4-Trifloxy-9-SEM-β-Carboline: Preparation and Synthetic Utility

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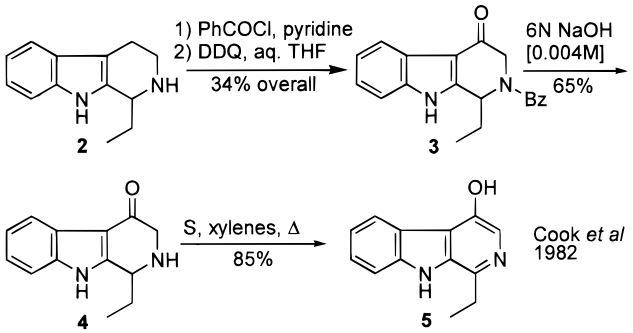
Numerous compounds with a β-carboline nucleus have been shown to possess CNS (central nervous system) activity, particularly at brain benzodiazepine receptors.[1] We were especially interested in preparing a variety of 4-substituted β-carbolines for biological evaluation since betacarbolines with 4-substitution and lacking substitution at the 3-position are not well represented in the literature. Syntheses typically involve introduction of the latent 4-substituent in the first synthetic step, Michael addition[2] of indole to a β-substituted nitroolefin. Reduction to a tryptamine[3], ring closure (either Pictet−Spengler[4] or Bischler-Napieralski[5]), and aromatization[6] have generally been used to complete the synthesis. For the purposes of rapid SAR (structure activity relationship) development, however, this linear approach was impractical, and we required instead a common advanced intermediate suitable for facile derivitization to generate a diverse group of 4-substituted β-carbolines.

An obvious target to fulfill these requirements would then be the 4-halo or 4-trifloxy-β-carbolines which would be readily derivatized through well-established palladium and nickel catalyzed cross coupling reactions. None of the four 4-halo or the 4-trifloxy derivatives lacking additional ring substitution have ever been reported. The synthesis and derivatization of the first such 4-trifloxy-β-carboline is the subject of this note.

The first report of a 4-hydroxy-β-carboline of which we are aware comes from the French patent literature.[7]

Scheme 1



4-Alkoxy derivatives are described, yet no synthesis, characterization data, or reference to the presumed 4-hydroxy precursor is given. In 1982, however, Cook[8] described fully the synthesis of 1-ethyl-4-hydroxy-β-carboline **5** from the tetrahydro-β-carboline two as shown in Scheme 1. The key step was installation of the 4-keto functionality via oxidation with DDQ[9] in aqueous THF. Saponification of the benzamide to furnish aminoketone (**4**) and sulfur promoted aromatization completed the synthesis. Two practical limitations of this methodology precluded its use for our purposes, however. The saponification was performed under high dilution (0.004M) in 6 N NaOH due to the low solubility of ketoamide (**3**). In addition, the excellent water solubility of aminoketone (**4**) necessitated 48 h of continuous liquid/liquid extraction with methylene chloride to furnish the product in 65% isolated yield. We reasoned that use of an appropriate cosolvent might circumvent the use of high dilution, while introduction of a protecting group on the indole nitrogen should dramatically increase the organic solubility of an intermediate aminoketone, thereby allowing for standard extractive workup. A successful protecting group would also have to survive all subsequent synthetic steps (basic hydrolysis, oxidation, triflation, and coupling) and be easily removed following coupling. The SEM[10] group has been found to fulfill all of these requirements.

Our synthesis thus commences with preparation of ketoamide (**7**) in two steps from tetrahydro-β-carboline (53% overall) using the Cook[9e] protocol as shown in Scheme 2. Alkylation with SEM-Cl then provided **8** as a stable crystalline solid in 80% yield. When **8** was heated for 1 h at 100 °C in 1:1 6N NaOH:MeOH (0.13M), consumption of starting material was observed with formation of two new products by TLC. These species proved to be the anticipated product, aminoketone (**9**), and 4-hydroxy-β-carboline[11] derivative (**10**). By simply stirring the reaction mixture at ambient temperature in an open flask, air oxidation to **10** was realized in 84%

