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Syntheses of Functionalized 1,4-Disubstituted γ-Carbolines

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We report the complete synthesis of a variety of 1,4-disubstituted γ-carbolines. These compounds are of particular interest for their involvement in many biological processes and are believed to possess various medicinal activities. A large number of *N*-tosylaldimines were condensed with indoles affording an array of 3-aminomethyl indoles. Subsequent additions, followed by intramolecular cyclization, afforded an array of 1,2-dihydro-3*H*-γ-carbolones in good yield. Upon subsequent aromatization, the corresponding fully aromatic functionalized 1-aryl-4-hydroxy-γ-carbolines resulted.

Introduction

β-Carbolines, pyrido[3,4-*b*]indoles, are of interest to the pharmaceutical industry due to their close relationship with natural products such as tryptophan as well as their numerous reported biological activities.[1] Through the years, a number of reports have shown that γ-carbolines, pyrido[4,3-*b*]indoles, also possess similar biological activities.[2] Several substituted γ-carbolines have been synthesized and examined in a series of in vitro and in vivo pharmacological tests and have demonstrated antipsychotic,[3] antibiotic,[4] antitumor,[5] and other related activities.[6,7]

There exists no general efficient synthetic route that allows for the formation of highly functionalized γ-carbolines, especially those that contain substituents in the 1- and 4-positions. Of the methods reported, the most widely used for γ-carboline formation, the Fischer synthesis, often fails completely, or proceeds in low yields unless forcing thermal conditions are used or an activated pyridine ring is employed.[7,8] An alternative approach is the Grabe−Ullman synthesis and its subsequent modifications.[9] This reaction involves the preparation of a phenyl-substituted triazolopyridine followed by elimination of nitrogen gas upon thermal degradation at temperatures ranging between 190 and 500 °C. Microwave irradiation has also proven successful on several substrates.[10] Likewise, Bunyan and co-workers report the formation of a small series of γ-carbolines by the ring closure of internally generated 2-nitrosobiphenyls, which were synthesized in situ.[11,12] This reaction proceeds in moderate yields and the products are limited to alkyl-substituted carbolines. In summary, many of these previously reported methods employing intramolecular cyclization proceed in low yields, are limited to nonfunctional substrates, or involve extreme thermal conditions.

The γ-carbolines formed in several cases were actually byproducts formed while attempting to synthesize the more notable β-carbolines. Robinson and Thornley,[13] for example, were attempting to synthesize β-carbolines when they developed a unique three-step γ-carboline synthesis employing 4-chloropyridine and *o*-phenylenediamine in a catalytic palladium(II) coupling reaction.

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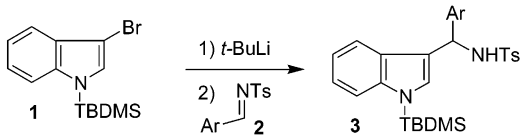
Likewise, Rönner and co-workers[14] also produced γ-carbolines as byproducts using the palladium-catalyzed condensation of tryptophan derivatives with glucose. This route is very limited in substitution due to the starting materials.

A couple of examples where γ-carbolines were the object of synthesis involve the intramolecular coupling of a boronic acid with *o*-fluoroiodopyridine by a Suzuki-type reaction employing a Pd(0) species.[15] Although seemingly an efficient conversion, it does involve the synthesis of specialty starting materials, and the authors report that the overall three-step process is limited to nonacid-sensitive substrates.[15] Most recently, Larock and co-workers[16] developed a novel palladium-catalyzed iminoannulation of internal alkynes. This unique method allows for the introduction of functionality into both the 3- and 4-positions of γ-carbolines. Additionally, Larock's group has shown that γ-carbolines substituted in the 3-position, some of which possess 4-annularization, are readily available by a novel palladium/copper-catalyzed intramolecular cyclization reaction of alkynyl indoles.[17] These γ-carboline derivatives have been found to act as cardiovascular agents or 5-HT_3 receptor antagonists.[18] Because of these recent advances and the importance of this class of compounds, we report a general synthesis and novel approach to afford the complimentary series of γ-carbolines that are substituted in the 1- and 4-positions.

