Synthesis of Metabolites of the Ah Receptor Ligand 6-Formylindolo[3,2-*b*]carbazole

Niklas Wahlström,[a,b] Ivan Romero,[a] and Jan Bergman*[a,b]

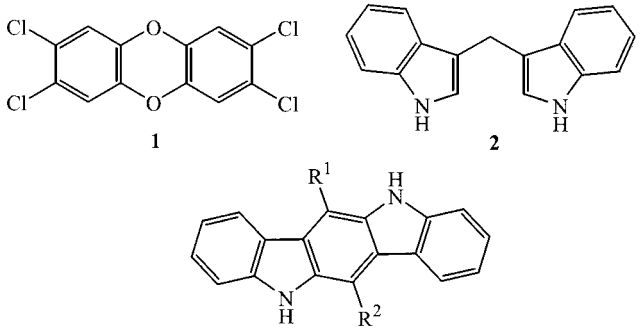
Keywords: Bis(indoles) / Acylations / Ah receptor / 6-Formylindolo[3,2-*b*]carbazole / Metabolite

Synthesis of the five mono- and di-hydroxylated metabolites of the aryl hydrocarbon receptor high affinity ligand 6-formylindolo[3,2-*b*]carbazole is described. The structures of the metabolites were unequivocally established as 2-hydroxy-, 8-hydroxy-, 2,10-dihydroxy-, 4,8-dihydroxy- and 2,8-dihydroxyindolo[3,2-*b*]carbazole-6-carboxaldehyde.

Introduction

The aryl hydrocarbon (Ah) receptor is an intracellar protein present in all rodent cells examined to date.[1] In the cell, the Ah receptor is involved in the primary detoxification of nonpolar substances, such as polyaromatic hydrocarbons, and xenobiotics like the highly toxic environmental pollutant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, **1**). The Ah receptor triggers the expression of many enzymes (including cytochrome P-4501A1) involved in detoxification processes.[2] Natural ligands for this receptor include di(indol-3-yl)methane (**2**) and indolo[3,2-*b*]carbazole (ICZ, **3**),[3] which are transformation products from the essential amino acid tryptophan. Irradiation of a tryptophan solution in water gives two ICZ derivatives that have been isolated[4] and structurally corroborated by independent syntheses to be 6-formylindolo[3,2-*b*]carbazole (**4a**)[5] and 6,12-diformylindolo[3,2-*b*]carbazole (**4b**).[5] The monoformylated ICZ derivative **4a** exhibits the highest binding affinity for the Ah receptor so far observed.[6] Further investigations of **4a** showed that the Ah receptor expression induced by **4a** is both rapid and transient, which seems to be a prerequisite for an endogenous ligand.[7] Additionally, the Ah receptor activation of an endogenous ligand has been suggested to be involved in the degradation of the ligand.[7]

Recently, indolo[3,2-*b*]carbazole-6-carbaldehyde (**4a**) was metabolized by incubation with an activated cytochrome P-4501A1 system in vivo. The resulting metabolites were isolated by HPLC and characterized using mass spectrometry and NMR spectroscopy.[8] Since two of the three metabolite fractions separated contained two substances, the NMR spectra displayed overlapping signals. Therefore, it was not possible to determine the relative position (2 or 3) of the hydroxy group in the A-ring (Figure 1) of these metabolites. We embarked on the synthesis of the assigned metabolites **5a**−**b** and **5d**−**f** (Figure 2) with the objective of establishing the substitution patterns of the hydroxylated metabolites, and to determine the activity and toxicity of the pure products.



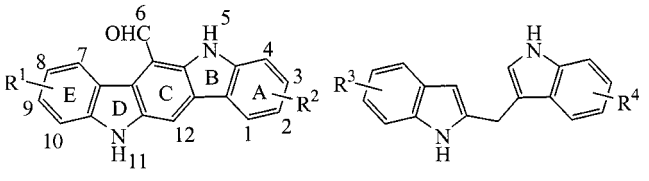
3 $R^1 = R^2 = H$
4a $R^1 = CHO$, $R^2 = H$
4b $R^1 = R^2 = CHO$

Figure 1. Potent aryl hydrocarbon receptor ligands **1**−**4b**

Results and Discussion

In our first approach, the di(indolyl)methanes **6a**−**g**,[9] were initially acylated using dichloroacetyl chloride and pyridine in THF to give the corresponding acylated products (exemplified here by compound **7**).[5,8] Ring closure and hydrolysis of the dichloromethyl compound **7** produced directly the desired aldehyde functionality. However, when the di(indolyl)methanes **7** were substituted with more than

[a] Unit for Organic Chemistry, CNT, Department of Biosciences at NOVUM, Karolinska Institute, Novum Research Park, 141 57 Huddinge, Sweden
Fax: (internat.) +46-8-6081501
E-mail: jabe@biosci.ki.se
[b] Södertörn University College, 141 04 Huddinge, Sweden



5a R^1 = H, R^2 = 2-OH
5b R^1 = 8-OH, R^2 = OH
5c R^1 = H, R^2 = 3-OH
5d R^1 = 8-OH, R^2 = 2-OH
5e R^1 = 8-OH, R^2 = 4-OH
5f R^1 = 10-OH, R^2 = 2-OH

6a R^3 = R^4 = H
6b R^3 = 5-OMe, R^4 = H
6c R^3 = H, R^4 = 5'-OMe
6d R^3 = H, R^4 = 6'-OMe
6e R^3 = 5-OMe, R^4 = 5'-OMe
6f R^3 = 7-OMe, R^4 = 5'-OMe
6g R^3 = 5-OMe, R^4 = 7'-OMe

Figure 2. ICZs **5a**−**f** with atom numbering outlined and the (indol-2-yl)(indol-3-yl)methanes **6a**−**g**

one methoxy group the co-formation of a decarbonylated by-product, **8**, resulted in an inseparable mixture of ICZ derivatives. As an example of this, the bis(indole) **7** was prepared from **6e** (Scheme 1). The ratio of products in the mixture resulting from treatment of **7** with various acids under the conditions outlined in Table 1 indicates that the extent of decarbonylation increased (formation of **8**) with higher temperature and increasing acid strength. (Table 1).

Table 1. Result from acid induced cyclisation of **7**

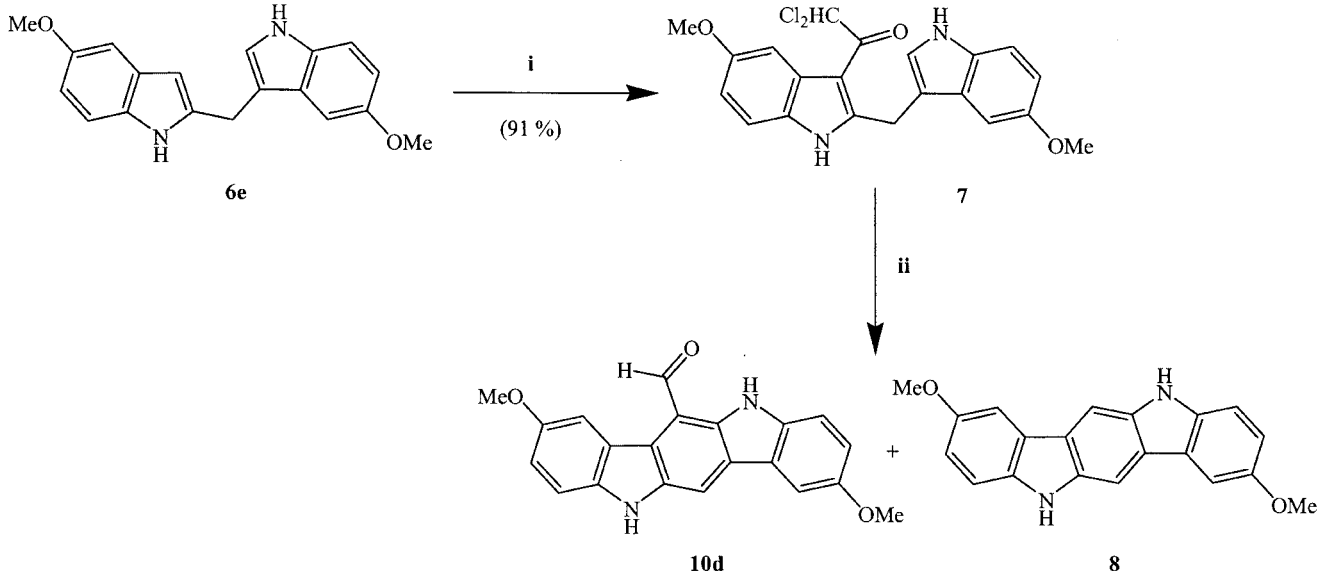
Entry	[h][a]	Catalyst	*T* [°C]	Ratio **10d**:**8**[b] [c]
1	6	2 M HCl	78	1:1
2	1.5	CH_3SO_3H	100	2:1
3	20	CH_3SO_3H	50	9:2
4	5.5	CF_3SO_3H	50	1:2
5	0.4	CF_3SO_3H	100	1:20

[a] Reaction time. [b] Determined by ^{1}H NMR after workup of reaction. [c] Yields were not determined.

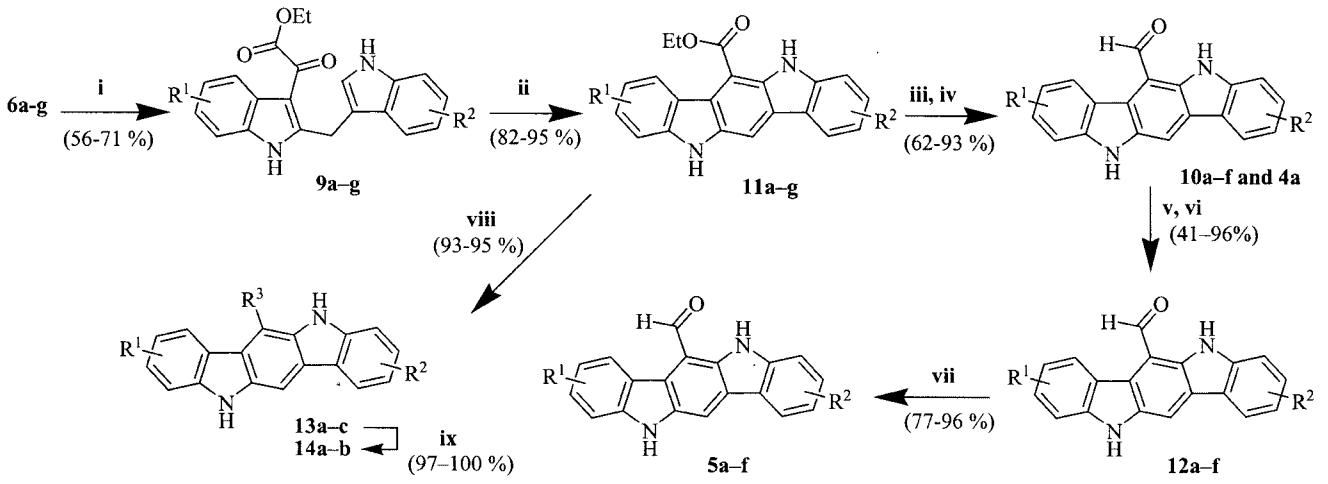
While attempting to increase the solubility of the mixture containing **10d** by protection of the nitrogen atoms, we noted the instability of the *N*,*N*′-diBoc derivative of **10d**. This sensitivity towards deprotection of the carbamate adjacent to the formyl group was attributed to electron donation by the methoxy group *para* to the nitrogen as well as the driving force of formation of a hydrogen bond between the formyl group and the NH proton. As a consequence of these difficulties, the first route was abandoned.

