The Free Internet Journal
for Organic Chemistry

Paper

Archive for
Organic Chemistry

Arkivoc **2018,** part v, 140-149

A new approach to the pyrrolo[3,4-*b*]indole ring system

Jeanese C. Badenock, Heidi L. Fraser, and Gordon W. Gribble*

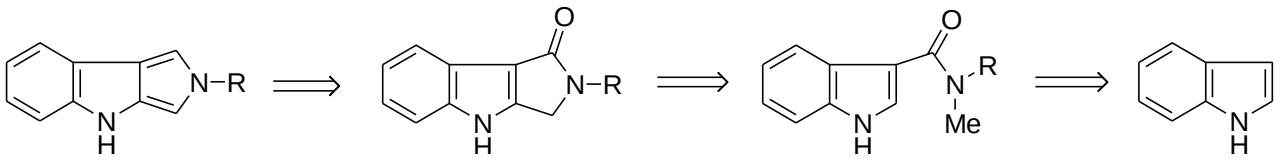
Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA
ggribble@dartmouth.edu

Dedicated to the memory of Martin E. Kuehne

Received 03-27-2018 **Accepted** 04-26-2018 **Published on line** 06-11-2018

Abstract

We report an approach to the pyrrolo[3,4-*b*]indole ring system that involves a new synthesis of pyrrolo[3,4-*b*]indol-1(2*H*)ones, which are known precursors to pyrrolo[3,4-*b*]indoles. 3-Trifluoroacetylindole is prepared from indole and converted into indole carboxamides upon reaction with lithiated amines. Subsequent C-2 bromination followed by a tri-*n*-butyltin hydride induced 1,5-radical translocation and 5-*endo*-*trig* cyclization affords 3,4-dihydropyrrolo[3,4-*b*]indol-1(2*H*)-one which upon reduction with DIBAL by the method of Kreher gives pyrrolo[3,4-*b*]indole.

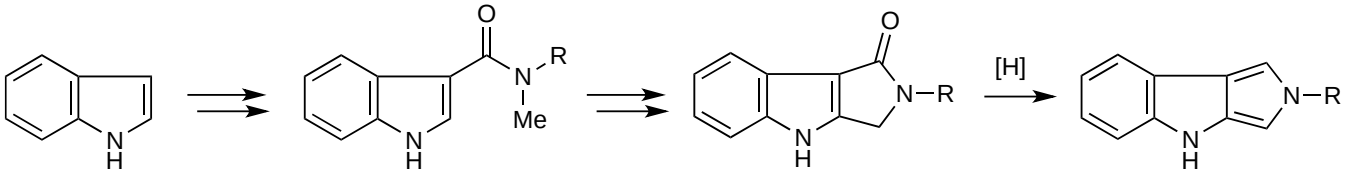


Keywords: Indole, pyrrolo[3,4-*b*]indole, pyrrolo[3,4-*b*]indolone, amidation, bromination

Introduction

In continuation of our interest in the synthesis and chemistry of pyrrolo[3,4-*b*]indoles,[1-6] we now describe a new synthesis of the pyrrolo[3,4-*b*]indole ring system that starts with indole itself. Our previous routes to this ring system utilized a pre-functionalized indole (e.g., 2- and 3-nitroindole, 2,3-dimethylindole). Furthermore, some of the previous syntheses of pyrrolo[3,4-*b*]indoles by Welch,[7] Sha,[8-10] Kreher,[11,12] Srinivasan,[13] Snyder,[14] and Solé[15] used a Fischer indolization of the appropriate 2,3-pyrrolidinedione or 2,4-pyrrolidinedione[16-18] to afford the corresponding pyrrolo[3,4-*b*]indol-3(2*H*)-one or pyrrolo[3,4-*b*]indol-1(2*H*)-one, followed by reduction to the 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole or the pyrrolo[3,4-*b*]indole ring system.[7,11,12]

We envisioned a synthesis of the pyrrolo[3,4-*b*]indole (**1**) ring system via the corresponding pyrrolo[3,4-*b*]indol-1(2*H*)one (**2**) that could be fashioned from a suitable indole amide (**3**) via radical methodology (Scheme 1).