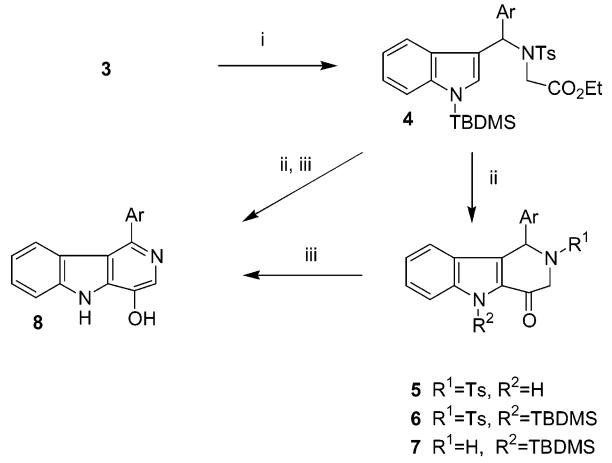
In the β-carboline series it was found that the more saturated tetrahydro-precursors possessed multidrug resistance.[19] This led to their attempted synthesis by many groups who mainly used the Pictet−Spengler synthesis.[20] However, much less is known about the synthesis and biological activity of their counterparts, the corresponding tetrahydro-γ-carbolines.[21]

The lack of commercially available 3-aminomethyl indoles has impeded the development of a novel synthetic approach to afford a large selection of functionalized γ-carbolines. We recently reported the development of a procedure for the facile synthesis of the 3-substituted aminomethyl indoles.[22] With this in place, we now report the development of a methodology that allows for control of the substituents, not only in the 1-position, but also in the 4-position of the tetrahydro-γ-carboline if desired. By altering the substitution in these two positions, compounds of varying binding abilities should be obtainable. Therefore, this synthetic approach could be easily manipulated to produce compounds with maximum pharmacological/biological effect.

SCHEME 1



SCHEME 2 [a]



[a] Reagents: (i) NaOEt, $BrCH_2CO_2Et$, (ii) Bentonite K-10 Clay, (iii) NaOH.

Discussion

Our goal was to start with readily available indole and to proceed by a method allowing for the control of substitution of various groups into the 1- and 4-positions in the final γ-carboline product. We reached this goal as follows. Treatment of 3-bromo-1-*tert*-butyldimethyl silyl indole (**1**) with *tert*-butyllithium followed by condensation with a variety of freshly prepared *N*-tosylaldimines[23] (**2**) affords the corresponding 1-protected-3-arylaminomethyl indoles (**3**) in good yields (Scheme 1).[22] This procedure allows for a wide variety of aryl substituents containing both electron-withdrawing and electron-donating functionalities to be introduced. Eventually the aryl substituent on **2** will become the 1-position aryl group of the final γ-carboline molecule. Therefore, altering the tosylaldimines (**2**) allows for direct control of the substituent in the 1-position.

Subsequent treatment of **3**, with sodium ethoxide followed by addition of ethyl bromoacetate affords compound **4** (Scheme 2). A variety of bases were employed in an attempt to optimize yields; however, it was discovered that sodium ethoxide afforded higher yields than other bases such as sodium hydroxide, sodium hydride, or sodium methoxide. When the 1,2-dihydro-3-*H*-γ-carbolone (**5**) was the target molecule, treatment of **4** with a variety of Lewis acids readily afforded this product by intramolecular cyclization. We elected to proceed via the carbolone (**5**) rather than the tetrahydro-γ-carboline, which could be produced by a Pictet−Spengler synthesis. By doing so, it becomes possible to vary substituents in the 4-position of the γ-carboline intermediate in addition to the aforementioned 1-position. The desired carbolone (**5**) was afforded in lower yields than expected, due to

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TABLE 1. Structure and Yields of Compound 4

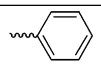
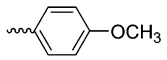
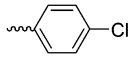
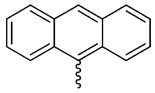
entry	Ar =	SM	Product	Yield
1		**3a**	**4a**	86
2		**3b**	**4b**	72
3		**3c**	**4c**	63
4		**3d**	**4d**	61
5		**3e**	**4e**	59
6		**3f**	**4f**	43
7		**3g**	**4g**	61

TABLE 2. Synthesis of 1,2-Dihydro-3-*H*-γ-carbolone by Intramolecular Cyclization

entry	starting material	product (yield %)
1	**4a**	**5a** (61); **6a** (9); **7a** (21)
2	**4b**	**5b** (45); **6b** (4); **7b** (17)
3	**4c**	**5c** (57); **6c** (16); **7c** (11)

contamination with **6** and **7**. A variety of Lewis acids such as $BF_3{*}Et_2O$, PPA, $ZnCl_2$, $AlCl_3$, $TiCl_4$, K-10 Clay, and P_2O_5 were examined as cyclizing catalysts with yields of **5** ranging from trace amounts to about 60%. The highest yield was achieved by employing Bentonite K-10 Clay. It has been noted that esters undergo either acylation (ring closure) or alkylation depending upon the choice of catalyst and it is believed that occurred in this case.[24] It was discovered that stronger Lewis acids, such as $TiCl_4$, frequently afforded a variety of products as noted by the increased formation of **6** and **7**. Since any of the compounds **5**, **6**, or **7**, when reacted with base, afforded the desired carboline **8**, it was unnecessary to isolate or purify the group of compounds that resulted from the acid-catalyzed cyclization step. Thus, a direct conversion from **4** to **8** was achieved in good yields, and when the carbolone **5** was the desired goal, this scheme allowed for its facile synthesis as well.