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(2) (a) Kozikowski, A. P.; Chen, Y.-Y. *J. Org. Chem.* **1981**, *46* (25), 5248. (b) Hartman, P. J.; Noland, W. E. *J. Am. Chem. Soc.* **1954**, *76*, 3227. (c) Noland, W. E.; Christensen, G. M., Sauer, G. L.; Dutton, G. G. S. *J. Am. Chem. Soc.* **1955**, *77*, 456. (d) Lehmann, J.; Jiang, N.; Behncke, A. *Arch. Pharm. (Weinheim, Ger.)* **1993**, *326, 6* (10), 813. (e) Cook, J. M.; Skolnick, P.; McKernan, R.; Cox, E. D.; Diaz-Arauzo, H.; Huang, Q.; Reddy, M. S.; Ma, C.; Harris, B. *J. Med. Chem.* **1998**, *41* (14), 2537.

(3) For recent examples, see: (a) Rodriguez, R.; Diez, A.; Rubiralta, M.; Giralt, E. *Heterocycles* **1996**, *43* (3), 513. (b) Dubois, L.; Dorey, G.; Potier, P.; Dodd, R. *Tetrahedron: Asymmetry* **1995**, *6* (2), 455.

(4) (a) Pandit, U.K.; Hiemstra, H. C.; Bieraugel, H.; Wijnberg, M. *Tetrahedron* **1983**, *39* (23), 3981. (b) Cook, J. M.; Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M. *J. Org. Chem.* **1979**, *44* (4), 535.

(5) (a) Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991**, *56* (8), 2701. (b) Martin, S. F.; Benage, B.; Hunter, J. E. *J. Am. Chem. Soc.* **1988**, *110* (17), 5925.

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(7) Corbiere, J. 19 Nov. **1981**, D'Invention 81 21650. No. de publication 2, 516, 512.

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(9) (a) Bergman, J.; Carlsson, R.; Misztal, S. *Acta Chem. Scand. B* **1976**, *30*, 853. (b) Yonemitsu, O.; Oikawa, Y. *J. Org. Chem.* **1977**, *42*, 1213. (c) Yonemitsu, O.; Oikawa, Y.; Yoshioka, T.; Mohri, K. *Heterocycles* **1979**, *12* (11), 1457. (d) Yonemitsu, O.; Oikawa, Y.; Yoshioka, T.; Mohri, K. *J. Chem. Res. Synth.* **1981**, 194. (e) Cook, J. M.; Hagen, T. J.; Narayanan, K.; Names, J. *J. Org. Chem.* **1989**, *54* (9), 2170.

(10) SEM = Trimethysilylethoxymethyl.

(11) For a seven step synthesis of 4-hydroxy-9-benzyl β-carboline by an entirely different route, see: Murakami, Y.; Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y. *Tetrahedron* **1997**, *53* (5), 1593.

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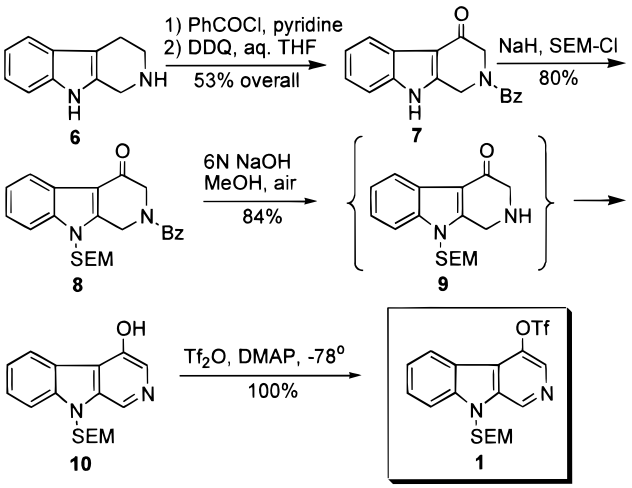
Scheme 2

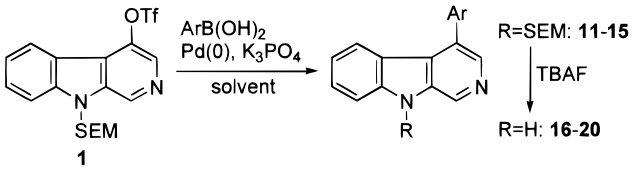


isolated yield. The need for a separate oxidation step, typically performed with sulfur or palladium at high temperature,[1d,6] was thus conveniently eliminated. The reasons for this facile oxidation of **9** (vs **4**) were not investigated, yet the 9-SEM group might act to stabilize the presumed benzylic radical, thereby facilitating oxidation with ambient oxygen. Alcohol **10** was then triflated in quantitative yield with Tf_2O/DMAP at low temperature to generate title compound **1** as a stable crystalline solid. Triflations using tertiary amine bases invariably gave lower yields with formation of colored impurities. The synthesis of **1** was thus completed in five steps from commercial starting material.

