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A novel palladium-catalyzed synthesis of β-carbolines: application in total synthesis of naturally occurring alkaloids

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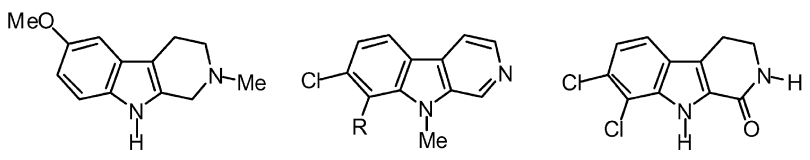
Abstract—Two naturally occurring β-carbolines, 6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline and bauerine A, have been prepared using a Stille-type coupling, followed by a palladium-phosphine catalyzed N-heteroannulation as the key steps.

We have recently developed a relatively mild palladium-phosphine catalyzed reductive N-heteroannulation of 2-nitrostyrenes forming indoles[1–6] and 1,2-dihydro-4(3*H*)-carbazolones[7] in good to excellent yields. A variety of 2-nitrostyrenes having electron-donating or electron-withdrawing substituents on the aromatic ring furnished indoles in good to excellent yield. Using this methodology as the key step, we have reported short syntheses of some naturally occurring indole alkaloids.[8] As a continuation of our interest in the synthesis of biologically active molecules utilizing this methodology, we envisioned a short synthesis of β-carbolines. Herein is reported the synthesis of two naturally occurring β-carbolines, 6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline (**1**) and bauerine A (Fig. 1). The synthesis of **1** also constitutes a formal total synthesis of the oxindole alkaloid, horsfiline.[9]

1. Results and discussion

Two naturally occurring β-carboline alkaloids, 6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline (**1**) and bauerine A, were selected as our synthetic targets (Fig. 1). β-Carboline **1** has been isolated from a variety of plant sources, for example, *Phalaris tuberosa*[10] and *Horsfieldia superba*.[9] Bauerine A was isolated by Moore et al. from the blue–green alga *Dichotrix baueriana*.[11] Two additional chlorine containing β-carbolines, bauerines B–C, were also isolated from the same source. The bauerine alkaloids show activity against herpes simplex virus type 2. A short synthesis of bauerine B was reported by Queguiner and co-workers a few years ago.[12] However, the methodology used for bauerine B is not suitable for the synthesis of bauerine A due to potential formation of isomeric products in one of the key steps.

Synthesis of 6-methoxy-1,2,3,4-tetrahydro-β-carboline (**1**) was initially examined to evaluate the feasibility of the proposed route to β-carboline alkaloids. Tri-*n*-butyl-(5-methyl-2-nitro-phenyl)stannane (**4**) was prepared from commercially available 4-nitroanisole in three steps (Scheme 1). Amination of 4-nitroanisole with *O*-methyl-hydroxylamine according to a literature procedure gave 5-methoxy-2-nitro-aniline (**2**).[13] Transformation of **2**, via reaction of the corresponding diazonium salt with potassium iodide, gave 2-iodo-4-methoxy-1-nitro-benzene (**3**) in 71%



1 **Bauerine A** (R = H) **Bauerine B** (R = Cl) **Bauerine C**

Figure 1.

Keywords: palladium; catalysis; alkaloids; carboline.

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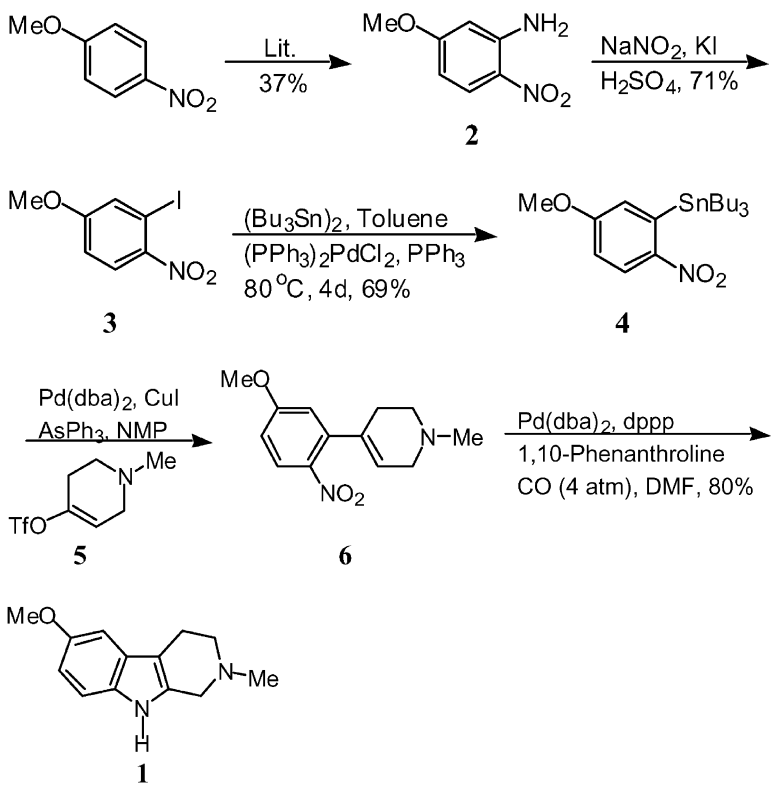
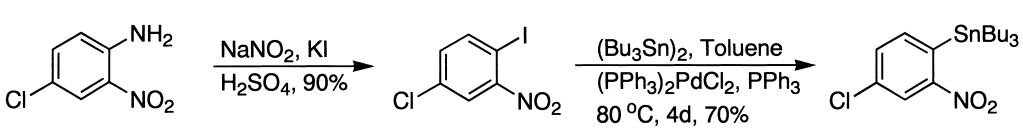


Scheme 1.