Experimental Section

General Procedures. Reagents were obtained from commercial suppliers and were used without further purification except as noted. Melting points are uncorrected. FTIR spectra of samples were obtained either as KBr pellets or on NaCl disks. ^{1}H NMR and ^{13}C NMR were determined at 300 and 75 MHz, respectively, in $CDCl_3$ unless otherwise noted, and chemical shifts are reported downfield from TMS. Coupling constants, *J*, are reported in Hz. THF was distilled from a sodium/benzophenone ketal-pair and CH_2Cl_2 from P_2O_5, all under nitrogen. All moisture-sensitive reactions and reagent transfers were carried out under either nitrogen or argon. Thin-layer chromatography (TLC) was performed on precoated silica gel sheets with glass backing. Preparative column chromatography was performed on an Isco-100s automated flash column chromatograph system employing pre-packed silica gel columns 60 Å (200−400 mesh).

TABLE 3. Synthesis of γ-Carboline (8) by Direct Conversion of 4

entry	starting material	product	yield (%)
1	**4a**	**8a**	35
2	**4b**	**8b**	31
3	**4c**	**8c**	28
4	**4d**	**8d**	33
5	**4e**	**8e**	43
6	**4f**	**8f**	18
7	**4g**	**8g**	26

General Procedure. Preparation of 3 from 1. To a stirred solution of 3-bromo-1-(*tert*-butyldimethylsilyl)indole[25] (**1**; 0.5 g, 1.6 mmol) in freshly distilled THF (15 mL), cooled to −78 °C, was added a solution of *t*-BuLi (2.1 mL of a 1.7 M solution in pentane, 3.6 mmol). The mixture was allowed to stir for 15 min before the rapid addition of 1.1 equiv of the corresponding tosylaldimine (**2**; 1.7 mmol) in 30 mL of freshly distilled THF. The solution was allowed to stir at room temperature for 24 h. The reaction mixture was quenched with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with H_2O (2 × 15 mL) and dried over $MgSO_4$. The resulting organic layer was concentrated with the aid of a rotary evaporator to afford a brown, viscous oil. Purification with flash column chromatography employing silica gel and a solvent system of EtOAc: hexanes (1:4) afforded compounds **3a**−**g**, respectively, in good yields.[22]

General Procedure. Preparation of 4 from 3. Into a 50-mL RB flask was placed a sample of compound **3** (2.01 mmol) dissolved in 30 mL of freshly distilled THF, and this mixture was allowed to stir under a positive flow of N_2 for 15 min. Sodium ethoxide (2.21 mmol) was added to the stirred solution and stirring was continued for an additional 30 min before ethyl bromoacetate (2.52 mmol) was added. The resulting solution was heated at reflux for 3.5 h and allowed to cool slowly to room temperature before being quenched with 10 mL of H_2O. The resulting solution was extracted with CH_2Cl_2 (3 × 25 mL), washed with H_2O (3 × 15 mL), and dried over $MgSO_4$ before being concentrated on a rotary evaporator. The final traces of solvent were removed under vacuum for 12 h. Gradient flash column chromatography (hexane:ethyl acetate) was performed to afford the desired purified product.

[[[1-TBDMS-1*H*-indol-3-yl]-phenyl-methyl]-(toluene-4-sulfonyl)-amino]-acetic acid ethyl ester (4a): A viscous red oil, 86% yield. FTIR 3466, 3051, 2956, 2916, 2854, 1716, 1638, 1451, 1415, 1264, 1140, 1093, 1010, 969, 896, 803, 741 cm^{-1}. ^{1}H NMR δ 7.79 (d, J = 9, 1H), 7.74−7.71 (m, 1H), 7.64−7.61 (m, 1H), 7.51 (d, J = 9, 1H), 7.36−7.26 (m, 4H), 7.24 (s, 1H), 7.30−7.10 (m, 5H), 6.62 (s, 1H), 4.19 (s, 2H), 4.10 (q, J = 6, 2H), 2.40 (s, 3H), 1.17 (t, J = 3, 3H), 0.92 (s, 9H), 0.60 (s, 6H). ^{13}C NMR δ 144.0, 141.9, 136.7, 130.2, 128.7, 128.1, 126.0, 124.1, 123.6, 122.0, 121.3, 120.7, 120.1, 119.2, 113.8, 111.0, 102.7, 40.3, 34.8, 31.5, 26.4, 23.8, 19.5, 14.1. Anal. Calcd for $C_{32}H_{40}N_2O_4SSi$: C, 66.63; H, 6.99; N, 4.86. Found: C, 66.28; H, 7.14; N, 4.61.

