Ortho-Directed Metalation of 3-Carboxy-β-carbolines: Use of the SmI_2-Cleavable 9-*N*-(*N*′,*N*′-Dimethylsulfamoyl) Blocking Group for the Preparation of 9-*N*-Deprotected 4-Amino Derivatives via Azide Introduction or a Palladium-Catalyzed Cross-Coupling Reaction

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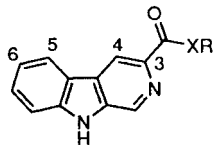
β-Carboline-3-carboxylic esters and amides (**1**, X = O or NH, R = alkyl group) are a pharmacologically important class of compounds, displaying a wide range of activities by virtue of their high-affinity interactions with the benzodiazepine receptors of the central nervous

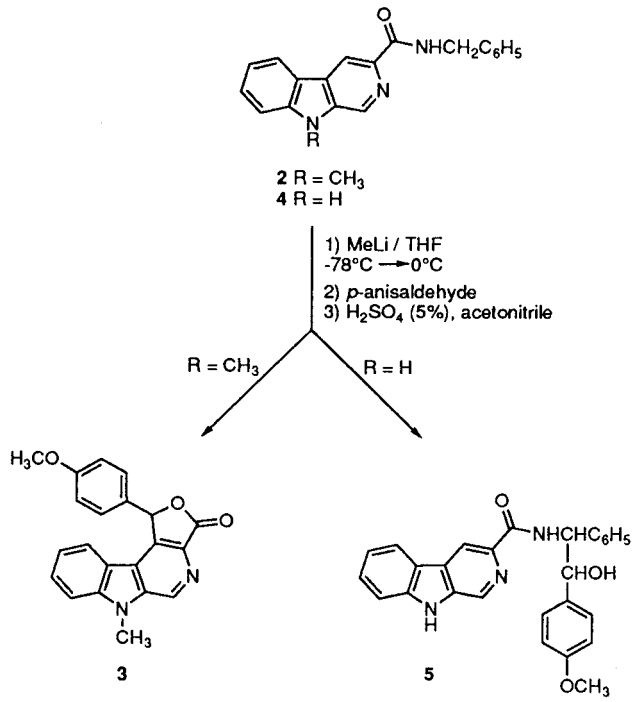


1 X = O, NH ; R = alkyl

system.[1] These activities (anxiolytic, hypnotic, mnesic, anticonvulsant) are intrinsically dependent on, and highly modulable by, the type of substituents incorporated at the 4 and 5 or 6 positions of the β-carboline nucleus.[2] In the search for molecules having a narrower range of activities and, especially, devoid of the undesirable side effects encountered in the clinical use of most current benzodiazepine receptor ligands (notably: tolerance, physical dependence, ataxia, and amnesia),[3] the incorporation of functional groups on the 3-carboxy-β-carboline nucleus is a major objective. In addition to the modulation of biological properties which such groups may themselves confer to these compounds, they provide handles by which a large number of derivatives may be prepared and studied pharmacologically.

It is with these objectives in mind that, in recent years, efforts have been made to introduce the amine function onto the 3-carboxy-β-carboline nucleus. Thus, 5-, 6-, and 7-amino-β-carboline-3-carboxylic esters have been prepared by reduction of the corresponding nitro-β-carbolines, the latter being synthesized either from the appropriate nitroindole or by direct electrophilic nitration of the β-carboline ring.[4−6] Because substituents at the C-4 position of 3-carboxy-β-carbolines have been shown

Scheme 1



to have a particularly powerful influence on the pharmacological profiles of these compounds with respect to the benzodiazepine receptor,[2] the synthesis of a 4-amino-3-carboxy-β-carboline derivative appeared to us to be a worthwhile goal. In this regard, we recently described the first synthesis of a 4-amino derivative of a β-carboline-3-carboxamide via treatment of the 4-carboxylic acid with diphenyl phosphorazidate.[7] Unfortunately, the low yield of this Curtius-type rearrangement together with the large number of steps necessary to obtain the starting carboxylic acid (based on Neef and co-workers' methodology for preparing 4-substituted 3-carboxy-β-carbolines)[5] made the pharmacological and synthetic exploitation of this 4-amino derivative unrealizable. These difficulties motivated our investigation of ortho-directed lithiation techniques[8] as a general method of directly introducing substituents at C-4 of 3-carboxy-β-carbolines.

As also previously described by us (Scheme 1),[9] the anion of β-carboline **2** (in which the *N*-benzylcarboxamide at C-3 is the ortho-directing group) can be selectively generated at C-4 using methyllithium as the metalating agent and reacted with an electrophile such as *p*-anisaldehyde to give the 4-substituted β-carboline derivative **3** in high yield. In these preliminary model studies, the free 9-NH was protected by a methyl group for

(1) Braestrup, C.; Nielsen, M.; Olsen, C. E. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 2288.
(2) For reviews, see: (a) Gardner, C. R.; Tully, R. W.; Hedgecock, C. J. R. *Prog. Neurobiol.* **1993**, *40*, 1. (b) Gardner, C. R. *Prog. Neurobiol.* **1988**, *31*, 425. (c) Dodd, R. H. *Eur. Bull. Cogn. Psychol.* **1992**, *12*, 484.
(3) Lader, M. *Adv. Biochem. Pharmacol.* **1995**, *48*, 135.
(4) Settimj, G.; Del Giudice, M. R.; Ferretti, R.; Gatta, F. *J. Heterocycl. Chem.* **1988**, *25*, 1391.
(5) Neef, G.; Eder, U.; Huth, A.; Rahtz, D.; Schmiechen, R.; Seidelmann, D. *Heterocycles* **1983**, *20*, 1295.
(6) Derivatives of 4-amino-3-carboxy-α-carboline have been recently prepared for the same purpose: Forbes, I. T.; Johnson, C. N.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 275.
(7) Dorey, G.; Dubois, L.; Prado de Carvalho, L.; Potier, P.; Dodd, R. H. *J. Med. Chem.* **1995**, *38*, 189.
(8) For reviews concerning ortho-directed metalation, see: (a) Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187. (b) Snieckus, V. *Chem. Rev. (Washington, D.C.)* **1990**, *90*, 879.
(9) Mehta, A.; Dodd, R. H. *J. Org. Chem.* **1993**, *58*, 7587.

