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Synthesis and alkylation of indolo[3,2-*b*]carbazoles

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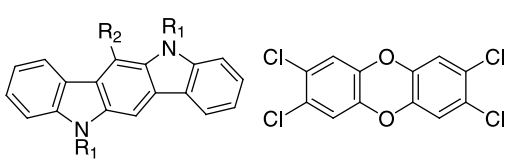
Abstract—Double Fischer cyclisation was used to prepare indolo[3,2-*b*]carbazole and its 2,8-di-OMe, OH, Br and F-derivatives. *N*-monosubstituted derivatives of indolo[3,2-*b*]carbazole (methyl, hydroxymethyl, dimethylaminoethyl) were obtained starting from 5,11-di-Boc-indolo[3,2-*b*]carbazole.

1. Introduction and background

Indolo[3,2-*b*]carbazole[1] (ICZ) **1a** (Fig. 1) is a molecule of considerable biological significance, since it is formed in vivo after consumption of cruciferous vegetables such as cabbage and Brussels sprouts.[2] ICZ has a strong affinity to the TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, **2**) receptor (Ah-receptor), and recently it has been demonstrated that 6-formylindolo[3,2-*b*]carbazole[3] (**3a**) has an extremely strong affinity to the TCDD receptor, in fact even stronger than the highly toxic dioxin TCDD itself.[4] The TCDD receptor is very important in the primary detoxification of unpolar substances, as this receptor triggers the expression of many enzymes (including cytochrome 1A1) involved in this process. Furthermore, in certain animals, the development of a proper liver and immune system are dependent on a working receptor.[5]

Although indole-3-carbinol, indole and 3-formylindole under acidic conditions all produce **1a**,[6] the low yields obtained and the complex product pattern prohibits the use of these simple approaches for synthetic purposes. In the simple condensation of indole with aldehydes, indolo[3,2-*b*]carbazole derivatives are produced, however, this strategy only works for aromatic aldehydes or with sterically hindered aliphatic aldehydes like *iso*-propanal.[7] For preparative purposes, compound **1a** can be prepared by double Fischer indolisation of the bis-phenylhydrazone of cyclohexane-1,4-dione under conditions described by Robinson.[8] Under slightly different conditions (HCl/EtOH) the yield of **1a** is much lower and an array of other products, including heterohelicenes,[9] are formed. Compound **1a** can also be prepared by Suzuki coupling of 1,4-dibromo-3,6-dinitrobenzene with phenylboronic acid and followed by reductive cyclisation, induced by $P(OEt)_3$.[10]



1a R_1=R_2=H
3a R_1=H, R_2=CHO
3b R_1=Me, R_2=H
3c R_1=Et, R_2=H

2

Figure 1.

In this paper, the preparation of ICZ and derivatives thereof via double Fischer cyclisation of diarylhydrazones (**4**) has been studied using several condensing agents. The preferred synthetic route for preparation of **1a** was found to be a modification of Robinson's method, e.g. (H_2SO_4 in AcOH). Several phosphorus containing agents like PPA, PCl_3 and polyphosphoric acid trimethylsilylester (PPSE) gave not only ICZ (i.e. the linear isomer), but also the angular isomer, indolo[2,3-*c*]carbazole (**5a**), the structure of which was confirmed by an independent synthesis.[11] Furthermore, several mono- and disubstituted *N*,*N*′-derivatives of **1a** have been prepared to enable determination of their activities.

2. Results and discussion

In contrast with the numerous studies concerning the affinities and activities of ICZ and particularly 6-formylindolo[3,2-*b*]carbazole (**3a**) very little is known about their metabolic fate.[4,12,13] As certain carbazole derivatives are hydroxylated in the benzene rings,[14] a similar transformation might also metabolise indolo[3,2-*b*]carbazole. One of the most likely metabolites would be 2,8-dihydroxyindolo[3,2-*b*]carbazole (**6**). As a precursor for **6** we planned

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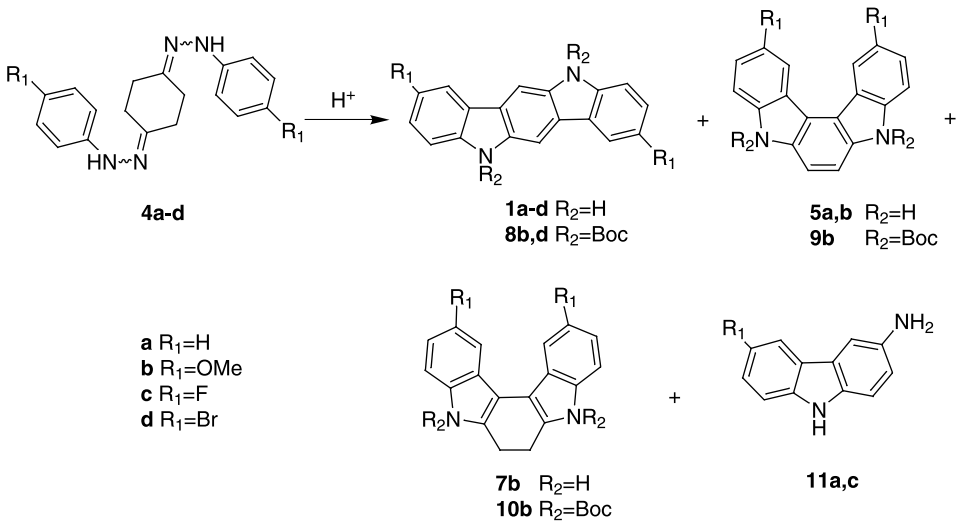


Scheme 1.

to synthesise 2,8-dimethoxy- and 2,8-dibromoindolo[3,2-*b*]carbazoles (**1b**,**d**).

The bishydrazones **4** were obtained in 50–60% yield by condensation of *p*-methoxy, *p*-F- or *p*-Br-phenylhydrazines, respectively, with cyclohexane-1,4-dione in EtOH in the absence of acid and used immediately. For the synthesis of **1b** PPSE[15] was the only medium that yielded the desired compound. The best results were obtained by adding the freshly prepared powdered phenylhydrazone **4b** portionwise to PPSE at 100–105°C (Scheme 1).

The angular isomer 2,11-dimethoxyindolo[2,3-*c*]carbazole (**5b**) and 6,7-dihydro-2,11-dimethoxy-indolo[2,3-*c*]carbazole (**7b**) were obtained as co-products. Attempts to use Boc-protection to separate the residual mixture of products were unsuccessful, since the retention values of the Boc-protected products **8b**–**10b** are very close. The Boc-protected dihydro derivative **7b** underwent dehydrogenation readily to give **5b**, especially in the presence of silica gel. The angular isomer **5b** is soluble in CH_3CN and it was isolated from the reaction mixture upon washing with CH_3CN, followed by column chromatography and sublimation at 215°C. For the isolation of **1b**, the remaining mixture of **1b** and **7b** was refluxed with Pd/C in the presence of air, resulting in a mixture consisting mainly of **1b**, which was *N*-Boc-protected and purified by column chromatography to produce **8b** in 20% yield (from **4b**). Finally, **8b** was crystallised from 1,4-dioxane and deprotected at 205°C/0.1 mm Hg to produce 2,8-dimethoxyindolo[3,2-*b*]carbazole (**1b**) in quantitative yield (from **8b**). The structures of **1b** and **5b** were established by NOEDIF experiments. Thus, saturation of the singlet 6/12-H in **1b** produced a NOE enhancement of the signal 7/1-H on 16%, which correlates to a proximity in space of the protons and confirms the structure of the 3,2-*b* isomer. Analogous experiments for **5b** did not display any NOE enhancement in the intensity of the signals.