[[[1-TBDMS-1*H*-indol-3-yl]-(4-methoxy-phenyl)-methyl]-(toluene-4-sulfonyl)-amino]-acetic acid ethyl ester (4b): A yellow powder, 72% yield, mp 110−112.5 °C. FTIR 3279, 3051, 2947, 2854, 1747, 1612, 1550, 1550, 1509, 1451,

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1306, 1254, 1156, 1093, 1031, 969, 917, 839, 813 cm^{-1}. ^{1}H NMR δ 7.82 (d, J = 6, 2H), 7.50 (d, J = 6, 2H), 7.40 (d, J = 9, 1H), 7.15 (d, J = 9, 2H), 6.93 (d, J = 9, 1H), 6.97−6.69 (m, 2H), 6.40 (s, 1H), 5.80 (d, J = 6, 2H), 5.47 (d, J = 9, 1H), 4.20 (q, J = 6, 2H), 3.75 (s, 2H), 3.72 (s, 3H), 2.31 (s, 3H), 0.99 (t, J = 9, 3H), 0.87 (s, 9H), 0.48 (s, 6H). ^{13}C NMR δ 169.5, 158.8, 142.6, 141.8, 137.7, 132.6, 130.0, 129.2, 128.4, 127.1, 121.5, 120.0, 119.5, 119.4, 118.0, 113.9, 113.6, 60.8, 58.5, 55.2, 54.6, 46.4, 26.2, 21.4, 19.3, 13.8. Anal. Calcd for $C_{33}H_{42}N_2O_5SSi$: C, 65.31; H, 6.98; N, 4.62. Found: C, 65.67; H, 7.03; N, 4.34.

[[[1-TBDMS-1*H*-indol-3-yl]-(4-chloro-phenyl)-methyl]-(toluene-4-sulfonyl)-amino]-acetic acid ethyl ester (4c): A yellow oil, 63% yield. FTIR 3373, 3051, 2947, 2864, 1742, 1597, 1545, 1488, 1451, 1420, 1337, 1265, 1207, 1161, 1088, 1016, 969, 896, 839, 808, 740, 699 cm^{-1}. ^{1}H NMR δ 7.83 (d, J = 9, 2H), 7.54 (d, J = 9, 1H), 7.46−7.42 (m, 1H), 7.31 (d, J = 9, 2H), 7.24 (d, J = 9, 2H), 7.18−6.88 (m, 4H), 6.69 (s, 1H), 6.43 (s, 1H), 5.83 (d, J = 3, 1H), 3.82 (q, J = 6, 2H), 2.42 (s, 3H), 2.36 (s, 2H), 1.01 (t, J = 9, 3H), 0.88 (s, 9H), 0.50 (s, 6H). ^{13}C NMR δ 156.2, 146.6, 142.0, 136.3, 131.5, 130.5, 130.3, 129.2, 128.2, 128.1, 128.0, 126.0, 124.7, 121.9, 120.1, 120.1, 117.4, 114.0, 50.7, 29.7, 26.2, 21.2, 19.3, 14.1. Anal. Calcd for $C_{32}H_{39}ClN_2O_4SSi$: C, 62.88; H, 6.43; N, 4.58. Found: C, 62.55; H, 6.22; N, 4.88.

[[[1-TBDMS-1*H*-indol-3-yl]-pyridin-2-yl-methyl]-(toluene-4-sulfonyl)-amino]-acetic acid ethyl ester (4d): A yellow powder, 61% yield, mp 87.5−93 °C. FTIR 3435, 3051, 2978, 1737, 1633, 1592, 1420, 1332, 1265, 1161, 1093, 1021, 896, 808, 740, 704 cm^{-1}. ^{1}H NMR δ 8.36 (d, J = 6, 2H), 7.86 (d, J = 6, 2H), 7.78−7.45 (m, 4H), 7.35 (d, J = 6, 1H), 7.20−6.78 (m, 3H), 6.78 (s, 1H), 5.78 (d, J = 3, 1H), 4.01 (q, J = 6, 2H), 2.43 (s, 3H), 2.32 (s, 2H), 1.13 (t, J = 3, 3H), 0.75 (s, 9H), 0.45 (s, 6H). ^{13}C NMR δ 169.3, 143.4, 141.5, 137.1, 133.3, 131.8, 129.4, 129.3, 128.6, 128.3, 128.0, 121.9, 119.9, 119.6, 117.3, 114.6, 113.9, 60.9, 58.3, 54.4, 54.3, 46.6, 26.1, 21.4, 19.2, 13.7. Anal. Calcd for $C_{31}H_{39}N_3O_4SSi$: C, 64.44; H, 6.80; N, 7.27. Found: C, 64.13; H, 7.12; N, 6.93.