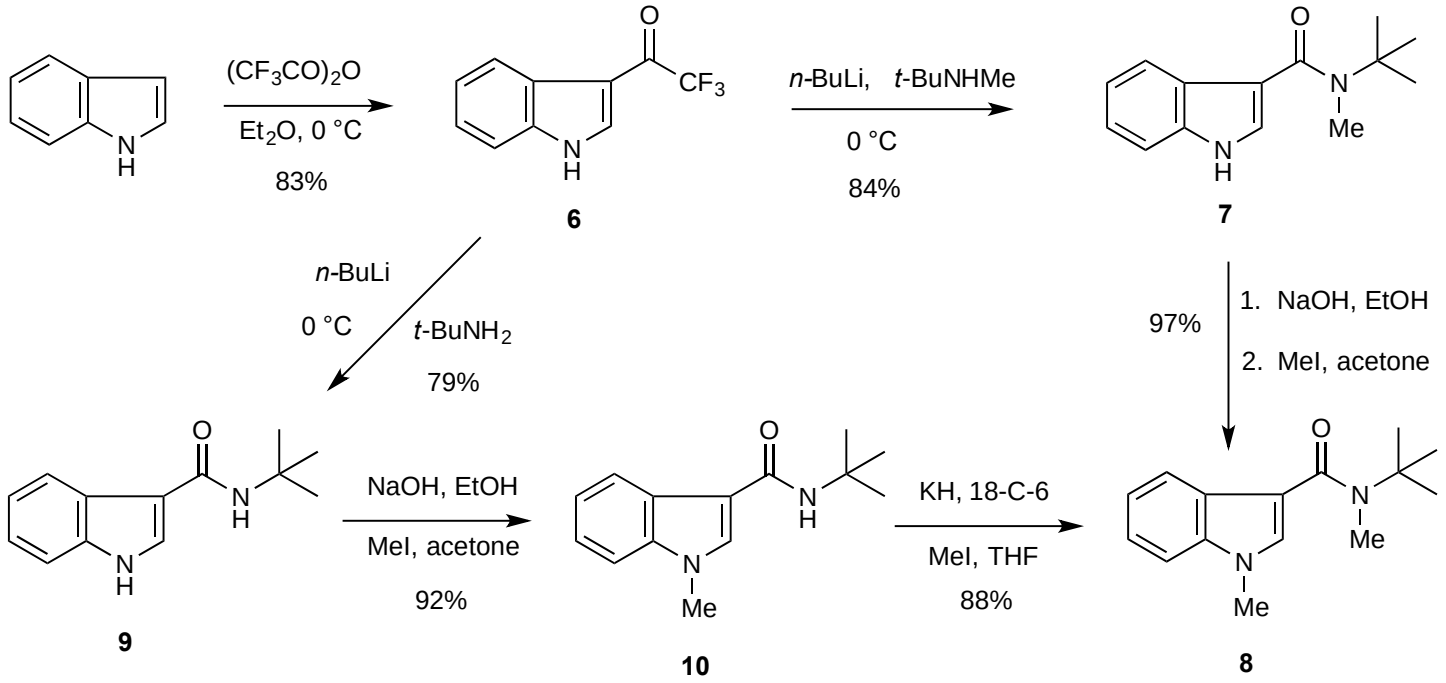
Scheme 1

Results and Discussion

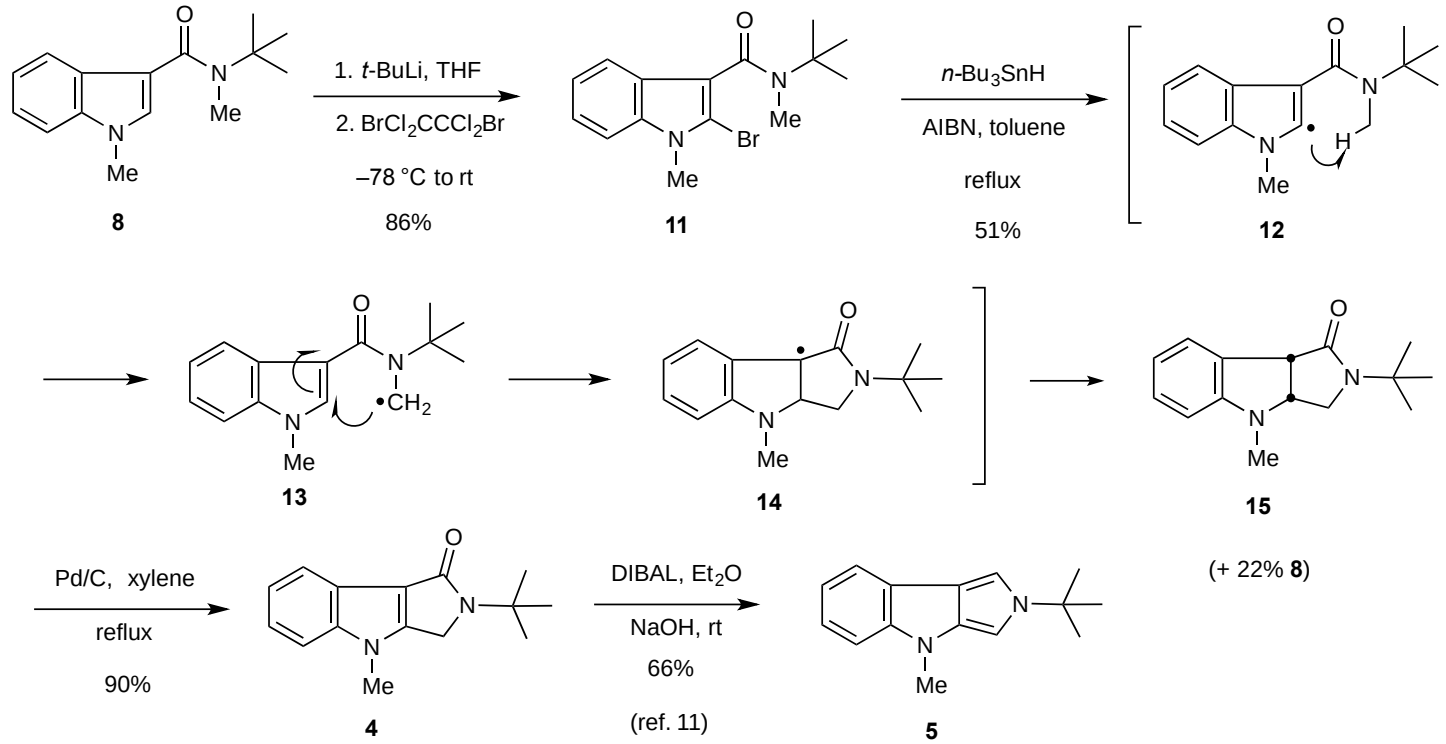
Our syntheses of 2-(*t*-butyl)-3,4-dihydro-4-methylpyrrolo[3,4-*b*]indol-1(2*H*)-one (**4**) and, by reduction, to the corresponding 2-(*t*-butyl)-2,4-dihydro-4-methylpyrrolo[3,4-*b*]indole (**5**), both of which were prepared by Kreher[12] via a Fischer-indole strategy, are depicted in Schemes 2 and 3. Indole was trifluoroacetylated to the known 3-trifluoroacetylindole (**6**)[19] and then aminated[20] with the anion of methyl-*t*-butylamine to afford amide **7** in excellent yield. Treatment of **7** with sodium hydroxide followed by iodomethane then gave amide **8**. However, the expense of methyl-*t*-butylamine led us to vary the synthesis of **8**. Thus, amination of **6** with *t*-butylamine/*n*-BuLi gave amide **9** in 79% yield. Sequential two-step methylation of **9** to **10** and then to **8** was accomplished in 81% overall yield. Amide **8** was identical as prepared by both methods (Scheme 2).

