(bromomethyl)1-carbethoxy-4-iodoindole (**5**) (1.23 g, 3.01 mmol), water (5 mL, 5.00 g, 278 mmol), and CH_3CN (16 mL). The suspension was heated to 50 °C at which time it became a homogeneous, yellow solution. After 10 min at 50 °C, TLC analysis showed no remaining starting material. The reaction mixture was allowed to cool to rt and was then poured into a separatory funnel containing ethyl acetate (20 mL) and water (20 mL). The organic layer was collected and washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, and filtered, and the solvents were removed to leave 825 mg (79%) of a yellow solid, mp = 109–111 °C. An analytical sample was prepared by recrystallization from ethanol to give a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, J = 8.10 Hz, 1H), 7.62 (m, 2H), 6.96 (t, J = 7.95 Hz, 1H), 4.94 (d, J = 5.40 Hz, 2H), 4.43 (q, J = 7.20 Hz, 2H), 2.39 (t, J = 6.30 Hz, 1H), 1.42 (t, J = 7.20 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.0, 136.5, 134.0, 130.8, 125.7, 125.6, 121.5, 115.2, 84.1, 63.5, 56.5, 14.4; IR (film, cm^{-1}) 3407 (br), 1735, 1422. Anal. Calcd for $C_{12}H_{12}NO_3I$: C, 41.76; H, 3.50; N, 4.06. Found: C, 41.70; H, 3.45; N, 4.22.

3-[(Benzylamino)methyl]-1-carbethoxy-4-iodoindole (7). Into a flask fitted with a reflux condenser were placed 3-(bromomethyl)-1-carbethoxy-4-iodoindole (**5**) (210 mg, 0.51 mmol), THF (10 mL), benzylamine (0.28 mL, 2.6 mmol), and K_2CO_3 (0.36 g, 2.6 mmol). The mixture was heated to reflux for 12 h and then poured into a separatory funnel containing ether (25 mL) and water (25 mL). The organic layer was collected and washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography (66:33:1 hexane:ethyl acetate:triethylamine) to give 182 mg (82%) of a white solid, mp = 83–85 °C. An analytical sample was prepared by recrystallization from acetonitrile: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, J = 8.2 Hz, 1H), 7.66 (dd, J = 8.1, 1.6 Hz, 1H), 7.61 (s, 1H), 7.37–7.21 (m, 5H), 6.95 (dd, J = 8.3, 7.8 Hz, 1H), 4.43 (q, J = 6.9 Hz, 2H), 4.08 (s, 2H), 3.87 (s, 2H), 1.83 (s, 1H), 1.41 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) d 150.1, 140.0, 136.6, 134.4, 131.0, 128.3, 126.9, 125.7, 125.6, 120.1, 115.2, 84.4, 63.4, 53.3, 44.1, 14.5; IR (KBr, cm^{-1}) 3319, 2991, 1736, 1417. Anal. Calcd for $C_{19}H_{19}N_2O_2I$: C, 52.55; H, 4.41; N, 6.45. Found: C, 52.70; H, 4.40; N, 6.58.

8. Into a flask were placed 3-(bromomethyl)-1-carbethoxy-4-iodoindole (**5**) (456 mg, 1.12 mmol), KCN (78 mg, 1.20 mmol), and DMF (3 mL). The mixture was heated to 50 °C and was allowed to stir overnight. The mixture was then poured into a separatory funnel containing ether (25 mL) and water (25 mL). The organic layer was collected, and washed with water (2 × 25 mL) and brine (25 mL), dried over $MgSO_4$, and filtered, and the solvents were removed to leave a yellow oil. The product was purified by flash chromatography (9:1 hexane:ethyl acetate) to give 302 mg (76%) of a white solid, mp = 122–124 °C. An analytical sample was prepared by recrystallization from ethanol to give a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, J = 8.40 Hz, 1H), 7.78 (s, 1H), 7.67 (d, J = 7.50 Hz, 1H), 7.01 (t, J = 7.80 Hz, 1H), 4.48 (q, J = 7.20 Hz, 2H), 4.16 (d, J = 1.50 Hz, 2H), 1.46 (t, J = 7.20 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.7, 136.4, 134.6, 129.3, 126.4, 125.9, 116.9, 115.5, 111.2, 83.8, 63.9, 16.6, 14.5; IR (film, cm^{-1}) 2987, 2249, 1743, 1422, 1377. Anal. Calcd for $C_{13}H_{11}N_2O_2I$: C, 44.09; H, 3.13; N, 7.91. Found: C, 43.84; H, 2.81; N, 7.62.