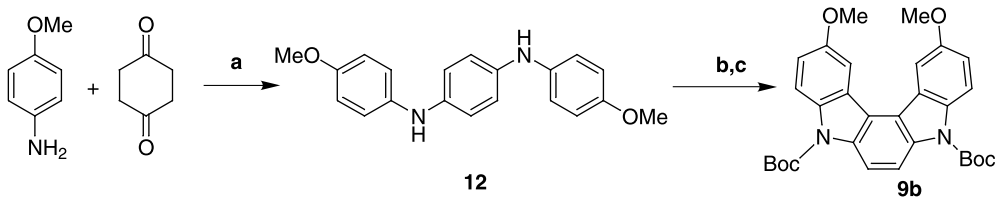
2,8-Difluoroindolo[3,2-*b*]carbazole (**1c**) was obtained in 26–48% yield together with 3-amino-6-fluorocarbazole **11c** (20–60%) after intramolecular condensation of **4c** in polyphosphoric acid at 190°C. It is necessary to heat **4c** swiftly from 10 to 70°C, otherwise the yield of **1c** significally decreased. This ring closure experiment suffered from variable reproducibility and other cyclisation media such as $AcOH/H_2SO_4$, PPSE or TsOH/toluene did not provide any improvements. The fluoroindolocarbazole **1c** was purified by refluxing in acetonitrile. Starting from the bis-bromophenylhydrazone **4d**, formation of 5,11-dibromo-indolo[3,2-*b*]carbazole (**1d**) could only be effected in a mixture of $AcOH-H_2SO_4$ (4:1) and progressed in 25% yield. The crude bromoindolocarbazole **1d** was protected with Boc_2O to **8d**, a compound that was easily purified by reflux in dioxane and filtration. The Boc-groups in **8d** were eliminated at 195°C/0.1 mm Hg during 5 h to produce **1d**. Yields for products of Fischer cyclisation of **4a**–**d** presented in Table 1.

It should be noted that double Fischer cyclisation to prepare indolocarbazoles can be successfully performed under very strong acidic conditions. Attempts to perform cyclisations without isolation of the unstable intermediate **4** mainly gave monocyclised products.

Due to the relatively low yield of **1b** an alternative synthesis, involving a cyclisation, catalyzed by $Pd(OAc)_2$, was attempted (Scheme 2). This technique has recently been used for the synthesis of 6,12-dicarboethoxyindolo[3,2-*b*]carbazole in high yield.[7] However, cyclisation of the diarylamine **12** with equimolar amount of $Pd(OAc)_2$ resulted only in the formation of 2,11-dimethoxy indolo[2,3-*c*]carbazole (**5b**), isolated in its Boc-protected form **9b**, identical with the previous sample obtained vide supra.

Table 1. Yields of products from Fischer cyclisation of the phenylhydrazones **4**

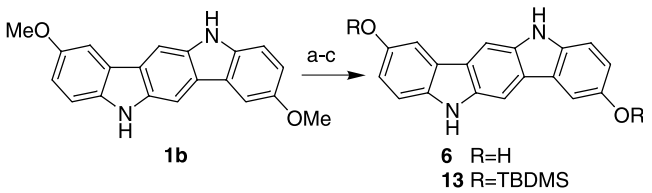
Hydrazones **4a–d**	Yields of products (%)			
	1a–d	**5a–d**	**7a–d**	**11a–d**
4a	47	0	0	16
4b	20	11	ca 15	0
4c	49	0	0	21
4d	24	0	0	0



Scheme 2. (**a**) PhH, reflux (13%); (**b**) $Pd(OAc)_2$, AcOH, reflux; (**c**) Boc_2O/DMAP, THF (10% for **b** and **c**).

We attempted to get the 2,8-dimethoxyindolocarbazole **1b** by exchanging the bromine atoms in 2,8-dibromoindolo[3,2-*b*]carbazole with methoxy groups. However, heating **1d** in DMF or DMA for 3 h with 5–10 eq. of CH_3ONa and 3–5 eq. of CuI did not provide more than 30% of **1b**. Harsher reaction conditions or prolonged reaction times resulted in increased degradation of the indolocarbazoles.

2,8-Dihydroxyindolo[3,2-*b*]carbazole **6** was obtained by demethylation of **1b** by 20 eq. BBr_3 at −78°C to 21°C (Scheme 3). *O*-Protection with *t*-$BuMe_2SiCl$ in the presence of imidazole in DMF gave the quite soluble product **13**, which was purified by column chromatography. Deprotection of the TBDMS group was performed with *n*-Bu_4NF to give **6** in 70% yield starting from **1b**.



Scheme 3. (**a**) BBr_3 (20 eq.), CH_2Cl_2, −78→21°C, 48 h; (**b**) *t*-$BuMe_2SiCl$, imidazole, DMF; (**c**) *n*-Bu_4NF, THF (70% for **a**–**c**).

N-Alkylated derivatives of ICZ have attracted considerable interest. They are readily obtained in high yields by treating ICZ with dialkyl oxalates under basic conditions, a methodology that has previously been used for alkylation of indoles and carbazoles.[16] Dialkylated derivatives of **1a**, e.g. **3b** and **c**, have earlier been tested for high affinity as TCDD-receptor ligands.[17] In view of the high activity of **14a** (Fig. 2) and the strong propensity of **14b** to stabilise triplex forms of synthetic DNA and RNA,[18] it appeared to be of considerable interest to synthesise related compounds such as **15b** (Fig. 3) in the ICZ series.

N,*N*-Dimethylaminoethylation of ICZ was performed with commercial 2-dimethylamino-1-chloroethane·HCl in DMSO with NaH as a base. When slightly more than 2 eq. of the alkylation reagent was used the dialkylated product **15a** was the sole product. Reducing the number of

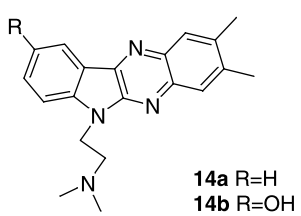
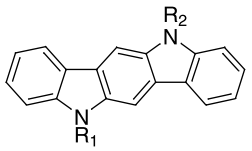


Figure 2.