Our approach to the conversion of amide **8** to lactam **4** was predicated on a radical cyclization methodology that we reported in a similar system some years ago (Scheme 3).[21] Thus, lithiation at C-2 of amide **8** followed by quenching with $BrCl_2CCCl_2Br$[22] gave the expected 2-bromoindole **11** in 86% yield. Treatment of **11** with tri-*n*-butyltin hydride and AIBN in toluene afforded the cyclized indoline **15** (51% yield) along with the debrominated indole **8** (22% yield). This reaction involves bromine abstraction to give the 2-indolyl radical **12**, which abstracts a methyl hydrogen (1,5-H) to give the α-amidoyl radical **13**. This radical cyclizes (5-*endo*-*trig*) to the indole C-2 position giving the product **15** after hydrogen atom abstraction by **14**. The relative lability of **15**, although fully characterized, precluded forming crystals suitable for X-ray analysis. Indeed, prolonged exposure of **15** to air led to a blue-colored solid. Dehydrogenation of **15** to the known **4** was accomplished in 90% yield using Pd/C in refluxing xylene.[23] Interestingly, other oxidation methods to install the indole double bond in indoline **15** resulted in no oxidation and only starting material was recovered (e.g. DDQ,

chloranil, NBS, $PdCl_2$, air/DMSO). Reduction of **4** with DIBAL according to the procedure of Kreher[11] gave pyrrolo[3,4-*b*]indole **5** in 66% yield.