In order to overcome these problems, another route was employed. The di(indolyl)methanes **6a**−**g** were acylated by using ethyl oxalyl chloride/pyridine in THF to produce the esters **9a**−**g** (Scheme 2, Table 2). Facile ring closure of **9a**−**g** was performed with methanesulfonic acid in 1,4-dioxane to produce ICZs **11a**−**g** in yields higher than 82% (Scheme 2, Table 3). The esters **11a**−**g** were reduced with lithium aluminum hydride to their corresponding alcohols, which were subsequently dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to the aldehydes **10a**−**f** (Scheme 2, Table 3). This series of operations prevented the formation of the decarbonylated indolocarbazoles from precursors containing the dichloro functionality (i.e.) **7**. In this fashion, indolo[3,2-*b*]carbazole-6-carboxaldehyde (**4a**) could be obtained in 89% yield from ethyl indolo[3,2-*b*]carbazole-6-carboxylate (**11a**).

Demethylation of **10a**−**f** with excess boron tribromide in dichloromethane produced the crude hydroxylated indolocarbazoles **5a**−**f**. Before purification, the hydroxy groups were protected as their silyl ethers using *tert*-butyldimethylsilyl chloride and imidazole in DMF to give **12a**−**f** (Table 3) after silica gel column chromatography. Deprotection with tetrabutylammonium fluoride in THF produced the hydroxylated metabolites **5a**−**b** and **5d**−**f** in pure form (Scheme 2, Table 4). By comparison with spectroscopic data reported previously,[8] we determined that the hydroxy



Scheme 1. i. Pyridine, $Cl_2CHCOCl$, THF ii. Ethanol/1,4-dioxane, 2 M HCl or $MeSO_3H$ or CF_3SO_3H.



Scheme 2. i. Pyridine, $ClCOCO_2Et$, THF ii. $MeSO_3H$, 1,4-dioxane iii. $LiAlH_4$, THF iv. DDQ, 1,4-dioxane v. BBr_3, CH_2Cl_2 vii. TBSCl, imidazole, DMF vii. TBAF, THF viii. BBr_3, CH_2Cl_2 ix. Heat

Table 2. Acylation products **9a**−**f** from di(indolyl)methanes **6a**−**g**

Compound	R^1	R^2	Yield [%]
9a	H	H	88[a]
9b	H	5′-OMe	67
9c	5-OMe	H	65
9d	H	6′-OMe	56
9e	5-OMe	5′-OMe	64
9f	5-OMe	7′-OMe	71
9g	7-OMe	5′-OMe	63

[a] Synthesized previously in similar yield.[5]

Table 3. Indolo[3,2-*b*]carbazoles **11a**−**g**, **10a**−**f** and **12a**−**f**

Compound	R^1	R^2	Yield [%]
11a	H	H	92[a]
11b	H	2-OMe	90
11c	8-OMe	H	88
11d	H	3-OMe	89
11e	8-OMe	2-OMe	95
11f	8-OMe	4-OMe	86
11g	10-OMe	2-OMe	82
4a	H	H	89
10a	H	2-OMe	87
10b	8-OMe	H	82
10c	H	3-OMe	62
10d	8-OMe	2-OMe	93
10e	8-OMe	4-OMe	78
10f	10-OMe	2-OMe	82
12a	H	2-OTBS	70
12b	8-OTBS	H	44
12c	H	3-OTBS	45
12d	8-OTBS	2-OTBS	44
12e	8-OTBS	4-OTBS	41
12f	10-OTBS	2-OTBS	72

[a] Synthesized previously in 88% yield.[5]

group occupies the 2-position of the A-ring (Figure 1). The considerable variation in the solubility of the different metabolites influenced their workup strategies. With two

Table 4. Indolo[3,2-*b*]carbazoles **5a**−**f**, **13a**−**c** and **14a**−**b**

Compound	R^1	R^2	R^3	Yield [%]
5a	H	2-OH	–	95
5b	8-OH	H	–	96
5c	H	3-OH	–	77
5d	8-OH	2-OH	–	77
5e	8-OH	4-OH	–	98
5f	10-OH	2-OH	–	84
13a	H	H	CO_2H	93
13b	8-OH	2-OH	CO_2H	95
13c	H	2-OH	CO_2H	93
14a	8-OH	2-OH	H	100
14b	H	2-OH	H	97

hydroxy functionalities in the A and E-rings (Figure 1) of compounds **10**, **12** and **5**, the solubilities were much improved. On the other hand, compounds with only one hydroxy functionality present had lower solubilities. The methoxyindolocarbazole **10b** and the metabolite 8-hydroxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (**5b**) were even more insoluble than indolo[3,2-*b*]carbazole-6-carboxaldehyde (**4a**). Several of the tetra- and penta-cyclic compounds prepared co-crystallized with small amounts of 1,4-dioxane or ethyl acetate. These solvents could not be removed by conventional methods and the compounds were purified by sublimation at high temperature and under high vacuum. The ester **11a** was hydrolyzed with 2 M sodium hydroxide in ethanol to give **13a** (Scheme 2, Table 4). The esters **11e** and **11b** were simultaneously demethylated and hydrolyzed to give the acids **13b**−**c** (Scheme 2, Table 4). In both cases, these acids were decarboxylated to give the hydroxy indolocarbazoles **14a**−**b** in 97−100% yield.

Conclusions

In summary, we have synthesized the five primary metabolites **5a**−**b** and **5d**−**f** of the highly potent aryl hydrocarbon

receptor ligand indolo[3,2-*b*]carbazole-6-carboxaldehyde (**4a**) and thus have determined unambiguously the substitution pattern of their hydroxy groups. These results will enable further studies on the affinity and toxicity of these metabolites.

Experimental Section

General Remarks: NMR spectra were obtained with a Bruker Avance 300 DPX spectrometer (Bruker, Newark, USA) operating at 300 MHz or a Jeol Eclipse +500 FT NMR spectrometer (Jeol Ltd., Tokyo, Japan) operating at 500 MHz. Spectra were recorded in [D_6]acetone, [D_6]DMSO or $CDCl_3$, using the residual solvent as internal standard at 300.1 or 500.2 MHz for ^{1}H and 75.5 or 125.8 MHz for ^{13}C at 298 K unless stated otherwise. Coupling constants and chemical shifts are given in Hz and ppm, respectively. IR spectra were recorded with a Perkin−Elmer FT-IR 1600 spectrophotometer. Melting points were determined using the capillary method on a Büchi B-545 or on a Heizbank Kofler hotbench and are uncorrected. Mass spectra were recorded using an LC/MS system operating in the electrospray ionization (ESI) mode at 70 eV. HRMS (FAB) experiments were performed by E. Nilsson, Kemicentrum, Lund, Sweden. Elemental analyses were performed by H. Kolbe Microanalytisches Laboratorium, Mülheim an der Ruhr, Germany. All reagents were of standard purity and used as received from Lancaster, Aldrich, Biosynth or Merck. Solvents were purified by distillation or were of HPLC grade and used as received. Dichloromethane was distilled from CaH_2 and stored over activated molecular sieves prior to use. 1,4-Dioxane was stored over sodium. THF was distilled from sodium/benzophenone. Chromatographic separations were performed on silica gel 60 (230−400 mesh). Reactions were monitored by thin-layer chromatography, on silica gel coated plates containing a fluorescent indicator.

2,2-Dichloro-1-[5-methoxy-2-(5-methoxy-1*H*-indol-3-ylmethyl)-1*H*-indol-3-yl]ethanone (7): Dichloroacetyl chloride (1.10 mL, 11.42 mmol) was added dropwise via syringe to a solution of 5-methoxy-2-(5-methoxy-1*H*-indol-3-ylmethyl)-1*H*-indole (**6e**) (2.80 g, 9.14 mmol) and pyridine (0.92 mL, 11.42 mmol) in THF (50 mL) under argon at −10 °C. The resulting suspension was then stirred at 21 °C for 5 h when a saturated aqueous solution of NH_4Cl (0.50 mL) was added. EtOAc (100 mL) and water (50 mL) were added, and the organic phase was separated, washed with 2 M HCl (40 mL), saturated aq. $NaHCO_3$ (40 mL), followed by water (50 mL) and finally brine (2 × 40 mL) before drying over Na_2SO_4. Evaporation at 30 °C gave a white-greenish semi-solid that was subjected to column chromatography (aluminum oxide) using a gradient elution by EtOAc/hexane (40−100%). Fractions containing the product were concentrated, and evaporated at 30 °C with Et_2O/hexane to give the acylated bis(indole) **7** (3.47 g, 91%) as a yellow solid. An analytical sample was crystallized from CH_2Cl_2/hexane. M.p. 65 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3320, 2934, 2830, 1632, 1585, 1463, 1214, 1107, 1026, 800 cm^{-1}. ^{1}H NMR (300.1 MHz; [D_6]acetone): δ = 10.84 (br. s, 1 H), 10.09 (br. s, 1 H), 7.61 (d, *J* = 2.3 Hz, 1 H), 7.34−7.24 (m, 4 H), 7.00 (d, *J* = 2.4 Hz, 1 H), 6.83−6.76 (m, 2 H), 4.72 (s, 2 H), 3.87 (s, 3 H), 3.70 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]acetone): δ = 181.9 (s), 157.3 (s), 155.1 (s), 151.8 (s), 132.9 (s), 131.2 (s), 128.7 (s), 128.3 (s), 125.8 (d), 113.5 (d), 113.1 (d), 112.9 (d), 112.9 (d), 110.4 (s), 108.9 (s), 104.7 (d), 101.0 (d), 71.5 (d), 56.0 (q), 55.9 (q), 26.0 (t) ppm. HRMS (FAB) calcd. for $C_{21}H_{18}Cl_2N_2O_3$ 416.0694 [M]$^+$; found 416.0703.

Procedure for the Preparation of 9a−g: Ethyl oxalyl chloride (12 mmol) was added dropwise during 10 min to a solution of di(indolyl)methane (8 mmol) and pyridine (12 mmol) in THF (50 mL) under argon at 0 °C. The temperature was then increased to 21 °C and the mixture stirred for 4−8 h. EtOAc (150 mL) was added and the mixture was washed with 2 M HCl (50 mL), satd. $NaHCO_3$ (60 mL), then water (50 mL) and finally brine (100 mL) before drying over Na_2SO_4. The solvents were concentrated to give a yellow solid. The solid was suspended in CH_2Cl_2 (50 mL) and stirred until homogeneous. The precipitate was collected, washed with CH_2Cl_2 and then dried to give **9** as a light yellowish solid. The solvent was concentrated to give an additional small crop of **9**.