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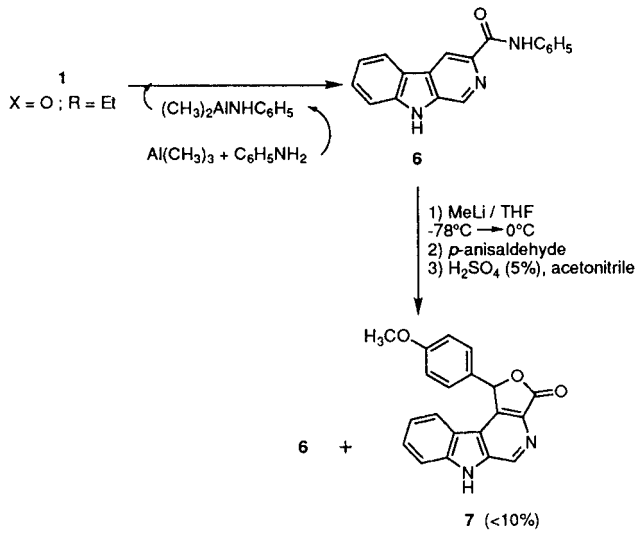
Scheme 2



simplicity.[10] However, such a group is known to interfere with receptor binding[11] and, moreover, cannot be easily removed.[12] Following our initial report concerning ortho-directed metalation of β-carboline-3-carboxamides, Mulzer and co-workers presented a similar reaction using a methoxymethyl blocking group at the 9-N position of the β-carboline and amidomagnesium chlorides as the metalating species.[13] Conversion rates were, however, generally quite low, and moreover, removal of the methoxymethyl blocking groups from the products was not described. Since, in our experience, efficient removal of this blocking group can be problematic, we preferred to find a more appropriate 9-N-protecting group before proceeding with the preparation, via this route, of 4-substituted (and, particularly, 4-amino) β-carbolines suitable for pharmacological evaluation. We describe herein the results of this investigation.

We first studied the effects on ortho-metalation of having no protecting group whatsoever at the 9-N position. Thus, reaction of compound **4** (prepared by analogy with **2**,[9,14] from ethyl β-carboline-3-carboxylate (**1**), trimethylaluminum, and benzylamine) with up to 5 equiv of methyllithium at −78 °C in THF followed by addition of *p*-anisaldehyde resulted in the formation of the benzylic alkylation product **5** (Scheme 1) as the only isolable product. To circumvent this parasitic reaction pathway,[15] the possibility of utilizing an *N*-phenylcarboxamide (as in **6**, Scheme 2) as an ortho-directing group was examined.[15,16] Amide **6** was thus prepared by the reaction of trimethylaluminum and aniline with ethyl β-carboline-3-carboxylate (**1**, X = O, R = Et).[2,14] Treatment of **6** in THF at −78 °C with methyllithium followed by addition of *p*-anisaldehyde and acid treatment of the worked-up reaction mixture (to promote cyclization of the initially formed alcohol to the lactone)[9] gave only poor yields of the desired ortho-substituted derivative **7** (<10% as estimated by ^{1}H NMR spectroscopy of the crude product, the rest being unreacted starting material). Attempts to increase the yield of the C-4-alkylated product **7** by varying reaction times, temperature, and/or the number of equivalents of base were unsuccessful.

Due to the free 9-NH of β-carboline **7** obviously having an adverse effect on proton abstraction at C-4,[17] an appropriate protecting group was sought for the former position. Recent reports have demonstrated the usefulness of the *N*-*tert*-butyldimethylsilyl (TBDMS) group for the protection of indole NH prior to lithiation at either the C-3 position (via halogen exchange)[18] or the C-4 position (via ortho-directed lithiation).[19] However, our attempts to prepare the analogous 9-N TBDMS derivative of ethyl β-carboline-3-carboxylate (**1**, X = O, R = Et) under similar conditions (LDA, TBDMS chloride, THF) met with failure, only starting material being recovered. Although TLC of the reaction mixture indicated that some *N*-silylated product was formed, this product did not survive standard workup conditions. The N−Si bond of β-carbolines appears to be extremely labile, probably due to the additional delocalization of the nitrogen lone pair compared to indole. Attention was then turned to more classical N-protecting groups such as *tert*-butyloxycarbonyl, benzyloxycarbonyl, acetyl, and tosyl.[20] However, all these groups were cleaved under the strongly basic conditions of the metalation reaction.

The *N*,*N*-dimethylsulfamoyl group has been shown to be an excellent N-protecting group for the lithiation of imidazole, being stable in the presence of alkyllithium reagents and removable in high yield under acidic conditions.[21] Since a dialkylsulfamoyl moiety can also be regarded as an ortho-directing group in metalation reactions (and has, in fact, served such a role in the imidazole field and elsewhere),[21,22] there was some apprehension that, introduced at the 9-N position of the β-carboline nucleus, this group could favor anion formation at C-1 and/or C-8. However, molecular models showed that this possibility was unlikely, the coordinating oxygen atoms of the sulfamoyl group being too distant to allow effective anion stabilization at these two positions.

The 9-*N*-(dimethylsulfamoyl)-β-carboline derivative **8** was thus prepared in 93% yield by sequential treatment of compound **6** with sodium hydride and *N*,*N*-dimethyl-

(10) Shortly after our report of the ortho-metalation of 3-carboxy-β-carbolines (ref 9), Queguiner and co-workers described experiments using 3-carboxy-α-carbolines as substrates and in which the 9-N position was similarly methylated: Papamicaël, C.; Dupas, G.; Bourguignon, J.; Queguiner, G. *Tetrahedron Lett.* **1994**, *35*, 4099.

(11) Cain, M.; Weber, R. W.; Guzman, F.; Cook, J. M.; Barker, S. A.; Rice, K. C.; Crawley, J. N.; Paul, S. M.; Skolnick, P. *J. Med. Chem.* **1982**, *25*, 1081.

(12) Although we reported (ref 9) that **2** could be demethylated using sequential treatment with benzoyl peroxide and sodium hydroxide, this methodology proved incompatible with many of the 4-substituted β-carbolines synthesized from **2** by the ortho-metalation route.

(13) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Synthesis* **1995**, 1225.

(14) Hirabayashi, T.; Itoh, K.; Sakai, S.; Kishi, Y. *J. Organomet. Chem.* **1970**, *25*, 33.