With multigram quantities of triflate **1** in hand, we turned our attention to its reactivity under palladium catalysis. The results obtained for Suzuki coupling[12] of triflate **1** are shown in Table 1. Suzuki coupling of p-methoxyphenylboronic acid with triflate **1** under the original conditions[12] ($Pd(PPh_3)_4$, K_3PO_4, *p*-dioxane) provided adduct **11** in 86% yield (Table 1). When these conditions were applied to phenyl-, *m*-tolyl- and 2-naphthylboronic acids, however, only trace amounts of coupling products were observed. Use of $PdCl_2$dppf with K_3PO_4 proved to be more general, although the choice of solvent proved critical. Phenyl adduct **12** was obtained in 61% yield using THF. The *m*-tolyl product **13** was obtained in 67% yield in *p*-dioxane, yet use of DME led to a lower yield. No product was obtained using DME as solvent for 2-naphthylboronic acid, yet in THF, naphthyl product **14** was obtained in 55% yield. Use of *p*-chlorophenyl boronic acid in *p*-dioxane gave the adduct **15** in 53% yield. In addition to the desired coupling products, small amounts of reduced β-carboline (**35**) and the product of triflate hydrolysis, 4-hydroxy species **10**, were generally formed. We next moved our attention to the Kumada[13] coupling for further preparation of 4-substituted β-carbolines.

Cross coupling of triflate **1** with both aryl and alkyl Grignard reagents was found to be a general method for construction of 4-substituted β-carbolines as shown in Tables 2 and 3. Two key parameters to the success of

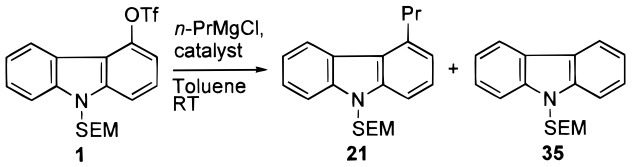
Table 1. Suzuki Couplings[a] of Triflate 1 and Aryl Boronic Acids



entry	aryl group	solvent	coupling product (%)	deprotected product (%)
1	4-OMePh	dioxane	**11** (86)	**16** (79)
2	Ph	THF	**12** (61)	**17** (65)
3	3-MePh	dioxane	**13** (67)[b]	**18** (84)
4	2-naphthyl	THF	**14** (55)[c]	**19** (85)
5	4-ClPh	dioxane	**15** (53)	**20** (82)

[a] Isolated yields after flash chromatography. $PdCl_2$dppf/K_3PO_4 was used in all cases except entry 1 where $Pd(PPh_3)_4$/K_3PO_4 was used. [b] 57% yield in DME. [c] No reaction in DME.

Table 2. Ratio of Coupling Product 21 to Reduced Product 35[a]



entry	catalyst	coupling **21**:reduced **35**
1	$NiCl_2(Ph_3P)_2$	15:85[c]
2	$PdCl_2(Ph_3P)_2$	20:80[f]
3	$Ni(acac)_2$	29:71[b]
4	$NiCl_2$dppf	35:65[d]
5	$PdCl_2$dppf	92:8[f]
6	$NiCl_2$dchxpe	45:55[b]
7	$NiCl_2$dppb	55:45[b]
8	$NiCl_2$dppp	55:45[c]
9	$NiCl_2$dppe	96:4[e]
10	$PdCl_2$dppe	70:30[f]

[a] All reactions were run using 1.5 equiv PrMgCl, 10 mol % catalyst at 0.05 M in toluene, and ratios were measured by HPLC. [b] Ratio measured after 1 h at room temperature. [c] Ratio measured after 18 h at room temperature. [d] 3.0 equiv PrMgCl, 20 mol % catalyst. Ratio measured after 20 h at room temperature and 5 h at 55 °C. [e] Ratio measured after 30 min at room temperature. [f] Ratio measured after 1 h at 55 °C.