9. Into a flask were placed 3-(bromomethyl)-1-carbethoxy-4-iodoindole (**5**) (964 mg, 2.36 mmol), dimethyl malonate (1.30 mL, 1.50 g, 11.37 mmol), K_2CO_3 (1.66 g, 12.01 mmol), 18-crown-6 (47 mg, 0.18 mmol), and benzene (10 mL). The resulting mixture was allowed to stir at rt for 4 h and then poured into a separatory funnel containing ether (30 mL) and water (30 mL). The organic layer was collected and washed with water (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, and filtered, and the solvents were removed via rotary evaporation to leave a brownish solid. The product was recrystallized from ethanol to yield 889 mg (82%) of a white solid: mp = 102–104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, J = 8.40 Hz, 1H), 7.67 (d, J = 7.50 Hz, 1H), 7.47 (s, 1H), 6.96 (t, J = 8.40 Hz, 1H), 4.45 (q, J = 6.90 Hz, 2H), 4.01 (t, J = 7.80 Hz, 1H), 3.71 (s, 6H), 3.53 (d, J = 7.50 Hz, 2H), 1.43 (t, J = 6.90 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 149.9, 136.3, 134.6, 130.4, 125.9, 125.7, 117.5, 115.2, 84.3, 63.5, 52.9, 52.6, 24.8, 14.5; IR (film, cm^{-1}) 2952, 1737, 1420. Anal. Calcd for $C_{17}H_{18}NO_6I$: C, 44.46; H, 3.95; N, 3.05. Found: C, 44.60; H, 4.06; N, 3.19.

10. Into a flask were placed 3-(bromomethyl)-1-carbethoxy-4-iodoindole (**5**) (110 mg, 0.27 mmol), ethyl cyanoacetate (0.43 mL, 457 mg, 4.04 mmol), K_2CO_3 (43 mg, 0.311 mmol), 18-crown-6

(12 mg, 0.05 mmol), and benzene (3 mL). The resulting mixture was allowed to stir at rt for 15 h, and then it was poured into a separatory funnel containing ether (15 mL) and water (15 mL). The organic layer was collected and washed with water (2 × 15 mL) and brine (15 mL), dried over $MgSO_4$, and filtered, and the solvents were removed via rotary evaporation to leave a yellow oil. The product was isolated by flash chromatography (85:15 hexane:ethyl acetate) to give 88 mg (75%) of a yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, J = 8.10 Hz, 1H), 7.68 (d, J = 6.90 Hz, 1H), 7.67 (s, 1H), 7.01 (t, J = 8.10 Hz, 1H), 4.46 (q, J = 7.40 Hz, 2H), 4.27 (q, J = 7.40 Hz, 2H), 4.10 (dd, J = 6.30, 9.30 Hz, 1H), 3.83 (dd, J = 6.30, 14.4 Hz, 1H), 3.27 (dd, J = 9.30, 14.4 Hz, 1H), 1.45 (t, J = 7.40 Hz, 3H), 1.30 (t, J = 7.40 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 149.9, 136.6, 134.8, 130.0, 127.1, 126.2, 116.1, 115.6, 115.5, 84.0, 63.7, 62.9, 39.4, 25.9, 14.3, 14.0; IR (film, cm^{-1}) 2983, 2250, 1747, 1465; HRMS (EI) calcd for $C_{17}H_{17}N_2O_4I$ 440.0235, found 440.0237 amu.