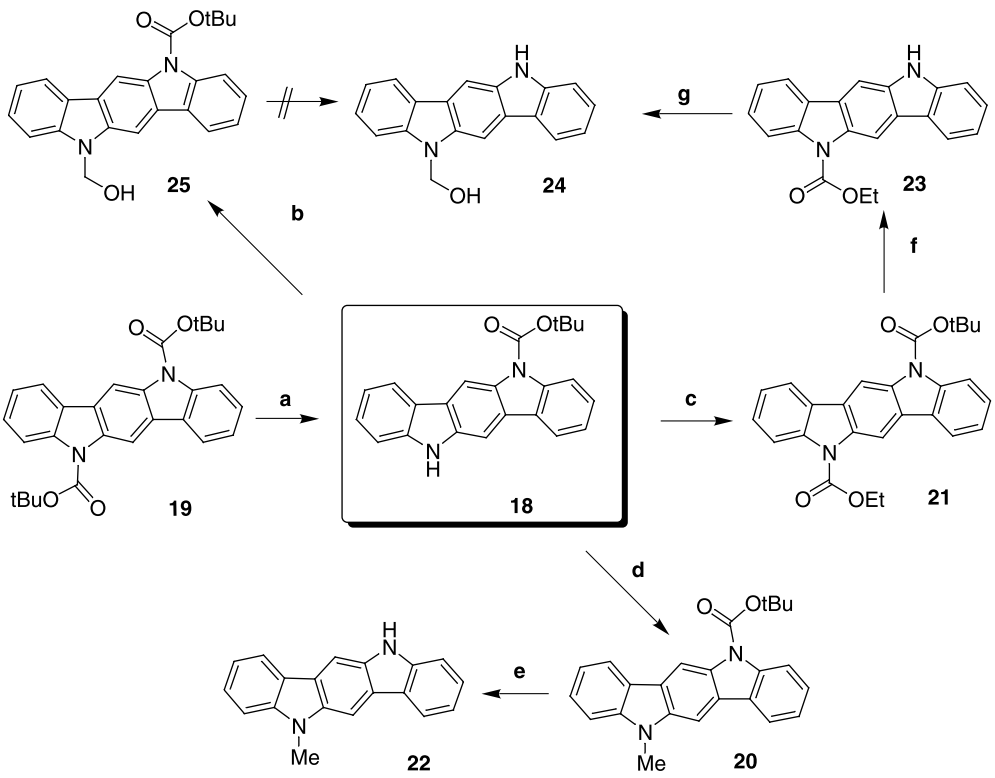


15a $R_1=R_2=CH_2CH_2N(CH_3)_2$
15b $R_1=H$, $R_2=CH_2CH_2N(CH_3)_2$
16 $R_1=R_2=CH_2N(CH_3)_2$
17 $R_1=R_2=CH_2OH$

Figure 3.

equivalents of $Me_2NCH_2CH_2Cl$ used produced a mixture of **15a** and **b**, which could be separated by column chromatography. The ease of the preparation of this type of compound and its good solubility (in e.g. $CHCl_3$) should assist the characterisation of ICZ and its derivatives. In connection with the preparation of **15a**, its lower and less stable homologue **16**, was readily obtained by reaction of **1a** with formaldehyde and dimethylamine in the presence of acetic acid in hot *N*,*N*-dimethylacetamide. In the absence of dimethylamine 5,11-dihydroxymethylindolo[3,2-*b*]carbazole (**17**) was readily prepared. We next wanted to develop a method to selectively obtain unsymmetrical alkyl derivatives of **1a**, including **15b** (Scheme 4).

The key compound for this synthesis was 5-*t*-butyloxycarbonylindolo[3,2-*b*]carbazole (**18**). In the next step we planned to introduce other substituents, such as methyl, hydroxymethyl and 2-dimethylaminoethyl in the molecule and then remove the Boc group. We obtained 5,11-di-*t*-butyloxycarbonylindolo[3,2-*b*]carbazole (**19**)[19] and removed one protecting group with 4–5 eq. of *n*-BuLi (depending on the scale) at 0°C to form the monoprotected derivative **18** in 72% yield. It was necessary to monitor the reaction carefully by TLC to avoid the removal of both protecting groups, but because of insolubility it is difficult to check for the presence of ICZ by TLC. MonoBoc-ICZ **18** was purified by column chromatography and crystallised from dioxane. The disubstituted unsymmetrical derivatives **20** and **21** were obtained by treatment of 5-*t*-butyloxycarbonylindolo[3,2-*b*]carbazole with MeI or ClCOOEt in two phase systems in 86 and 84% yields, respectively. *N*-Boc-deprotection of **20** was carried out at 210°C/0.1 mm Hg to provide analytically pure crystals of 5-methylindolo[3,2-*b*]carbazole (**22**). 5-Ethoxycarbonylindolo[3,2-*b*]carbazole (**23**) was obtained by treatment of **21** in TFA/CH_2Cl_2 and crystallised from CH_3CN in 83% yield. Attempts to use $LiAlH_4$ for this purpose caused selective elimination of COOEt to give **18**. Finally 5-hydroxymethylindolo[3,2-*b*]carbazole (**24**) was obtained in 90% yield by rapid reduction of **23** with $LiAlH_4$ at 0°C and purified by column chromatography then suspending the product in acetone and collecting the solid. Due to its



Scheme 4. (**a**) *n*-BuLi, THF, 0°C, NH_4Cl, 21°C (72%); (**b**) H_2CO, EtOH (88%); (**c**) i. NaOH, CH_2Cl_2, Bu_4NHSO_4 ii. $ClCO_2Et$ (84%); (**d**) NaOH, CH_2Cl_2, Bu_4NBr ii. MeI (86%); (**e**) 200°C/0.1 mm Hg (quant.); (**f**) 10% TFA/CH_2Cl_2 (83%); (**g**) $LiAlH_4$, THF 0°C (90%).

thermal instability, all attempts to crystallise **24** were unsuccessful. While examining an alternative route to **24** 5-Boc-11-hydroxymethylindolo[3,2-*b*]carbazole (**25**) was obtained in 88% yield by treatment of **18** with an excess of 37% formaldehyde. Despite several attempts to deprotect **25** to give **24**, by using basic or acidic catalysis or reduced pressure (at 160°C), no satisfactory results could be obtained. It should be noted that compounds **20** and **21** could be easily obtained, directly without isolation of **18**, by treating the reaction mixture, obtained from the mono-deprotection of **19**, with ClCOOEt or MeI, but in this case the purification of the target compounds from by-products (5,11-diethoxycarbonyl- or 5,11-dimethylindolo[3,2-*b*]carbazoles) is troublesome.

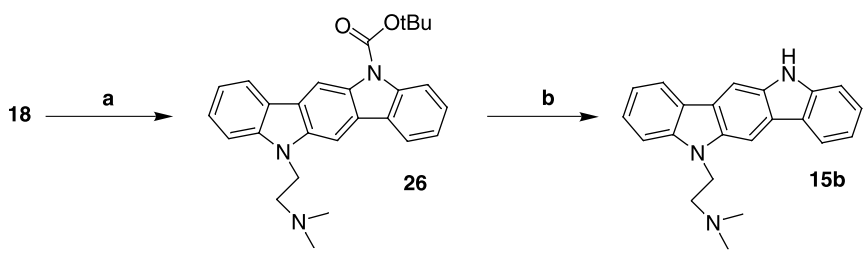
The *N*-alkylation of **18** to introduce 2-dimethylaminoethyl substituent was troublesome. Satisfactory results were only obtained by treatment **18** with *t*-BuOK and freshly prepared 2-dimethylamino-1-chloroethane in DMF (Scheme 5). Under these conditions 5-Boc-11-(2-dimethylaminoethyl)-indolo[3,2-*b*]carbazole **26** was obtained in 60% yield. Boc-deprotection of **26** took place only under strongly basic conditions, at room temperature for 72 h in 1.5 M NaOMe to give **15b** in 73% yield.