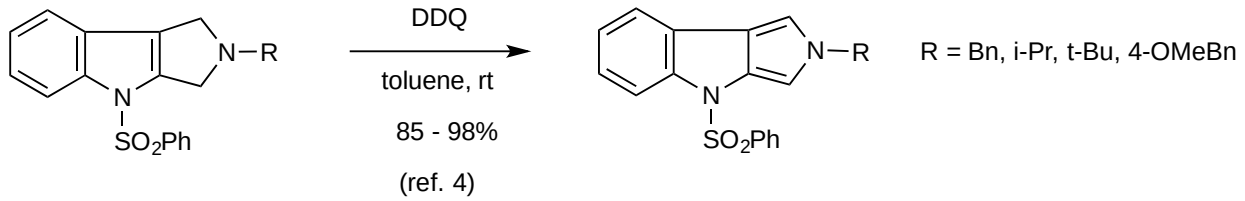


Scheme 2



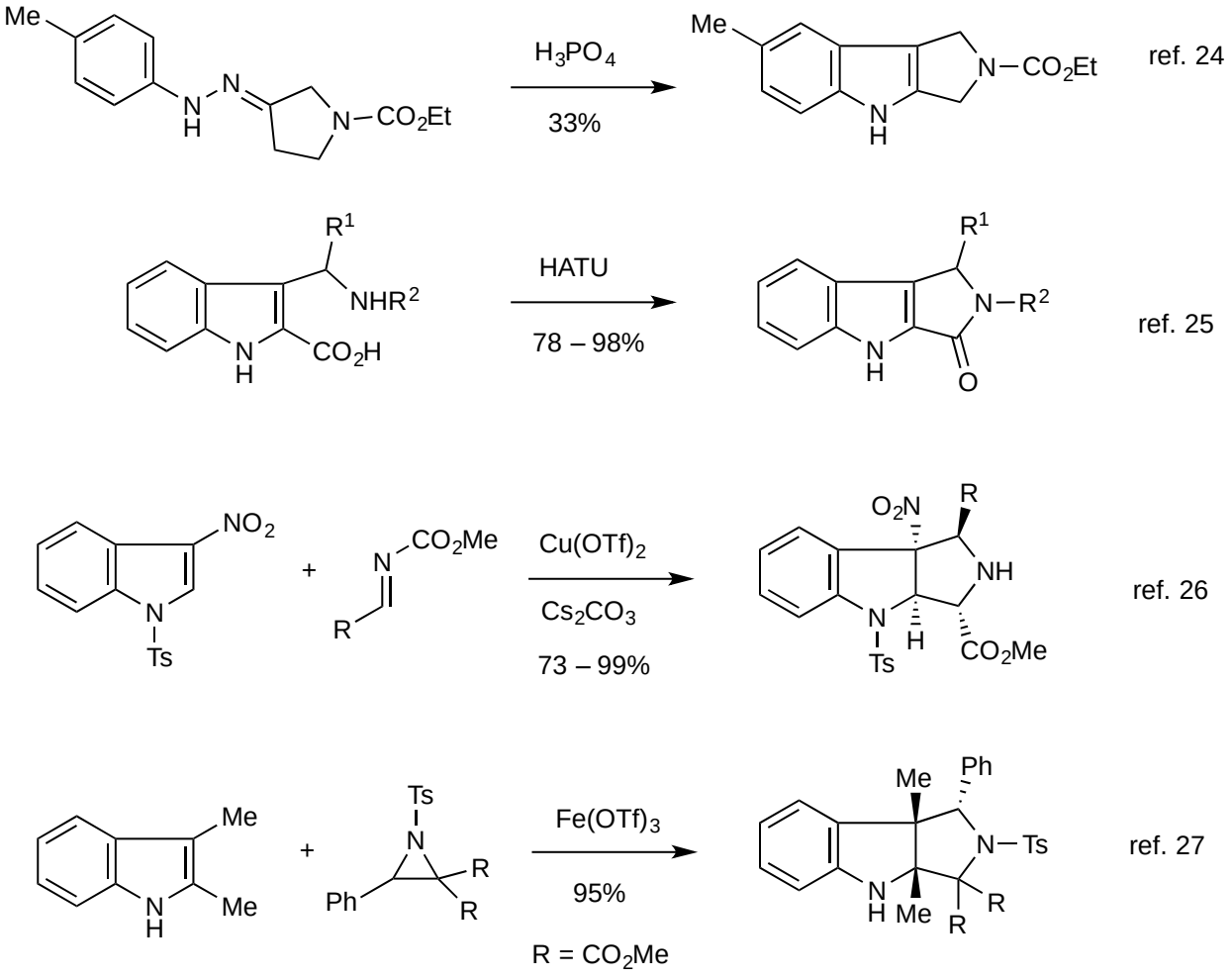
Scheme 3

An important extension of our methodology is that $LiAlH_4$ reduction of pyrrolo[3,4-*b*]indolones like **4** should yield the corresponding 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole, as shown by Welch.[7] Thus, we have reported previously that the latter can be oxidized to the pyrrolo[3,4-*b*]indole ring system, albeit with a different indole *N*-protecting group (Scheme 4).[4]



Scheme 4

It should be noted that other syntheses of pyrrolo[3,4-*b*]indolones and pyrrolo[3,4-*b*]indolines have been reported in recent years,[24-27] but which do not involve a radical cyclization/dehydrogenation methodology. These are shown in Scheme 5.



Scheme 5

Conclusions

In conclusion, we have described a new approach to the pyrrolo[3,4-*b*]indole ring system that involves pyrrolo[3,4-*b*]indol-1(2*H*)one precursors that were initially employed by Welch and Kreher to synthesize pyrrolo[3,4-*b*]indoles by hydride reduction. Our new synthesis of pyrrolo[3,4-*b*]indol-1(2*H*)ones is atom economical and utilizes indole and aliphatic amines as the key ingredients, thus avoiding the necessity of preparing substituted 2,4-pyrrolidinediones that are required for a Fischer indole synthesis strategy.

Experimental Section

General. Melting points were determined on a Laboratory Devices Mel Temp capillary melting point apparatus, in open capillaries and are uncorrected. Thin layer chromatography (TLC) was performed on Whatman brand 20 x 20 cm polyester backed silica plates with fluorescent indicator. Plates were visualized by 254 nm UV light. Alternative visualization was accomplished by dipping the plate into a solution of ceric ammonium sulfate in 10% aqueous H_2SO_4 then drying. Flash chromatography was carried out using Silicycle ultra pure silica gel 60A (Angstrom). ^{1}H (300 MHz), ^{13}C (75 MHz), and ^{19}F (282.2 MHz) NMR spectra were recorded on a Varian XL-300 Fourier transform spectrometer unless otherwise indicated (by frequency) in which they were recorded on a Varian Unity plus spectrometer: ^{1}H (500 MHz) and ^{13}C (125 MHz). The chemical shifts are reported in δ (ppm) using the δ 7.27 signal of C*H*Cl_3 (^{1}H-NMR) and the δ 77.23 signal of *C*DCl_3 (^{13}C-NMR), the δ 4.87 signal of CD_3O*H* (^{1}H-NMR) and the δ 49.15 signal of *C*D_3OD (^{13}C-NMR), the δ 2.51 signal of $(CH_3)_2SO$ (^{1}H-NMR) and the δ 39.50 signal of $(CD_3)_2SO$ (^{13}C-NMR), or the δ 2.05 signal of $CO(CD_3)CD_2H$ (^{1}H-NMR) and δ 29.92 signal of $CO(CD_3)_2$ (^{13}C-NMR) and the 0.00 signal of C*F*Cl_3 (Freon 11) (^{19}F NMR) as internal standards. The apparent multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), the number of protons, and the coupling constants (in Hz) are reported where appropriate. Infrared spectra (IR) were recorded with a Perkin Elmer Series 1600 FTIR spectrophotometer and are referenced to the 1601 cm^{-1} band of polystyrene. IR spectra were obtained using either neat compounds (film) or solid potassium bromide pellets (KBr) and are reported in reciprocal centimeters. Ultraviolet (UV) spectra were recorded on a Hewlett-Packard 8451A Diode Array UV spectrophotometer and are reported in nanometers. Low-resolution mass spectra and high-resolution mass spectrometry (HRMS) were also performed at the University of Illinois (Urbana-Champaign) mass spectrometry laboratory. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA). Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under N_2. All amines and dichloromethane (CH_2Cl_2) were distilled in the presence of calcium hydride. All alkyllithium reagents were standardized prior to use by titration against diphenylacetic acid in dilute THF. Azobisisobutyronitrile (AIBN) was recrystallized from ethanol. *N*-Bromosuccinimide was recrystallized prior to use from water and dried in vacuo in the presence of phosphorus pentoxide. Potassium hydride (KH) was purchased from Aldrich as a 35% dispersion in mineral oil. Sodium hydride (NaH) was purchased from Acros as a 60% dispersion in mineral oil. The hydrides were washed with hexanes under N_2 to remove the mineral oil and then dried under vacuum. 1,2-Dibromo-1,1,2,2-tetrachloroethane ($BrCl_2CCCl_2Br$) was dried by dissolving the white solid in ether, drying over sodium sulfate, filtering under gravity, and removing the solvent in vacuo, prior to use. Unless otherwise indicated, all other reagents and solvents were purchased from commercial sources and were used without further purification. Inert atmospheres of nitrogen or argon were predried by flow through a column of Drierite 4 mesh with indicator. All reactions were done under a positive flow of nitrogen unless otherwise stated. Degassing was accomplished with a Firestone valve using the freeze, pump,