(15) Benzylic alkylation of the benzylamido group has sometimes been observed in ortho-directed lithiation reactions; see, for example: Epsztajn, J.; Bieniek, A.; Plotka, M. W. *J. Chem. Res., Synop.* **1986**, 20.

(16) Epsztajn, J.; Bieniek, A.; Plotka, M. W.; Suwald, K. *Tetrahedron* **1989**, *45*, 7469.

(17) A similar observation was made by Mulzer and co-workers, ref 13.

(18) Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 10.

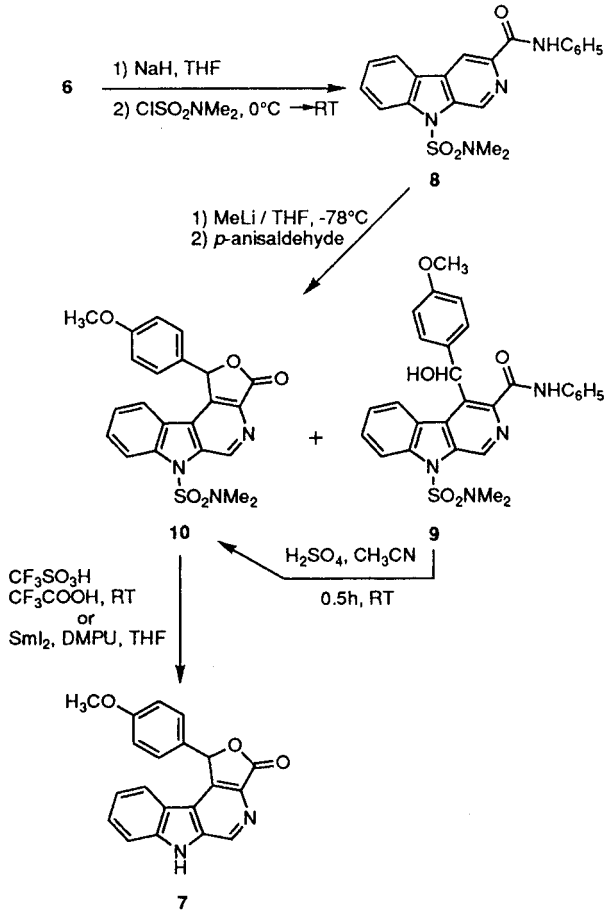
(19) Griffen, E. J.; Roe, D. G.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 1484.

(20) The *N*-benzyl group was also considered. However, in view of the likelihood of benzylic alkylation of this group under the conditions of the ortho-lithiation reaction (ref 15) and the necessity of utilizing drastic conditions to remove it (ref 6), this possibility was not pursued.

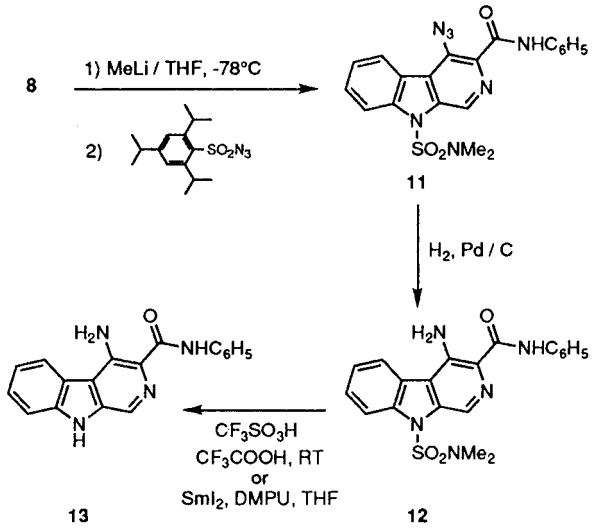
(21) Chadwick, D. J.; Ngochindo, R. I. *J. Chem. Soc., Perkin Trans. 1* **1984**, 481.

(22) Marsais, F.; Cronnier, A.; Trecourt, F.; Queguiner, G. *J. Org. Chem.* **1987**, *52*, 1133.

Scheme 3



Scheme 4



sulfamoyl chloride in THF (Scheme 3). Reaction of **8** with ~3 equiv of methyllithium for 45 min at −78 °C followed by addition of *p*-anisaldehyde led to formation of a mixture of the C-4-substituted *β*-carboline **9** and its lactonized derivative **10**. Compound **9**, not isolated, was converted into **10** by treatment of the reaction mixture with sulfuric acid in acetonitrile for 30 min at rt.[9] The yield of **10** resulting from these three operations (lithiation, electrophilic substitution, cyclization) was 90%. It should be noted that, though the overall yield of ortho-metalation product **10** is substantially the same as that obtained in the case of the *N*-methyl derivative **2**,[9] the dimethylsulfamoyl protecting group has a favorable effect on ortho-metalation in that generation of the C-4 anion is apparently more rapid in the case of **8** (45 min at −78 °C instead of 2 h at −78 °C followed by 20 min at 0 °C for **2**) and furthermore requires a smaller excess of methyllithium reagent (3 equiv instead of 5 equiv for **2**).

Removal of the dimethylsulfamoyl protecting group, essential to our objective of preparing pharmacologically relevant *β*-carboline derivatives, proved initially to be difficult. Application to **10** of the reaction conditions shown to achieve complete deprotection of *N*-(dimethylsulfamoyl)imidazole derivatives (2 M HCl, 4 h reflux)[21] led to formation of only traces of deprotected product **7**. Increasing the reflux time or acid concentration led to product decomposition as did the use of a basic medium (aqueous LiOH). Finally, on the basis of reaction conditions used to remove *N*-sulfonyl protecting groups in peptides,[23] complete deprotection of **10**, to give **7**, was obtained in excellent yield by the action of a mixture (1:10) of trifluoromethanesulfonic acid and trifluoroacetic acid for 1 h at rt.

There have been a number of recent reports concerning the deprotection of *N*-(arylsulfonyl)amines using samarium diiodide.[24] We were thus curious to see if the *N*,*N*-dimethylsulfamoyl group could also be cleaved by this reagent. Compound **10** was thus treated at rt with excess SmI_2 in THF in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU). After 1 h, complete deprotection of **10** was observed by TLC, and the product, compound **7**, was isolated in 73% yield. This represents a very useful and mild alternative to the acidic cleavage of this protecting group described above.