[[[1-TBDMS-1*H*-indol-3-yl]-(2-trifluoromethyl-phenyl)-methyl]-(toluene-4-sulfonyl)-amino]-acetic acid ethyl ester (4e): A yellow oil, 59% yield. FTIR 3269, 3051, 2937, 2854, 1742, 1597, 1550, 1493, 1467, 1451, 1420, 1337, 1311, 1239, 1213, 1161, 1119, 1036, 964, 927, 896, 808, 735, 709, 678 cm^{-1}. ^{1}H NMR δ 7.82 (d, J = 6, 2H), 7.75 (d, J = 9, 2H), 7.59 (t, J = 6, 1H), 7.42 (t, J = 6, 1H), 7.39−7.33 (m, 3H), 7.23 (d, J = 6, 1H), 7.20−6.73 (m, 2H), 6.28 (s, 1H), 6.20 (d, J = 3, 1H), 5.12 (d, J = 3, 1H), 3.47 (q, J = 6, 2H), 2.45 (s, 3H), 2.41 (s, 2H), 1.08 (t, J = 9, 3H), 0.77 (s, 9H), 0.42 (s, 6H). ^{13}C NMR δ 170.0, 168,7, 143.4, 141.7, 136.9, 131.7, 130.8, 129.7, 129.6, 129.5, 129.4, 129.0, 128.4, 127.4, 127.1, 122.1, 120.1, 118.6, 117.9, 114.1, 61.4, 55.1, 50.5, 48.3, 26.1, 21.5, 19.2, 14.1. Anal. Calcd for $C_{33}H_{39}F_3N_2O_4SSi$: C, 61.47; H, 6.10; N, 4.34. Found: C, 61.14; H, 5.86; N, 3.97.

[[[1-TBDMS-1*H*-indol-3-yl]-thiophen-2-yl-methyl]-(toluene-4-sulfonyl)-amino]-acetic acid ethyl ester (4f): A brown powder, 43% yield, mp 87.5−93 °C. FTIR 3373, 3051, 2948, 2854, 2304, 1752, 1732, 1602, 1550, 1472, 1451, 1420, 1332, 1265, 1213, 1161, 1093, 1021, 964, 896, 839, 813, 740, 699, 668 cm^{-1}. ^{1}H NMR δ 7.83 (d, J = 9, 1H), 7.55 (d, J = 9, 2H), 7.41 (t, J = 9, 1H), 7.26−6.98 (m, 3H), 6.97 (d, J = 9, 2H), 6.97−6.89 (m, 2H), 6.68 (s, 1H), 6.09 (d, J = 9, 1H), 4.11 (q, J = 18, 2H), 2.38 (s, 2H), 2.32 (s, 3H), 0.91 (t, J = 6, 3H), 0.86 (s, 9H), 0.54 (s, 6H). ^{13}C NMR δ 169.3, 145.1, 142.7, 142.2, 141.6, 137.5, 129.8, 129.2, 129.0, 126.5, 125.7, 125.1, 121.8, 119.8, 119.7, 119.2, 117.4, 113.9, 60.8, 54.7, 51.1, 46.1, 26.1, 21.4, 19.2. Anal. Calcd for $C_{30}H_{38}N_2O_4S_2Si$: C, 61.82; H, 6.57; N, 4.81. Found: C, 61.71; H, 6.32; N, 5.18.

[[Anthracen-9-yl-[1-TBDMS-1*H*-indol-3-yl]-methyl]-(toluene-4-sulfonyl)-amino]-acetic acid ethyl ester (4g): A yellow oil, 61% yield. FTIR 3373, 3051, 2958, 2916, 2854, 1732, 1602, 1451, 1420, 1264, 1156, 1093, 1010, 964, 896, 839, 809, 735, 704 cm^{-1}. ^{1}H NMR δ 8.17 (m, 2H), 7.86 (d, J = 9, 2H), 7.54 (d, J = 12, 2H), 7.43 (d, J = 6, 1H), 7.36 (t, J = 6, 1H), 7.22 (s, 1H), 7.13 (t, J = 9, 2H), 6.98 (t, J = 6, 2H), 6.76 (d, J = 6, 2H), 6.68 (s, 1H), 6.33 (d, J = 9, 2H), 5.76 (d, J = 6, 1H), 4.19 (q, J = 3, 2H), 3.91 (s, 2H), 2.05 (s, 3H), 0.86 (t, J = 6, 3H), 0.79 (s, 9H), 0.42 (s, 6H). ^{13}C NMR δ 186.7, 146.6, 142.0, 136.3, 131.5, 130.5, 130.3, 129.2, 128.1, 128.0, 126.0, 124.7, 121.9, 120.1, 120.1, 117.4, 114.0, 100.3, 96.3, 93.8, 50.7, 31.9, 29.7, 26.3, 21.2, 14.1. Anal. Calcd for $C_{40}H_{44}N_2O_4SSi$: C, 70.97; H, 6.55; N, 4.14. Found: C, 71.36; H, 6.46; N, 3.83.