Ethyl 2-(5-Methoxy-1*H*-indol-3-ylmethyl)-1*H*-indol-3-yl]-2-oxoacetate (9b): An analytical sample was crystallized from MeCN. Yellow crystals, M.p. 193.5−194.5 °C. IR (KBr) = 3382, 3229, 1732, 1563, 1457, 1267, 1168, 1025, 756 cm^{-1}. ^{1}H NMR (300.1 MHz; [D_6]DMSO): δ = 12.21 (s, 1 H), 10.83 (s, 1 H), 7.78−7.75 (m, 1 H), 7.46−7.43 (m, 1 H), 7.28−7.18 (m, 3 H), 7.16 (d, *J* = 2.3 Hz, 1 H), 7.00 (d, *J* = 2.3 Hz, 1 H), 6.73 (dd, *J* = 8.8, 2.4 Hz, 1 H), 4.47 (s, 2 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 3.70 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]DMSO): δ = 181.5 (s), 166.1 (s), 153.1 (s), 150.9 (s), 135.4 (s), 131.3 (s), 127.0 (s), 126.1 (s), 124.5 (d), 122.9 (d), 122.4 (d), 119.3 (d), 122.2 (d), 112.1 (d), 111.2 (d), 109.6 (s), 107.6 (s), 100.1 (d), 61.6 (t), 55.2 (q), 23.6 (t), 13.7 (q) ppm. MS (ESI): *m*/*z* = 377 [M + 1]$^+$, 375 [M − 1]$^-$. $C_{22}H_{20}N_2O_4$ (376.4): calcd. C 70.20, H 5.36, N 7.44; found C 70.15, H 5.31, N 7.41.

Ethyl 2-[5-Methoxy-2-(1*H*-indol-3-ylmethyl)-1*H*-indol-3-yl]-2-oxoacetate (9c): An analytical sample was crystallized from MeCN. Yellow crystals, M.p. 191.0−193.5 °C. IR (KBr): $\tilde{\nu}$ = 3370, 3202, 1737, 1596, 1558, 1464, 1183, 1028, 748 cm^{-1}. ^{1}H NMR (500.2 MHz; [D_6]DMSO): δ = 12.00 (s, 1 H), 10.99 (s, 1 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 8.2 Hz, 1 H), 7.34−7.31 (m, 2 H), 7.16 (d, *J* = 1.8 Hz, 1 H), 7.07 (dd, *J* = 7.8, 7.4 Hz, 1 H), 6.95 (dd, *J* = 7.8, 6.9 Hz, 1 H), 6.83 (dd, *J* = 8.7, 2.3 Hz, 1 H), 4.42 (s, 2 H), 4.23 (q, 2 H, 6.8 Hz), 3.76 (s, 3 H), 1.19 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (125.8 MHz; [D_6]DMSO): δ = 181.3 (s), 166.1 (s), 155.7 (s), 150.6 (s), 136.2 (s), 130.1 (s), 127.2 (s), 126.6 (s), 124.0 (d), 121.2 (d), 118.6 (d), 118.0 (d), 112.9 (d), 112.1 (d), 111.5 (d), 109.7 (s), 107.7 (s), 102.2 (d), 61.6 (t), 55.3 (q), 23.6 (t), 13.7 (q) ppm. MS (ESI): *m*/*z* = 377 [M + 1]$^+$, 375 [M − 1]$^-$. $C_{22}H_{20}N_2O_4$ (376.4): calcd. C 70.20, H 5.36, N7.44; found C 70.34, H 5.36, N 7.39.

Ethyl 2-[6-Methoxy-2-(1*H*-indol-3-ylmethyl)-1*H*-indol-3-yl]-2-oxoacetate (9d): An analytical sample was crystallized from EtOAc. Yellow crystals, M.p. 211.0−214.0 °C. IR (KBr): $\tilde{\nu}$ = 3389, 3339, 1726, 1601, 1459, 1267, 1164, 1027 cm^{-1}. ^{1}H NMR (300.1 MHz; [D_6]DMSO): δ = 12.14 (s, 1 H), 10.77 (s, 1 H), 7.79−7.75 (m, 1 H), 7.44−7.40 (m, 1 H), 7.31 (d, *J* = 8.6 Hz, 1 H), 7.23−7.17 (m, 2 H), 7.03 (d, *J* = 2.2 Hz, 1 H), 6.86 (d, *J* = 2.2 Hz, 1 H), 6.62 (dd, *J* = 8.6, 2.3 Hz, 1 H), 4.42 (s, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 3.74 (s, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]DMSO): δ = 182.4 (s), 166.9 (s), 156.5 (s), 151.7 (s), 137.8 (s), 136.2 (s), 127.1 (s), 123.8 (d), 123.5 (d), 123.3 (d), 122.0 (s), 120.3 (d), 119.6 (d), 113.1 (d), 110.6 (s), 109.7 (d), 108.5 (s), 95.5 (d), 62.5 (t), 56.0 (q), 24.5 (t), 14.6 (q) ppm. MS (ESI): *m*/*z* = 375 [M − 1]$^-$,377 [M + 1]$^+$. $C_{22}H_{20}N_2O_4$ (376.4): calcd. C 70.20, H 5.36, N7.44; found C 70.17, H 5.40, N 7.48.

Ethyl 2-[5-Methoxy-2-(5-methoxy-1*H*-indol-3-ylmethyl)-1*H*-indol-3-yl]-2-oxoacetate (9e): An analytical sample was crystallized from EtOAc/MeCN as yellow crystals. M.p. 209−211 °C. IR (KBr) =

3372, 3198, 1734, 1625, 1591, 1557, 1472, 1375, 1278, 1217, 1029, 799 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]DMSO): δ = 12.04 (s, 1 H), 10.81 (s, 1 H), 7.33 (d, *J* = 8.8 Hz, 1 H), 7.29 (d, *J* = 2.3 Hz, 1 H), 7.25 (d, *J* = 8.8 Hz, 1 H), 7.12 (d, *J* = 2.3 Hz, 1 H), 6.96 (d, *J* = 2.3 Hz, 1 H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.72 (dd, *J* = 8.7, 2.3 Hz, 1 H), 4.39 (s, 2 H), 4.25 (q, *J* = 7.0 Hz, 2 H), 3.76 (s, 3 H), 3.69 (s, 3 H), 1.20 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 181.3 (s), 166.1 (s), 155.7 (s), 153.1 (s), 150.7 (s), 131.3 (s), 130.1 (s), 127.2 (s), 127.0 (s), 124.5 (d), 112.9 (d), 112.1 (d), 112.0 (d), 111.2 (d), 109.6 (s), 107.6 (s), 102.1 (d), 100.0 (d), 61.6 (t), 55.3 (q), 55.2 (q), 23.6 (t), 13.7 (q) ppm. MS (ESI): *m*/*z* = 405 [M − 1]$^-$, 407 [M + 1]$^+$. $C_{23}H_{22}N_2O_5$ (406.4): calcd. C 67.97, H 5.46, N 6.89; found C 67.96, H 5.40, N 6.79.

Ethyl 2-[5-Methoxy-2-(7-methoxy-1*H*-indol-3-ylmethyl)-1*H*-indol-3-yl]-2-oxoacetate (9f): Yellow crystals from MeCN. M.p. 143 °C (dec.). IR (neat): ṽ = 3312, 3190, 1714, 1578, 1460, 1260, 1212, 1024 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]acetone): δ = 11.14 (s, 1 H), 9.98 (s, 1 H), 7.49 (d, *J* = 8.1 Hz, 1 H), 7.28 (d, *J* = 8.8 Hz, 1 H), 7.17 (d, *J* = 2.1 Hz, 1 H), 7.15−7.10 (m, 2 H), 6.78−6.73 (m, 2 H), 4.59 (s, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 3.87 (s, 3 H), 3.75 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 181.2 (s), 166.1 (s), 155.7 (s), 150.7 (s), 146.2 (s), 130.1 (s), 128.2 (s), 127.2 (s), 126.3 (s), 123.6 (d), 119.2 (d), 113.0 (d), 112.1 (d), 110.9 (d), 110.1 (s), 107.6 (s), 102.1 (d), 101.7 (d), 61.6 (t), 55.3 (q), 55.1 (q), 23.7 (t), 13.7 (q) ppm. MS (ESI): *m*/*z* = 405 [M − 1]$^-$, 407 [M + 1]$^+$. HRMS (FAB) calcd. for $C_{23}H_{22}N_2O_5$ 406.1529 [M]$^+$, found 406.1533.

Ethyl 2-[7-Methoxy-2-(5-methoxy-1*H*-indol-3-ylmethyl)-1*H*-indol-3-yl]-2-oxoacetate (9g): Yellow crystals from MeCN. M.p. 157.0−159.0 °C. IR (KBr): ṽ = 3356, 1719, 1619, 1579, 1458 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]acetone): δ = 11.11 (br. s, 1 H), 9.97 (br. s, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 7.17−7.10 (m, 3 H), 6.78−6.73 (m, 2 H), 4.59 (s, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 3.87 (s, 3 H), 3.75 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]acetone): δ = 182.2 (s), 166.7 (s), 154.4 (s), 150.0 (s), 146.6 (s), 132.2 (s), 128.7 (s), 128.0 (s), 125.9 (s), 124.8 (d), 123.5 (d), 112.9 (d), 112.4 (d), 112.2 (d), 111.3 (s), 109.6 (s), 104.0 (d), 100.6 (d), 61.7 (t), 55.3 (2 × q), 24.0 (t), 13.7 (q) ppm. MS (ESI): *m*/*z* = 407 [M − 1]$^-$, 405 [M + 1]$^+$. HRMS (FAB) calcd. for $C_{23}H_{22}N_2O_5$ 406.1529 [M]$^+$, found 406.1530.

Procedure for the Preparation of 11a−g: $MeSO_3H$ (2.0 mL) was added dropwise to a solution of **9** (4.0 mmol) in 1,4-dioxane (100 mL) at 21 °C under nitrogen. The mixture was heated at reflux for 1 hfollowed by cooling to 21 °C and addition of silica (10 g). The solvents were evaporated and the remaining solid purified with column chromatography on silica eluting with $CHCl_3$/hexane (gradient 0−100%) yielding the indolocarbazoles **11** as yellow solids.

Ethyl Indolo[3,2-*b*]carbazole-6-carboxylate (11a): (92%) Identical in all respects with a reference that was prepared in a yield of 88%.[5]

Ethyl 2-Methoxyindolo[3,2-*b*]carbazole-6-carboxylate (11b): Yellow solid. (90%) This substance starts to decompose around 70 °C and finally melts between 159.5−160.5 °C. IR (KBr): ṽ = 3410, 1675, 1488, 1298, 1202, 1153 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.51 (s, 1 H), 10.78 (s, 1 H), 8.76 (d, *J* = 8.2 Hz, 1 H), 8.51 (s, 1 H), 7.88 (d, *J* = 2.4 Hz, 1 H), 7.61 (d, *J* = 8.7 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.45 (dd, *J* = 7.8, 7.2 Hz, 1 H), 7.16 (dd, *J* = 7.7, 7.6 Hz, 1 H), 7.10 (dd, *J* = 8.7, 2.5 Hz, 1 H), 4.69 (q, *J* = 7.1 Hz, 2 H), 3.90 (s, 3 H), 1.53 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 167.2 (s), 153.1 (s), 141.7 (d), 136.4 (s), 135.9 (s), 134.8 (s), 126.1 (s), 124.9 (d), 123.4 (s), 122.0 (s), 121.3 (s), 120.2 (s), 117.6 (d), 115.4 (d), 112.2 (d), 110.7 (d), 106.9 (d), 105.0 (s), 103.3 (d), 60.8 (t), 55.6 (q), 14.5 (q) ppm. MS (ESI): *m*/*z* = 359 [M + 1]$^+$, 357 [M − 1]$^-$. $C_{22}H_{18}N_2O_3$ (358.4): calcd. C 73.73, H 5.06, N 7.82; found C 73.81, H 4.95, N 7.76.