and thaw method with argon. All references to "water" or "H_2O" correspond to reverse osmosis deionized (RODI) water. "Brine" is a saturated aqueous sodium chloride solution. All volume descriptions for extractions and washes are approximate. "In vacuo" refers to solvent removal first by rotary evaporation followed by a lower pressure environment (≤ 0.2 Torr). Reaction temperatures ranging between –75 °C and –40 °C were achieved using a CO_2/isopropanol bath. Reaction temperatures ranging between 0 °C and 10 °C were achieved using a ice/sodium chloride bath. Anhydrous reactions were performed with glassware dried for 24 h at a temperature of 120 °C or greater then assembled hot and cooled under an atmosphere of nitrogen. Alternatively, glassware was assembled, flame dried, cooled under an atmosphere of nitrogen, and the drying/cooling process was repeated.

2,2,2-Trifluoro-1-(1*H*-indol-3-yl)ethan-1-one (6). This compound was prepared according to the procedure of Mackie.[19] To a stirred solution of trifluoroacetic anhydride (11.6 mL, 82.1 mmol, 2.4 eq.) in Et_2O (85 mL) at 0 °C was added a solution of indole (4.0 g, 34.2 mmol, 1 eq.) in Et_2O (24 mL) over 1 h via an addition funnel. The solution was stirred at 0 ^oC for 8 h. The Et_2O solution was washed with saturated $NaHCO_3$ (3 x 100 mL) and H_2O (2 x 75 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo to give a white solid which was recrystallized from Et_2O to give **6** (6.02 g, 83%) as white crystals: mp 209-210 °C (lit.[19] mp 208 °C); ^{1}H-NMR ($CDCl_3$) δ 11.6 (s, 1H), 8.36 (m, 1H), 8.29 (m, 1H), 7.58 (m, 1H), 7.30 (m, 2H); ^{13}C-NMR ($CO(CD_3)_2$) δ 205.9, 136.7, 126.5, 124.7, 123.7, 121.9, 119.5, 115.6, 112.9, 110.1; ^{19}F-NMR ($CFCl_3$) δ –73.4.

***N*-(*tert*-Butyl)-*N*-methyl-1*H*-indole-3-carboxamide (7).** To a stirred solution of *t*-butylmethylamine (2.8 mL, 23.5 mmol, 5 eq.), in THF (40 mL) at 0 °C under nitrogen was added slowly *n*-BuLi (9.4 mL, 23.5 mmol, 2.5 M in hexanes, 5 eq.). The solution was stirred at 0 °C for 2 h. To the anion was added 3-trifluoroacetylindole (**6**) (1.0 g, 4.69 mmol, 1 eq.) in THF (40 ml) at 0 °C. The reaction mixture was allowed to gradually warm to rt over 18 h then poured onto ice H_2O (75 mL) and stirred for 4 h. The aqueous solution was extracted with CH_2Cl_2 (4 x 75 mL). The organic extracts were combined, washed with brine (2 x 50 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil. This was purified by flash chromatography (2:1 hexanes: EtOAc) to give **7** as a yellow solid (0.91 g, 84%): ^{1}H-NMR ($CDCl_3$) δ 9.44 (bs, 1H), 7.65-7.68 (m, 1H), 7.32-7.35 (m, 2H), 7.14-7.21 (m, 2H), 3.03 (s, 3H), 1.57 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 169.6, 135.7, 127.8, 125.1, 122.3, 120.7, 120.4, 114.9, 111.8, 56.3, 35.2, 27.9; IR (KBr) 3444, 3167, 2945, 1587, 1536, 1446, 1123, 1011 cm^{-1}; UV (95% EtOH) δ_{max} 296 nm.; MS *m/z* 230 (M^+), 215, 144, 116, 89, 72 (100%). An analytical sample was obtained via iterative recrystallizations from CH_2Cl_2/hexanes: mp 220-222 °C. *Anal.* Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.80; H, 7.82; N, 12.08.

***N*-(*tert*-Butyl)-*N*,1-dimethyl-1*H*-indole-3-carboxamide (8), Method A.** To a stirred suspension of NaOH (78.9 mg, 1.97 mmol, 1.3 eq.) in EtOH (50 mL) was added the amide **7** (349.1 mg, 1.52 mmol, 1 eq.) neat. The solution was stirred for 2 h at rt to allow for complete dissolution. The EtOH was removed under reduced pressure, and the residue was dissolved in acetone (25 mL). The suspension was stirred for 5 min, treated with MeI (0.1 mL, 1.52 mmol, 1 eq.) and stirred overnight at rt (*ca*. 8 h). The solution was filtered under gravity, and the filtrate was then concentrated in vacuo to give a yellow oil. The oil was the triturated repeatedly with Et_2O to yield **8** as a light yellow solid (359 mg, 97%). The solid was homologous by TLC and ^{1}H-NMR. All spectral data was identical to those of **8** prepared by Method B (*vide infra*).