11. Into a flask were placed 1-carbethoxy-3-(hydroxymethyl)-4-iodoindole (**6**) (349 mg, 1.01 mmol), CH_2Cl_2 (3 mL), and MnO_2 (2.27 g, 26.11 mmol). After 45 min at rt, TLC analysis showed no remaining starting material. The reaction mixture was filtered through Celite, and the solvent was removed via rotary evaporation to leave a white solid. The product was recrystallized from ethanol to yield 312 mg (90%) of a white solid: mp = 124–125 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 11.19 (s, 1H), 8.40 (s, 1H), 8.31 (d, J = 8.40 Hz, 1H), 7.81 (d, J = 7.50 Hz, 1H), 7.08 (t, J = 7.95 Hz, 1H), 4.51 (q, J = 6.90 Hz, 2H), 1.47 (t, J = 6.90 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.6, 149.5, 136.8, 135.8, 131.9, 130.2, 126.4, 121.2, 115.3, 83.2, 64.6, 14.4; IR (film, cm^{-1}) 2985, 1758, 1664. Anal. Calcd for $C_{12}H_{10}NO_3I$: C, 42.01; H, 2.94; N, 4.08. Found: C, 42.24; H, 3.12; N, 4.15.

12. Into an autoclave were placed 1-carbethoxy-3-(hydroxymethyl)-4-iodoindole (**6**) (116 mg, 0.336 mmol), $Cl_2Pd(PPh_3)_2$ (23 mg, 0.03 mmol), Et_3N (0.20 mL, 145 mg, 1.43 mmol), and DMF (2 mL). The autoclave was flushed three times with CO and then pressurized to 600 psig. The mixture was heated to 35–45 °C for 16 h and then allowed to cool to rt and poured into a separatory funnel containing ether (30 mL) and water (30 mL). The organic layer was collected and washed with water (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, and filtered, and the solvents were removed via rotary evaporation to leave an orange solid. The product was recrystallized from ethanol to give 64 mg (78%) of a white solid: mp = 156–157 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (bs, 1H), 8.08 (d, J = 7.20 Hz, 1H), 7.43 (m, 2H), 5.78 (d, J = 1.50 Hz, 2H), 4.47 (q, J = 6.90 Hz, 2H), 1.47 (t, J = 6.90 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 150.8, 132.7, 131.3, 126.3, 122.5, 120.2, 119.1, 117.0, 110.6, 68.4, 63.9, 14.4; IR (film, cm^{-1}) 2980, 2935, 1737, 1709, 1634. Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.45; H, 4.46; N, 5.71.

13. Into an autoclave were placed 3-[(benzylamino)methyl]-1-carbethoxy-4-iodoindole (**7**) (182 mg, 0.42 mmol), $Cl_2Pd(PPh_3)_2$ (29 mg, 0.04 mmol), Et_3N (0.25 mL, 1.81 mmol), and DMF (10 mL). The autoclave was flushed three times with CO and then pressurized to 600 psig. The mixture was heated to 45 °C for 12 h and then allowed to cool to rt and poured into a separatory funnel containing ether (30 mL) and water (30 mL). The organic layer was collected and washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, and filtered, and the solvents were removed via rotary evaporation to leave a black solid. The product was purified by flash chromatography (methylene chloride, then 20:1 methylene chloride:acetonitrile) to give 120 mg (85%) of a white solid: mp = 131–132 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.00 (m, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.45–7.23 (m, 7H), 4.86 (s, 2H), 4.74 (d, J = 2.0 Hz, 2H), 4.48 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.4, 150.91, 137.0, 132.3, 130.0, 128.6, 128.1, 127.5, 125.9, 121.0, 120.7, 119.0, 118.2, 111.0, 63.5, 50.6, 46.5, 14.3; IR (KBr, cm^{-1}) 3122, 1739, 1644, 1290. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.47; H, 5.47; N, 8.22.