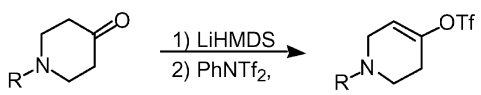
yield. Palladium-catalyzed reaction of **3** with hexa-*n*-butylditin in toluene at 80°C for 4 days furnished arylstannane **4** in 69% yield.[14] Stille coupling of **4** with vinyl triflate **5**, using bis(dibenzylideneacetone)-palladium(0) (5 mol%), triphenylarsine (20 mol%), and copper iodide (10 mol%) in *N*-methylpyrrolidine (NMP) gave the expected coupling product **6** in good yield. Synthesis of **5** from *N*-methyl-4-piperidone and related Stille cross-coupling reactions have been reported.[15]

Palladium-catalyzed N-heteroannulation of **6** under conditions previously employed to prepare indoles (conditions A),[2] palladium diacetate (6 mol%), triphenylphosphine (24 mol%), and carbon monoxide (4 atm) in acetonitrile at 70°C (60 h), gave a 7:3 mixture of **6** and the expected product **1**. Palladium–phenanthroline complexes have been shown to be particularly active catalysts for the reductive carbonylation of nitrobenzenes to give isocyanates.[16] We have previously successfully employed this type of catalyst system for the preparation of 1,2-dihydro-4(3*H*)-carbazolones.[7] Application of the modified conditions (conditions B), bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$, 6 mol%), 1,3-bis(diphenylphosphino)propane (dppp, 12 mol%), 1,10-phenanthroline (12 mol%), and CO (6 atm) in dimethylformamide (DMF, 80°C, 12 h), gave the expected 6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline (**1**) in 80% yield. It should be noted that the described route cannot compete with previously published syntheses of **1**.[17,18] However, it demonstrates the feasibility of the key steps for the preparation of β-carboline type alkaloids.

Based on the successful completion of the synthesis of **1**, we decided to pursue a synthesis of bauerine A using a related synthetic relay. Formation of a diazonium salt from 4-chloro-2-nitroaniline (**7**) followed by reaction with potassium iodide, using a modification of a published procedure,[19] gave 4-chloro-1-iodo-2-nitrobenzene (**8**) in 90% yield. Reaction of **8** with hexa-*n*-butylditin catalyzed by palladium as described above furnished tri-*n*-butyl-(4-chloro-2-nitro-phenyl)stannane (**9**) in 70% yield (Scheme 2). Three different *N*-protected vinyl triflates were prepared from 4-piperidone. In addition to the known *N*-benzyl-[20,21] and *N*-BOC-protected[22] vinyl triflates **10** and **11**, the *N*-tosyl-protected vinyl triflate **12** was prepared from the corresponding *N*-protected piperidones[23] using *N*-phenyltrifluoromethansulfonamide and lithium hexamethyldisilazide (LiHMDS) (Scheme 3). A fourth compound, 4-iodo-*N*-benzyl-1,2,5,6-tetrahydropyridine (**13**) was prepared in 70%



Scheme 2.



10 (R = Bn, 75%)
11, (R = BOC, 71%)
12, (R = Ts, 80%)

Scheme 3.

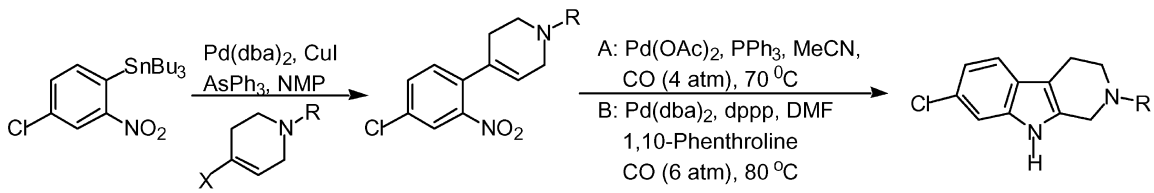
yield in a three-step reaction sequence from commercially available 3-butyne-1-ol according to a literature procedure.[24]

Stille cross-coupling of **10** with arylstannane **9** using $Pd(dba)_2$ (5 mol%), triphenylarsine (20 mol%), and copper iodide (10 mol%) in NMP at 50°C gave the expected product **14** (Scheme 4). However, the coupling product could not be completely separated from a substantial amount of tin-containing impurities even after extensive purification. The impurity co-elutes upon chromatography and was only partially removed by bulb-to-bulb distillation. To a much lesser extent, the problem of co-eluting, tin-containing, impurities was also encountered upon palladium-catalyzed reaction of vinyl iodide **13** with arylstannane **9**. To improve the purity of the Stille coupling product, **11** and **12** were used, and the cross-coupling products **15** and **16** were obtained. The latter compounds were readily purified by column chromatography on silica gel to give pure products in 50 and 62% yield, respectively.

Palladium catalyzed N-heteroannulation of **14**, formed from coupling of **13** with **9**, under standard reaction conditions (conditions A) gave the tetrahydro-β-carboline **17** in 61% yield (from **13**, Scheme 4). For the *N*-tosyl and *N*-BOC protected Stille coupling products **15** and **16**, the modified reaction conditions B were required for complete transformation to afford the tetrahydro-β-carbolines **18** and **19**. Considering the substantially lower yield of **19** compared to **17** and **18**, the former, N-tosylated compound, was not further pursued for the synthesis of bauerine A.