In summary, the symmetrical 2,8-disubstituted OMe, F and Br indolo[3,2-*b*]carbazoles have been synthesised by double Fischer cyclisations. It was demonstrated that besides the linear isomer, the angular isomer indolo[2,3-*c*]carbazole was also produced during these cyclisations. Demethylation of 2,8-dimethoxyindolo[3,2-*b*]carbazole with BBr_3 gave dihydroxy-ICZ in high yield. Several *N*-monosubstituted indolo[3,2-*b*]carbazoles were prepared in moderate yields starting from 5,11-di-BocICZ.

3. Experimental

3.1. General methods

^1H and ^{13}C NMR spectra were obtained on a Bruker DPX 300 (300 MHz) instrument. Chemical shifts are reported in δ, ppm and coupling constants (*J*) are given in Hz. IR spectra were recorded on Perkin–Elmer 1600 FT-IR



Scheme 5. (**a**) *t*-BuOK, DMF, $(CH_3)_2NCH_2CH_2Cl$ (60%); (**b**) 1.5N CH_3ONa, 72 h (73%).

spectrophotometer using KBr films. Mass-spectra were obtained by electron impact (EI) method on a SSQ 710 Finnigan spectrometer. High resolution mass spectra was performed by Einor Nilsson, University of Lund, Sweden. Melting points (uncorrected) were determined on a Büchi B-545 apparatus or a Reichert Kofler hot stage. Column chromatography was carried out by using Merck Kieselgel F_{254} or Aluminium oxide 90 (70–230 mesh). The substances were developed with the van Urk reagent (2% *p*-dimethylaminobenzaldehyde in EtOH–50% H_2SO_4, 1:1).

3.1.1. Cyclohexane-1,4-dione bisphenylhydrazone (4a). Cyclohexane-1,4-dione bisphenylhydrazone **4a** was obtained in accordance with Ref. 20 in 98% yield by boiling a mixture of cyclohexane-1,4-dione (5.6 g, 45 mmol) and phenylhydrazine (10.9 mL, 110 mmol) in ethanol (90 mL) for 3 min in the presence of glacial acetic acid (0.1 mL). Mp 150°C (lit.[20] 150–151°C).

3.1.2. Indolo[3,2-*b*]carbazole (1a) (a modification of Robinson's[8] method). Compound **4a** (8.80 g, 30 mmol) was added portionwise to a mixture of AcOH and H_2SO_4 (1:4, 40 mL), cooled to 0°C. After 5 min of stirring the mixture was quickly heated to 50–55°C, and thereafter, the temperature was increased slowly. At 84–87°C the mixture changed colour from bright raspberry to grey-green and the temperature jumped up to 110°C. The reaction mixture was kept at this temperature for 10–15 min, then allowed to cool and left overnight, before the mixture was diluted with EtOH. After 1 h a greenish precipitate was collected, washed carefully with water to neutral pH and dried to give pure **1a** (3.07 g, 40%). To increase the yield the first 100 mL of washings was combined with the mother liquid, and the mixture was evaporated in vacuo to remove EtOH and part of the AcOH. The rest was diluted with EtOH, and the precipitate obtained (mainly containing **1a**) was collected and washed carefully with water, dried and finally purified by reflux in DMF. The insoluble residue was collected and dried at 140°C for 24 h to give further **1a** (0.53 g, total yield 47%). The filtrate after removing the second precipitate was diluted with water and basified by 2 M NaOH to pH 9. The resulting fine precipitate was collected, and washed carefully with water to give pure 3-aminocarbazole **11a** (yield 16%). Mp 254–255°C (lit.[21] 254°C). IR (KBr) 3401, 3048, 1608, 1584, 1495, 1461, 1325, 1226, 1143, 860, 804, 743 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.76 (1H, NH), 7.91 (1H, d, J=7.6 Hz), 7.41 (1H, d, J=8.2 Hz), 7.31 (1H, d, J=2.3 Hz), 7.28 (1H, dd, J=7.6, 7.4 Hz), 7.22 (1H, d, J=8.0 Hz), 7.04 (1H, dd, J=8.0, 7.4 Hz), 6.82 (1H, dd, J=8.2, 2.3 Hz), 4.61 (2H, NH_2); ^{13}C NMR (DMSO-d_6) δ 141.13 (s), 140.15 (s), 132.76 (s), 124.72 (s), 123.00 (d), 122.15 (s), 119.70 (d), 117.36 (d), 115.14 (d), 111.06 (d), 110.61 (d), 103.77 (d).

3.1.3. Cyclohexane-1,4-dione *bis*-(*p*-methoxyphenyl)-hydrazone (4b). A suspension of *p*-methoxyphenylhydrazine hydrochloride (3.5 g, 20 mmol) in water (50 mL) was stirred rapidly for 10 min before 2 M NaOH (10 mL) was added dropwise. *p*-Methoxyphenylhydrazine began to precipitate during the addition and 2 min after completion of addition, the precipitate was collected and dried under vacuum on the filter wrapped in foil to give *p*-methoxyphenylhydrazine (2.34 g, 85%), mp 63–64°C (lit.[22] 64–65°C).

To a solution of cyclohexane-1,4-dione (0.905 g, 8.08 mmol) in absolute EtOH (30 mL) was added freshly prepared *p*-methoxyphenylhydrazine (2.03 g, 14.70 mmol) in several portions. The reaction mixture was stirred for 20 min under light protection, then cooled in an ice bath. The solid was collected, washed with cold EtOH (5 mL), and dried in the same manner as *p*-methoxyhenylhydrazine to give **4b** (1.75 g, 68%) as a brown powder. Mp 115°C (decomp.) The product stored at −18°C. MS EI *m*/*z*: 351 $[M-1]^+$ (100); IR (KBr) 3428, 1604, 1509, 1239, 1085, 1032, 824 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.32 (2H, s, NH), 7.03 (4H, d, J=9.0 Hz), 6.77 (4H, d, J=9.0 Hz), 3.64 (6H, s, OMe), 2.60 (4H, m, CH_2), 2.53 (4H, m, CH_2); ^{13}C NMR (DMSO-d_6) δ 152.13 (s), 146.41 (s), 140.72 (s), 114.15 (d), 113.44 (d), 55.14 (q), 29.30 (t), 25.72 (t).