14. Into an autoclave were placed indole **9** (220 mg, 0.479 mmol), $Cl_2Pd(PPh_3)_2$ (26 mg, 0.04 mmol), Et_3N (0.28 mL, 203 mg, 2.0 mmol), and CH_3CN (2 mL). The autoclave was flushed three times with CO and then pressurized to 600 psig. The mixture was then heated to 95–100 °C, and the pressure was readjusted to 600 psig. The reaction was allowed to stir at 95–100 °C for 16 h and then allowed to cool to rt and poured into a separatory funnel containing ether (50 mL) and water (50 mL). The organic layer was collected and washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered, and the solvents were removed via rotary evaporation to leave a brown oil. The product was isolated by flash chromatography (4:1 hexane:ethyl acetate) to yield 117 mg (68%) of a white solid, mp = 138–140 °C. An analytical sample was prepared by recrystallization from ethanol: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (br, 1H), 7.74 (d, J = 7.50 Hz, 1H), 7.54 (br s, 1H), 7.43 (t, J = 7.95 Hz, 1H), 4.48 (q, J = 7.20 Hz, 2H), 3.85 (d, J = 1.20 Hz, 2H), 1.46 (t, J = 7.20 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 188.9, 168.3, 150.4, 134.3, 133.3, 126.0, 125.9, 122.6, 120.6, 120.3, 112.6, 68.7, 63.3, 53.0, 29.5, 14.3; IR (film, cm^{-1}) 3125, 2956, 1732, 1694, 1613. Anal. Calcd for $C_{18}H_{17}NO_7$: C, 60.17; H, 4.77; N, 3.90. Found: C, 60.23; H, 4.62; N, 3.92.

16. To a flask were added **9** (197 mg, 0.43 mmol), triphenylphosphine (21 mg, 0.08 mmol), (trimethylsilyl)acetylene (65 μL, 0.47 mmol), copper(I) iodide (18 mg, 0.09 mmol), triethylamine (0.19 mL, 1.39 mmol), palladium acetate (7 mg, 0.03 mmol), and DMF (4 mL). The mixture was heated to 70 °C for 14 h, after which time it was allowed to cool and was poured into a separatory funnel containing ether (20 mL) and saturated $CuSO_4$ solution (20 mL). The organic layer was collected and washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and filtered, and the solvents were removed to leave a dark oil. The product was isolated by flash chromatography (4:1 hexane:ethyl acetate) to give 153 mg (84%) of a yellow oil. This material was estimated to be greater than 94% pure by ^1H NMR. An analytical sample was prepared by recrystallization from hexanes at −78 °C to give 124 mg (67%) of a white powder: mp = 60–61 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, J = 8.4 Hz, 1H), 7.39 (s, 1H), 7.37 (dd, J = 7.6, 1.0 Hz, 1H), 7.22 (t, J = 8.2, 7.6 Hz, 1H), 4.44 (q, J = 7.10 Hz, 2H), 4.05 (t, J = 8.20 Hz, 1H), 3.68 (s, 6H), 3.57 (d, J = 8.20 Hz, 2H), 2.87 (t, J = 7.10 Hz, 3H), 0.23 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 150.5, 136.0, 129.9, 128.8, 124.6, 124.3, 117.8, 115.9, 114.7, 103.4, 98.1, 63.3, 52.5, 52.4, 24.9, 14.3, 0.3; IR (KBr, cm^{-1}) 2962, 2144, 1733. Anal. Calcd for $C_{22}H_{27}NO_6Si$: C, 61.52; H, 6.34; N, 3.26. Found: C, 61.39; H, 6.27; N, 3.29.