Removal of the benzyl group from **17** was readily achieved using a number of reagents. Unfortunately, attempted debenzylation using Pd/C on $Ba(OH)_2$ and ammonium formate[25] in refluxing methanol, Pd/C and formic acid (aq., 4.4%) in methanol,[26] or $Pd(OH)_2$/C and ammonium formate gave the dechlorinated product **20** in 85–91% yield, as the formate salt (Scheme 5). Methylation of the pyrrole nitrogen, using sodium hydride and methyl iodide in THF at 0°C, gave **22** in 81% yield. The benzyl protecting was removed in quantitative yield, again accompanied with the facile and complete dechlorination, to give **23**.

Aromatization of 1,2,3,4-tetrahydro-β-carbolines, without substituents on the six-membered nitrogen ring is not a



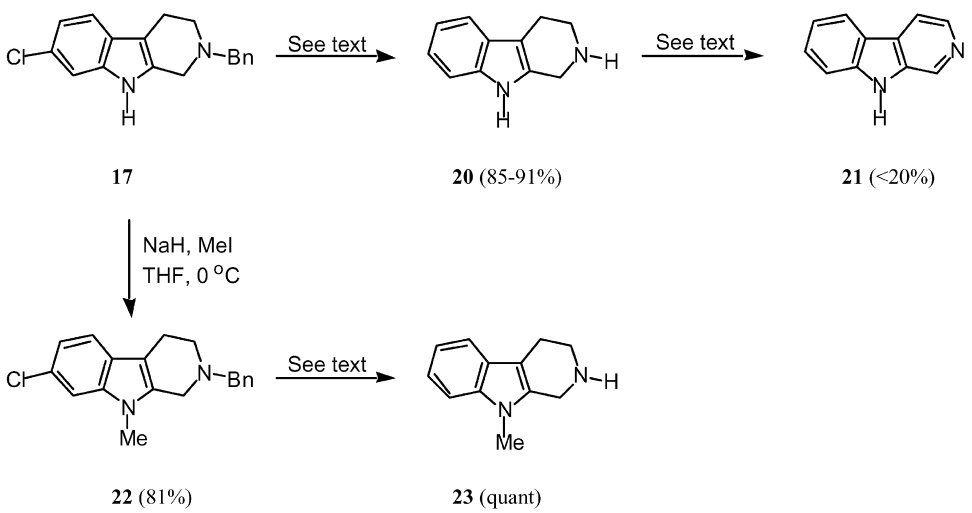
9

10 (R = Bn, X = OTf)
11 (R = BOC, X = OTf)
12 (R = Ts, X = OTf)
13 (R = Bn, X = I)

14
15 (50%)
16 (62%)

17 (61% from **13**, using A)
18 (81%, using B)
19 (50%, using B)

Scheme 4.



17

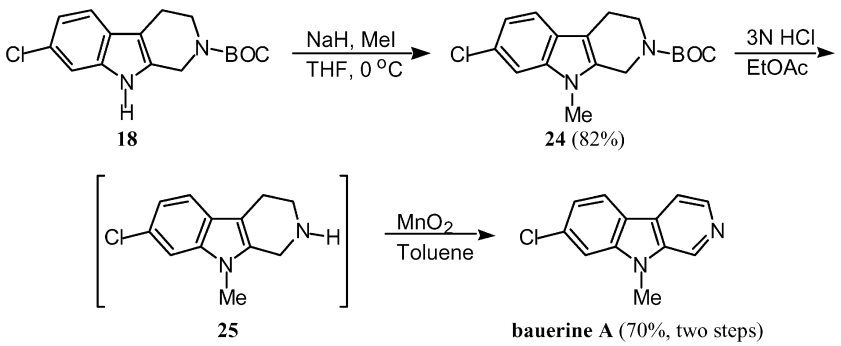
20 (85-91%)

21 (<20%)

22 (81%)

23 (quant)

Scheme 5.



Scheme 6.

trivial transformation.[27] Using **20** as a model substrate, commonly used oxidizing reagents, such as manganese dioxide,[28] selenium dioxide,[29] palladium on carbon,[30] iodosobenzene,[31] or palladium on barium carbonate in butanol[32] gave unsatisfactory results. The starting material was usually recovered together with minor amounts of the expected aromatized product **21** (<20%).

Next, we turned our focus to the *N*-BOC protected annulation product **18**. Tetrahydro-β-carboline **18** was N-methylated in 82% yield (Scheme 6). The BOC protecting group was removed by treatment with 3N HCl in ethyl acetate at ambient temperature affording tetrahydro-β-carboline **25** in almost quantitative yield. The deprotected carboline was difficult to purify and was therefore used in the next step without prior purification. Oxidation of **25** was achieved employing MnO_2 in refluxing toluene to give bauerine A in 70% yield. Thus, the first total synthesis of bauerine A was completed in 7 linear steps, in 18% overall yield, from commercially available starting materials.

In conclusion, we have achieved the synthesis of two naturally occurring β-carbolines employing two successive palladium catalyzed reactions, namely, a Stille coupling followed by a reductive N-heteroannulation. Further application for the total synthesis of some chiral β-carbolines is currently underway in our laboratories.