General Procedure. Preparation of 5 from 4. Into a 50-mL RB flask was placed a sample of compound **4** (8.42 mmol) dissolved in 25 mL of freshly distilled THF. The solution was allowed to stir under a positive flow of N_2 for 15 min. To the stirred solution was added 1.00 g of Bentonite K-10 clay. The resulting solution was heated in an 80 °C oil bath for 12 h. Upon completion, the reaction mixture was cooled, then diluted with 20 mL of CH_2Cl_2 and vacuum filtered with the aid of a Büchner funnel to remove the clay from the reaction mixture. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Final traces of solvent were removed under vacuum for 4 h. Gradient flash column chromatography (hexane:ethyl acetate) was performed to afford the desired product **5**.

1-Phenyl-2-(toluene-4-sulfonyl)-1,2,3,5-tetrahydro-pyrido[4,3-*b*]indol-4-one (5a): A brown oil, 61% yield. FTIR 3650, 3522, 3134, 3004, 3051, 2916, 1719, 1492, 1441, 1368, 1259, 1171, 1124, 1088, 989, 746, 678 cm^{-1}. ^{1}H NMR δ 8.18 (br s, 1NH), 7.78 (d, J = 6, 2H), 7.62−7.40 (m, 2H), 7.31 (d, J = 6, 2H), 7.17−7.02 (m, 7H), 4.97 (s, 1H), 4.32 (s, 1H), 2.35 (s, 3H). ^{13}C NMR δ 185.6, 146.3, 141.6, 136.3, 134.6, 134.0, 133.8, 128.7 (overlapping peak), 127.8, 125.8, 124.9, 122.2, 121.8, 121.5, 119.7, 109.8, 51.7, 50.3, 22.4. Anal. Calcd for $C_{24}H_{20}N_2O_3S$: C, 69.21; H, 4.84; N, 6.73. Found: C, 68.97; H, 5.13; N, 6.49.

1-(4-Methoxy-phenyl)-2-(toluene-4-sulfonyl)-1,2,3,5-tetrahydro-pyrido[4,3-*b*]indol-4-one (5b): Dark oil, 45% yield. FTIR 3414, 3187, 3049, 2981, 2918, 1710, 1657, 1587, 1478, 1448, 1376, 1352, 1312, 1227, 1181, 1054, 1024, 1018, 998, 761 cm^{-1}. ^{1}H NMR δ 8.26 (br s, 1NH), 7.51 (d, J = 6, 2H), 7.35 (d, J = 6, 2H), 7.21−7.15 (m, 3H), 7.07 (t, J = 6, 1H), 7.04 (d, J = 6, 1H), 6.89 (d, J = 6, 1H), 6.81 (d, J = 6, 2H), 5.07 (s, 1H), 4.05 (s, 2H), 3.77 (s, 3H), 1.55 (s, 3H). ^{13}C NMR δ 158.9, 143.6, 142.9, 139.1, 137.6, 136.6, 132.5, 129.7, 129.2, 128.4, 127.2, 126.5, 125.4, 119.9, 119.4, 116.6, 113.7, 111.2, 55.2, 30.2, 29.7, 22.7. Anal. Calcd for $C_{25}H_{22}N_2O_4S$: C, 67.25; H, 4.97; N, 6.27. Found: C, 67.04; H, 5.16; N, 6.19.

1-(4-Chloro-phenyl)-2-(toluene-4-sulfonyl)-1,2,3,5-tetrahydro-pyrido[4,3-*b*]indol-4-one (5c): A brown oil, 57%. FTIR 3352, 3097, 3081, 2975, 2961, 1719, 1643, 1602, 1302, 1156, 1093, 906, 813 cm^{-1}. ^{1}H NMR δ 8.46 (br s, 1NH), 7.79−7.68 (m, 3H), 7.34−7.09 (m, 9H), 5.07 (s, 1H), 4.31 (s, 1H), 2.39 (s, 3H). ^{13}C NMR δ 187.4, 146.7, 146.3, 142.3, 137.9, 135.9, 133.8, 130.3, 129.6, 129.1, 126.5, 125.2, 124.8, 122.6, 121.1, 120.8, 110.6, 52.3, 48.7, 23.1. Anal. Calcd for $C_{24}H_{19}ClN_2O_3S$: C, 63.92; H, 4.25; N, 6.21. Found: C, 64.01; H, 4.52; N, 5.93.