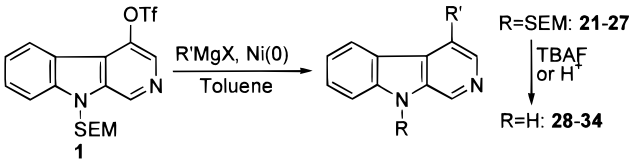
the reaction were found to be ligand choice and rate of Grignard addition. A set of 10 catalyst/ligand combinations were examined in the coupling of triflate **1** with n-PrMgCl as detailed in Table 2. Mixtures of desired product **21** and reduced species **35** were formed. The best results were obtained using $PdCl_2$dppf (entry 5) and $NiCl_2$dppe (entry 9), with the nickel species proving to be slightly superior. The use of large bite angle ligands with palladium and small bite angle ligands with nickel gave the highest selectivities.

It is interesting to note that $Ni(acac)_2$ (Table 3, entry 3), which performs admirably in the coupling of aryl Grignard's,[14] is a very poor ligand for the coupling of *n*-propylmagnesium chloride. We found that rapid addition of the Grignard reagent often had a deleterious effect on the reaction leading to low yields and incomplete conversions.[18] We thus developed a protocol where only

(12) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.
(13) (a) Kumada, M.; Tamao, K.; Sumitani, K. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (b) Kumada, M.; Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S-i.; Nakajima, I.; Minato, A. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958. (c) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144.

(14) Snieckus, V.; Sengupta, S.; Leite, M., Raslan, D. S.; Quesnelle, C. A. *J. Org. Chem.* **1992**, *57*, 4066.

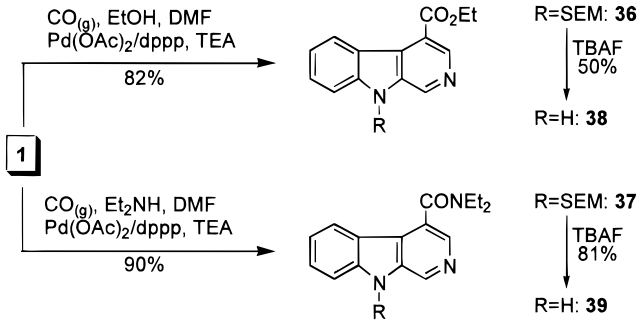
Table 3. Kumada Couplings of Triflate 1 with Grignard Reagents[a]



entry	R group	coupling conditions	coupling product (%)	deprotected product (%)
1	propyl	$NiCl_2$dppe	**21** (89)	**28** (86)[b]
2	cyclohexyl	$NiCl_2$dppe	**22** (57)	**29** (66)[b]
3	benzyl	$Ni(acac)_2$	**23** (55)	**30** (98)[b]
4	4-MePh	$Ni(acac)_2$	**24** (53)	**31** (60)[c]
5	3-OMePh	$Ni(acac)_2$	**25** (54)	**32** (74)[c]
6	4-*t*-BuPh	$Ni(acac)_2$	**26** (76)	**33** (68)[c]
7	4-CF_3Ph	$Ni(acac)_2$	**27** (93)	**34** (80)[c]

[a] Isolated yields after flash chromatography. All reactions in toluene. [b] Aqueous HCl deprotection. [c] TBAF deprotection.

Scheme 3

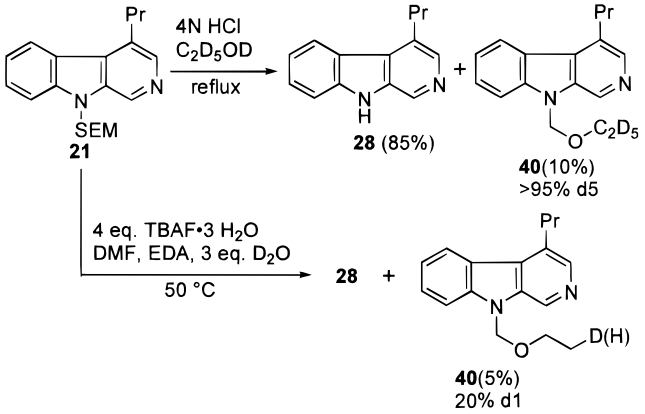


enough Grignard was added to reduce nickel(II) to nickel(0),[13] with the remainder being added via syringe pump over a period of 4−6 h. Use of cyclohexylmagnesium chloride (Table 3, entry 2) and benzylmagnesium chloride (entry 3) furnished product under similar conditions. A series of commercially available aryl Grignard reagents (entries 4−7) were coupled analogously in good yield using exclusively $Ni(acac)_2$ as catalyst.