2. Experimental

2.1. General procedures

All NMR spectra were determined in $CDCl_3$ at 270 MHz (^{1}H NMR) and 67.5 MHz (^{13}C NMR) unless otherwise stated. The chemical shifts are expressed in δ values relative to Me_4Si (0.0, ^{1}H and ^{13}C), $CDCl_3$ (77.0, ^{13}C), or DMSO-d_6 (39.5, ^{13}C) internal standards. ^{1}H–^{1}H spin–spin coupling constants are reported as calculated from spectra; thus, a slight difference between J_{ab} and J_{ba} is usually obtained. Results of APT (attached proton test) ^{13}C NMR experiments are shown in parentheses where, relative to $CDCl_3$, (−) denotes CH_3 or CH and (+) denotes CH_2 or C. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Toluene, hexanes, dimethylformamide (DMF), triethylamine, methanol, and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed in oven-dried glassware under an argon atmosphere unless otherwise stated. Solvents were removed from crude reaction mixtures and products on a rotary evaporator at water aspirator pressure. Melting points were determined on a MelTemp and are uncorrected. Elemental analyses were performed by Alantic Microlab Inc. (Norcross, GA). High-resolution mass-spectra analyses were performed at University of California Riverside Mass Spectrometry Facility (Riverside, CA).

2.1.1. 2-Iodo-4-methoxy-1-nitro-benzene (3).[33] 5-Methoxy-2-nitroaniline (**2**)[13] (400 mg, 2.38 mmol) was dissolved in H_2SO_4 (conc., 5 mL) and cooled to 0°C in an ice-bath. To this solution was added dropwise a solution of $NaNO_2$ (197 mg, 2.85 mmol) in H_2SO_4 (conc., 5 mL). The resulting diazonium salt solution was stirred at 0°C for 30 min, and then slowly allowed to warm to room temperature over 2 h. The diazonium salt solution was added dropwise (15 min) to an ice–water solution of KI (592 mg, 3.56 mmol) at 0°C, and the resulting mixture was stirred for an additional 2 h. The solution was made basic with NaOH (aq., 10%) and extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was removed at reduced pressure to give **3** (470 mg, 1.68 mmol, 71%) as a yellow solid. No further purification was required. Mp 65°C; ^{1}H NMR δ 7.96 (d, J=9 Hz, 1H), 7.52 (d, J=2.5 Hz, 1H), 6.97 (dd, J=9, 2.5 Hz), 3.85 (s, 3H); ^{13}C NMR δ 162.3 (+), 144.8 (+), 127.2 (−), 126.9 (−), 113.9 (−), 88.0 (+), 56.0 (−).

2.1.2. Tri-*n*-butyl (5-methoxy-2-nitro-phenyl)stannane (4). To a mixture of 2-iodo-4-methoxy-1-nitrobenzene (**3**) (450 mg, 1.61 mmol) in dry toluene (15 mL) under argon was added, hexa-n-butylditin (890 μL, 1.76 mmol), followed by $PdCl_2(PPh_3)_2$ (11 mg, 0.015 mmol), and triphenylphosphine (8.4 mg, 0.032 mmol). The reaction mixture was stirred at 80°C for 5 days. Upon completion of the reaction, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with ammonium hydroxide solution (aq., 3×10 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed at reduced pressure. The crude product was purified by chromatography (hexanes) to give **4** (487 mg, 1.10 mmol, 69%) as a pale yellow oil. ^{1}H NMR δ 8.31 (d, J=9.0 Hz, 1H), 7.1 (d, J=2.7 Hz, 1H), 6.92 (dd, J=9.0, 2.7 Hz, 1H), 3.90 (s, 3H), 1.47 (m, 6H), 1.39 (m,

6H), 1.12 (m, 6H), 0.86 (t, J=7.1 Hz, 9H); ^{13}C NMR δ 163.2 (+), 146.5 (+), 143.3 (+), 126.4 (−), 122.1 (−), 113.3 (−), 55.6 (−), 28.8 (+), 27.2 (+), 13.5 (−), 11.0 (+); IR (neat) 2955, 1571, 1500, 1463, 1331, 1230 cm^{-1}. HRMS (DCI) calcd for $C_{19}H_{37}N_2O_3Sn$ ($M^+NH_4^+$) 461.1826, found 461.1827.

2.1.3. 4-(5-Methoxy-2-nitro-phenyl)-1-methyl-1,2,3,6-tetrahydro-pyridine (6). To a solution of **4** (360 mg, 8.15 mmol) in *N*-methylpyrrolidinone (1.5 mL), under argon, was added 1-methyl-4-[(trifluoromethanesulfonyl)-oxy]-1,2,3,6-tetrahydropyridine (**5**)[15] (200 mg, 8.15 mmol), $Pd(dba)_2$ (23.4 mg, 0.40 mmol), triphenylarsine (49.9 mg, 0.16 mmol), and copper iodide (15.5 mg, 0.081 mmol). The reaction mixture was stirred at 50°C for 10 h. The reaction mixture was allowed to cool to ambient temperature and was diluted with CH_2Cl_2 (100 mL). The organic phase was washed with ammonium hydroxide (aq., 3×10 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residual NMP together with unknown tin impurities were removed by bulb–bulb distillation. The residue was purified by chromatography (hexanes–EtOAc, 2:8) to give **6** (166 mg, 0.66 mmol, 82%) as a faint yellow oil. ^{1}H NMR δ 8.05 (d, J=9 Hz, 1H), 6.86 (dd, J=9.0, 2.7 Hz, 1H), 6.75 (d, J=2.7 Hz, 1H), 3.86 (s, 3H), 3.10 (q, J=3.3 Hz, 2H), 2.7 (t, J=5.5 Hz, 2H), 2.42 (s, 3H), 2.39 (m, 2H); ^{13}C NMR δ 163.0 (+), 141.3 (+), 135.4 (+), 127.1 (−), 123.1 (−), 115.8 (−), 113.1 (−), 55.9 (−), 54.5 (+), 52.0 (+), 45.8 (−), 3.3 (+); IR (neat) 1575, 1513 cm^{-1}. HRMS (DCI) calcd for $C_{13}H_{16}N_2O_3$ 248.1161 (M^+), found 248.1158.