17. To a flask were added **9** (126 mg, 0.27 mmol), PPh_3 (10 mg, 0.038 mmol), CuI (8 mg, 0.042 mmol), phenylacetylene (33 μL, 0.30 mmol), NEt_3 (0.12 mL, 0.87 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol), and DMF (2.5 mL). The reaction mixture was heated to 70 °C for 15 h, after which time it was allowed to cool to rt and was poured into a separatory funnel containing ether (20 mL) and saturated aqueous $CuSO_4$ (20 mL). The organic layer was collected and washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and filtered, and the solvents were removed by rotary evaporation to leave a yellow oil. The product was purified by flash chromatography (85:15 hexane:ethyl acetate) to give 88 mg (75%) of a white solid: mp = 103–105 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, J = 8.20 Hz, 1H), 7.5–7.2 (m, 8H), 4.43 (q, J = 7.20 Hz, 2H), 4.07 (t, J = 7.90 Hz, 1H), 3.63 (d, J = 7.90 Hz, 2H), 3.52 (s, 6H), 1.42 (t, J = 7.10 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 150.4, 135.9, 131.4, 129.2, 128.3, 128.2, 128.0, 124.7, 124.4, 123.0, 117.7, 115.7, 114.7, 92.6, 87.8, 63.4, 52.5, 25.3, 14.5; IR (KBr, cm^{-1}) 3460, 3121, 3005, 2958, 2204, 1731, 1426, 1325, 1231. Anal. Calcd for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N, 3.23. Found: C, 69.31; H, 5.31; N, 3.29.

18. To a flask were added **9** (85 mg, 0.18 mmol), PPh_3 (3 mg, 0.011 mmol), vinyltributyltin (59 μL, 0.20 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and THF (2 mL). The reaction mixture was heated to 85 °C for 15 h, after which time it was allowed to cool to rt and was poured into a separatory funnel containing ether (20 mL) and water (20 mL). The organic layer was collected and washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and filtered, and the solvents were removed via rotary evaporation to leave a yellow oil. The product was purified by flash chromatography (85:15 hexane:ethyl acetate) to yield 58 mg (87%) of a white solid: mp = 91–93 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, J = 7.60 Hz, 1H), 7.4–7.2 (m, 4H), 5.66 (d, J = 16.9, 1.0 Hz, 1H), 5.36 (dd, J = 11.1, 1.7 Hz, 1H), 4.41 (q, J = 6.90 Hz, 2H), 3.79 (t, J = 7.60 Hz, 1H), 3.69 (s, 6H), 3.40 (d, J = 7.70 Hz, 2H), 1.40 (t, J = 6.90 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 150.5, 136.1, 134.5, 132.2, 126.7, 124.7, 124.2, 120.9, 117.6, 117.2, 114.6, 63.2, 52.7, 52.0, 26.9, 14.5; IR (KBr,

cm^{-1}) 2990, 1740, 1432, 1254, 1099. Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.76; H, 5.83; N, 3.92.

19. To a flask were added the boronate ester (61 mg, 0.32 mmol), prepared from the hydroboration reaction of 3-methyl-1-butyne with catechol borane, **9** (99 mg, 0.22 mmol), triphenylphosphine (6.0 mg, 0.02 mmol), $Pd(OAc)_2$ (2.5 mg, 0.01 mmol), K_2CO_3 (61 mg, 0.44 mmol), and THF (2 mL). Finally, methanol (8.9 μL, 0.22 mmol) was added, and the reaction was heated to 70 °C for 15 h. The mixture was poured into a separatory funnel containing ether (20 mL) and water (20 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, and filtered, and the solvents were removed to give a brown oil. The product was purified by flash chromatography (4:1 hexane:ethyl acetate) to yield 70 mg (79%) of a pale yellow oil:[6] ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12–8.08 (m, 1H), 7.40 (s, 1H), 7.26–7.24 (m, 2H), 6.95 (dd, J = 15.4, 1.1 Hz, 1H), 6.12 (dd, J = 15.4, 7.2 Hz, 1H), 4.45 (q, J = 7.4 Hz, 2H), 3.84 (t, J = 7.5 Hz, 1H), 3.72 (s, 6H), 3.45 (d, J = 7.6 Hz, 2H), 2.58–2.46 (m, 1H), 1.44 (t, J = 7.4 Hz, 3H), 1.11 (d, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 151.0, 142.0, 136.6, 132.9, 127.1, 125.2, 124.8, 124.6, 121.6, 118.1, 114.3, 63.6, 53.1, 52.8, 32.3, 27.5, 22.8, 15.0; IR (neat, cm^{-1}) 2959, 1735, 1428, 1252.

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