The reactivity of triflate **1** under carbonylative conditions was also examined as shown in Scheme 3. When treated under 100 psi CO at 100 °C using a $Pd(OAc)_2$/dppp combination,[15] the acylated adducts **36** and **37** were obtained in high yield.

The syntheses of the 4-substituted β-carbolines were completed by removal of the SEM protecting group. Two different protocols were employed: aqueous HCl/EtOH and tetrabutylammonium fluoride (TBAF)/DMF/1,2-ethylenediamine (EDA). Our initial attempts using aqueous HCl/EtOH[16] gave the deprotected material along with ca. 15% of a side product which turned out to be the (nondeuterated) species corresponding to **40**. Better results, without formation of this side product, were obtained with THF in place of EtOH. While the aqueous HCl/THF protocol was suitable for several species, it gave mixtures of desired product and hydrolysis byproducts

Scheme 4



when applied to *p*-*tert*-butylphenyl adduct **26**, *p*-trifluoromethylphenyl adduct **27**, and ester **36**. Use of TBAF trihydrate in THF or DMF together with EDA[17] was found to be a completely general method and was applied successfully in all cases. Deprotection yields were generally high and are shown in Tables 1 and 3. Surprisingly, small amounts of ethoxymethyl species **40** were formed also when TBAF/DMF/EDA was used. We have investigated the mechanism of their formation through deuterium labeling studies. When propyl adduct **21** was hydrolyzed in aqueous HCl/C_2D_5OD, analysis of minor component **40** by ^1H NMR showed > 95% d_5 incorporation (Scheme 4). Compound **40** was thus shown to be formed exclusively by attack of the solvent ethanol on the intermediate methyleneiminium ion. When **21** was treated with four equivalents of TBAF trihydrate in the presence of 3 equiv added D_2O, ^1H NMR analysis of minor product **40** showed ca. 20% deuterium incorporation in the terminal methyl group. The curious situation thus exists in which no protiodesilylation occurs under acidic conditions, yet under the basic conditions (excess EDA) of the TBAF deprotection, byproduct formation occurs *only via* protiodesilylation, with residual water on the TBAF reagent being the proton source.

In summary, a series of novel 4-substituted β-carbolines have been prepared from 4-trifloxy-9-SEM-β-carboline. Use of palladium and nickel catalyzed cross coupling and carbonylation reactions have allowed for the facile preparation of 4-aryl, -alkyl, and -acyl β-carboline derivatives from a common advanced intermediate.

Experimental Section

General. All melting points are uncorrected. ^1H and ^{13}C NMR spectra were generally obtained at 400 and 100 MHz, respectively. Elemental analysis were performed by QTI Analyses, NJ. All chemicals were obtained from commercial sources and used as received unless otherwise noted. Anhydrous solvents from Aldrich were generally used directly. $NiCl_2$dppb was prepared following the method of Frauenrath et al.[19] and $NiCl_2$dppf using the method of Rudie et al.[20] *p*-Trifluoro-methylphenylmagnesium bromide was prepared in a standard fashion in diethyl ether from *p*-bromobenzotrifluoride and magnesium powder (Aldrich). See Supporting Information for all compounds not discussed here.

9-SEM-ketoamide (8). To a solution of 12.0 g of ketoamide **7** (41.4 mmol, 1 equiv) in 90 mL of DMF at ambient temperature under N_2 was cautiously added 1.04 g of NaH (43.4 mmol, 1.05

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(20) Rudie, A. W.; Lichtenberg, D. W.; Katcher, M. L.; Davison, A. *Inorg. Chem.* **1978**, *17*, 2859−2863.