General Procedure. Preparation of 8 from 4. Into a 50-mL RB flask was placed a sample of compound **4** (8.42 mmol) dissolved in 25 mL of freshly distilled THF. The solution was allowed to stir under a positive flow of N_2 for 15 min. To the stirred solution was added 1.00 g of Bentonite K-10 clay. The resulting solution was heated in an 80 °C oil bath for 12 h. The reaction mixture was cooled and vacuum filtered with the aid of a Büchner funnel to remove the clay from the reaction mixture. To the resulting combined organic layer was added 20 mL of THF, NaOH (16.84 mmol), and tetrabutylammonium bromide (0.84 mmol). The solution was heated at reflux for 6 h, allowed to slowly cool to room temperature, diluted with 20 mL of CH_2Cl_2, and neutralized with 1 M HCl. The resulting solution was washed with H_2O (3 × 20 mL) and brine (1 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Final traces of solvent were removed under vacuum for 4 h. Gradient flash column chro-

matography (hexane:ethyl acetate) was performed to afford the desired product **8**.

General Procedure. Preparation of 8 from 5. Compound **5** was dissolved in 25 mL of freshly distilled THF and allowed to stir for 15 min before the addition of NaOH (16.84 mmol) and tetrabutylammonium bromide (0.84 mmol). The resulting solution was heated at reflux for 6 h and then allowed to slowly cool to room temperature, diluted with 20 mL of CH_2Cl_2, and neutralized with 1 M HCl. The resulting solution was washed with H_2O (3 × 20 mL) and brine (1 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Final traces of solvent were removed under vacuum for 4 h. Gradient flash column chromatography (hexane:ethyl acetate) was performed to afford the desired product **8**.

1-Phenyl-5*H*-pyrido[4,3-*b*]indol-4-ol (8a): A yellow oil, 35% yield (from **4**). FTIR 3406, 2956, 2910, 2852, 1733, 1634, 1577, 1536, 1455, 1415, 1334, 1258, 1091, 1016, 860, 802 cm^{-1}. ^1H NMR δ 7.91 (br s, 1H), 7.73 (d, J = 6, 1H), 7.40−7.34 (m, 2H), 7.19−7.12 (m, 4H), 7.02−6.97 (m, 1H), 6.67 (d, J = 6, 1H), 5.89 (s, 1H), 4.25 (s, 1H). ^{13}C NMR δ 144.0, 136.7, 134.7, 128.7, 128.2, 127.1, 126.1, 124.5, 123.6, 122.2, 121.9, 119.9, 119.8, 119.2, 119.2. Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.21; H, 4.58; N, 10.43.

1-(4-Methoxy-phenyl)-5*H*-pyrido[4,3-*b*]indol-4-ol (8b): A yellow oil, 31% yield (from **4**). FTIR 3406, 2921, 2863, 1611, 1577, 1513, 1455, 1340, 1299, 1241, 1172, 1086, 1033, 849, 808, 739, 704 cm^{-1}. ^1H NMR δ 8.01 (br s, 1H), 7.79 (d, J = 6, 2H), 7.55 (d, J = 6, 2H), 7.30−7.17 (m, 1H), 7.14−7.09 (m, 1H), 6.97 (t, J = 9, 1H), 6.73 (d, J = 9, 1H), 6.72 (s, 1H), 4.82 (br s, 1H), 3.75 (s, 3H). ^{13}C NMR δ 189.9, 158.9, 143.6, 142.9, 136.6, 129.7, 129.2, 128.4, 125.4, 124.0, 122.5, 119.9, 116.6, 113.7, 11.2, 54.6. Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.09; H, 4.75; N, 9.51.

1-(4-Chloro-phenyl)-5*H*-pyrido[4,3-*b*]indol-4-ol (8c): A yellow oil, 28% yield (from **4**). FTIR 3383, 3291, 3059, 2956, 2922, 1646, 1599, 1547, 1489, 1461, 1414, 1328, 1299, 1218, 1155, 1091, 1027, 1010, 808, 738, 716, 629 cm^{-1}. ^1H NMR δ 8.04 (br s, 1H), 7.75 (s, 1H), 7.44 (d, J = 9, 2H), 7.35 (d, J = 9, 2H), 7.24−6.98 (m, 3H), 6.61 (d, J = 6, 1H), 5.80 (s, 1H). ^{13}C NMR δ 140.4, 139.6, 136.7, 135.1, 124.0, 123.0, 122.7, 121.5, 120.1, 119.6, 119.4, 118.7, 116.9, 111.3, 110.4, 110.3, 109.1. Anal. Calcd for $C_{17}H_{11}ClN_2O$: C, 69.28; H, 3.76; N, 9.50. Found: C, 68.93; H, 3.54; N, 9.79.