***N*-(*tert*-Butyl)-1*H*-indole-3-carboxamide (9).** To a stirred solution of *t*-butylamine (16.4 mL, 157 mmol, 5 eq.), in THF (56 mL) at -78 ^oC under nitrogen was added slowly *n*-BuLi (62.6 mL, 157 mmol, 2.5 M in hexanes, 5 eq.). The solution was stirred at -78 ^oC for 1 h. To the anion was added a solution of 3-trifluoroacetylindole (**6**) (6.67 g, 31.3 mmol, 1 eq.) in THF (50 mL) at 0 °C. The reaction mixture was allowed to gradually warm to rt over 12 h. This was poured onto ice H_2O (100 mL) and stirred for 2 h before the aqueous solution was extracted with

CH_2Cl_2 (1 x 65 mL). The entire solution was filtered through Celite® to separate the emulsion that formed. The aqueous layer was further extracted with CH_2Cl_2 (3 x 65 mL). The organic layers were combined, washed with brine (1 x 100 mL), dried (Na_2SO_4), and concentrated in vacuo to give a dark yellow oil. The oil was purified by flash chromatography (2:1 hexanes: EtOAc) to give **9** as a pale yellow solid (6.76 g, 79%): ^{1}H-NMR ($CDCl_3$) δ 9.60 (s, 1H), 7.89-7.85 (m, 1H), 7.68 (d, 1H, *J* 2.8 Hz), 7.41-742 (m, 1H), 7.26-7.21 (m, 2H), 5.94 (s, 1H), 1.55 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 165.5, 136.7, 128.5, 124.3, 122.5, 121.3, 119.1, 113.0, 112.5, 51.5, 29.3; IR (film) 3399, 3231, 2964, 1627, 1538, 1449, 1231, 737 cm^{-1}; MS *m/z* 216 (M^+), 161, 144, 116, 89. An analytical sample was obtained via iterative recrystallizations from Et_2O: mp 188-190 °C. *Anal.* Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.14; H, 7.41; N, 12.87.

***N*-(*tert*-Butyl)-1-methyl-1*H*-indole-3-carboxamide (10).** To a stirred suspension of NaOH (1.27 g, 31.8 mmol, 1.3 eq.) in EtOH (100 mL) was added amide **9** (5.28 g, 24.4 mmol, 1 eq.) neat. The solution was stirred for 2 h at rt. The EtOH was removed under reduced pressure, and the residue was dissolved in acetone (100 mL). The suspension was stirred for 15 min, treated with MeI (2 mL, 31.8 mmol, 1.3 eq.) and stirred overnight. The yellow solution was filtered under gravity, and the filtrate was concentrated in vacuo to give a pale yellow oil. The oil was triturated repeatedly with Et_2O to yield 5.19 g of **10** as a white solid (92%): ^{1}H-NMR ($CDCl_3$) δ 7.90 (m, 1H), 7.62 (s, 1H), 7.37-7.23 (m, 3H), 5.82 (s, 1H), 3.80 (s, 3H), 1.52 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 164.7, 137.3, 132.3, 125.2, 122.4, 121.3, 119.8, 112.2, 110.1, 51.4, 33.2, 29.3; IR (KBr) 3444, 3367, 3100, 2956, 1622, 1533, 1456, 1278, 1111, 744 cm^{-1}; UV (95% EtOH) δ_{max} 298 nm; MS *m/z* 230 (M^+), 174, 158 (100%), 130, 103, 77, 42. An analytical sample was obtained via iterative recrystallizations from Et_2O: mp 200-201.5 °C. *Anal.* Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.92; H, 7.86; N, 12.08.

***N*-(*tert*-Butyl)-*N*,1-dimethyl-1*H*-indole-3-carboxamide (8), Method B.** To a stirred suspension of KH (117 mg, 2.93 mmol, 1.2 eq.) in THF (10 mL) was added 18-crown-6 (775 mg, 2.93 mmol, 1.2 eq.) neat. The suspension was stirred at 0 °C under nitrogen for 1 h, at which time was added amide **10** (561.3 mg, 2.44 mmol, 1 eq.) in THF (34 mL) via an addition funnel. The solution was stirred at 0 °C for 1 h, treated with MeI (0.2 mL, 2.93 mmol, 1.2 eq.), and stirred overnight. The solution was poured onto ice H_2O (100 mL) and stirred thoroughly. The white solid that formed was collected by vacuum filtration and dried under vacuum to give the amide **8** as a white solid (516 mg, 88%). The filtrate was extracted with CH_2Cl_2 (3 x 65 mL) and the organic extracts were washed with brine (2 x 50 mL), dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil. Trituration of the oil with Et_2O gave the desired amide **8** as a white solid (12.5 mg). Total yield of **8** was 88% (529 mg). Both solids were homologous by TLC and ^{1}H-NMR; ^{1}H-NMR ($CDCl_3$) δ 7.68-7.71 (dd, 1H, *J*′ 1.4 Hz, *J*″ 7.3 Hz), 7.46 (s, 1H), 7.19-7.35 (m, 3H), 3.81 (s, 3H), 3.06 (s, 3H), 1.57 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 169.4, 136.8, 132.4, 126.1, 122.4, 121.2, 121.0, 114.4, 109.9, 56.4, 35.5, 33.4, 28.1; IR (KBr) 3458, 3113, 2975, 1627, 1533, 1474, 1363, 325, 1238, 1132, 1086 cm^{-1}; UV λ_{max} (95% EtOH) 218, 264, 290, 332, 348 nm. An analytical sample of **8** was obtained via iterative recrystallizations from Et_2O: mp 165-166 °C. *Anal.* Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.67; H, 8.30; N, 11.44.