2.1.4. 6-Methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline (1).[14] To an oven dried, threaded ACE glass pressure tube was added **6** (160 mg, 0.64 mmol), $Pd(dba)_2$ (22 mg, 0.038 mmol), 1,3-bis(diphenylphosphino)propane (15.9 mg, 0.038 mmol), 1,10-phenanthroline (15.3 mg, 0.077 mmol), and DMF (5 mL). The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction mixture was heated at 90°C (oil bath temperature) under CO (6 atm) until all starting material was consumed (12 h), as judged by TLC. The reaction mixture was filtered through a Celite pad, and the pad was washed with CH_2Cl_2 (10 mL). The solvent was removed under reduced pressure, and crude product was purified by chromatography (CH_2Cl_2–MeOH, 8:2) to give **1** (111 mg, 0.51 mmol, 80%) as a pale yellow solid.

2.1.5. 4-Chloro-1-iodo-2-nitro-benzene (8).[19] The procedure by Liedholm was followed with a few modifications. A solution of 4-chloro-2-nitroaniline (**7**) (2.60 g, 15.0 mmol) in H_2SO_4 (conc., 25 mL) was cooled to 0°C in an ice-bath. To the solution was added dropwise a solution of $NaNO_2$ (1.24 g, 18.0 mmol) in H_2SO_4 (conc., 15 mL). The resulting diazonium salt solution was stirred at 0°C for 30 min and then slowly allowed to warm to room temperature over 2 h. The diazonium salt solution was added dropwise (15 min) to an ice–water solution of KI (3.73 g, 22.5 mmol) at 0°C and stirred for another 2 h at °C. The reaction mixture was made basic with NaOH (aq., 10%) and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent was removed at reduced pressure to give **10** (3.90 g, 13.8 mmol, 90%, literature yield 54%) as a yellow solid. Mp 59°C; ^{1}H NMR δ 8.00 (d, J=5.9 Hz, 1H), 7.86 (d, J=2.3 Hz, 1H), 7.28 (dd, J=6.9, 2.3 Hz, 1H); ^{13}C NMR δ 142.6 (−), 135.2 (+), 133.5 (−), 125.6 (−), 83.5 (+).

2.1.6. Tri-*n*-butyl-(4-chloro-2-nitro-phenyl)stannane (9). To a mixture of 4-chloro-1-iodo-2-nitro-benzene (**8**) (1.00 g, 3.52 mmol) in dry toluene (25 mL), under argon, was added, hexa-*n*-butylditin (1.94 mL, 3.85 mmol), followed by $PdCl_2(PPh_3)_2$ (24.5 mg, 0.035 mmol), and triphenylphosphine (18 mg, 0.068 mmol). The resulting reaction mixture was stirred at 80°C for 4 days. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with ammonium hydroxide solution (aq., 3×10 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (hexanes) to give **9** (1.11 g, 2.48 mmol, 70%) as a pale yellow oil. ^{1}H NMR δ 8.29 (d, J=1.2 Hz, 1H), 7.58 (m, 2H), 1.48 (m, 6H), 1.33(m, 6H), 1.14 (m, 6H), 0.85 (t, J=7.3 Hz, 9H); ^{13}C NMR δ 154.1 (+), 138.5 (−), 135.2 (+), 133.3 (−), 124.1 (−), 28.8 (+), 27.2 (+), 13.7 (−), 11.0 (+); IR (neat) 2955, 1525, 1456, 1343 cm^{-1}. Anal. calcd for $C_{18}H_30ClNO_2Sn$: C, 48.41; H, 6.77. Found: C, 48.78; H, 6.60.

2.1.7. *N*-(4-Methylphenylsulfonyl)-4-[(trifluoromethanesulfonyl)oxy]-1,2,3,6-tetrahydropyridine (12). To a freshly prepared solution of LDA in THF (10 mL), from diisopropylamine (243 mL, 1.73 mmol) and *n*-BuLi (2 M in hexane, 0.86 mL, 1.73 mmol) at −78°C, was added a solution of *N*-(4-methylphenylsulfonyl)-4-piperidone (400 mg, 1.58 mmol) in THF (5 mL). The resulting mixture was stirred at −78°C for 30 min where after a solution of *N*-phenyltrifluoromethanesulfonimide (400 mg, 1.58 mmol) in THF (8 mL) was added dropwise. After stirring for an additional 1 h, the solution was allowed to slowly warm to ambient temperature. The solvent was removed, and the residue was purified by chromatography (hexanes–EtOAc, 19:1) to give **12** (485 mg, 1.25 mmol, 80%) as a colorless oil that solidified in the freezer. Mp 69°C; ^{1}H NMR δ 7.68 (d, J=8.3 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H), 5.73 (m, 1H), 3.79 (q, J=3.0 Hz, 2H), 3.37 (q, J=8.5 Hz, 2H), 2.48 (m, 2H), 2.44 (s, 3H); ^{13}C NMR δ 146.3 (+), 144.2 (+), 133.1 (−), 129.9 (−), 127.4 (−), 114.3 (−), 43.3 (+), 42.7 (+), 27.8 (+), 21.4 (−); IR (neat)1352, 1166 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{14}F_3NO_5S_2$ 385.0265 (M^+), found 385.0258.