Ethyl 8-Methoxyindolo[3,2-*b*]carbazole-6-carboxylate (11c): Yellow solid. (77%) This substance starts to decompose at 169.5 °C and finally melts at 187.0 °C. IR (KBr): ṽ = 3465, 3406, 1712, 1461, 1303, 1215, 1171, 1143 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.31 (s, 1 H), 10.91 (s, 1 H), 8.44 (s, 1 H), 8.27−8.24 (m, 2 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.47−7.41 (m, 2 H), 7.19 (dd, *J* = 7.5, 7.4 Hz, 1 H), 7.12 (dd, *J* = 8.8, 2.5 Hz, 1 H), 4.70 (q, *J* = 7.1 Hz, 2 H), 3.86 (s, 3 H), 1.53 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 167.2 (s), 151.9 (s), 141.2 (s), 136.7 (s), 135.9 (s), 135.6 (s), 126.2 (d), 123.3 (s), 121.6 (s), 121.4 (s), 120.3 (d), 119.8 (s), 118.5 (d), 115.7 (d), 111.4 (d), 111.2 (d), 107.5 (d), 106.9 (d), 104.8 (s), 60.8 (t), 55.6 (q), 14.5 (q) ppm. MS (ESI): *m*/*z* = 357 [M − 1]$^-$, 359 [M + 1]$^+$. HRMS (FAB) calcd. for $C_{22}H_{18}N_2O_3$ 358.1317 [M]$^+$, found 358.1319.

Ethyl 3-Methoxyindolo[3,2-*b*]carbazole-6-carboxylate (11d): Yellow solid. M.p. 225−227 °C. IR (KBr): ṽ = 3459, 3400, 1717, 1619, 1514, 1308, 1247, 1205, 1155, 818, 745 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.45 (s, 1 H), 10.83 (s, 1 H), 8.71 (d, *J* = 8.2 Hz, 1 H), 8.35 (s, 1 H), 8.13 (d, *J* = 8.5 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 7.41 (dd, *J* = 7.7, 7.2 Hz, 1 H), 7.23 (d, *J* = 1.9 Hz, 1 H), 7.13 (dd, *J* = 7.6, 7.3 Hz, 1 H), 6.81 (dd, *J* = 8.5, 2.0 Hz, 1 H), 4.68 (q, *J* = 7.1 Hz, 2 H), 3.87 (s, 3 H), 1.52 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 167.2 (s), 159.0 (s), 142.6 (s), 141.3 (s), 135.8 (s), 135.3 (s), 125.7 (d), 124.(d), 123.6 (s), 121.4 (s), 121.1 (d), 118.7 (s), 117.6 (d), 115.3 (s), 110.6 (d), 107.6 (d), 105.8 (d), 105.0 (s), 95.3 (d), 60.8 (t), 55.2 (q), 14.5 (q). MS (ESI): *m*/*z* = 357 [M − 1]$^-$. $C_{22}H_{18}N_2O_3$ (358.4): calcd. C 73.73, H 5.06, N 7.82; found C 73.61, H 4.98, N 7.75.

Ethyl 2,8-Dimethoxyindolo[3,2-*b*]carbazole-6-carboxylate (11e): Yellow solid. M.p. 70−75 °C dec. IR (KBr): ṽ = 3464, 3294, 1681, 1485, 1294, 1215, 1197, 1158, 803 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]acetone): δ = 10.36 (s, 1 H), 10.34 (s, 1 H), 8.54 (d, *J* = 2.5 Hz, 1 H), 8.47 (s, 1 H), 7.77 (d, *J* = 2.5 Hz, 1 H), 7.56 (d, *J* = 8.7 Hz, 1 H), 7.46 (d, *J* = 8.8 Hz, 1 H), 7.14−7.07 (m, 2 H), 4.73 (q, *J* = 7.1 Hz, 2 H), 3.91 (s, 3 H), 3.91 (s, 3 H), 1.58 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]acetone): δ = 168.5 (s), 154.8 (s), 153.7 (s), 138.6 (s), 138.2 (s), 137.3 (s), 137.1 (s), 124.9 (s), 123.7 (s), 123.4 (s), 122.1 (s), 116.9 (d), 116.4 (d), 112.8 (d), 111.9 (d), 109.5 (d), 108.0 (d), 106.0 (d), 104.1 (s), 61.6 (t), 56.3 (q), 56.2 (q), 15.2 (q) ppm. MS (ESI): *m*/*z* = 387 [M − 1] $^-$. $C_{23}H_{20}N_2O_4$ (388.4): calcd. C 71.12, H 5.19, N 7.21; found C 71.08, H 5.25, N 7.16.

Ethyl 4,8-Dimethoxyindolo[3,2-*b*]carbazole-6-carboxylate (11f): Eluent 0−50% $CHCl_3$/hexane. Yellow solid. M.p. 176.0−177.5 °C. IR (KBr): ṽ = 3484, 3404, 1709, 1676, 1514, 1293, 1257, 1214, 1144, 798 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]acetone): δ = 10.40 (br. s, 1 H), 9.97 (br. s, 1 H), 8.55 (br. s, 1 H), 8.44 (s, 1 H), 7.78 (d, *J* = 7.7 Hz, 1 H), 7.47 (d, *J* = 8.8 Hz, 1 H), 7.18−7.03 (m, 3 H), 4.76 (q, *J* = 7.0 Hz, 2 H), 4.06 (s, 3 H), 3.93 (s, 3 H), 1.62 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]acetone): δ = 168.7 (s), 153.8 (s), 146.6 (s), 138.2 (s), 137.7 (s), 137.6 (s), 131.7 (s), 124.9 (s), 124.3 (s), 123.3 (s), 122.0 (s), 120.7 (d), 117.1 (d), 113.7 (d), 112.0 (d), 109.4 (d), 108.4 (d), 107.9 (d), 106.1 (s), 61.9 (t), 56.3 (q), 56.1 (q), 15.1 (q) ppm. MS (ESI): *m*/*z* = 387 [M − 1]$^-$, 389 [M + 1]$^+$. $C_{23}H_{20}N_2O_4$ (388.4): calcd. C 71.12, H 5.19, N 7.21; found C 71.03, H 5.14, N 7.16.

Ethyl 2,10-Dimethoxyindolo[3,2-*b*]carbazole-6-carboxylate (11g): Yellow solid. M.p. 170.5−172.5 °C. IR (KBr): ṽ = 3456, 3347,

1714, 1487, 1255, 1205, 1148 cm^{-1}. ^1H NMR (300.1 MHz; [D_6]acetone): δ = 10.55 (s, 1 H), 10.37 (s, 1 H), 8.56 (s, 1 H), 8.52 (d, *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 2.3 Hz, 1 H), 7.57 (d, *J* = 8.8 Hz, 1 H), 7.12−7.00 (m, 3 H), 4.70 (q, *J* = 7.1 Hz, 2 H), 3.19 (s, 3 H), 3.92 (s, 3 H), 1.57 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]acetone): δ = 168.5 (s), 154.9 (s), 146.6 (s), 138.8 (s), 137.1 (s), 136.4 (s), 133.5 (s), 124.8 (s), 124.1 (s), 123.7 (s), 122.5 (s), 119.3 (d), 119.0 (d), 116.4 (d), 112.8 (d), 108.4 (d), 107.1 (d), 106.0 (s), 104.0 (d), 61.1 (t), 56.2 (q), 56.0 (q), 15.0 (q) ppm. MS (ESI): *m*/*z* = 387 $[M - 1]^-$, 389 $[M + 1]^+$. $C_{23}H_{20}N_2O_4$ (388.4): calcd. C 71.12, H 5.19, N 7.21; found C 71.04, H 5.15, N 7.16.

Representative Procedure for the Preparation of 4a, 10b and 10c: Ethyl Indolo[3,2-*b*]carbazole-6-carboxylate (**11a**) (343 mg, 1.00 mmol) dissolved in THF (12 mL) was added dropwise to a suspension of $LiAlH_4$ (228 mg, 6.00 mmol) in THF (40 mL) below −10 °C under argon. The reddish suspension was then stirred for 1 h at −10 °C, and then at 0 °C for 3.5 h. The cooling bath was removed and a saturated aqueous solution of NH_4Cl was added to quench the excess $LiAlH_4$. EtOAc (200 mL) and water (100 mL) were then added to the suspension. The organic phases were separated and the water phase extracted with EtOAc (2 × 100 mL). The combined organic phases were then washed with brine (2 × 100 mL) and finally dried with $MgSO_4$. Evaporation of the solvents produced a yellow solid (290 mg) which was dissolved by gentle heating in 1,4-dioxane (60 mL) under argon. A solution of DDQ (227 mg, 1.00 mmol) in dioxane (3 mL) was added over 10 min. The resulting suspension was stirred for 48 h to ensure complete dehydrogenation. EtOAc (300 mL) and a saturated aqueous solution of $NaHCO_3$ (100 mL) were added and the mixture stirred for 1 h. The precipitate formed was collected and washed with an excess of water and EtOAc. The yellow solid was dried at 240 °C and 0.12 mbar to give 77 mg of **4a**. The organic solvents from the washings were separated and the aqueous phase extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL) and dried with $MgSO_4$. Evaporation of the solvents produced a further 163 mg of **4a**.

Indolo[3,2-*b*]carbazole-6-carboxaldehyde (4a): Spectral and physical data were identical with a reference sample.[5]

8-Methoxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (10b): The aldehyde **10b** was prepared from **11c** in a similar manner to that for **4a**. Yellow solid, M.p. 341.0−345.5 °C. IR (KBr): $\tilde{\nu}$ = 3462, 3383, 3351, 1659, 1484, 1458, 1213, 1088, 810, 752 cm^{-1}. ^1H NMR (500.2 MHz; [D_6]DMSO): δ = 11.73 (s, 1 H), 11.43 (s, 1 H), 11.33 (s, 1 H), 8.57 (s, 1 H), 8.28 (d, *J* = 7.3 Hz, 1 H), 8.02 (d, *J* = 2.3 Hz, 1 H), 7.73 (d, *J* = 7.8 Hz, 1 H), 7.52 (d, *J* = 8.7 Hz, 1 H), 7.44 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.23 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.16 (dd, *J* = 8.7, 2.3 Hz, 1 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (125.8 MHz; [D_6]DMSO): δ = 190.0 (d), 152.9 (s), 141.6 (s), 136.7 (s), 135.4 (s), 126.2 (d), 123.3 (s), 121.4 (s), 121.3 (s), 121.0 (s), 120.3 (d), 119.2 (d), 116.6 (d), 112.2 (d), 112.0 (s), 112.0 (d), 110.1 (d), 106.6 (d), 55.7 (q) ppm (one carbon resonance not observed). MS (FIA): *m*/*z* = 315 $[M + H]^+$. $C_{20}H_{14}N_2O_2$ (314.3): calcd. C 76.42, H 4.49, N 8.91; found C 76.34, H 4.44, N 8.85.