2-Bromo-*N*-(*tert*-butyl)-*N*,1-dimethyl-1*H*-indole-3-carboxamide (11). To a stirred solution of the methylated amide **8** (816 mg, 3.34 mmol, 1 eq.) in THF (40 mL) at -78 °C was added slowly *t*-BuLi (3.0 mL, 5.01 mmol, 1.7 M in hexanes, 1.5 eq.). The solution was stirred at –78 °C for 1 h, then warmed to rt over 30 min before recooling to –78 °C. At this time the anion was treated with dried 1,2-dibromo-1,1,2,2-tetrachloroethane (1.63 g, 5.01 mmol, 1.5 eq.) in THF (20 mL). The solution warmed to rt overnight then poured onto ice H_2O (100 mL) and stirred for 2 h. No precipitate formed upon stirring. The aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL). The organic layers were combined, washed with brine (1 x 100 mL), dried (Na_2SO_4), and concentrated in vacuo to give a brown oil. Purification using flash column chromatography (2:1 hexanes: EtOAc) gave bromide **11** as a yellow solid (887 mg, 86%); ^{1}H-NMR ($CDCl_3$) δ 7.57-7.71 (dt, 1H, *J*′ 1.2 Hz, *J*″ 8.0 Hz), 7.14-7.34 (m, 3H),

3.76 (s, 3H), 2.96 (s, 3H), 1.57 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 167.1, 136.4, 125.8, 122.5, 121.0, 119.6, 114.7, 114.2, 109.5, 56.5, 34.2, 31.5, 28.0; IR (film) 3456, 3052, 2979, 1627, 1516, 1466, 1386, 1386, 1332 1265 cm^{-1}; UV λ_{max} (95% EtOH) 212, 266, 290, 332, 348 nm; MS *m/z* 323 (M^+), 307, 268, 236 (100%), 208, 169, 158, 129. An analytical sample of **11** was obtained via iterative recrystallizations from Et_2O: mp 105-106 °C. *Anal*. Calcd for $C_{15}H_{19}BrN_2O$: C, 55.74; H, 5.92; N, 8.67; Br, 24.72. Found: C, 56.13; H, 5.94; N, 8.64; Br, 24.42.

2-(*tert*-Butyl)-4-methyl-3,3a,4,8b-tetrahydropyrrolo[3,4-*b*]indol-1(2*H*)-one (15). To a refluxing solution of bromide **11** (869 mg, 2.69 mmol, 1 eq.) in degassed toluene (60 mL) under Ar, was added *n*-Bu_3SnH (0.9 mL, 3.23 mmol, 1.2 eq.) and AIBN (88.0 mg, 0.54 mmol, 0.2 eq.) in degassed toluene (20 mL) dropwise over 24 h via a Kontes® constant addition funnel. The solution was refluxed for a total of 48 h then cooled to rt. The solvent was removed in vacuo and the resulting residue was chromatographed (2:1 hexanes: EtOAc) to give dihydroindole **15** (334 mg) in 51% yield and the reduced compound **8** in 22% yield (144 mg) as pale yellow solids; ^{1}H-NMR ($CDCl_3$) δ 7.31-7.34 (d, 1H, *J* 7.3 Hz), 7.08-7.13 (td, 1H, *J*′ 1.1 Hz, *J*″ 7.7 Hz), 6.70-6.73 (td, 1H, *J*′ 0.7 Hz, *J*″ 7.3 Hz), 6.41-6.43 (d, 1H, *J* 7.7 Hz), 4.01-4.07 (qd, 1H, *J*′ 1.5 Hz, *J*″ 9.2 Hz), 3.93-3.95 (d, 1H, *J* 9.2 Hz), 3.66-3.71 (dd, 1H, *J*′ 5.5 Hz, *J*″ 10.3 Hz), 3.56-3.59 (dd, 1H, *J*′ 1.5 Hz, *J*″ 10.3 Hz), 2.80 (s, 3H), 1.38 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 172.5, 152.0, 128.4, 126.1, 124.9, 118.6, 106.6, 63.4, 54.3, 51.1, 50.7, 34.4, 27.6; IR (film) 2975, 2877, 2243, 1674, 1607, 1488, 1413, 1365, 1285 cm^{-1}; MS *m/z* 244 (M^+), 187, 158 (100%), 144, 131,103, 89, 77. An analytical sample of **15** was obtained via iterative recrystallizations from Et_2O: mp 100-100.5 °C**.** *Anal*. Calcd for $C_{15}H_{18}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.83; H, 8.34; N, 11.39.

2-(*tert*-Butyl)-4-methyl-3,4-dihydropyrrolo[3,4-*b*]indol-1(2*H*)-one (4). To a solution of the dihydroindole **15** (41.5 mg, 0.17 mmol, 1 eq.) in xylenes (5 mL) was added Pd/C (10% Pd, 40.3 mg, 0.38 mmol, 2.2 eq.). The mixture was heated at reflux for 14 h. No more starting material was present by TLC. The catalyst was removed by filtration through Celite® and washed thoroughly with toluene. The filtrate was collected and concentrated in vacuo to give lactam **4** as a white crystalline solid (37.2 mg) in 90% yield. The solid was homologous by TLC: mp 171-172 °C (lit.[11] mp 175 °C); ^{1}H-NMR ($CDCl_3$) δ 7.87-7.89 (dd, 1H, *J*′ 1.2 Hz, *J*″ 7.1 Hz), 7.20-7.29 (m, 3H), 4.30 (s, 2H), 3.67 (s, 3H), 1.54 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 168.6, 151.8, 142.2, 123.0, 122.6, 121.9, 121.0, 120.9, 110.4, 55.1, 43.8, 31.5, 29.2; IR (film) 2977, 2253, 1661, 1560, 1454, 1404, 1344 cm^{-1}.