3.1.4. Indolisation of cyclohexane-1,4-dione bis-(*p*-methoxyphenyl)-hydrazone (4b) in PPSE. A mixture of P_2O_5 (4.97 g, 35 mmol) and $(Me_3Si)_2O$ (11.90 mL, 56 mmol) in CH_2Cl_2 (35 mL) was refluxed for 35 min, before the flask was equipped with a distillation head and the solvent was evaporated in vacuo. The temperature was quickly raised to 160°C, whereafter the heating was stopped. The mixture was allowed to cool to 107°C and then compound **4b** (1.73 g, 4.92 mmol) was added in small portions to the freshly prepared PPSE. The temperature of reaction mixture was kept between 104 and 112°C for 5 min and then poured into iced water. After 1 h a precipitate was slowly filtered off, washed carefully with water, 0.5 M NaOH solution and finally water to give a crude mixture of **1b**,**5b** and **7b** (1.12 g). The mixture was suspended in CH_3CN (30 mL), refluxed for 5 min and filtered. The acetonitrile solution, containing mainly **5b** was purified by column chromatography (hexane–EtOAc 2:1) to give **5b** (165 mg, 11% from **4b**). Sublimation of this material at 213–215°C at 0.1 mm Hg for 24 h gave analytically pure 2,11-dimethoxyindolo[2,3-*c*]carbazole (**5b**) as a fine greenish powder. The residue, which after washing with acetonitrile contained mainly **1b** and **7b**, was refluxed for 12 h in diglyme in the presence of 5% Pd/C (70 mg) and air. Once all of **7b** had degradated (as judged by TLC), the solid, containing Pd/C, was filtered and washed with DMF and acetone. The combined filtrate was evaporated in vacuo and the residue was treated with Boc_2O (1.52 g, 6.95 mmol) and DMAP (0.193 g, 1.58 mmol) in THF (12 mL) for 4 h at room temperature. The reaction mixture was diluted with $CHCl_3$, washed twice with water, dried ($MgSO_4$), evaporated in vacuo. The remaining residue was purified twice by column chromatography (hexane–EtOAc 2.2:1) and then (hexane–EtOAc 5:1) to give 5,11-di-*t*-butyloxycarbonyl-2,8-dimethoxyindolo[3,2-*b*]carbazole (**8b**) (503 mg, 20%, calc. for **4b**). The product was crystallised from dioxane to give slightly pinkish crystals. The substance **8b** was deprotected during 8 h at 205°C, 0.1 mm Hg to give a quantitative yield of 2,8-dimethoxyindolo[3,2-*b*]carbazole (**1b**) as a fine greenish powder.

3.1.5. 2,8-Dimethoxyindolo[3,2-*b*]carbazole (1b). Mp >410°C. Anal. calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 75.83; H, 4.97; N, 8.68. IR (KBr) 3401,

1522, 1489, 1467, 1279, 1216, 1204, 1157, 1031, 841, 818, 798, 607 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.73 (2H, s, NH), 8.05 (2H, s, H-6/12), 7.75 (2H, d, J=2.5 Hz, H-1/7), 7.34 (2H, d, J=8.4 Hz, H-4/10), 7.00 (2H, dd, J=8.4, 2.5 Hz, H-3/9), 3.85 (6H, s, OMe); ^{13}C NMR (DMSO-d_6) δ 152.39 (s), 136.06 (s), 136.62 (s), 122.93 (s), 122.83 (s), 114.52 (d), 111.05 (d), 103.31 (d), 100.47 (d), 55.67 (q).

3.1.6. 2,11-Dimethoxyindolo[2,3-*c*]carbazole (5b). Mp 231–232°C. Anal. calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found: C, 76.11; H, 5.26; N, 8.65. IR (KBr) 3389, 3346, 1576, 1489, 1479, 1292, 1219, 1143, 1091, 1038, 789, 602 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.24 (2H, s, NH), 8.14 (2H, d, J=2.2 Hz, H-1/12), 7.57 (2H, s, H-6/7), 7.50 (2H, d, J=8.8 Hz, H-4/9), 7.08 (2H, dd, J=8.8, 2.2 Hz, H-3/10), 3.99 (6H, s, OMe); ^{13}C NMR (DMSO-d_6) δ 152.37 (s), 134.99 (s), 134.31 (s), 122.02 (s), 115.07 (s), 133.88 (d), 111.84 (d), 110.47 (d), 104.28 (d), 55.25 (q).

3.1.7. 6,7-Dihydro-2,11-dimethoxy-indolo[2,3-*c*]carbazole (7b). The substance was identified by NMR in the reaction mixture after cyclisation of **4b**. ^1H NMR (DMSO-d_6) δ 10.81 (2H, s, NH), 7.22 (2H, d, J=8.8 Hz, H-4/9), 7.05 (2H, d, J=2 Hz, H-1/12), 6.69 (2H, dd, J=8.7, 2.3 Hz, H-3/10), 3.98 (4H, s, CH_2), 3.78 (6H, s, OMe).

3.1.8. 5,11-Di-(*t*-butoxycarbonyl)-2,8-dimethoxyindolo[3,2-*b*]carbazole (8b). Undergoes Boc-deprotection at temperature over 220°C; HRMS calcd for $C_{30}H_{32}N_2O_6$ 516.2260, found 516.2263; IR (KBr) 1716, 1490, 1449, 1434, 1380, 1306, 1202, 1155, 1022 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.91 (2H, bs, H-6/12), 8.15 (2H, d, J=9.0 Hz, H-4/10), 7.56 (2H, d, J=2.9 Hz, H-1/7), 7.07 (2H, dd, J=9.0, 2.9 Hz, H-3/9), 3.96 (6H, s, OMe), 1.83 (18H, s, 2×Boc); ^{13}C NMR ($CDCl_3$) δ 156.26 (s), 151.49 (s), 135.87 (s), 133.70 (s) 127.40 (s), 126.06 (s), 117.31 (d), 115.34 (d), 107.03 (d), 103.06 (d), 83.90 (s), 56.03 (q), 28.59 (q).

3.1.9. 5,8-Di-(*t*-butoxycarbonyl)-2,11-dimethoxyindolo[2,3-*c*]carbazole (9b). Mp 175–176°C. HRMS calcd for $C_{30}H_{32}N_2O_6$ 516.2260, found 516.2249; IR (KBr) 2976, 1719, 1484, 1316, 1157, 1122, 1027, 814, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.56 (2H, s, H-6/7), 8.36 (2H, d, J=9.1 Hz, H-4/9), 8.19 (2H, d, J=2.5 Hz, H-1/12), 7.15 (2H, dd, J=9.1, 2.5 Hz, H-3/10), 4.01 (6H, s, OMe), 1.80 (18H, s, 2×Boc). ^{13}C NMR ($CDCl_3$) δ 155.71 (s), 151.11 (s), 136.29 (s), 133.54 (s), 126.41 (s), 119.63 (s), 117.17 (d), 115.34 (d), 114.45 (d), 106.77 (d), 84.10 (s), 56.00 (q), 28.61 (q).

3.1.10. 5,8-Di-(*t*-butoxycarbonyl)-6,7-dihydro-2,11-dimethoxyindolo[2,3-*c*]carbazole (10b). The sample of **10b** was obtained by Boc-protection of the mixture **1b**, **5b** and **7b** (obtained after condensation of **4b**) by excess of Boc_2O in the presence of DMAP, followed by separating by preparative TLC (hexane–CH_2Cl_2 2:1; R_f(**10b**)=0.22, R_f(**9b**)=0.15, R_f(**8b**)=0.12). EI/MS (70 eV) (*m/z*): 518 $[M]^+$ (100); ^1H NMR ($CDCl_3$) δ 8.03 (2H, d, J=9.0 Hz, H-4/9), 7.00 (2H, d, J=2.8 Hz, H-1/12), 6.94 (2H, dd, J=9.0, 3.0 Hz, H-3/10), 4.32 (4H, s, CH_2), 3.90 (6H, s, OMe), 1.76 (18H, s, Boc).