With these exploratory results in hand, substrate **8** was then employed for the preparation of a fully deprotected 4-amino-3-carboxy-*β*-carboline derivative, one of our primary goals in applying ortho-directed metalation technology to *β*-carbolines. Thus, ortho-lithiation of **8** using our standard conditions (2.5 equiv of methyllithium in THF, 45 min−1 h at −78 °C) followed by addition of 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide, 3 equiv)[25,26] gave, after hydrolytic workup, 92% of the 4-azido-*β*-carboline derivative **11** (Scheme 4). The presence of an azide function in **11** was indicated by a sharp band at 2136 cm^{-1} in the infrared spectrum, while the ^1H NMR spectrum confirmed the C-4 position of the azide, the characteristic singlet observed at 9.20 ppm for the proton at this position in precursor **8** having disappeared. The 4-amino derivative **12** was then obtained in 95% yield by catalytic hydrogenation of **11** over palladium on carbon. Treatment of **12** with trifluoromethanesulfonic acid and trifluoroacetic acid (1:10) for 2 h at rt then provided the deprotected 4-amino-*β*-carboline-3-carboxamide derivative **13** in 95% yield. Deprotection of **12** using SmI_2−DMPU also gave **13** in practically quantitative yield.

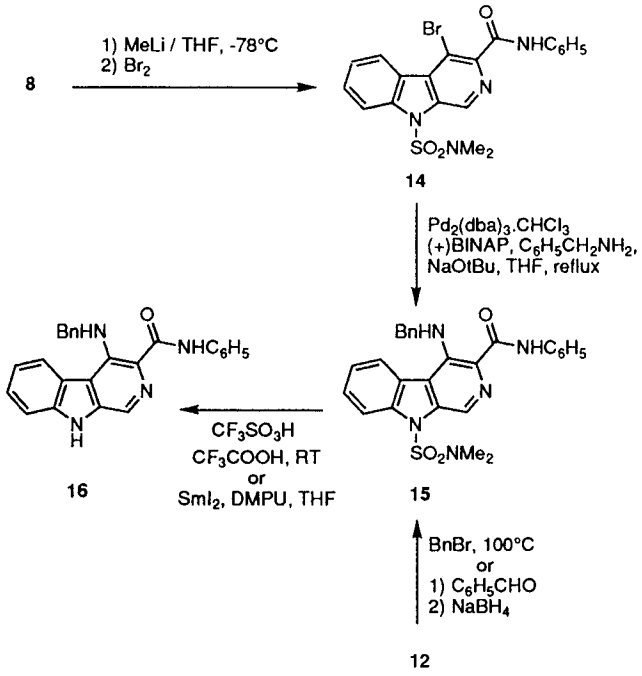
(23) Yajima, H.; Takeyama, M.; Kanaki, J.; Nishimura, O.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 3752.

(24) (a) Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602. (b) Goulaouic-Dubois, C.; Guggisberg, A.; Hesse, M. *J. Org. Chem.* **1995**, *60*, 5969. (c) Knowles, H.; Parsons, A. F.; Pettifer, R. M. *Synlett* **1997**, 271.

(25) (a) Leffler, J. E.; Tsuno, Y. *J. Org. Chem.* **1963**, *28*, 902. (b) Harmon, R. E.; Wellman, G.; Gupta, S. K. *J. Org. Chem.* **1973**, *38*, 11.

(26) Trisyl azide has been shown to be a more effective azide-transfer reagent than the more commonly employed tosyl azide: Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881.

Scheme 5



As an obvious means of preparing novel pharmacologically relevant β-carboline derivatives, we next investigated alkylation of the amine function of **12**. Initial efforts using benzyl bromide as the model alkylating agent in the presence of bases (NaH, K_2CO_3, or Et_3N) gave only traces of the *N*-benzyl derivative **15** (Scheme 5). However, when a solution of **12** in benzyl bromide was heated at 100 °C for 24 h, compound **15** was obtained in 62% yield. The same product **15** was formed, though in lower yield (35%), when **12** was treated with benzaldehyde and then with sodium borohydride. The low nucleophilic character of this aromatic amine, together with the steric hindrance provided by the 3-anilide group, is no doubt responsible for this relatively poor reactivity. An alternative route to 4-(*N*-alkylamino)-3-carboxy-β-carboline derivatives was suggested by the recent work of Buchwald and co-workers.[27] These authors have shown that bromopyridines can be effectively coupled to primary and secondary alkylamines using a $Pd_2(dba)_3$–BINAP complex as catalyst. As shown in Scheme 5, this methodology can also be applied to 3-carboxamido-β-carbolines, as illustrated by the formation of the 4-benzylamino derivative **15**. Thus, ortho-metalation of **8** with methyllithium followed by reaction of the anion with bromine for 15 min at −78 °C provided the 4-bromo-β-carboline **14** in quantitative yield. The latter was treated with $Pd_2(dba)_3$ (0.1 equiv), BINAP (0.2 equiv), benzylamine (1.5 equiv), and sodium *tert*-butoxide in THF at reflux for 16 h, affording the desired 4-benzylamino derivative **15** in 52% yield. Finally, compound **15** was deprotected using SmI_2 to give **16** in 89% yield.

In conclusion, the introduction of the *N*,*N*-dimethylsulfamoyl moiety as a stable but easily removed blocking group for the 9-N position of 3-carboxy-β-carbolines now permits preparation, via ortho-directed metalation techniques, of 4-substituted derivatives directly amenable to pharmacological evaluation. The value of this procedure is exemplified by the highly efficient preparation of the 4-amino-3-carboxy-β-carboline **13**, a derivative of which has previously been synthesized only by a multistep, low-yielding pathway.[7] Moreover, the success of the combination of ortho-directed metalation, palladium-catalyzed cross-coupling, and SmI_2-promoted removal of the 9-N-protecting group suggests that this may be a method of choice for the preparation of 4-amino-3-carboxy-β-carboline derivatives in particular and 4-substituted derivatives in general. This possibility is presently being investigated.