3-Methoxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (10c): The aldehyde **10c** was prepared from **11d** in a similar manor as for **4a**. Yellow solid. This sample gradually becomes darker and finally melts between 374.0−379.0 °C. IR (KBr): $\tilde{\nu}$ = 3377, 1654, 1617, 1310, 1243, 745 cm^{-1}. ^1H NMR (300.1 MHz; [D_6]DMSO): δ = 11.61 (s, 1 H), 11.56 (s, 1 H), 11.33 (s, 1 H), 8.52 (d, *J* = 8.1 Hz, 1 H), 8.46 (s, 1 H), 8.54 (d, *J* = 8.5 Hz, 1 H), 7.58 (d, *J* = 8.1 Hz, 1 H), 7.46 (dd, *J* = 7.6, 7.3 Hz, 1 H), 7.30 (d, *J* = 2.1 Hz, 1 H), 7.18 (dd, *J* = 7.3, 7.2 Hz, 1 H), 6.85 (dd, *J* = 8.5, 2.2 Hz, 1 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]DMSO): δ = 190.1 (d), 159.0 (s), 143.1 (s), 141.3 (s), 135.5 (s), 134.8 (s), 126.0 (d), 124.3 (d), 123.6 (s), 121.2 (d), 121.1 (s), 120.2 (s), 118.7 (d), 115.0 (s), 112.2 (s), 111.3 (d), 108.9 (d), 108.0 (d), 96.0 (d), 55,3 (q) ppm. MS (FIA): *m*/*z* = 313 $[M - H]^-$. HRMS (FAB) calcd. for $C_{20}H_{14}N_2O_2$ 314.1055 $[M]^+$, found 314.1051.

Representative Procedure for the Preparation of 10a, 10d and 10f: Ethyl 2-methoxyindolo[3,2-*b*]carbazole-6-carboxylate (**11b**) (1.08 g, 3.00 mmol) dissolved in THF (40 mL) was added dropwise to a suspension of $LiAlH_4$ (1.37 g, 36.00 mmol) in THF (50 mL) below −10 °C under argon. The reddish suspension was then stirred for 1 h at −10 °C, and then at 0 °C for 3.5 h. The cooling bath was removed and a saturated aqueous solution of NH_4Cl was added to quench the excess $LiAlH_4$. The suspension was diluted with EtOAc (200 mL) and water (100 mL) and then the organic phases were separated. The water phase was extracted with EtOAc (2 × 100 mL) and the combined organic phases were washed with brine (2 × 100 mL) and finally dried with $MgSO_4$. Evaporation of the solvents produced a yellow solid that was dissolved by gentle heating in 1,4-dioxane (100 mL). DDQ (0.68 g, 3.00 mmol) dissolved in 1,4-dioxane (6 mL) was added dropwise during 15 minutes under argon at 40 °C. After 15 h at 21 °C, 1 M NaOH (100 mL) and EtOAc (300 mL) were added. The organic phases were separated and the aqueous phase extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with water (100 mL), then brine (2 × 100 mL) and dried with $MgSO_4$. The solvents were evaporated onto silica (5 g) and the residue subjected to gravity column chromatography (silica) with EtOAc as eluent to give indolocarbazole **10a** (0.82 g, 87%) as an orange solid.

2-Methoxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (10a): Orange solid. M.p. 282.5−284.0 °C. IR (KBr): $\tilde{\nu}$ = 3391, 3375, 1657, 1487, 1463, 1215, 1086, 1031 cm^{-1}. ^1H NMR (300.1 MHz; [D_6]DMSO): δ = 11.61 (s, 1 H), 11.56 (s, 1 H), 11.34 (s, 1 H), 8.60 (s, 1 H), 8.54 (d, *J* = 8.1 Hz, 1 H), 7.89 (d, *J* = 1.9 Hz, 1 H), 7.64 (d, *J* = 8.7 Hz, 1 H), 7.59 (d, *J* = 8.2 Hz, 1 H), 7.48 (dd, *J* = 7.7, 7.3 Hz, 1 H), 7.19 (dd, *J* = 7.6, 7.4 Hz, 1 H), 7.08 (dd, *J* = 8.7, 2.2 Hz, 1 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]DMSO): δ = 189.8 (d), 153.5 (s), 141.6 (s), 136.3 (s), 135.9 (s), 134.4 (s), 126.4 (d), 124.5 (d), 123.5 (s), 121.7 (s), 120.9 (s), 118.8 (d), 115.3 (d), 112.7 (d), 112.2 (s), 111.4 (d), 110.1 (d), 103.4 (d), 55.6 (q) ppm (one carbon resonance not observed). MS (ESI): *m*/*z* = 313 $[M - H]^-$. $C_{20}H_{14}N_2O_2$ (314.3): calcd. C 76.42, H 4.49, N 8.91; found C 76.52, H 4.37, N 8.92.

2,8-Dimethoxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (10d): The aldehyde **10d** was prepared from **11e** using the same procedure as for **10a**. Orange-reddish solid. M.p. 312.0 °C (dec.). IR (neat): $\tilde{\nu}$ = 3388, 3355, 2992, 2834, 1654, 1620, 1484, 1296, 2307, 1082, 1027, 812, 797 cm^{-1}. ^1H NMR (500.2 MHz; [D_6]DMSO): δ = 11.56 (s, 1 H), 11.42 (s, 1 H), 11.31 (s, 1 H), 8.57 (s, 1 H), 7.99 (d, *J* = 2.3 Hz, 1 H), 7.87 (d, *J* = 2.2 Hz, 1 H), 7.63 (d, *J* = 8.7 Hz, 1 H), 7.51 (d, *J* = 8.7 Hz, 1 H), 7.15 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.07 (dd, *J* = 8.7, 2.2 Hz, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (125.8 MHz; [D_6]DMSO): δ = 189.8 (d), 153.5 (s), 152.9 (s), 136.8 (s), 136.3 (s), 136.0 (s), 135.1 (s), 123.4 (s), 121.8 (s), 121.5 (s), 121.0 (s), 116.6 (d), 115.3 (d), 112.7 (d), 112.2 (d), 111.9 (s), 110.3 (d), 106.5 (d), 103.4 (d), 55.7 (q), 55.6 (q) ppm. MS (ESI): *m*/*z* = 345 $[M + 1]^+$, 343 $[M - 1]^-$. $C_{21}H_{16}N_2O_3$ (344.4): calcd. C 73.24, H 4.68, N 8.13; found C 73.20, H 4.61, N 8.15.

2,10-Dimethoxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (10f): The aldehyde **10f** was prepared from **11g** using the same procedure as

for **10a**. Red solid. M.p. 295.0−296.0 °C. IR (KBr): $\tilde{\nu}$ = 3429, 3206, 2993, 2832, 1646, 1617, 1595, 1559, 1486, 1249, 1217, 1070 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.73 (s, 1 H), 11.57 (s, 1 H), 11.31 (s, 1 H), 8.55 (s, 1 H), 8.09 (d, *J* = 7.8 Hz, 1 H), 7.85 (d, *J* = 2.3 Hz, 1 H), 7.64 (d, *J* = 8.8 Hz, 1 H), 7.16−7.05 (m, 3 H), 4.04 (s, 3 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 189.8 (d), 153.5 (s), 145.8 (s), 136.3 (s), 135.9 (s), 134.3 (s), 131.9 (s), 123.4 (s), 122.1 (s), 121.7 (s), 119.3 (d), 116.8 (d), 115.4 (d), 112.8 (d), 111.9 (s), 110.6 (d), 106.5 (d), 103.2 (d), 55.6 (q), 55.4 (q) ppm (one carbon resonance not observed). MS (ESI): *m*/*z* = 345 $[M + 1]^+$. HRMS (FAB) calcd. for $C_{21}H_{16}N_2O_3$ 344.1161 $[M]^+$, found 344.1166.

4,8-Dimethoxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (10e): Ethyl 4,8-Dimethoxyindolo[3,2-*b*]carbazole-6-carboxylate (**11f**) (405 mg, 1.04 mmol) dissolved in THF (10 mL) was added during 10 minutes to a suspension of $LiAlH_4$ (490 mg, 12.51 mmol) in THF (40 mL) at −10 °C under nitrogen, and then stirred for an additional period of 4 h. The temperature was then raised to 21 °C over 2 h. The cooling bath was then removed and a saturated aqueous solution of NH_4Cl (2 mL) was carefully added. EtOAc (200 mL) and water (100 mL) were added and the organic phases were separated. The water phase was extracted with EtOAc (2 × 75 mL). The combined organic phases were washed with brine (2 × 100 mL) and then dried with $MgSO_4$ and then evaporated to give a yellow solid. This solid was dissolved in 1,4-dioxane (40 mL) under nitrogen and warmed to 40 °C. DDQ (236 mg, 1.04 mmol) dissolved in 1,4-dioxane (4 mL) was added over 15 minutes and the reaction mixture stirred for 14 h at 21 °C. EtOAc (300 mL) and a saturated aqueous solution of $NaHCO_3$ (150 mL) were added. The organic phase was separated, and the aqueous phase extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with water (2 × 100 mL) and brine (2 × 100 mL) and then dried with $MgSO_4$. As the solvents were reduced in volume, a red solid precipitated. The solid was collected and washed with EtOAc and then dried to give 130 mg of **10f**. Another crop gave an additional 96 mg of **10f**. Silica (3 g) was added to the filtrate and the solvents were removed. Column chromatography (silica) with EtOAc as eluent produced a further 55 mg of the yellow-reddish indolocarbazole **10f**. The total yield of **10f** was 281 mg (78%). M.p. 292.5−296.5 °C. IR (KBr): $\tilde{\nu}$ = 3435, 3409, 2923, 2852, 1655, 1605, 1487, 1259, 1211, 1073, 802 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.45 (s, 1 H), 11.30 (s, 1 H), 10.95 (s, 1 H), 8.56 (s, 1 H), 8.23 (d, *J* = 2.4 Hz, 1 H), 7.90 (d, *J* = 7.7 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 1 H), 7.24−7.10 (m, 3 H), 4.04 (s, 3 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 190.9 (d), 152.7 (s), 145.3 (s), 136.9 (s), 136.4 (s), 135.8 (s), 130.5 (s), 123.5 (s), 122.7 (s), 121.1 (s), 120.9 (s), 120.3 (d), 116.8 (d), 113.1 (d), 112.2 (s), 112.0 (d), 110.3 (d), 107.5 (d), 106.9 (d), 55.7 (q), 55.6 (q) ppm. MS (ESI): *m*/*z* = 343 $[M - 1]^-$. HRMS (FAB) calcd. for $C_{21}H_{16}N_2O_3$ 344.1161 $[M]^+$, found 344.1164.

Representative Procedure for the Preparation of the Silylated Indolocarbazoles 12a, 12c−f: BBr_3 (1 M in CH_2Cl_2, 3.66 mL, 10 equiv.) was added during 25 minutes to a suspension of 2-methoxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (**10a**) (115 mg, 0.36 mmol) in CH_2Cl_2 (50 mL) at −78 °C under argon. After addition was complete, the temperature was slowly raised to 21 °C and the mixture stirred for 12 h. The suspension was then cooled to 0 °C and a saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the resulting slurry stirred 1 h. The bulk of the dichloromethane was evaporated and the precipitate dissolved in EtOAc (100 mL) and water (50 mL). The organic layer was separated and the aqueous phase extracted with EtOAc (100 mL). The combined organic phases were washed with brine (50 mL) and dried with $MgSO_4$ and the solvents evaporated to produce the crude indolocarbazole **12a** as a yellow solid. This solid was dissolved in DMF (10 mL) under argon. Imidazole (249 mg, 3.66 mmol) and *tert*-butyldimethylsilyl chloride (551 mg, 3.66 mmol) were added and the solution stirred until the starting material disappeared (90 min) as judged from TLC. EtOAc (100 mL) and water (50 mL) were added and the organic phase separated. The aqueous phase was extracted with EtOAc (100 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL) and then dried with $MgSO_4$. Evaporation produced a semisolid that was subjected to column chromatography with EtOAc/hexane (0−20%) as eluent. The silylated indolocarbazole **12a** was obtained in 110 mg (72%) as an orange-reddish solid.