2.1.8. 1-Benzyl-4-(4-chloro-2-nitro-phenyl)-1,2,3,6-tetrahydropyridine (14). To a solution of **9** (830 mg, 1.86 mmol) in NMP (5 mL), under argon, was added **10** (597 mg, 1.86 mmol), $Pd(dba)_2$ (53 mg, 0.093 mmol), triphenylarsine (113 mg, 0.37 mmol), and copper iodide (35 mg, 0.18 mmol). The resulting mixture was stirred at 50°C (oil-bath temperature) for 10 h. After cooling to ambient temperature, the mixture was diluted with CH_2Cl_2 (200 mL), washed with ammonium hydroxide (aq., 3×10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvents were evaporated under reduced pressure. The remaining NMP was removed by bulb-to-bulb distillation under vacuum, followed by purification of the residue by chromatography (hexanes–EtOAc, 9:1) to give 415 mg of a pale yellow oil. The oil was

a mixture of **14** (by ^{1}H NMR) and an unidentified tin-containing impurity. All attempts to further purify **14** were unsuccessful.

Similar reaction of **9** (939 mg, 2.10 mmol) with **13** (600 mg, 2.11 mmol), in the presence of $PdCl_2(PPh_3)_2$ (74 mg, 0.10 mmol), triphenylphosphine (55 mg, 0.21 mmol), and copper iodide (40 mg, 0.21 mmol) in NMP (4 mL), as described above, gave after purification by chromatography (hexanes–EtOAc, 9:1) **14** (469 mg) as a pale yellow oil. The product was contaminated with a small amount of an unknown tin-containing impurity. Spectral data from the mixture: ^{1}H NMR δ 7.85 (d, J=1.9 Hz, 1H), 7.49 (dd, J=8.2, 2.1 Hz, 1H), 7.36 (m, 6H), 5.61 (m, 1H), 3.65 (s, 2H), 3.12 (m, 2H), 2.71 (t, J=5.7 Hz, 2H), 2.33 (m, 2H); ^{13}C NMR δ 148.2 (+), 137.7 (+), 136.0 (+), 132.9 (+), 132.4 (−), 131.7 (−), 128.8 (−), 128 (−), 126.8 (−), 124.9 (−), 123.8 (−), 62.1 (+), 52.4 (+), 49.1 (+), 29.5 (+); IR (neat) 1531, 1351 cm^{-1}; HRMS (DEI) calcd for $C_{18}H_{17}ClN_2O_2$ 328.0978 (M^+), found 328.0978.

2.1.9. 4-(4-Chloro-2-nitro-phenyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (15). Reaction of **9** (950 mg, 2.12 mmol) with **11** (710 mg, 2.12 mmol) in the presence of $Pd(dba)_2$ (61.5 mg, 0.10 mmol), triphenylarsine (131 mg, 0.42 mmol), copper iodide (40 mg, 0.21 mmol) in NMP, as described above, gave after chromatography (hexanes EtOAc, 9:1) **15** (450 mg, 1.32 mmol, 62%) as an oil. ^{1}H NMR δ 7.91 (d, J=1.9 Hz, 1H), 7.55 (dd, J=8.1, 2.1 Hz, 1H), 7.26 (d, J=1.6 Hz, 1H), 5.6 (s, 1H), 4.03 (br s, 2H), 3.63 (t, J=5.4 Hz, 2H), 2.30 (br s, 2H), 1.49 (s, 9H); 13C NMR δ 154.5 (+), 148.1 (+), 135.9 (+), 133.6 (+), 133.4 (+), 132.8 (−), 131.8 (−), 124.4 (−), 79.6 (+), 29.0 (+), 28.2 (−); IR (neat) 2930, 1693, 1537, 1415, 1365, 1238, 1169, 1112 cm^{-1}. HRMS (CI) calcd for $C_{16}H_{23}ClN_3O_4$ 356.1377 ($M^+NH_4^+$), found 356.1362.

2.1.10. 4-(4-Chloro-2-nitro-phenyl)-2-(4-methylphenyl-sulfonyloxy)-1,2,3,6-tetrahydropyridine (16). To a solution of **9** (540 mg, 1.21 mmol) in NMP (2 mL) was added vinyl triflate **12** (467 mg, 1.21 mmol) under argon, followed by $Pd(dba)_2$ (34.7 mg, 0.060 mmol), triphenylarsine (74.1 mg, 0.24 mmol), and copper iodide (23 mg, 0.12 mmol). The reaction mixture was worked up as described above to give after purification by chromatography (hexanes–EtOAc, 9:1) **16** (239 mg, 0.60 mmol, 50%) as a pale yellow solid. Mp 111°C; ^{1}H NMR δ 7.91 (d, J=2.1 Hz, 1H), 7.71 (d, J=8.2 Hz, 2H), 7.5 (dd, J=8.3, 2.1 Hz, 1H), 7.37 (d, J=7.9 Hz, 1H), 7.2 (d, J=8.1 Hz, 2H), 5.55 (m, 1H), 3.71 (m, 2H), 3.34 (t, J=5.5 Hz, 2H), 2.45 (s, 3H), 2.39 (m, 2H); ^{13}C NMR δ 143.7 (+), 133.8 (+), 133.1 (+), 131.9 (−), 129.7 (−), 129.6 (−), 127.5 (−), 124.3 (−), 121.6 (−), 44.8 (+), 42.7 (+), 29.5 (+), 21.4 (−); IR (CCl_4) 1595, 1337, 1163, 980 cm^{-1}. Anal. calcd for $C_{18}H_{17}ClN_2O_4S$: C, 55.03; H, 4.36. Found: C, 54.75; H, 4.37.