equiv) in portions over 15 min. After 30 min, a solution of 7.69 mL of SEM-Cl (43.4 mmol, 1.05 equiv) in 20 mL of DMF was added dropwise over 30 min. After 1 h at ambient temperature, 200 mL of half-saturated NaCl was added, and the mixture was extracted with EtOAc (4 × 200 mL). The combined EtOAc layers were washed with saturated NaCl (2x), dried ($MgSO_4$), and the solvents were removed in vacuo to give 25 g of oil which was then chromatographed on Si gel eluting with 2:1 Hex:EtOAc to give 13.4 g of **8** (77%) as a colorless crystalline solid, mp = 97−98 °C. ^{1}H NMR (C_6D_6) δ: 8.73 (d, J = 7.5 Hz, 1H), 7.43 (d, J = 6.2 Hz, 2H), 7.34−7.27 (m, 5H), 7.14 (m, 1H), 4.98 (br s, 2H), 4.87 (br s, 2H), 4.10 (br s, 2H), 0.86 (br s, 2H), 0.00 (s, 9H). ^{13}C NMR (C_6D_6) δ: 186.55 (s), 170.49 (s), 137.61 (s), 135.25 (s), 130.17 (d), 128.64 (d), 127.71 (d), 125.00 (s), 124.14 (d), 123.65 (d), 122.16 (d), 112.65 (s), 110.30 (d), 72.76 (t), 66.49 (t), 55.59 (br t), 39.54 (br t), 17.73 (t), −1.48 (q). Anal. Calcd for $C_{24}H_{28}N_2O_3Si$: C, 68.54; H, 6.71; N, 6.66. Found: C, 68.38; H, 6.68; N, 6.48.

9-SEM-4-hydroxy-β-carboline (10). To a solution of 13.0 g of **8** (30.9 mmol, 1 equiv) in 120 mL MeOH at ambient temperature under N_2 was added 120 mL 6M NaOH, and the mixture was refluxed for 1.5 h. The mixture was then allowed to cool to 23 °C, opened to the air, and stirred vigorously for 36 h. The MeOH was then removed in vacuo and the residual liquid extracted with EtOAc (3 × 250 mL), the combined EtOAc layers were washed with H_2O (2 × 300 mL) and dried ($MgSO_4$), and the solvents were removed in vacuo to give 10.5 g of a pink solid. Recrystallization (EtOAc) gave 7.00 g of pure **10** as pale yellow crystals, mp = 201−203 °C. Chromatography of the mother liquors on Si gel (EtOAc) gave an additional 1.16 g. Total 8.16 g, 84% yield. ^{1}H NMR (C_6D_6) δ: 9.08 (d, J = 7.7 Hz, 1H), 8.91 (s, 1H), 8.67 (s, 1H), 7.51−7.43 (m, 2H), 7.40 (t, J = 7.1 Hz, 1H), 5.24 (s, 2H), 3.40 (t, J = 7.6 Hz, 2H), 0.81 (t, J = 7.7 Hz, 2H), −0.07 (s, 9H). ^{13}C NMR (C_6D_6) δ: 152.64 (s), 140.98 (s), 138.82 (s), 127.45 (d), 125.65 (d), 124.98 (d), 122.03 (d), 121.97 (s), 120.93 (d), 119.22 (s), 109.47 (d), 72.41 (t), 65.83 (t), 17.34 (t), −1.75 (q). Anal. Calcd for $C_{17}H_{22}N_2O_2Si$: C, 64.93; H, 7.05; N, 8.91. Found: C, 64.92; H, 6.93; N, 8.79.