2-(*tert*-Butyldimethylsilyloxy)indolo[3,2-*b*]carbazole-6-carboxaldehyde (12a): Orange solid. M.p. 296.5−298.5 °C. IR (KBr): $\tilde{\nu}$ = 3433, 3234, 2955, 2929, 2857, 1649, 1618, 1597, 1464, 1264, 1085, 900 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.57 (s, 1 H), 11.56 (s, 1 H), 11.33 (s, 1 H), 8.60 (s, 1 H), 8.54 (d, *J* = 8.1 Hz, 1 H), 7.75 (d, *J* = 2.3 Hz, 1 H), 7.62−7.58 (m, 2 H), 7.48 (dd, *J* = 7.5, 7.3 Hz, 1 H), 7.19 (dd, *J* = 7.2, 7.1 Hz, 1 H), 6.98 (dd, *J* = 8.6, 2.3 Hz, 1 H), 1.02 (s, 9 H), 0.25 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 189.8 (d), 148.4 (s), 141.6 (s), 136.7 (s), 136.0 (s), 134.4 (s), 126.4 (d), 124.5 (d), 123.3 (s), 122.0 (s), 121.8 (s), 120.9 (s), 119.4 (d), 118.8 (d), 112.5 (d), 112.1 (s), 111.4 (d), 110.4 (d), 110.3 (d), 25.7 (q), 18.0 (q), −4.4 (q) ppm. MS (ESI): *m*/*z* = 415 $[M + 1]^+$, 413 $[M - 1]^-$. $C_{25}H_{26}N_2O_2Si$ (414.6): calcd. C 72.43, H 6.32, N 6.76; found C 72.28, H 6.30, N 6.67.

3-(*tert*-Butyldimethylsilyloxy)indolo[3,2-*b*]carbazole-6-carboxaldehyde (12c): The silylated ICZ **12c** was prepared from **10c** using the same procedure as for **12a**. Orange solid. M.p. 318.5−323.0 °C. IR (KBr): $\tilde{\nu}$ = 3424, 3387, 2954, 2928, 2857, 1650, 1622, 1248, 1152, 859 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.58 (s, 1 H), 11.56 (s, 1 H), 11.33 (s, 1 H), 8.51 (d, *J* = 8.1 Hz, 1 H), 8.46 (s, 1 H), 8.12 (d, *J* = 8.4 Hz, 1 H), 7.58 (d, *J* = 8.1 Hz, 1 H), 7.46 (dd, *J* = 8.0, 7.2 Hz, 1 H), 7.27 (d, *J* = 2.1 Hz, 1 H), 7.19 (dd, *J* = 7.9, 7.2 Hz, 1 H), 6.75 (dd, *J* = 8.4, 2.1 Hz, 1 H), 1.00 (s, 9 H), 0.26 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 190.0 (d), 154.5 (s), 143.0 (s), 141.3 (s), 135.5 (s), 134.8 (s), 126.1 (d), 124.3 (d), 123.5 (s), 121.1 (d), 121.0 (s), 120.5 (s), 118.8 (d), 115.7 (s), 112.7 (d), 112.2 (s), 111.4 (d), 109.0 (d), 102.7 (d), 25.6 (q), 18.0 (q), −4.4 (q) ppm. $C_{25}H_{26}N_2O_2Si$ (414.6): calcd. C 72.43, H 6.32, N 6.76; found C 72.29, H 6.26, N 6.67.

2,8-Bis(*tert*-butyldimethylsilyloxy)indolo[3,2-*b*]carbazole-6-carboxaldehyde (12d): The silylated ICZ **12d** was prepared from **10d** using the same procedure as for **12a**. Red solid. M.p. 268 °C (dec.). IR (neat): $\tilde{\nu}$ = 3430, 2954, 2928, 2856, 1647, 1595, 1471, 1259, 1191, 1079, 891, 778 cm^{-1}. ^1H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.57 (s, 1 H), 11.38 (s, 1 H), 11.20 (s, 1 H), 8.47 (s, 1 H), 7.99 (d, *J* = 2.1 Hz, 1 H), 7.74 (d, *J* = 2.3 Hz, 1 H), 7.58 (d, *J* = 8.6 Hz, 1 H), 7.47 (d, *J* = 8.7 Hz, 1 H), 7.05 (dd, *J* = 8.7, 2.2 Hz, 1 H), 6.98 (dd, *J* = 8.6, 2.3 Hz, 1 H), 1.02 (s, 9 H), 1.01 (s, 9 H), 0.25 (s, 6 H), 0.24 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 189.3 (d) 148.4 (s), 147.7 (s), 137.2 (s), 136.8 (s), 136.5 (s), 135.2 (s), 123.4 (s), 122.1 (s), 121.3 (s), 121.1 (s), 120.2 (d), 119.4 (d), 114.0 (d), 112.4 (d), 112.0 (s), 111.9 (d), 110.5 (s), 110.4 (d), 25.7 (q), 25.7 (q), 18.0 (s), 18.0 (s), −4.4 (2 × q) ppm. MS (ESI): *m*/*z* = 545 $[M + 1]^+$, 543 $[M - 1]^-$. HRMS (FAB) calcd. for $C_{31}H_{40}N_2O_3Si_2$ $[M]^+$ 544.2577, found 544.2592.

4,8-Bis(*tert*-butyldimethylsilyloxy)indolo[3,2-*b*]carbazole-6-carboxaldehyde (12e): The silylated ICZ **12e** was prepared from **10e**

using the same procedure as for **12a**. Orange solid. M.p. 209.0−211.5 °C. IR (neat): $\tilde{\nu}$ = 3420, 3387, 2952, 2928, 2856, 1653, 1604, 1476, 1266, 1205, 893, 836, 777 cm^{-1}. ^1H NMR (300.1 MHz; [D_6]acetone): δ = 11.38 (s, 1 H), 10.63 (br. s, 1 H), 10.56 (br. s, 1 H), 8.56 (s, 1 H), 7.95 (d, *J* = 2.3 Hz, 1 H), 7.87 (d, *J* = 7.8 Hz, 1 H), 7.54 (d, *J* = 8.7 Hz, 1 H), 7.19−7.12 (m, 2 H), 7.04 (dd, *J* = 7.7, 0.8 Hz, 1 H), 1.18 (s, 9 H), 1.08 (s, 9 H), 0.37 (s, 6 H), 0.31 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]acetone): δ = 191.0 (d), 149.9 (s), 142.0 (s, 1 H), 138.6 (s), 137.3 (s), 136.5 (s), 134.6 (s), 125.1 (s), 124.8 (s), 123.3 (s), 122.8 (s), 121.7 (d), 121.4 (d), 116.7 (d), 114.9 (d), 114.8 (d), 113.5 (s), 113.0 (d), 111.1 (d), 26.3 (2 × q), 19.0 (s), 18.9 (s), −4.0 (q), −4.1 (q) ppm. MS (ESI): *m*/*z* = 543 [M − 1]$^-$, 545 [M + 1]$^+$. HRMS (FAB) calcd. for $C_{31}H_{40}N_2O_3Si_2$ [M]$^+$ 544.2577, found 544.2570.

2,10-Bis(*tert*-butyldimethylsilyloxy)indolo[3,2-*b*]carbazole-6-carboxaldehyde (12f): The silylated ICZ **12f** was prepared from **10f** using the same procedure as for **12a**. The red solid starts to decompose at 210 °C and finally melts at 245.0 °C. IR (neat): $\tilde{\nu}$ = 3463, 3425, 3375, 2950, 2923, 2850, 1655, 1619, 1461, 1267, 1251, 1100, 891, 827, 778 cm^{-1}. ^1H NMR (300.1 MHz; [D_6]acetone): δ = 11.40 (s, 1 H), 11.05 (br. s, 1 H), 10.28 (br. s, 1 H), 8.57 (s, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 7.70−7.67 (m, 2 H), 7.13 (dd, *J* = 7.9, 7.8 Hz, 1 H), 7.07−7.03 (m, 2 H), 1.11 (s, 9 H), 1.06 (s, 9 H), 0.38 (s, 6 H), 0.28 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]acetone): δ = 190.6 (d), 150.3 (s), 142.7 (s), 138.0 (s), 137.6 (s), 135.8 (s), 135.8 (s), 124.8 (s), 124.4 (s), 124.3 (s), 123.6 (s), 120.8 (d), 120.7 (d), 118.4 (d), 115.7 (d), 113.5 (s), 113.3 (d), 111.3 (d), 111.2 (d), 26.4 (q), 26.3 (q), 19.1 (s), 18.9 (s), −3.8 (q), −4.1 (q) ppm. MS (ESI): *m*/*z* [M + 1]$^+$ 545, [M − 1]$^-$ 543. HRMS (FAB) calcd. for $C_{31}H_{40}N_2O_3Si_2$ 544.2577 [M]$^+$, found 544.2569.

8-(*tert*-Butyldimethylsilyloxy)indolo[3,2-*b*]carbazole-6-carboxaldehyde (12b): BBr_3 (1 M in CH_2Cl_2, 10 mL, 10.00 mmol) was added over 30 minutes to a cooled (−78 °C) suspension of 8-methoxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (**10b**) (314 mg, 1.00 mmol) in CH_2Cl_2 (80 mL). The temperature of the resulting suspension was raised to 21 °C over 26 h, and after that time demethylation was complete as judged by TLC (eluent 75% EtOAc/hexane). A saturated aqueous solution of $NaHCO_3$ (30 mL) was added and the dichloromethane removed under reduced pressure. The precipitate was filtered and washed with excess water and then dried at 60 °C and 0.01 mbar to give a red solid. The solid was suspended in DMF (15 mL) under argon, followed by addition of imidazole (410 mg, 6.00 mmol) and *tert*-butyldimethylsilyl chloride (754 mg, 5.00 mmol). The mixture was stirred for 48 h and then poured into water (200 mL) and extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with water (3 × 50 mL) and brine (50 mL) before drying over $MgSO_4$. Evaporation produced the crude product that was subjected to column chromatography on silica with EtOAc/hexane (0−50%) as eluent. The silylated indolocarbazole **12b** was obtained in 184 mg (44%) as an orange solid. An analytical sample was recrystallized from toluene. M.p. 322.0−326.5 °C. IR (neat): $\tilde{\nu}$ = 3401, 3340, 2954, 2928, 2856, 1661, 1604, 1476, 1458, 1263, 1205, 894, 807, 775, 732 cm^{-1}. ^1H NMR (300.1 MHz; [D_6]DMSO): δ = 11.76 (s, 1 H), 11.46 (s, 1 H), 11.23 (s, 1 H), 8.57 (s, 1 H), 8.28 (d, *J* = 7.6 Hz, 1 H), 8.03 (d, *J* = 2.2 Hz, 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 7.49−7.41 (m, 2 H), 7.23 (dd, *J* = 7.9, 7.1 Hz, 1 H), 7.06 (dd, *J* = 8.7, 2.2 Hz, 1 H), 1.02 (s, 9 H), 0.26 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]DMSO): δ = 189.5 (d), 147.7 (s), 141.6 (s), 137.2 (s), 135.8 (s), 135.5 (s), 126.3 (d), 123.4 (s), 121.4 (s), 121.3 (s), 121.2 (s), 121.0 (s), 120.4 (d), 120.3 (d), 119.2 (d), 114.1 (d), 111.9 (d), 111.9 (d), 110.0 (d), 25.8 (q), 18.0 (s), −4.4 (q) ppm. $C_{25}H_{26}N_2O_2Si$ (414.6): calcd. C 72.43, H 6.32, N 6.76; found C 72.29, H 6.28, N 6.63.