3.1.11. 2,8-Dihydroxyindolo[3,2-*b*]carbazole (6). To a precooled (−78°C) suspension of **1b** (171 mg, 0.54 mmol) in dry CH_2Cl_2 (20 mL), a 1 M solution of BBr_3 in dichloromethane (21.64 mmol, 21.64 mL) was added during 25 min under a stream of Ar. The reaction mixture was stirred at −78°C for 10 h, and then during 9 h the temperature was allowed to increase to 21°C. The ambient temperature was kept for 24 h before the mixture was cooled to 0°C, slowly quenched by addition of a saturated NH_4Cl solution (2 mL), then diluted with H_2O (100 mL) and neutralised with NaOH solution. The resulting dark precipitate, mainly containing the hydroxyindolocarbazole **6**, was collected and washed with water and $CHCl_3$. To increase the solubility, **6** was then *O*-protected by TBDMS. Thus *t*-$BuMe_2SiCl$ (812 mg, 5.41 mmol) and imidazole (368 mg, 5.41 mmol) were added to a suspension of the precipitate in DMF (12 mL). After stirring at 21°C for 2 h the reaction was complete (as judged by TLC in hexane–EtOAc 2:1). The reaction mixture was poured onto ice, extracted with EtOAc, dried over $MgSO_4$, evaporated and then purified by flash chromatography (hexane–EtOAc 2:1) to give 2,8-di(*t*-butyldimethylsilyloxy)indolo[3,2-*b*]carbazole (**13**) (212 mg, 76%) as a light yellow powder. Then a solution of **13** (200 mg, 0.39 mmol) in THF (25 mL) was treated with *n*-Bu_4NF (1N solution in THF, 3.10 mL) at room temperature. After 5 min of stirring the deprotection was complete (TLC in hexane–EtOAc 2:1). The resulting suspension was diluted with EtOAc (100 mL) and washed with brine and then water. The combined organic solvents were then evaporated in vacuo to give **7** (103 mg, 92% from **13**) as a fine grey-greenish powder. Mp >410°C. HRMS calcd for $C_{18}H_{12}N_2O_2$ 288.0899, found 288.0923; IR (KBr) 1716, 1490, 1449, 1434, 1380, 1306, 1202, 1155, 1022 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.50 (2H, s, NH-5/11), 8.81 (2H, s, OH-2/8), 7.88 (2H, s, H-6/12), 7.46 (2H, d, J=2.2 Hz, H-1/7), 7.23 (2H, d, J=8.6 Hz, H-4/10), 6.86 (2H, dd, J=8.6, 2.2 Hz, H-3/9); ^{13}C NMR (DMSO-d_6) δ 149.72 (s), 135.61 (s), 135.26 (s), 123.23 (s) 122.58 (s), 114.70 (d), 110.78 (d), 105.02 (d), 100.11 (d).

3.1.12. 2,8-Di(*t*-butyldimethylsilyloxy)indolo[3,2-*b*]carbazole (13). Mp 194°C (decomp.). HRMS calcd for $C_{30}H_{40}N_2O_2Si_2$ 516.2628, found 516.2624; IR (KBr) 3391, 3102, 1586, 1461, 1396, 1325, 1195, 1155, 847, 810, 598 cm^{-1}; ^1H NMR (acetone-d_6) δ 9.86 (2H, s, NH-5/11), 8.08 (2H, s, H-6/12), 7.64 (2H, d, J=2.4 Hz, H-1/7), 7.35 (2H, d, J=8.6 Hz, H-4/10), 6.96 (2H, dd, J=8.6, 2.4 Hz, H-3/9), 1.05 (18H, s, *t*-Bu), 0.26 (12H, s, Me); ^{13}C NMR (acetone-d_6) δ 149.05 (s), 137.96 (s), 137.29 (s), 124.93 (s), 124.41 (s), 119.78 (d), 111.73 (d), 111.14 (d), 101.45 (d), 26.29 (q), 18.91 (s), −3.50 (q).

3.1.13. Bis(*p*-methoxyphenyl)phenylenediamine (12). A mixture of cyclohexane-1,4-dione (1.12 g, 10 mmol) and *p*-methoxyaniline (2.46 g, 20 mmol) in benzene (60 mL) was refluxed under Dean-Stark conditions. After 18 h the *p*-methoxyaniline was consumed (TLC hexane–EtOAc, 2:1) to produce a complex mixture. The mixture was kept for 24 h without treatment before **12** (R_f 0.65, bright brown colour under van Urk reagent) crystallised from the reaction mixture. Recrystallisation from EtOH gave **12** (410 mg, 13%) as a light brown powder. Mp 202–203°C (lit.[23] 199.5°C). MS EI *m/z*: 320 $[M]^+$ (100); IR (KBr) 3393, 2832, 1514, 1498, 1239, 1028, 823, 810 cm^{-1}; ^1H NMR

(DMSO-d_6) δ 7.46 (2H, s, NH), 6.91 (4H, d, J=8.9 Hz, ArH), 6.87 (4H, s), 6.79 (4H, d, J=8.9 Hz, ArH), 3.68 (6H, s, OMe); ^{13}C NMR (DMSO-d_6) δ 152.57 (s), 138.20 (s), 137.19 (s), 118.15 (d), 117.73 (d), 114.59 (d), 55.18 (q).

3.1.14. Condensation of bis(*p*-methoxyphenyl)phenylenediamine (12) in the presence Pd(OAc)$_2$. Compound **12** (200 mg, 0.63 mmol) was dissolved in degassed AcOH (10 mL) under an Ar flow at room temperature and $Pd(OAc)_2$ (317 mg, 1.38 mmol) was added to the solution in one portion. The temperature was quickly raised to 100°C and kept so for 5 h, whereupon **12** had been consumed (as judged by TLC in hexane–EtOAc 2:1). Upon the completion of the reaction a palladium mirror was observed. The solvent was evaporated and the residue was treated with Boc_2O (861 mg, 3.94 mmol) and DMAP (49.6 mg, 0.41 mmol) in THF (15 mL). After the usual work up the mixture was purified by flash chromatography (hexane–EtOAc 1:1) to give **9b** (31 mg, 10%) as a single product. Spectral data and melting point are in accordance with data, described above for **9b**.

3.1.15. Cyclohexane-1,4-dione bis-(*p*-fluorophenyl)-hydrazone (4c). To a suspension of *p*-fluorophenylhydrazine hydrochloride (4.07 g, 25 mmol) in water (30 mL) was added at room temperature a solution of NaOH (1.00 g, 25 mmol) in water (30 mL). After 15 min of stirring the light yellow solution obtained was extracted with EtOAc (3×100 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated in vacuo to give *p*-fluorophenylhydrazine (2.91 g, 23.5 mmol, 94%). Mp 32–33°C (lit.[24] 34°C).