(27) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

Experimental Section

General.. Melting points are uncorrected. IR spectra of samples were obtained as KBr pellets. ^1H and ^{13}C NMR chemical shifts are given as δ values. TLC and preparative chromatography were performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with UV light (254 and 366 nm). All column chromatography was conducted on Merck 60 silica gel (230−240 mesh) at medium pressure (200 mbar). All solvents were distilled and stored over 4-Å molecular sieves before use. Solutions of methyllithium and samarium iodide were purchased from Aldrich Chemical Co. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

3-*N*-Benzyl-β-carboline-3-carboxamide (4). A solution of trimethylaluminum in heptane (6.2 mL of a 2.0 M solution, 12.4 mmol) was added dropwise at −10 °C under argon to anhydrous dichloromethane (40 mL). The solution was stirred for 10 min, benzylamine (0.68 mL, 6.2 mmol) was added dropwise, and stirring was continued at −10 °C for 20 min and then at rt for 1 h. A solution of ethyl β-carboline-3-carboxylate (**1**, X = O, R = Et) (1.5 g, 6.2 mmol) in dichloromethane (15 mL) was then added, and the mixture was refluxed for 24 h. After cooling and neutralization with 1 M HCl, the reaction mixture was extracted with dichloromethane and ethanol (200 mL of a 9:1 mixture), and the organic extract was washed with water (3 × 75 mL). The organic phase was evaporated to dryness under reduced pressure, and the residual solid was suspended in methanol and collected by filtration, affording compound **4** in 82% yield: mp 260 °C; ^1H NMR (DMSO-d_6, 250 MHz) δ 4.68 (2H, d, J = 6.4 Hz), 7.35−7.50 (6H, m), 7.71 (1H, t, J = 8.1 Hz), 7.78 (1H, d, J = 8.1 Hz), 8.52 (1H, d, J = 7.8 Hz), 8.99 (1H, s), 9.02 (1H, s), 9.33 (1H, t, J = 6.4 Hz, exchangeable with D_2O), 12.07 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 42.3, 112.2, 114.0, 119.9, 122.1, 126.6, 127.3, 128.1, 128.2, 128.5, 132.2, 137.1, 139.6, 139.8, 140.9, 164.8; IR (KBr) 3360, 3218, 1653, 1536 cm^{-1}; EIMS *m*/*z* 301 $(M)^+$. Anal. Calcd for $C_{19}H_{15}N_3O$: C, 75.75; H, 4.98; N, 13.95. Found: C, 75.63; H, 5.12; N, 13.88.

Attempted Ortho-Metalation of Compound 4. To a solution of compound **4** (200 mg, 0.66 mmol) in anhydrous THF (65 mL) held at −78 °C under argon for 30 min was added dropwise over 10 min a solution of methyllithium in THF (3.3 mL of a 1.0 M solution, 3.3 mmol). The solution was stirred for 2 h at −78 °C and then for 30 min at 0 °C before addition, at 0 °C, of freshly distilled *p*-anisaldehyde (0.4 mL, 3.3 mmol). After completion of the addition, the reaction mixture was allowed to come to rt, and stirring was maintained for 1 h. The solution was then cooled back to 0 °C, water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (2 × 15 mL) and dried over sodium sulfate, and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel (heptane−ethyl acetate, 1:1) affording compound **5** as a white solid in 54% yield: mp 205 °C; ^1H NMR (DMSO-d_6, 250 MHz) δ 3.80 (3H, s), 5.10 (0.5H, t, J = 3.0 Hz), 5.22 (0.5H, t, J = 5.4 Hz), 5.28−5.39 (1H, m), 5.84 (0.5H, d, J = 4.4 Hz, exchangeable with D_2O), 5.96 (0.5H, d, J = 4.6 Hz, exchangeable with D_2O), 6.92 (2H, dd, J = 8.7, 7.0 Hz), 7.24−7.44 (6H, m), 7.47 (1H, t, J = 8.7 Hz), 7.57 (2H, d, J = 7.6 Hz), 7.70 (1H, t, J = 8.0 Hz), 7.77 (1H, d, J = 8.0 Hz), 8.48 (1H, dd, J = 7.9 Hz), 8.84 (0.5H, s), 8.89 (0.5H, s), 9.06 (0.5H, s), 9.13 (0.5H, s), 9.25 (1H, t, J = 7.0 Hz, exchangeable with D_2O), 12.13 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 54.8, 58.5, 58.8, 74.1, 74.6, 112.2, 112.9, 113.1, 113.8, 113.9,

120.0, 120.8, 122.2, 126.6, 127.0, 127.3, 127.4, 127.7, 127.9, 128.1, 128.6, 132.4, 132.6, 134.3, 135.4, 137.2, 139.2, 139.4, 140.1, 141.0, 142.1, 158.1, 163.6, 164.0; IR (KBr) 3370, 3272, 1625, 1532 cm^{-1}; CIMS *m/z* 438 $(MH)^+$. Anal. Calcd for $C_{27}H_{23}N_3O_3 \cdot 0.65H_2O$: C, 72.19; H, 5.45; N, 9.32. Found: C, 72.14; H, 5.62; N, 9.33.

3-*N*-Phenyl-*β*-carboline-3-carboxamide (6). Using the procedure employed for the preparation of benzylamide **4**, reaction of trimethylaluminum (5 mL of a 2.0 M solution in hexane, 10 mmol) with aniline (0.38 mL, 4.2 mmol) and then with **1** (X = O, R = Et) (1.20 g, 5 mmol) afforded compound **6** in 80% yield: mp 285 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 7.23 (1H, t, J = 7.4 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.50 (2H, d, J = 7.6 Hz), 7.73 (1H, t, J = 8.4 Hz), 7.80 (1H, d, J = 8.4 Hz), 8.07 (2H, d, J = 7.8 Hz), 8.56 (1H, d, J = 7.8 Hz), 9.11 (2H, s), 10.72 (1H, s, exchangeable with D_2O), 12.16 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 112.3, 114.5, 119.8, 120.0, 120.8, 122.3, 123.3, 128.4, 128.6, 128.7, 132.2, 137.3, 138.7, 139.2, 141.1, 163.2; IR (KBr) 3307, 3212, 1648, 1540 cm^{-1}; EIMS *m/z* 287 $(M)^+$, 195 $(M - NHC_6H_5)^+$. Anal. Calcd for $C_{18}H_{13}N_3O \cdot 0.25H_2O$: C, 74.08; H, 4.66; N, 14.40. Found: C, 74.13; H, 4.62; N, 14.34.