Representative Procedure for the Preparation of the Hydroxylated Indolocarbazoles 5a−e: Tetrabutylammonium fluoride (1 M in THF, 0.37 mL, 0.37 mmol) was added to a solution of 2-(*tert*-butyldimethylsilyloxy)indolo[3,2-*b*]carbazole-6-carboxaldehyde (**12a**) (70 mg, 0.169 mmol) in THF (12 mL) at 0−2 °C under argon. After 10−20 min the reaction was complete as judged by TLC. A buffer solution (pH 7.4, 60 mL) was added and the resulting slurry stirred for 30−60 min. A yellow-brownish solid was collected and washed with excess water before drying at reduced pressure. The dried solid was boiled 3 times in hexane, each time carefully removing the solvents with a pipette. The insoluble indolocarbazole **5a** was obtained in 48 mg (95%) as a yellow-brownish solid.

In the spectroscopic data of the metabolites **5a−b** and **5d−f**, the ^1H NMR spectra ([D_6]acetone) is included for comparison with the previous data.[8] Due to the low solubility of **5a−b** and **5d−f**, ^{13}C NMR spectra in [D_6]acetone could not be recorded.

2-Hydroxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (5a): This orange solid starts to decompose at 341.5 °C and finally melts between 351.0−354.5 °C. IR (KBr): $\tilde{\nu}$ = 3391, 3375, 1657, 1487, 1463, 1215, 1086, 1031 cm^{-1}. ^1H NMR (500.2 MHz; [D_6]acetone, 294 K): δ = 11.43 (s, 1 H), 10.98 (br. s, 1 H), 10.65 (br. s, 1 H), 8.52 (3, 1H), 8.49 (d, *J* = 8.2 Hz, 1 H), 8.06 (s, 1 H), 7.65 (d, *J* = 2.3 Hz, 1 H), 7.63 (d, *J* = 8.7 Hz, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.48 (ddd, *J* = 7.8, 6.8, 0.9 Hz, 1 H), 7.24 (ddd, *J* = 7.8, 6.8, 0.9 Hz, 1 H), 7.05 (dd, *J* = 8.7, 2.3 Hz, 1 H) ppm. ^1H NMR (300.1 MHz; [D_6]DMSO): δ = 11.53 (s, 1 H), 11.44 (s, 1 H), 11.32 (s, 1 H), 9.04 (br. s, 1 H), 8.53 (d, *J* = 7.8 Hz, 1 H), 8.47 (s, 1 H), 7.59−7.54 (m, 3 H), 7.47 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.18 (dd, *J* = 7.8, 7.3 Hz, 1 H), 6.94 (dd, *J* = 8.7, 1.8 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]DMSO): δ = 189.7 (d), 151.0 (s), 141.5 (s), 136.0 (s), 135.4 (s), 134.2 (s), 126.3 (d), 124.5 (d), 123.4 (s), 122.0 (s), 121.6 (s), 121.0 (s), 118.7 (d), 115.6 (d), 112.5 (d), 112.1 (s), 111.4 (d), 110.0 (d), 105.2 (d) ppm. MS EI(30 eV): *m*/*z* (%) = 300 (41) [M]$^+$, 73 (97), 60 (100). HRMS (FAB) calcd. for $C_{19}H_{12}N_2O_2$ [M]$^+$ 300.0899, found 300.0910.

8-Hydroxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (5b): The hydroxyindolocarbazole **5b** was prepared from **12b** using the same procedure as for **5a**. Brick red solid. M.p. 371.0−373.5 °C. IR (neat): $\tilde{\nu}$ = 3428, 3387, 3309, 1643, 1597, 1476, 1196, 1085, 819, 756 cm^{-1}. ^1H NMR (500.2 MHz; [D_6] acetone, 294 K): δ = 11.36 (s, 1 H), 11.17 (br. s, 1 H), 10.44 (br. s, 1 H), 8.56 (s, 1 H), 8.23 (d, *J* = 7.8 Hz, 1 H), 8.04 (s, 1 H), 7.88 (d, *J* = 1.8 Hz, 1 H), 7.79 (d, *J* = 8.2 Hz, 1 H), 7.50−7.45 (m, 2 H), 7.25 (dd, *J* = 7.4, 7.3 Hz, 1 H), 7.11 (dd, *J* = 8.2, 1.8 Hz, 1 H) ppm. ^1H NMR (500.2 MHz; [D_6]DMSO): δ = 11.66 (s, 1 H, N*H*-5), 11.27 (s, 1 H, N*H*-11), 11.23 (s, 1 H, C*H*O-6), 9.03 (s, 1 H, O*H*-8), 8.53 (s, 1 H, C*H*-12), 8.27 (d, *J* = 7.3 Hz, 1 H, C*H*-1), 7.83 (d, *J* = 1.8 Hz, 1 H, C*H*-7), 7.73 (d, *J* = 7.8 Hz, 1 H, C*H*-4), 7.44−7.41 (m, 2 H, C*H*-3 and C*H*-10), 7.22 (dd, *J* = 7.8, 7.3 Hz, 1 H, C*H*-2), 7.03 (dd, *J* = 8.7, 2.3 Hz, 1 H, C*H*-9) ppm. ^{13}C NMR (125.8 MHz; [D_6]DMSO): δ = 189.4 (d), 150.4 (s), 141.5 (s), 136.0 (s), 135.5 (s), 135.2 (s), 126.2 (d), 123.1 (s), 121.3 (2 × s), 121.3 (s), 120.3 (d), 119.2 (d), 116.6 (d), 112.1 (s), 112.0 (d), 111.9 (d), 110.0 (d), 108.6 (d) ppm. MS EI(70 eV): *m*/*z* (%) = 300 (21) [M]$^+$, 272 (9), 242 (9), 87 (10), 74 (17), 73 (61), 64 (39), 63 (22), 61 (18), 60 (100). HRMS (FAB) calcd. for $C_{19}H_{12}N_2O_2$ [M]$^+$ 300.0899, found 300.0887.

3-Hydroxyindole[3,2-*b*]carbazole-6-carboxaldehyde (5c): The hydroxyindolocarbazole **5c** was prepared from **12c** using the same procedure as for **5a**. Yellow solid. M.p. 380 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3377, 1654, 1617, 1310, 1243, 745 cm^{-1}. ^1H NMR (500.2 MHz; [D_6]acetone, 294 K): δ = 11.42 (s, 1 H), 11.01 (s, 1 H), 10.62 (s, 1

H), 8.58 (s, 1 H), 8.45 (d, J = 7.8 Hz, 1 H), 8.43 (s, 1 H), 8.02 (d, J = 8.2 Hz, 1 H), 7.60 (d, J = 8.2 Hz, 1 H), 7.45 (dd, J = 8.2, 6.9 Hz, 1 H), 7.26 (d, J = 2.3 Hz, 1 H), 7.22 (dd, J = 7.4, 6.8 Hz, 1 H), 6.81 (dd, J = 8.2, 2.3 Hz, 1 H) ppm. ^{13}C NMR (125.8 MHz; [D$_6$]acetone): δ = 190.8 (d), 158.3 (s), 144.4 (s), 142.5 (s), 136.8 (s), 136.1 (s), 126.8 (d), 125.3 (s), 124.9 (d), 122.6 (s), 121.9 (d), 121.7 (s), 120.0 (d), 115.7 (s), 113.4 (s), 112.2 (d), 109.9 (d), 109.2 (d), 98.6 (d) ppm. HRMS (FAB) calcd. for $C_{19}H_{12}N_2O_2$ 300.0899 $[M]^+$ found 300.0898.

2,8-Dihydroxyindolo[3,2-*b*]carbazole-12-carboxaldehyde (5d): The hydroxyindolocarbazole **5d** was prepared from **12d** using the same procedure as for **5a**. Red solid. M.p. 383.0−385.5 °C. IR (KBr): $\tilde{\nu}$ = 3429, 3315, 1640, 1594, 1475, 1189, 1079 cm^{-1}. ^{1}H NMR (500.2 MHz; [D$_6$]acetone, 294 K): δ = 11.32 (s, 1 H), 10.94 (br. s, 1 H), 10.36 (br. s, 1 H), 8.46 (s, 1 H), 8.05 (s, 1 H), 8.02 (s, 1 H), 7.86 (J = 2.2 Hz, 1 H), 7.63 (d, J = 2.3 Hz, 1 H), 7.61 (d, J = 8.7 Hz, 1 H), 7.47 (d, J = 8.7 Hz, 1 H), 7.10 (dd, J = 8.7, 2.3 Hz, 1 H), 7.04 (dd, J = 8.7, 2.2 Hz, 1 H) ppm. ^{1}H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.36 (s, 1 H), 11.87 (s, 2 H), 9.03 (s, 1 H), 9.00 (s, 1 H), 8.40 (s, 1 H), 7.80 (d, J = 2.1 Hz, 1 H), 7.56 (d, J = 2.2 Hz, 1 H), 7.52 (d, J = 8.6 Hz, 1 H), 7.40 (d, J = 8.7 Hz, 1 H), 7.01 (dd, J = 8.7, 2.1 Hz, 1 H), 6.93 (dd, J = 8.6, 2.2 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 189.0 (d), 151.0 (s, 1 H), 150.4 (s), 136.0 (2 × s), 135.4 (s), 135.0 (s), 123.2 (s), 122.0 (s), 121.4 (s), 121.2 (s), 116.5 (d), 115.4 (d), 112.4 (d), 111.9 (d), 111.9 (s), 110.1 (d), 108.5 (d), 105.2 (d) ppm. MS (ESI): m/z = 317 $[M - 1]^-$, 315 $[M + 1]^+$. HRMS (FAB) calcd. for $C_{19}H_{12}N_2O_3$ 316.0848 $[M]^+$ found 316.0844.

4,8-Dihydroxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (5e): The hydroxyindolocarbazole **5e** was prepared from **12e** using the same procedure as for **5a**. Red solid. M.p. 393.0 °C (dec.). IR (neat): $\tilde{\nu}$ = 3384, 1630, 1593, 1462, 1273, 1185, 793 cm^{-1}. ^{1}H NMR (500.2 MHz; [D$_6$]acetone, 294 K): δ = 11.36 (s, 1 H), 10.76 (br. s, 1 H), 10.44 (br. s, 1 H), 9.01 (s, 1 H), 8.52 (s, 1 H), 8.06 (s, 1 H), 7.89 (d, J = 2.3 Hz, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.49 (d, J = 8.7 Hz, 1 H), 7.13−7.09 (m, 2 H), 6.99 (d, J = 7.8 Hz, 1 H) ppm. ^{1}H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.28 (s, 1 H), 11.27 (s, 1 H), 11.23 (s, 1 H), 9.95 (br. s, 1 H), 9.03 (br. s, 1 H), 8.48 (s, 1 H), 7.83 (d, J = 1.5 Hz, 1 H), 7.75 (d, J = 7.7 Hz, 1 H), 7.42 (d, J = 8.7 Hz, 1 H), 7.11−7.01 (m, 2 H), 6.88 (d, J = 7.7 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 189.7 (d), 150.4 (s), 142.7 (s), 136.1 (s), 135.6 (s), 134.9 (s), 130.0 (s), 123.5 (s), 123.3 (s), 121.4 (s), 121.3 (s), 120.4 (d), 116.7 (d), 112.2 (s), 112.1 (d), 111.9 (d), 111.4 (d), 110.1 (d), 108.6 (d) ppm. MS (ESI): m/z = 315 $[M - 1]^-$, 317 $[M + 1]^+$. HRMS (FAB) calcd. for $C_{19}H_{12}N_2O_3$ 316.0848 $[M]^+$, found 316.0852.