2.1.11. 2-Benzyl-7-chloro-1,2,3,4-tetrahydro-1*H*-β-carboline (17). To an oven dried, threaded ACE glass pressure tube was added **14** (469 mg, 1.43 mmol), $Pd(OAc)_2$ (19.2 mg, 0.085 mmol), PPh_3 (90 mg, 0.34 mmol), and MeCN (5 mL). The tube was fitted with a pressure head, and the solution was saturated with CO (four cycles of 4 atm of CO). The reaction mixture was heated at 70°C (oil-bath temperature) under CO (4 atm) until all starting material was consumed (15 h), as judged by TLC. The solvent was evaporated under reduced pressure, and the crude product was purified by chromatography (hexanes–EtOAc, 8:2) to give **17** (380 mg, 1.28 mmol) as a white solid. The yield in two steps starting from **13** was 61%. Mp 164°C; ^{1}H NMR δ 7.65 (br s, NH, 1H), 7.38 (m, 7H), 7.05 (dd, J=8.2, 1.7 Hz, 1H), 3.76 (s, 2H), 3.61 (s, 2H), 2.89 (t, J=5.5 Hz, 2H), 2.78 (t, J=5.3 Hz, 2H); ^{13}C NMR δ 138.1 (+), 136.3 (+), 132.6 (+), 129.1 (−), 128.4 (−), 127.2 (−), 119.9 (−), 118.6 (−), 110.7 (−), 108.4 (+), 62.0 (+), 50.7 (+). 49.9 (+), 21.1 (+); IR (CCl_4) 3450, 2359, 1616, 1435 cm^{-1}. HRMS (DEI) calcd for $C_{18}H_{17}ClN_2$ 328.0978 (M^+), found 328.0978.

2.1.12. 1,2,3,4-Tetrahydro-β-carboline (20).[33] To a stirred suspension of **17** (200 mg, 0.67 mmol) and $Pd(OH)_2$/C (200 mg, ca. 20% palladium) in dry methanol (20 mL) was added ammonium formate (210 mg, 3.33 mmol) under an argon atmosphere. The mixture was stirred at reflux until disappearance of starting material (TLC, 3.5 h). After cooling to ambient temperature, the suspension was filtered through a Celite pad, and the pad was washed with methanol (10 mL). The solvent was evaporated at reduced pressure to give **20** (106 mg, 0.62 mmol, 91%).

2.1.13. 7-Chloro-1,3,4,9-tetrahydro-β-carboline-2-carboxylic acid *tert*-butyl ester (18). Reaction of **15** (215 mg, 0.63 mmol) with CO in the presence of $Pd(dba)_2$ (21.9 mg, 0.038 mmol), 1.3-bis(diphenylphosphino)propane (15.7 mg, 0.038 mmol), 1,10-phenanthroline (15 mg, 0.075 mmol), in DMF (3 mL), as described for **1**, gave after chromatography (hexanes–EtOAc, 9:1) **18** (157 mg, 0.80 mmol, 81%) as a white solid. Mp 188°C; ^{1}H NMR δ 8.70 (br s, NH, 1H), 7.37 (d, J=8.3 Hz, 1H), 7.28 (d, J=1.7 Hz, 1H), 7.07 (dd, J=8.5, 1.6 Hz, 1H), 4.6 (s, 2H), 3.77 (t, J=5.7 Hz, 2H), 2.78 (t, J=5.7 Hz, 2H), 1.52 (s, 9H); 13C NMR (DMSO-d_6) δ IR (CCl_4) 3278, 1674 cm^{-1}. HRMS (DCI) calcd for $C_{16}H_2OClN_2O_2$ 306.1135 (MH^+), found 306.1130.

2.1.14. 7-Chloro-2-(4-methylphenylsulfonyloxy)-1,2,3,4-tetrahydro-1*H*-β-carboline (19). Reaction of **16** (230 mg, 0.58 mmol) with carbon monoxide in the presence of $Pd(dba)_2$ (20 mg, 0.034 mmol), 1.3-bis(diphenylphosphino)propane (14.4 mg, 0.035 mmol), 1,10-phenanthroline (13.9 mg, 0.07 mmol), in DMF (5 mL), as described above for **1**, gave after chromatography (hexanes–EtOAc, 7:3) **19** (105 mg, 0.29 mmol, 50%) as a pale yellow solid. Mp >250°C; ^{1}H NMR (DMSO-d_6) δ 6.78 (d, J=8.3 Hz, 2H), 6.48 (m, 4H), 6.05 (d, J=7.2 Hz, 1H), 3.36 (br s, 2H), 1.58 (br s, 2H), 1.45 (brs, 4H); ^{13}C NMR (DMSO-d_6) δ 143.6 (+), 136.3 (+), 133.6 (+), 130.5 (+), 129.9 (−), 127.2 (−), 125.6 (+), 125.0 (+), 118.9 (−), 118.8 (−), 110.8 (−), 106.5 (+), 43.8 (+), 43.2 (+), 20.9 (−), 20.7 (+); IR (CCl_4) 3384, 2361 cm^{-1}. HRMS (DCI) calcd for $C_{18}H_{18}ClN_2O_2S$ 361.0778, found 361.0766.