To a solution of cyclohexane-1,4-dione (1.34 g, 12 mmol) in absolute EtOH (44 mL), the freshly obtained *p*-fluorophenylhydrazine in absolute EtOH (12 mL) was added dropwise. After 0.5 h a light yellow powder began to precipitate. After stirring at 21°C for 1 h 40 min the starting material was consumed (TLC hexane–EtOAc 4:1) and the reaction mixture was cooled to 0°C. The solid was collected, washed with cold EtOH (4 mL) and dried. Concentration of the mother liquid gave an additional amount of solid **4c** (total amount 1.50 g, 46%). Mp 127°C (decomp.); MS EI *m/z*: 327 $[M-1]^+$ (100); IR (KBr) 3445, 1611, 1509, 1247, 1213, 1110, 1087, 826, 627 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.60 (2H, s, NH), 7.03 (4H, m), 6.99 (4H, m), 2.60 (4H, m), 2.53 (4H, m); ^{13}C NMR (DMSO-d_6) δ 145.34 (s, J_{C-F}=315.0 Hz), 124.32 (s), 115.10 (d, J_{C-F}=22.0 Hz), 113.29 (d, J_{C-F}=7.3 Hz), 113.10 (s), 29.34 (t), 25.77 (t).

3.1.16. Indolisation of cyclohexane-1,4-dione bis-(*p*-fluorophenyl)hydrazone (4c) in PPA. The *p*-fluorophenylhydrazone **4c** (1.00 g, 3.05 mmol) was mixed with polyphosphoric acid (PPA) (12.5 g) at 0°C. The mixture was heated quickly to 80°C and then more slowly (during 10–15 min) to 185°C. Between 60 and 80°C the colour of the mixture changed from dark brown-reddish to light brown, and after 150°C it became greenish-yellow. The mixture was kept at 185–190°C for 8–10 min, before it was allowed to cool down over 2 h. The reaction mixture then was diluted with 95% EtOH to 150 mL. A fine grey-greenish solid, containing **1c**, was slowly filtered off and washed with water to pH 7, and dried. The filtrate was partly evaporated in vacuo and diluted with water. The solid was collected, washed with water, and dried to give a crude mixture (60 mg, more than three products according NMR). The residual filtrate was basified with 2 M NaOH to pH 9. The solid was collected and washed with water to give 3-amino-6-fluorocarbazole (**11c**) (125 mg, 21%). The crude solid of **1c** was suspended in CH_3CN (50 mL), reflux for 10 min, collected and washed with hot acetonitrile to give **1c** (435 mg, 49%) as a fine greenish solid.

3.1.17. 2,8-Difluoroindolo[3,2-*b*]carbazole (1c). Mp >410°C. Anal. calcd for $C_{18}H_{10}F_2N_2$: C, 73.97; H, 3.45; N, 9.58. Found: C, 74.10; H, 3.35; N, 9.47; IR (KBr) 3404, 2863, 2610, 2359, 1617, 1587, 1529, 1490, 1468, 1438, 1286, 1238, 1189, 1150, 1076, 1024, 915, 869, 847, 802, 589 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.07 (2H, s, NH), 8.14 (2H, s, H-6/12), 8.05 (2H, dd, J_{H1-F}=9.4 Hz, J_{H1-H3}=2.3 Hz, H-1/7), 7.42 (2H, dd, J_{H4-H3}=8.7 Hz, J_{H4-F}=4.4 Hz, H-4/10), 7.22 (2H, td, J_{H3-H4}=8.8 Hz, J_{H3-F}=9.3 Hz, J_{H3-H1}=2.5 Hz, H-3/9); ^{13}C NMR (DMSO-d_6) δ 155.89 (d, C-2,8, J_{C2-F}=229.95 Hz), 136.83 (d, C-1′, $J_{C1'-F}$=132.15 Hz), 122.97 (s), 122.91 (s), 122.89 (s), 113.14 (d, C-1 or C-3, J_{C1-F}=25.05 Hz), 111.16 (d, C-4/10, J_{C4-F}=8.92 Hz), 105.98 (d, C-3 or C-1, J_{C3-F}=23.47 Hz), 101.13 (d, C-6/12).

3.1.18. 3-Amino-6-fluorocarbazole (11c). Mp 229–230°C (decomp.). MS EI *m/z*: 201 $[M+1]^+$ (100); IR (KBr) 3393, 1577, 1502, 1464, 1227, 1150, 868, 811, 585 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.72 (1H, s, NH), 7.69 (1H, dd, J_{H5-F}=9.5 Hz, J_{H5-H7}=2.5 Hz, H-5), 7.33 (1H, dd, J_{H8-H7}=8.8 Hz, J_{H8-F}=4.5 Hz, H-8), 7.20 (1H, d, J_{H4-H2}=2.0 Hz, H-4), 7.18 (1H, d, J_{H1-H2}=8.5 Hz, H-1), 7.11 (1H, td, J_{H7-H8}=8.9 Hz, J_{H7-F}=9.4 Hz, J_{H7-H5}=2.5 Hz, H-7), 6.78 (1H, dd, J=8.5, 2.3 Hz H-2), 4.51 (2H, bs, NH_2); ^{13}C NMR (DMSO-d_6) δ 155.89 (s, J_{C6-F}=230.0 Hz), 141.11 (s), 136.66 (s), 134.01 (s), 122.77 (s, J_{C-F}=4.1 Hz), 122.42 (s, J_{C-F}=9.4 Hz), 116.07 (d), 112.35 (d, J_{C-F}=25.2 Hz), 111.43 (d), 111.37 (d, J_{C8-F}=8.9 Hz), 105.12 (d, J_{C-F}=23.0 Hz), 103.81 (d).

3.1.19. Cyclohexane-1,4-dione bis(*p*-bromophenyl)-hydrazone (4d). To a solution of cyclohexane-1,4-dione (2.464 g, 22.0 mmol) in absolute EtOH (40 mL) a solution of *p*-bromophenylhydrazine hydrochloride (8.936 g, 40 mol) in absolute EtOH (50 mL) was added dropwise during 10 min at rt. A solid soon started to precipitate. The reaction mixture was kept at 40°C for 1.5 h and then cooled. The solid was collected and washed with cold EtOH (10–15 mL) and dried to give **4d** (4.360 g, 49%) as light yellow solid. The substance was stored at −18°C. Mp 148–149°C; MS EI *m/z*: 449 $[M-1]^+$ (100); IR (KBr) 3436, 2485, 1487, 1240, 1070, 1011, 830, 541 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.91 (2H, s), 7.29 (4H, d, J=8.8 Hz), 7.02 (4H, d, J=8.8 Hz), 2.67 (4H, m), 257 (4H, m); ^{13}C NMR (DMSO-d_6) δ 149.55 (s), 145.71 (s), 131.32 (d), 114.38 (d), 109.09 (s), 31.76 (t), 29.29 (t), 25.97 (t), 23.27 (t).