9-(*N*,*N*-Dimethylsulfamoyl)-3-*N*-phenyl-*β*-carboline-3-carboxamide (8). A solution of compound **6** (170 mg, 0.59 mmol) in anhydrous THF (20 mL) was treated at 0 °C under argon with sodium hydride (71 mg of a 50% dispersion in oil, 1.48 mmol). The mixture was stirred for 30 min at 0 °C, and *N*,*N*-dimethylsulfamoyl chloride (191 μL, 1.78 mmol) was then added. The reaction mixture was allowed to come to rt and stirred for a further 3 h. The solution was concentrated under reduced pressure, ethyl acetate (30 mL) was added to the residue, and the mixture was washed with water (3 × 15 mL). The combined aqueous washings were extracted with ethyl acetate (2 × 10 mL); the organic extracts were combined and dried over sodium sulfate. The crude reaction product remaining after removal of the solvents under reduced pressure was purified by column chromatography on silica gel (dichloromethane), affording compound **8** as a colorless solid (93%) which could be further purified by crystallization from dichloromethane−hexane: mp 192 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 3.01 (6H, s), 7.25 (1H, t, J = 7.7 Hz), 7.51 (2H, t, J = 8.5 Hz), 7.69 (1H, t, J = 7.8 Hz), 7.90 (1H, t, J = 8.3 Hz), 8.08 (2H, d, J = 8.2 Hz), 8.29 (1H, d, J = 8.5 Hz), 8.73 (1H, d, J = 7.8 Hz), 9.20 (1H, s), 9.53 (1H, s), 10.85 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 38.1, 114.4, 114.5, 120.1, 122.8, 123.7, 124.0, 128.6, 130.5, 134.2, 136.4, 138.4, 143.6, 162.4; IR (KBr) 3337, 1677, 1529, 1170 cm^{-1}; EIMS *m/z* 394 $(M)^+$, 302 $(M - NHC_6H_5)^+$, 286 $(M - SO_2NMe_2)^+$. Anal. Calcd for $C_{20}H_{18}N_4O_3S$: C, 60.90; H, 4.60; N, 14.20; S, 8.13. Found: C, 60.86; H, 4.58; N, 14.16; S, 8.42.

(*R*,*S*)-5-(*N*,*N*-Dimethylsulfamoyl)-10-(4-methoxyphenyl)furo[3,4-*c*]-*β*-carbolin-2(10*H*)-one (10). A solution of compound **8** (180 mg, 0.45 mmol) in anhydrous THF (40 mL) was treated dropwise at −78 °C under argon with a solution of methyllithium in THF (1.13 mL of a 1.0 M solution, 1.13 mmol). The reaction mixture was stirred for 45 min at −78 °C, and freshly distilled *p*-anisaldehyde (166 μL, 1.37 mmol) was then added dropwise over 5 min. Stirring was continued at −78 °C for 30 min and then for 2 h at rt. At the end of the reaction period, the solution was cooled to 0 °C, water (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were evaporated to dryness under reduced pressure, the residue was dissolved in acetonitrile (15 mL), and concentrated sulfuric acid (0.5 mL) was added. After 30 min of stirring, the solution was diluted with ethyl acetate (50 mL) and washed successively with aqueous sodium hydroxide (20 mL of a 10% solution), saturated aqueous sodium chloride solution (20 mL), and water (20 mL). The organic phase was dried (Na_2SO_4), the solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate−heptane, 1:3) affording compound **10** as a white powder (90%): mp 233 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 3.05 (6H, s), 3.86 (3H, s), 7.08 (2H, d, J = 8.4, 1.6 Hz), 7.39 (1H, s), 7.45−7.56 (4H, m), 7.83 (1H, t, J = 8.6 Hz), 8.31 (1H, d, J = 8.6 Hz), 9.79 (1H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 38.1, 55.1, 79.6, 114.5, 114.6, 120.4, 123.8, 124.0, 125.2, 126.5, 130.2, 130.6, 136.6, 137.4, 139.0, 139.4, 160.3, 167.6; IR (KBr) 1770, 1175 cm^{-1}; CIMS *m/z* 438 $(MH)^+$. Anal. Calcd for $C_{22}H_{19}N_3O_5S$: C, 60.39; H, 4.38; N, 9.60; S, 7.32. Found: C, 60.31; H, 4.54; N, 9.60; S, 7.14.

(*R*,*S*)-10-(4-Methoxyphenyl)furo[3,4-*c*]-*β*-carbolin-2(10*H*)-one (7). A solution of compound **10** (124 mg, 0.28 mmol) in trifluoromethanesulfonic acid and trifluoroacetic acid (5 mL of a 1:10 mixture) was stirred for 1 h at rt and then neutralized by addition of aqueous sodium hydroxide (4 N), resulting in formation of a precipitate. After addition of water (10 mL), the mixture was filtered, and the precipitate was washed successively with water, methanol, and ethyl acetate, providing compound **7** as a white solid in 89% yield: mp >300 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 3.85 (3H, s), 7.07 (2H, d, J = 8.6 Hz), 7.26 (1H, t, J = 7.4 Hz), 7.29 (1H, s), 7.44 (2H, d, J = 8.6 Hz), 7.49 (1H, d, J = 7.4 Hz), 7.67 (1H, t, J = 8.1 Hz), 7.83 (1H, d, J = 8.1 Hz), 9.33 (1H, s), 12.67 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 55.1, 79.4, 112.7, 114.4, 118.8, 120.7, 123.2, 127.3, 128.7, 130.0, 132.7, 137.5, 138.7, 160.1; IR (KBr) 1760 cm^{-1}; EIMS *m/z* 330 $(M)^+$. Anal. Calcd for $C_{20}H_{14}N_2O_3 \cdot 1.2H_2O$: C, 68.25; H, 4.70; N, 7.96. Found: C, 68.31; H, 4.59; N, 7.97.