1-Pyridin-2-yl-5*H*-pyrido[4,3-*b*]indol-4-ol (8d): A brown oil, 33% yield (from **4**). FTIR 3406, 2956, 1634, 1525, 1444, 1345, 1259, 1155, 1091, 1022, 930, 866, 803 cm^{-1}. ^1H NMR δ 8.03 (br s, 1H), 7.92 (d, J = 9, 1H), 7.46−7.42 (m, 2H), 7.38−7.33 (m, 3H), 7.19 (t, J = 6, 1H), 7.09 (t, J = 6, 1H), 6.99 (s, 1H), 4.45 (s, 1H). ^{13}C NMR δ 149.4, 136.3, 136.1, 132.8, 131.8, 127.3, 127.0, 124.0, 123.5, 122.2, 122.1, 119.6, 118.9, 113.0, 111.2, 110.9, 110.2. Anal. Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.39; H, 4.08; N, 15.99.

1-(2-Trifluoromethyl-phenyl)-5*H*-pyrido[4,3-*b*]indol-4-ol (8e): A yellow oil, 43% yield (from **4**). FTIR 3360, 3256, 2956, 1640, 1600, 1524, 1490, 1450, 1415, 1374, 1305, 1259, 1155, 1091, 1028, 906, 803, 745 cm^{-1}. ^1H NMR δ 8.36 (br s, 1H), 7.86 (d, J = 9, 1H), 7.76 (d, J = 9, 1H), 7.69 (d, J = 9, 1H), 7.59−7.47 (m, 1H), 7.40−7.30 (m, 2H), 7.20−7.17 (m, 1H), 6.97 (d, J = 9, 1H), 5.74 (s, 1H), 4.69 (s, 1H). ^{13}C NMR δ 188.2, 144.0, 136.7, 134.7, 128.7, 128.2, 127.1, 126.1, 124.5, 123.6, 122.2, 121.9, 119.9, 119.8, 119.2, 119.2, 111.0, 70.3. Anal. Calcd for $C_{18}H_{11}F_3N_2O$: C, 65.85; H, 3.38; N, 8.53. Found: C, 66.02; H, 3.57; N, 8.46.

1-Thiophen-2-yl-5*H*-pyrido[4,3-*b*]indol-4-ol (8f): A yellow oil, 18% yield (from **4**). FTIR 3406, 2944, 1640, 1548, 1455, 1426, 1339, 1288, 1259, 1224, 1184, 1155, 1086, 1034, 970, 849, 808, 739, 623 cm^{-1}. ^1H NMR δ 8.03 (br s, 1H), 7.57 (d, J = 9, 1H), 7.36 (d, J = 9, 1H), 7.12 (t, J = 6, 1H), 7.10−7.05 (m, 2H), 7.05 (s, 1H), 6.92 (s, 1H), 6.93−6.87 (m, 2H), 4.32 δ (s, 1H). ^{13}C NMR δ 196.4, 145.6, 128.3, 127.1, 126.7, 124.7, 123.7, 122.2, 119.7, 119.6, 119.5, 118.6, 115.3, 111.1, 110.8. Anal. Calcd for $C_{15}H_{10}N_2OS$: C, 67.65; H, 3.78; N, 10.52. Found: C, 67.78; H, 3.69; N, 10.35.

1-Anthracen-9-yl-5*H*-pyrido[4,3-*b*]indol-4-ol (8 g): An orange oil, 26% yield (from **4**). FTIR 3418, 2933, 2852, 1640, 1455, 1369, 1259, 1184, 1091, 1022, 964, 802 cm^{-1}. ^1H NMR δ 8.39 (br s, 1H), 8.23 (d, J = 9, 2H), 8.03 (d, J = 9, 2H), 7.93−7.87 (m, 8H), 7.46 (d, J = 6, 4H), 7.38 (t, J = 6, 1H), 7.14 (s, 1H), 7.06 (d, J = 6, 2H), 6.13 (s, 1H), 5.01 (s, 1H). ^{13}C NMR δ 147.6, 147.1, 139.1, 138.4, 134.0, 132.6, 131.7, 129.0, 127.2, 125.6, 125.0, 124.4, 124.0, 122.9, 119.9, 114.0, 109.9, 107.6, 92.4. Anal. Calcd for $C_{25}H_{16}N_2O$: C, 83.31; H, 4.47; N, 7.77. Found: C, 83.58; H, 4.63; N, 8.06.

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