9-SEM-4-trifloxy-β-carboline (1). A 500 mL three-neck RB flask at 23 °C under N_2 was charged with 5.84 g of alcohol **10** (18.6 mmol, 1 equiv), 9.07 g of DMAP (74.3 mmol, 4 equiv), 230 mL of CH_2Cl_2, and 23 mL of pyridine in the order given. The resulting solution was then cooled to −78 °C, and a solution of 3.43 mL of Tf_2O (20.4 mmol, 1.1 equiv) in 30 mL of CH_2Cl_2 was added dropwise over 20 min. After 1.5 h at −78 °C, a 0 °C bath was installed, and after 30 min at this temperature, 125 mL of saturated $NaHCO_3$ was added and the mixture was stirred vigorously. The phases were separated, the aqueous phase was reextracted with CH_2Cl_2, the combined CH_2Cl_2 layers were dried ($MgSO_4$), and the solvents removed in vacuo azeotroping with PhMe to give a solid. The solid was triturated with hexane and filtered to remove unreacted DMAP, and the filtrate chromatographed on Si gel eluting with 4:1 Hex:EtOAc to give 8.35 g of **1** (100 %) as a light yellow crystalline solid, mp = 74−75 °C. ^{1}H NMR (C_6D_6) δ: 8.95 (s, 1H), 8.73 (s, 1H), 8.60 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 5.09 (s, 2H), 3.30 (t, J = 7.7 Hz, 2H), 0.76 (t, J = 7.7 Hz, 2H), −0.09 (s, 9H). ^{13}C NMR (C_6D_6) δ: 141.48 (s), 141.42 (s), 138.51 (s), 132.79 (d), 132.35 (d), 129.51 (d), 124.05 (d), 121.92 (d), 121.72 (s), 119.21 (q, $^1J_{C-F}$ = 321 Hz), 118.80 (s), 110.45 (d), 72.65 (t), 66.45 (t), 17.57 (t), −1.58 (q). Anal. Calcd for $C_{18}H_{21}F_3N_2O_4SSi$: C, 48.42; H, 4.74; N, 6.27. Found: C, 48.15; H, 4.67; N, 6.17.

General Procedure 1. Suzuki coupling/SEM Deprotection. 4-(4′-methoxyphenyl)-β-carboline (16). A 10 mL RB flask at 23 °C under N_2 was charged with 154 mg of K_3PO_4 (0.725 mmol, 1.5 equiv), 200 mg of triflate **1** (0.483 mmol, 1 equiv), 81 mg of *p*-methoxyphenyl boronic acid (0.531 mmol, 1.1 (equiv), 28 mg $Pd(PPh_3)_4$ (0.024 mmol, 0.05 (equiv), and 2.5 mL of *p*-dioxane in the order given. The flask was placed in a preequilibrated 90 °C oil bath and heated for 4 h. The mixture was cooled to ambient temperature, diluted with 20 mL of H_2O, and extracted with EtOAc (2 × 20 mL). The combined EtOAc layers were washed with saturated $NaHCO_3$, dried ($MgSO_4$), and stripped in vacuo to give 250 mg of a brown oil which was chromatographed on silica eluting with 35% EtOAc in hexanes to give 168 mg (86%) of **11** as a yellow oil. To a solution of 160 mg of **11** (0.40 mmol, 1.0 (equiv) in 2.0 mL of THF was added 2.2 mL of 1 M TBAF/THF (2.2 mmol, 5.6 equiv) and 79 μL of ethylenediamine (1.19 mmol, 3 equiv). The mixture was heated at 50 °C for 48 h. The volatiles were removed in vacuo, and the residue was chromatographed on silica eluting with EtOAc to give 85 mg of **16** (79%) as a pale yellow solid, mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ: 11.80 (s, 1H), 8.90 (s, 1H), 8.18 (s, 1H), 7.61 (m, 4H), 7.50 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 8.6 Hz, 2H), 7.07 (t, J = 7.7 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 159.2 (s), 140.8 (s), 138.3 (d), 135.9 (s), 132.8 (d), 130.8 (s), 130.2 (d), 129.7 (s), 127.9 (d), 124.7 (s), 122.6 (d), 120.2 (s), 119.0 (d), 114.2 (d), 112.1 (d), 55.2 (q). EIMS M^+ 274. Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.70; H, 5.29; N, 10.20.