4-Azido-9-(*N*,*N*-dimethylsulfamoyl)-3-*N*-phenyl-*β*-carboline-3-carboxamide (11). A solution of compound **8** (271 mg, 0.69 mmol) in anhydrous THF (100 mL) was held at −78 °C under argon for 30 min before dropwise addition of methyllithium (1.72 mL of a 1.0 M solution in THF, 1.72 mmol) over 10 min. The violet-colored reaction mixture was stirred for 1 h at −78 °C, and a solution of trisyl azide (635 mg, 2.1 mmol) in THF (3 mL) was added dropwise over 5 min. The reaction mixture was stirred for a further 30 min at −78 °C, the cooling bath was removed, and stirring was continued for 2 h. At the end of this period, the reaction mixture was cooled to 0 °C and the reaction quenched by successive addition of acetic acid (560 μL), sodium acetate (167 mg), and methanol (1.6 mL). After 30 min, the solution was concentrated to one-half volume under reduced pressure, ethyl acetate (100 mL) was added, and the resulting solution was washed successively with water (30 mL), saturated aqueous sodium hydrogen carbonate (30 mL), and water (30 mL). The organic phase was dried over sodium sulfate and concentrated under reduced pressure leading to precipitation of compound **11** which was collected by filtration and washed with heptane (92% yield). Obtained as a white solid, compound **11** gradually turned bright yellow on contact with air: mp 195 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 2.99 (6H, s), 7.26 (1H, t, J = 7.7 Hz), 7.51 (2H, t, J = 7.7 Hz), 7.70 (1H, t, J = 7.6 Hz), 7.89 (1H, t, J = 8.2 Hz), 8.00 (1H, d, J = 7.9 Hz), 8.30 (1H, d, J = 8.2 Hz), 8.79 (1H, d, J = 7.6 Hz), 9.34 (1H, s), 10.94 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 38.1, 114.2, 120.0, 121.7, 123.9, 124.0, 124.3, 124.5, 128.7, 130.2, 130.5, 131.2, 136.4, 138.4, 139.0, 163.0; IR (KBr) 3340, 2136, 1681, 1525, 1171 cm^{-1}; HREIMS calcd for $C_{20}H_{17}N_7O_3S$ $[M]^+$ *m/z* 435.1113, found *m/z* 435.1101.

4-Amino-9-(*N*,*N*-dimethylsulfamoyl)-3-*N*-phenyl-*β*-carboline-3-carboxamide (12). A solution of compound **11** (250 mg, 0.57 mmol) in acetone and ethanol (40 mL of a 1:1 mixture) was hydrogenated for 45 min at atmospheric pressure in the presence of 10% palladium on carbon (150 mg). The reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure affording compound **12** as a white powder (95%) which could be crystallized in methanol: mp 216 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.98 (6H, s), 7.22 (1H, t, J = 7.5 Hz), 7.48 (1H, t, J = 7.8 Hz), 7.66 (1H, t, J = 7.8 Hz), 7.80 (2H, t, J = 8.2 Hz), 7.99 (2H, d, J = 8.2 Hz), 8.30 (1H, d, J = 8.4 Hz), 8.68 (1H, d, J = 7.9 Hz), 8.87 (1H, s), 10.70 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 38.1, 114.1, 116.7, 120.0, 122.6, 122.7, 122.9, 123.4, 123.7, 128.1, 128.6, 137.2, 137.9, 138.3, 142.5, 166.2; IR (KBr) 3485, 3334, 1662, 1524 cm^{-1}; CIMS *m/z* 410 $(MH)^+$. Anal. Calcd for $C_{20}H_{19}N_5O_3S$: C, 58.67; H, 4.68; N, 17.10; S, 7.83. Found: C, 58.64; H, 4.71; N, 16.91; S, 7.82.

4-Amino-3-*N*-phenyl-*β*-carboline-3-carboxamide (13). A solution of compound **12** (160 mg, 0.39 mmol) in trifluoromethanesulfonic acid and trifluoroacetic acid (3.3 mL of a 1:10 mixture) was stirred for 2 h at rt. The reaction mixture was neutralized by the addition of 4 N sodium hydroxide solution. Water (15 mL) was then added, and the mixture was extracted with ethyl acetate (40 mL). The organic phase was washed with water (15 mL) and dried over sodium sulfate, and the solvent

was removed under reduced pressure, affording compound **13** as a light-yellow powder in 95% yield: mp 292 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.19 (1H, t, J = 7.6 Hz), 7.42 (1H, t, J = 7.4 Hz), 7.49 (2H, t, J = 7.7 Hz), 7.64 (1H, t, J = 7.7 Hz), 7.75 (1H, d, J = 7.8 Hz), 7.97 (2H, d, J = 7.8 Hz), 8.42 (1H, s), 8.60 (1H, d, J = 7.8 Hz), 10.57 (1H, s, exchangeable with D_2O), 12.07 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 111.4, 118.5, 119.2, 119.5, 120.6, 121.8, 122.0, 122.6, 125.9, 128.3, 137.8, 138.4, 139.0, 143.0, 166.5; IR (KBr) 3496, 3341, 3297, 1642, 1513 cm^{-1}; CIMS m/z 303 (MH)$^+$. Anal. Calcd for $C_{18}H_{14}N_4O\cdot0.35H_2O$: C, 70.05; H, 4.80; N, 18.15. Found: C, 70.05; H, 4.84; N, 18.11.

4-Bromo-9-(*N*,*N*-dimethylsulfamoyl)-3-*N*-phenyl-*β*-carboline-3-carboxamide (14). A solution of compound **8** (200 mg, 0.51 mmol) in THF (40 mL) was treated dropwise at −78 °C under argon with a solution of methyllithium in THF (1.1 mL of a 1 M solution, 1.1 mmol). The reaction mixture was stirred for 1 h at −78 °C, bromine (57 μL, 1.1 mmol) was added dropwise, and stirring was continued for 15 min. After addition of water (10 mL), the solution was allowed to come to rt, and it was then evaporated to one-half volume and diluted with ethyl acetate (50 mL). The solution was washed with saturated aqueous ammonium chloride (20 mL) and water (20 mL). The organic phase was dried over sodium sulfate and evaporated to dryness under reduced pressure. The residual solid was suspended in methanol (5 mL) and collected by filtration, affording compound **14** as a white powder in quantitative yield: mp 220 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.02 (6H, s), 7.26 (1H, t, J = 7.5 Hz), 7.51 (2H, t, J = 7.7 Hz), 7.76 (1H, t, J = 7.5 Hz), 7.91 (2H, d, J = 7.7 Hz), 7.98 (1H, t, J = 8.5 Hz), 8.37 (1H, d, J = 8.5 Hz), 9.04 (1H, d, J = 7.9 Hz), 9.50 (1H, s), 10.84 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 37.5, 110.0, 114.1, 119.2, 122.1, 123.0, 123.4, 123.5, 128.4, 129.2, 130.5, 133.1, 135.2, 138.4, 139.1, 146.7, 163.7; IR (KBr) 3325, 1693, 1526, 1172 cm^{-1}; CIMS m/z 475 (MH$^+$, ^{81}Br), 473 (MH$^+$, ^{79}Br). Anal. Calcd for $C_{20}H_{17}BrN_4O_3S$: C, 50.75; H, 3.62; N, 11.84; S, 6.77. Found: C, 51.15; H, 3.82; N, 11.58; S, 6.75.