2.1.15. 2-Benzyl-7-chloro-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carboline (22). A solution of **17** (420 mg, 1.41 mmol) in THF (5 mL) was added dropwise, under argon, to a 0°C cold suspension of NaH (71 mg, 2.95 mmol) in THF (5 mL). After stirring for 45 min, iodomethane

(92 μL, 1.47 mmol) was added, and the reaction mixture was stirred at 0°C for 4 h. Upon completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure. The crude residue was purified by chromatography (hexanes–EtOAc, 85:15) to give **22** (355 mg, 1.14 mmol, 81%) as a yellow solid. Mp 138°C; ^{1}H NMR δ 7.38 (m, 7H), 7.05 (dd, J=8.2, 1.7 Hz, 1H), 3.8 (s, 2H), 3.65 (s, 2H), 3.5 (s, 3H), 2.86 (m, 2H), 2.81 (m, 2H); ^{13}C NMR δ 138.2 (+), 137.3 (+), 134.2 (+), 128.9 (−), 128.3 (−), 127.1 (−), 126.4 (+), 125.2 (+), 119.2 (−), 118.6 (−), 108.6 (−), 107.4 (+), 62.2 (+), 50.4 (+), 49.2 (+), 29.0 (−), 21.2 (+); IR (CCl_4) 2359, 1680 cm^{-1}. HRMS (DEI) calcd for $C_{19}H_{19}ClN_2$ 310.1237 (M^+), found 310.1230.

2.1.16. 9-Methyl-1,2,3,4-tetrahydro-β-carboline (23).[34] A suspension of **22** (200 mg, 0.64 mmol) and $Pd(OH)_2$/C (200 mg, ca. 20% palladium) in dry methanol (15 mL) was stirred under a hydrogen atmosphere (2.5 atm) at ambient temperature until the disappearance of the starting material (TLC, 15 h). The mixture was filtered through a Celite pad, and the pad was washed with methanol (10 mL). The solvent was evaporated at reduced pressure to give **23** (120 mg, 0.66 mmol, quantitative).

2.1.17. 7-Chloro-9-methyl-1,3,4,9-tetrahydro-β-carboline-2-carboxylic acid *tert*-butyl ester (24). Reaction of **18** (330 mg, 1.07 mmol) with NaH (54 mg, 2.25 mmol) and iodomethane (69 μL, 1.10 mmol) in THF, as described for **22**, gave after chromatography (hexanes–EtOAc, 9:1) 24 (347 mg, 1.07 mmol, 82%) as a white solid. Mp 152°C; ^{1}H NMR δ 7.32 (d, J=8.3 Hz, 1H), 7.13 (d, J=1.7 Hz, 1H), 7.01 (dd, J=8.5, 1.7 Hz, 1H), 4.55 (s, 2H), 3.7 (s, 2H), 3.48 (s, 3H), 2.7 (t, J=5.3 Hz, 2H), 1.5 (s, 9H); ^{13}C NMR δ 137.2 (+), 126.9 (+), 124.9 (+), 119.4 (−), 118.6 (−), 117.7 (−), 108.7 (−), 80.0 (−), 42.1 (+), 29.1 (−), 28.4 (−), 21.1 (+); IR (CCl_4) 2362, 1682 cm^{-1}. Anal. calcd for $C_{17}H_{21}ClN_2O_2$: C, 63.65; H, 6.60. Found: C, 63.72; H, 6.56.

2.1.18. Bauerine A. To a solution of **24** (120 mg, 0.37 mol) under argon, was added EtOAc (5 mL) and 3N HCl (aq., 2 mL), and the reaction mixture was stirred for 10 h. The progress of the reaction was monitored by TLC until all starting material was consumed. The reaction mixture was neutralized with $NaHCO_3$ (aq.) and extracted with EtOAc (3×25 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed at reduced pressure to give the crude product **25** (83 mg, 0.37 mmol). ^{1}H NMR δ 7.39 (d, J=8.3 Hz, 1H), 7.28 (d, J=1.8 Hz, 1H), 7.00 (dd, J=8.5, 1.6 Hz, 1H), 4.34 (s, 2H), 3.57 (s, 3H), 3.45 (t, J=5.7 Hz, 2H), 2.98 (t, J=4.7 Hz, 2H).

The crude product was dissolved in dry toluene (5 mL), and MnO_2 (85 mg, 0.98 mmol) was added under an argon atmosphere. The reaction mixture was stirred at 100°C (oil-bath temperature) for 4 h. The reaction mixture was filtered through a Celite pad, and the pad was washed with CH_2Cl_2 (10 mL). Solvent evaporation at reduced pressure, followed by purification of the crude product by chromatography (hexanes–EtOAc, 1:1), gave bauerine A (55 mg, 0.25 mmol, 70%) as a yellow solid. Spectral data are in all respects identical to literature data for bauerine A.

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