2-(*tert*-Butyl)-4-methyl-2,4-dihydropyrrolo[3,4-*b*]indole (5). This compound was prepared according to the procedure of Kreher.[11] To a solution of indolone **4** (34.1 mg, 0.14 mmol, 1 eq.) in anhydrous Et_2O (3 mL) was added dropwise DIBAL solution (0.16 mL, 0.16 mmol, 1.0 M in hexanes, 1.1 eq.). The solution was stirred for 24 h at rt. To this was added 10% NaOH (4 mL) and stirred for 1 h. The mixture was extracted repeatedly with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), and concentrated in vacuo to give a yellow solid. Flash column chromatography (4:1 hexanes: EtOAc) gave unchanged **4** (6.4 mg) and pyrroloindole **5** (17.0 mg) as a yellow oil, which turned green on standing. Total yield of **5** based on recovered starting material was 66%: ^{1}H-NMR ($CDCl_3$) δ 7.70-7.72 (dd, 1H, *J*′ 0.73 Hz, *J*″ 7.7 Hz), 7.22-7.28 (m, 1H), 7.11-7.14 (m, 2H), 7.00-7.04 (td, 1H, *J*′ = 1.1 Hz, *J*″ = 7.3 Hz), 6.58-6.59 (d, 1H, *J*′ = 1.8 Hz), 3.64 (s, 3H), 1.67 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 146.4, 137.8, 123.3, 121.0, 120.3, 117.5, 115.1, 107.7, 105.0, 91.5, 55.9, 31.4, 31.3. These data are in agreement with the literature data.[11]

Acknowledgements

This investigation was supported in part by the National Institutes of Health (GM58601) and by Dartmouth College.

References

1. Pelkey, E. T.; Gribble, G. W. *Chem. Commun.* **1997**, 1873.
2. Gribble, G. W.; Pelkey, E. T.; Switzer, F. L. *Synlett* **1988**, 1061.
3. Gribble, G. W.; Pelkey, E. T.; Simon, W. M.; Trujillo, H. A. *Tetrahedron* **2000**, *56*, 10133. https://doi.org/10.1016/S0040-4020(00)00858-9
4. Kishbaugh, T. L. S.; Gribble, G. W. *Synth. Commun.* **2002**, *32*, 2003. https://doi.org/10.1081/SCC-120004850
5. Pelkey, E. T.; Gribble, G. W. *Can. J. Chem.* **2006**, *84*, 1338. https://doi.org/10.1139/v06-075
6. Roy, S.; Kishbaugh, T. L. S.; Jasinski, J. P.; Gribble, G. W. *Tetrahedron Lett.* **2007**, *48*, 1313. https://doi.org/10.1016/j.tetlet.2006.12.125
7. Welch, W. M. *J. Org. Chem.* **1976**, *41*, 2031. https://doi.org/10.1021/jo00873a033
8. Sha, C.-K.; Chuang, K.-S.; Young, J.-J. *J. Chem. Soc., Chem. Commun.* **1984**, 1552.
9. Sha, C.-K.; Chuang, K.-S.; Wey, S.-J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 977. https://doi.org/10.1021/jo00873a033
10. Sha, C.-K.; Yang, J.-F. *Tetrahedron* **1992**, *48*, 10645. https://doi.org/10.1016/S0040-4020(01)88360-5
11. Kreher, R. P.; Dyker, G. *Z. Naturforsch Teil B: Chem. Sci.* **1987**, *42*, 473.
12. Dyker, G.; Kreher, R. P. *Chem.-Ztg.* **1988**, *112*, 235.
13. Jeevanandam, A.; Srinivasan, P. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2663. https://doi.org/10.1039/p19950002663
14. Daly, K.; Nomak, R.; Snyder, J. K. *Tetrahedron Lett.* **1997**, *38*, 8611. https://doi.org/10.1016/S0040-4039(97)10312-4
15. Solé, D.; Bennasar, M.-L.; Jiménez, I. *Org. Biomol. Chem.* **2011**, *9*, 4535. https://doi.org/10.1039/c1ob05087g
16. Southwick, P. L.; Previc, E. P.; Casanova, Jr., J.; Carlson, E. H. *J. Org. Chem.* **1956**, *21*, 1087. https://doi.org/10.1021/jo01116a009
17. Southwick, P. L.; Owellen, R. J. *J. Org. Chem.* **1960**, *25*, 1133. https://doi.org/10.1021/jo01077a017
18. Lowe, G. W.; Yeung, H. W. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2907. https://doi.org/10.1039/P19730002907
19. Mackie, R. K.; Mhatre, S.; Tedder, J. M. *J. Fluorine Chem.* **1977**, *10*, 437. https://doi.org/10.1016/S0022-1139(00)82425-2
20. Hassinger, H. L.; Soll, R. M.; Gribble, G. W. *Tetrahedron Lett.* **1998**, *39*, 3095. https://doi.org/10.1016/S0040-4039(98)00505-X
21. Gribble, G. W.; Fraser, H. L.; Badenock, J. C. *Chem. Commun.* **2001**, 805. https://doi.org/10.1039/b101859k
22. Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495. https://doi.org/10.1021/jo00034a058
23. Tanaka, H.; Murakami, Y.; Aizawa, T.; Torii, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3742. https://doi.org/10.1246/bcsj.62.3742

24. Ivachtchenko, A. V.; Frolov, E. B.; Mitkin, O. D.; Tkachenko, S. E.; Khvat, A. V. *Chem. Het. Cpds.* **2010**, *46*, 170.
https://doi.org/10.1007/s10593-010-0488-z
25. Ma, F.; Ma, L.; Lei, M.; Hu, L. *Monatsch. Chem.* **2014**, *145*, 1035.
https://doi.org/10.1007/s00706-014-1171-3
26. Awata, A.; Arai, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 10462.
https://doi.org/10.1002/anie.201405223
27. Liu, H.; Zheng, C.; You, S.-L. *Chin. J. Chem.* **2014**, *32*, 709.
https://doi.org/10.1002/cjoc.201400178