4-(*N*-Benzylamino)-9-(*N*,*N*-dimethylsulfamoyl)-3-*N*-phenyl-*β*-carboline-3-carboxamide (15). From the 4-Amino Derivative 12 and Benzyl Bromide: A solution of compound **12** (20 mg, 0.046 mmol) in benzyl bromide (2 mL) was heated at 100 °C for 24 h. The reaction mixture was cooled to 0 °C, saturated aqueous sodium hydrogen carbonate (1 mL) was added, and the mixture was extracted with dichloromethane (10 mL). The organic extract was washed with water (3 mL) and saturated aqueous sodium chloride (3 mL), dried over sodium sulfate, and evaporated to dryness under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate−heptane, 1:3) affording compound **15** as a white solid (62%): mp 183 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 2.99 (6H, s), 4 0.64 (2H, d, J = 6.7 Hz), 7.23 (1H, t, J = 7.5 Hz), 7.35−7.50 (6H, m), 7.69 (1H, t, J = 7.5 Hz), 7.86 (1H, t, J = 8.3 Hz), 7.92 (2H, d, J = 8.3 Hz), 8.33 (1H, d, J = 8.3 Hz), 8.35 (1H, d, J = 7.6 Hz), 8.44 (1H, t, J = 6.8 Hz, exchangeable with D_2O), 9.10 (1H, s), 10.79 (1H, s, exchangeable with D_2O); IR (KBr) 3326, 3262, 1653, 1526, 1169 cm^{-1}; CIMS m/z 500 (MH)$^+$. Anal. Calcd for $C_{27}H_{25}N_5O_3S$: C, 64.91; H, 5.04; N, 14.02; S, 6.42. Found: C, 64.66; H, 5.28; N, 14.15; S, 6.46.

From 12 and Benzaldehyde: A solution of compound **12** (50 mg, 0.12 mmol) and benzaldehyde (16 μL, 0.16 mmol) in 95% ethanol and THF (5 mL of a 5:1 mixture) was heated at 80 °C overnight. The solution was cooled and concentrated to dryness under reduced pressure. The residue was dissolved in dichloromethane (5 mL), the solution was cooled to 0 °C, and sodium borohydride (4.5 mg, 0.12 mmol) was added. The reaction mixture was allowed to come to rt, and stirring was maintained overnight at which time water (1 mL) was added followed by ethyl acetate (20 mL). The aqueous layer was removed, and the organic phase was washed with water (10 mL) and then with saturated aqueous sodium chloride (10 mL). The organic phase was dried (Na_2SO_4), the solvents were removed under reduced pressure, and the residue was purified by chromatography on silica gel (ethyl acetate−heptane, 1:3) affording compound **15** as a white solid (35%), identical in all respects with the compound obtained from **12** and benzyl bromide (above).

From the 4-Bromo Derivative 14: A mixture of compound **14** (37 mg, 0.08 mmol), benzylamine (13 μL, 0.12 mmol), tris-(dibenzylideneacetone)dipalladium(0) chloroform adduct (10 mg, 0.008 mmol), BINAP (10 mg, 0.016 mmol), and sodium *tert*-butoxide (19 mg, 0.2 mmol) in anhydrous THF (10 mL) was degassed by bubbling in argon for 5 min and then refluxed for 16 h. The reaction mixture was cooled to rt, diluted with dichloromethane (10 mL), and washed with saturated aqueous sodium chloride (10 mL) and water (10 mL). The organic phase was dried over sodium sulfate, the solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate−heptane, 1:3), affording compound **15** in 52% yield, identical in all respects with the compound obtained from **12** (above).

General Procedure for the Removal of the *N*,*N*-Dimethylsulfamoyl Blocking Group Using SmI_2. A solution of the dimethylsulfamoyl derivative (**10**, **12**, or **15**; 0.1 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (0.8 mmol) in anhydrous THF (10 mL) was treated dropwise, at rt under argon, with a solution of SmI_2 in THF (5 mL of a 0.1 M solution, 0.5 mmol). At the end of the reaction period (0.5−1 h, as indicated by TLC), 5% HCl solution (2 mL) was added, the solution was concentrated to one-half volume under reduced pressure, and ethyl acetate (20 mL) was added. The mixture was washed with water (10 mL) and saturated aqueous sodium chloride (10 mL). The organic phase was dried over sodium sulfate, the solvents were removed under reduced pressure, and the residue was purified as indicated. Prepared by this method were the following compounds.

7: 73% yield from **10** after suspension of the residue in dichloromethane and filtration; identical in all respects to the compound obtained by acid hydrolysis of **10** (above).

13: 97% yield from **12** after chromatography of the residue on silica gel (ethyl acetate−heptane, 1:2); identical in all respects to the compound obtained from acid hydrolysis of **12** (above).

4-(*N*-Benzylamino)-3-*N*-phenyl-*β*-carboline-3-carboxamide (16): 89% yield from **15** after chromatography of the residue on silica gel (dichloromethane); mp 162 °C (MeOH); ^{1}H NMR (DMSO-d_6, 250 MHz) δ 4.77 (2H, d, J = 6.9 Hz), 7.20 (1H, t, J = 6.9 Hz), 7.23−7.49 (8H, m), 7.69 (1H, t, J = 8.1 Hz), 7.81 (1H, d, J = 8.1 Hz), 7.93 (2H, d, J = 8.0 Hz), 8.22 (1H, d, J = 7.9 Hz), 8.66 (1H, s), 8.75 (1H, t, J = 6.9 Hz, exchangeable with D_2O), 10.72 (1H, s, exchangeable with D_2O), 12.24 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 51.0, 112.2, 120.0, 120.2, 120.5, 123.3, 123.4, 125.2, 127.0, 127.1, 128.4, 128.6, 138.3, 138.9, 139.7, 140.1, 145.4, 166.5; IR (KBr) 3414, 3317, 3298, 1636, 1529 cm^{-1}; CIMS m/z 393 (MH)$^+$. Anal. Calcd for $C_{25}H_{20}N_4O\cdot0.25H_2O$: C, 75.64; H, 5.21; N, 14.11. Found: C, 75.71; H, 5.36; N, 14.12.

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