2,10-Dihydroxyindolo[3,2-*b*]carbazole-6-carboxaldehyde (5f): Tetrabutylammonium fluoride (1 M in THF, 1.83 mL, 1.83 mmol) was added to a solution of **12f** (166 mg, 0.30 mmol) in THF (5 mL) at 0−2 °C under argon. After 15 min the reaction was complete as judged by TLC. A buffer solution (pH 7.4, 70 mL) was added and the resulting slurry stirred for 30−60 min. The mixture was extracted with EtOAc (200 mL). The organic solvents were washed with water (4 × 50 mL) and brine (2 × 50 mL) and dried with $MgSO_4$. Evaporation produced a red solid that was boiled 3 times in hexane, each time carefully removing the solvent with a pipette. Drying produced the indolocarbazole **5f** in 73 mg (84%) as a dark-reddish solid. This sample gradually becomes darker and darker and no melting point could be recorded below 410 °C. IR (neat): $\tilde{\nu}$ = 3383, 3341, 1634, 1619, 1561, 1329, 1196, 1098 cm^{-1}. ^{1}H NMR (500.2 MHz; [D$_6$]acetone, 294 K): δ = 11.39 (s, 1 H), 10.97 (br. s, 1 H), 10.54 (br. s, 1 H), 8.93 (br. s, 1 H), 8.55 (s, 1 H), 8.07 (s, 1 H), 7.95 (d, J = 7.8 Hz, 1 H), 7.64−7.62 (m, 2 H), 7.08−7.05 (m, 2 H), 6.97 (d, J = 7.3 Hz, 1 H) ppm. ^{1}H NMR (300.1 MHz; [D$_6$]DMSO): δ = 11.40 (s, 1 H), 11.33 (s, 1 H), 11.27 (s, 1 H), 9.94 (br. s, 1 H), 9.03 (s, 1 H), 8.41 (s, 1 H), 7.92 (d, J = 7.9 Hz, 1 H), 7.55−7.52 (m, 2 H), 7.01−6.88 (m, 3 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 189.7 (d), 151.0 (s), 143.2 (s), 135.9 (s), 135.4 (s), 134.2 (s), 131.9 (s), 123.1 (s), 122.3 (s), 122.2 (s), 121.9 (s), 119.4 (d), 115.5 (d), 115.2 (d), 112.6 (d), 111.8 (s), 110.3 (2 × d), 104.9 (d) ppm. MS (ESI): m/z = 317 $[M + 1]^+$, 315 $[M - 1]^-$. HRMS (FAB) calcd. for $C_{19}H_{12}N_2O_3$ 316.0848 $[M]^+$, found 316.0849.

Indolo[3,2-*b*]carbazole-6-carboxylic Acid (13a): The ester **11a** (920 mg, 2.80 mmol) was heated under nitrogen in a mixture of EtOH (150 mL) and 2 M NaOH (100 mL) at reflux for 12 h and was then cooled to 21 °C. The bulk of the solvents were removed until 10−15 mL remained. Water (200 mL) was added together with ice and 2 M HCl (250 mL). The precipitate formed was collected and washed with excess of water before drying in vacuo to give the acid **13a** in 0.78 g (93%) as a yellow solid. This material slowly lost the yellow color to a more grey-greenish color during attempted melting point measurements, and no value could be recorded. IR (KBr): $\tilde{\nu}$ = 3404, 1653, 1616, 1512, 1459, 1436, 1322, 1229, 741 cm^{-1}. ^{1}H NMR (300.1 MHz; [D$_6$]DMSO): δ = 13.53 (br. s, 1 H), 11.46 (s, 1 H), 10.98 (s, 1 H), 8.93 (d, J = 8.2 Hz, 1 H), 8.45 (s, 1 H), 8.25 (d, J = 7.7 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.42 (dd, J = 8.0, 7.2 Hz, 2 H), 7.20−7.10 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 168.9 (s), 141.6 (s), 141.1 (s), 136.1 (s), 135.2 (s), 126.1 (d), 126.0 (d), 125.5 (d), 123.2 (s), 121.6 (s), 121.4 (s), 120.4 (s), 120.2 (d), 118.4 (d), 117.6 (d), 111.6 (d), 110.5 (d), 106.4 (d), 105.9 (s) ppm. HRMS (FAB) calcd. for $C_{19}H_{12}N_2O_2$ 300.0899 $[M]^+$ found 300.0896.

Representative Procedure for the Preparation of 13b−c: BBr_3 (1 M in CH_2Cl_2, 4.63 mL, 4.63 mmol) was added dropwise to a solution of **11e** (92 mg, 0.23 mmol) in dry dichloromethane (20 mL) at −78 °C under argon. The cooling bath was then removed and the resulting suspension stirred at 21 °C until reaction was complete as judged by TLC (1−2 days). Ice/water (100 mL) was then added and the mixture extracted with EtOAc (4 × 75 mL). The combined organic solvents were washed with water and dried with $MgSO_4$. The solvents were reduced together with 500 mg of silica gel. Column chromatography (silica) with EtOAc/hexane (50−100%) as eluent produced the acid **13b** in 75 mg (95%) as a yellow solid. This material slowly changed from the yellow color to a more grey color during attempted melting point measurements, and no value could be recorded.

2,8-Dihydroxyindolo[3,2-*b*]carbazole-6-carboxylic Acid (13b): IR (KBr): $\tilde{\nu}$ = 3413, 1678, 1477, 1320, 1212, 1187, 1161, 808 cm^{-1}. ^{1}H NMR (300.1 MHz; [D$_6$]DMSO): δ = 13.30 (br. s, 1 H), 10.98 (s, 1 H), 10.54 (s, 1 H), 8.91 (s, 1 H), 8.76 (s, 1 H), 8.29 (d, J = 2.2 Hz, 1 H), 8.23 (s, 1 H), 7.51 (d, J = 2.2 Hz, 1 H), 7.47 (d, J = 8.6 Hz, 1 H), 7.30 (d, J = 8.6 Hz, 1 H), 6.95−6.88 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz; [D$_6$]DMSO): δ = 168.8 (s), 150.3 (s), 149.1 (s), 136.6 (s), 136.0 (s), 135.6 (s), 135.1 (s), 123.0 (s), 122.2 (s), 122.1 (s), 120.3 (s), 115.8 (d), 115. 3 (d), 111.9 (d), 110.5 (d), 110.3 (d), 106.3 (d),105.3 (s), 104.9 (d) ppm. HRMS (FAB) calcd. for $C_{19}H_{12}N_2O_4$ 332.0797 $[M]^+$, found 332.0803.

2-Hydroxyindolo[3,2-*b*]carbazole-6-carboxylic Acid (13c): The ICZ **13c** was prepared from **11b** using the same procedure as for **13b**. The eluent was EtOAc. This material slowly lost its yellow color to a more grey color upon attempted melting point measurements,

and no value could be recorded. IR (KBr): $\tilde{\nu}$ = 3460, 3405, 1678, 1656, 1485, 1432, 1298, 1216, 1155, 745 cm^{-1}. ^1H NMR (300.1 MHz; [D_6]DMSO): δ = 13.42 (br. s, 1 H), 11.35 (s, 1 H), 10.64 (s, 1 H), 8.93−8.90 (m, 2 H), 8.31 (s, 1 H), 7.54 (d, *J* = 2.2 Hz, 1 H), 7.51−7.48 (m, 2 H), 7.40 (t, *J* = 7.1 Hz, 1 H), 7.10 (dd, *J* = 7.2, 7.1 Hz, 1 H), 6.92 (dd, *J* = 8.6, 2.3 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]DMSO): δ = 168.9 (s), 150.4 (s), 141.6 (s), 136.9 (s), 135.1 (s), 134.7 (s), 125.8 (d), 125.5 (d), 123.2 (s), 122.2 (s), 121.5 (s), 120.4 (s), 117.5 (d), 115.5 (d), 112.0 (d), 110.5 (d), 106.4 (d), 105.4 (s), 105.0 (d) ppm. HRMS (FAB) calcd. for $C_{19}H_{12}N_2O_3$ 316.0848 $[M]^+$, found 316.0861.

Representative Procedure for Decarboxylation of the Acids 13b−c: The acid **13** was heated at 300 °C under argon for 10−15 min. The colour changed from yellow to gray-greenish after a few minutes. The isolated yields were almost quantitative.

2,8-Dihydroxyindolo[3,2-*b*]carbazole (14a): The spectroscopic data were identical to those of a reference sample.[10]

2-Hydroxyindolo[3,2-*b*]carbazole (14b): Greenish solid. M.p. > 410 °C. IR (KBr): $\tilde{\nu}$ = 3528, 3395, 1608, 1520, 1471, 1457, 1446, 1218, 1143, 845, 746 cm^{-1}. ^1H NMR (300.1 MHz; [D_6]DMSO): δ = 10.91 (s, 1 H), 10.60 (s, 1 H), 8.83 (s, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 8.02 (s, 1 H), 7.96 (s, 1 H), 7.49 (d, *J* = 2.4 Hz, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.35 (t, *J* = 7.0 Hz, 1 H), 7.25 (d, *J* = 8.5 Hz, 1 H), 7.10 (dd, *J* = 8.0, 7.8 Hz, 1 H), 6.88 (dd, *J* = 8.5, 2.0 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz; [D_6]DMSO): δ = 149.8 (s), 141.1 (s), 135.9 (s), 135.2 (s), 134.6 (s), 125.3 (d), 123.2 (s), 122.6 (2 × s), 122.5 (s), 120.1 (d), 117.5 (d), 114.8 (d), 110.8 (d), 110.4 (d), 105.0 (d), 100.3 (d), 100.2 (d) ppm.

Acknowledgments

We thank Dr. Tomasz Janosik for a constructive discussion during the preparation of this manuscript and Dr. Marcus Ruda for help with low resolution mass spectroscopic measurements.

[1] J. P. Whitlock, *Annu. Rev. Pharmacol. Toxicol.* **1999**, *39*, 103−125.
[2] D. W. Nebert, A. L. Roe, M. Z. Dieter, W. A. Solis, Y. Yang, T. P. Dalton, *Biochem. Pharmacol.* **2000**, *65*, 65−85.
[3] J. Bergman, T. Janosik, N. Wahlström, *Adv. Heterocycl. Chem.* **2001**, *80*, 1−71.
[4] A. Rannug, U. Rannug, H. Rosenkranz, L. Winqvist, R. Westerholm, E. Agurell, A. J. Grafström, *J. Biol. Chem.* **1987**, *262*, 15422−15427.
[5] J. Tholander, J. Bergman, *Tetrahedron* **1999**, *55*, 6243−6260.
[6] U. Rannug, A. Rannug, U. Sjoeberg, H. Li, R. Westerholm, J. Bergman, *Chem. Biol.* **1995**, *2*, 841−845.
[7] Y.-D. Wei, L. Bergander, U. Rannug, A. Rannug, *Arch. Biochem. Biophys.* **2000**, *383*, 99−107.
[8] L. Bergander, N. Wahlström, T. Alsberg, J. Bergman, A. Rannug, U. Rannug, *Drug Metab. Dispos.* **2003**, *31*, 233−241.
[9] N. Wahlström, B. Stensland, J. Bergman, *Synthesis*, manuscript accepted.
[10] L. N. Yudina, J. Bergman, *Tetrahedron* **2003**, *59*, 1265−1275.
Received February 10, 2004