General Procedure 2. Kumada Coupling/SEM Deprotection. 4-Benzyl-β-carboline (30). To a suspension of 447 mg of triflate **1** (1.0 mmol, 1.0 equiv) and 26 mg $Ni(acac)_2$ (0.1 mmol, 0.1 equiv) in 20 mL of toluene at room temperature under Ar was added 1.79 mL of 0.84 M benzylmagnesium chloride in Et_2O (1.5 mmol, 1.5 equiv). The resulting dark brown solution was stirred at room temperature for 1.5 h, then another 1.79 mL portion of Grignard was added and stirring continued. The reaction was quenched after 5 h with 15 mL of saturated aqueous NH_4Cl. The phases were separated, and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent gave a yellow oil which was purified by flash chromatography on silica using 35% EtOAc in hexanes (R_f = 0.42 for product) to give 211 mg of the coupling product **23**, 55% yield, and 20 mg of a 55:45 mixture of coupling product and reduced triflate **35**, (R_f = 0.31 for reduced triflate). The coupling product **23**, 211 mg, was dissolved in 10 mL of THF and 20 mL of 3M aq HCl. The solution was refluxed for 24 h after which THF was evaporated in vacuo. The aqueous phase was made basic with 10% NaOH and extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo gave 146 mg of a yellow solid which was triturated three times with Et_2O to afford 140 mg (98%) of pure **30**, mp = 210−213 °C. ^{1}H NMR ($CDCl_3$) δ: 9.37 (s, 1H), 8.94 (s, 1H), 8.29 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.48−7.58 (m, 2H), 7.22−7.34 (m, 6H), 4.66 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 141.11 (s), 140.35 (d), 139.31 (s), 132.32 (d), 129.09 (d), 129.00 (d), 128.50 (d), 128.31 (s), 126.85 (d), 124.35 (d), 121.81 (s), 120.61 (d), 111.99 (d), 37.65 (t). CIMS $(M+H)^+$ 259.1. Anal. Calcd for $C_{18}H_{14}N_2 \cdot 0.3H_2O$: C; 81.98, H; 5.58, N; 10.62. Found: C; 81.74, H; 5.55, N; 10.32.

General Procedure 3. Carbonylation/SEM Deprotection. 4-Diethylamido-β-carboline(39). To a 20 mL vial was added 250 mg of triflate **1** (0.56 mmol, 1.0 equiv), 13 mg $Pd(OAc)_2$ (0.056 mmol, 0.1 equiv), and 24 mg dppp (0.056 mmol, 0.1 equiv). To this was added 5 mL of DMF and 2.5 mL of Et_2NH. The vial was placed in a 60 mL of Parr bomb, and the reaction mixture was stirred under 100 psi CO for 10 h at 100 °C. The reaction mixture was diluted with water and extracted with EtOAc four times. The combined organic layer was washed two times with water, once with brine, and dried over $MgSO_4$. Evaporation of the solvent gave a brown oil which was purified by flash chromatography on silica using EtOAc (R_f = 0.35) to give 200 mg (90%) of **37** as a light yellow oil. The coupling product **37**, 200 mg (0.50 mmol, 1.0 equiv) was dissolved in 5 mL of DMF in a 25 mL flask fitted with a reflux condenser. Solid TBAF·$3H_2O$, 316 mg (1.0 mmol, 2.0 equiv), was added followed by 67 μL ethylenediamine (1.0 mmol, 2.0 equiv), and the yellow solution was stirred under argon at 50 °C for 24 h. TLC (7.5% MeOH/CH_2Cl_2) indicated incomplete conversion and another 1.0 mmol portion each of TBAF·$3H_2O$ and ethylenediamine was added. After a total of 48 h at 50 °C the reaction mixture was diluted with water and extracted three times with EtOAc. The combined organic layer was washed once with water, once with brine and dried over $MgSO_4$. Evaporation of the solvent gave a yellow oil which was purified by flash chromatography on silica using 7.5% MeOH/CH_2Cl_2 (R_f = 0.25) to give 110 mg (81%) of pure **39** as a waxy solid. ^{1}H NMR ($CDCl_3$) δ: 11.30 (s, 1H), 8.55 (s, 1H), 8.38 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.40 (m, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.16 (m, 1H), 3.83 (broad s, 2H), 3.28 (q, J = 7.0 Hz, 2H), 1.49 (t, J = 7.0 Hz, 3H), 1.03 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 169.51 (s), 141.70 (s), 136.55 (s), 135.02 (d), 134.60 (d), 129.05 (d), 125.60 (s), 125.05 (s), 122.97 (d), 120.42

(d), 120.05 (d), 112.55 (d), 43.88 (t), 40.15 (t), 14.75 (q), 13.51 (q). ESMS $(M+H)^+ = 268.3$. Anal. Calcd for $C_{16}H_{17}N_3O \cdot 0.1H_2O$: C; 71.41, H; 6.44, N; 15.61. Found: C; 71.40, H; 6.21, N; 15.51.

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Supporting Information Available: Complete synthetic details for the preparation of compounds **17**−**20**, **28**−**29**, **31**−**34**, and **38** as well as full characterization for every compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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