3.1.20. Indolisation of cyclohexane-1,4-dione bis-(*p*-bromophenyl)hydrazone (4d). Compound **4d** (4.350 g, 9.67 mmol) was suspended in a precooled (5°C) mixture of glacial acetic and sulfuric acids (4:1, 25 mL). The mixture was heated quickly to 60°C and thereafter the heating was

continued slowly to reflux. Above 80°C the dark brown solution transformed into a green-yellow suspension. The mixture was kept at reflux for 3–5 min and then allowed to cool to room temperature. After 1 h it was diluted with EtOH (55 mL). The resulting suspension formed was kept for 1 h, when the precipitate was collected, washed carefully with water and dried to give **1d** (1.05 g, 26%) as a fine greenish-yellow powder. For purification the product was Boc-protected with Boc_2O (2.44 g, 11.16 mmol) and DMAP (0.124 g, 1.01 mmol) in THF (30 mL) during 4 h. The reaction mixture was diluted with $CHCl_3$ (350 mL), washed twice with water and evaporated. The solid was suspended in acetonitrile (30 mL), refluxed during 5 min, filtered off, washed with hot acetonitrile (8 mL) and dried to give analytically pure **8d** (1.42 g, 91%). Boc-indolocarbazole **8d** was deprotected during 6 h at 200°C, 0.1 mm Hg to give a quantitative yield of pure **1d** as a fine greenish powder.

3.1.21. 2,8-Dibromoindolo[3,2-*b*]carbazole (1d). Mp >410°C. Anal. calcd for $C_{18}H_{10}N_2Br_2$: C, 52.21; H, 2.43; N, 6.76; Br, 38.59. Found: C, 52.29; H, 2.36; N, 6.70; Br, 38.48. IR (KBr) 3394, 1468, 1446, 1285, 1235, 1178, 1054, 848, 811 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.28 (2H, s, NH), 8.46 (2H, d, J=1.7 Hz, H-1/7), 8.21 (2H, s, H-6/12), 7.49 (2H, dd, J=8.5, 1.7 Hz, H-3/9), 7.41 (2H, d, J=8.5 Hz, H-4/10); ^{13}C NMR (DMSO-d_6) δ 139.89 (s), 135.50 (s), 127.98 (d), 124.44 (s), 122.93 (d), 122.26 (s), 112.40 (d), 109.61 (s), 101.28 (d).

3.1.22. 2,8-Dibromo-5,11-di-*t*-butyloxycarbonylindolo[3,2-*b*]carbazole (8d). Undergoes Boc-deprotection at temperatures above 270°C. HRMS calcd for $C_{28}H_{26}N_2Br_2O_4$ 612.0259, found 612.0258; IR (KBr) 3418, 1719, 1465, 1431, 1373, 1338, 1305, 1155, 1028, 811, 765 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.88 (2H, s), 8.18 (2H, d, J=2.0 Hz), 8.16 (2H, d, J=8.8 Hz), 7.59 (2H, dd, J=8.8, 2.0 Hz), 1.83 (18H, s, Boc); ^{13}C NMR ($CDCl_3$): δ 151.12 (CO), 138.29 (s), 130.31 (d), 128.19 (s), 125.38 (s), 122.82 (d), 118.06 (2C, d and s), 116.47 (s), 107.32 (d), 84.82 (s), 28.67 (q).

3.1.23. 5,11-Bis(2-dimethylaminoethyl)indolo[3,2-*b*]carbazole (15a). A suspension of **1a** (2.00 g, 8.0 mmol) in DMSO (25 mL) was added dropwise to a suspension of NaH (1.02 g, 95% in oil, 40.0 mmol) in DMSO (25 mL) under N_2 flow. Then the reaction mixture was heated to 35°C. After 0.5 h of stirring the hydrochloride of 2-dimethylamino-1-chloroethane (2.53 g, 17.6 mol) in DMSO (20 mL) was added dropwise. The mixture was stirred at the same temperature under N_2 flow until complete consumption of **1a** had occurred. After 3 h the reaction mixture was poured onto ice (700 mL). The fine yellow powder obtained was collected, washed with water and dried to give pure **15a** (2.41 g). The filtrate was extracted with CH_2Cl_2 (3×100 mL). The collected organic phases were washed with water, dried over Na_2SO_4, evaporated in vacuo and dried under reduced pressure to give more of **15a** (0.502 g, total yield 92%). Mp 180–181°C; MS EI m/z: 398 $[M]^+$ (100), 384 $[M-Me+1]^+$ (80), 340 $[M-4Me+2]^+$ (55), 295 $[M-CH_2CH_2NMe_2-2Me-1]^+$ (60). IR (KBr) 3423, 2940, 2756, 1610, 1508, 1469, 1446, 1264, 1117, 1020, 833, 741, 546 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21 (2H, d, J=7.6 Hz), 8.05 (2H, s), 7.52 (2H, d, J=8.2 Hz), 7.44 (2H, dd, J=7.5, 7.3 Hz), 7.24 (2H, dd, J=7.2, 8.2 Hz), 4.55 (4H, t, J=7.5 Hz, $N-CH_2$), 2.78 (4H, t, J=7.5 Hz, $-CH_2-NMe_2$), 2.43 (12H, s, Me); ^{13}C NMR ($CDCl_3$) δ 140.99 (s), 135.45 (s), 125.30 (d), 122.44 (s), 122.40 (s), 119.77 (d), 117.73 (d), 107.69 (d), 98.16 (d), 56.58 (t), 45.46 (q), 41.40 (t).

3.1.24. 5,11-Bis(dimethylaminomethyl)indolo[3,2-*b*]carbazole (16). To a precooled (0°C) 40% water solution of Me_2NH (3.16 mL, 25 mmol), acetic acid (2.28 mL, 40 mmol) was added slowly, whilst maintaining a temperature below 5°C, followed by 37% aqueous solution of H_2CO (1.50 mL, 20 mmol). The resulting mixture was stirred for 10 min at 0°C and then added slowly under Ar flow to a suspension of **1a** (512 mg, 2 mmol) in DMA (15 mL) at room temperature. The resulting suspension was heated to 90°C and kept at this temperature for 10 min. The reaction mixture was then cooled and the solvent was evaporated in vacuo. Water (20 mL) was added to the residue and the resulting solid was collected, washed with water and dried to give 470 mg of **16** (64%) as a cream solid. HRMS calcd for $C_{24}H_{26}N_4$ 370.2157, found 370.2174. Mp >200°C (decomp.). IR (KBr) 1612, 1506, 1455, 1358, 1264, 1243, 1150, 1040, 866, 734 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.37 (2H, s), 8.26 (2H, d, J=7.7 Hz), 7.66 (2H, d, J=7.9 Hz), 7.44 (2H, dd, J=7.5, 7.9 Hz), 7.20 (2H, dd, J=7.5, 7.7 Hz), 5.05 (4H, s, CH_2), 2.33 (12H, s, Me); ^{13}C NMR (DMSO-d_6) δ 141.94 (s), 136.45 (s), 125.67 (d), 122.49 (s), 122.24 (s), 120.16 (d), 118.42 (d), 109.75 (d), 100.08 (d), 65.36 (t), 42.72 (q).

3.1.25. 5,11-Bis(hydroxymethyl)indolo[3,2-*b*]carbazole (17). To a suspension of **1a** (512 mg, 2.00 mmol) in DMA (17 mL), K_2CO_3 (828 mg, 6.00 mmol) and 37% aqueous solution of H_2CO (1.80 mL, 24 mmol) were added under Ar flow. The mixture was quickly heated to 110°C and then kept at the same temperature during 10 min. The hot solution was filtered from unreacted **1a** and the solvent was evaporated in vacuo. Water (20 mL) was added to the residue and the resulting solid was collected, washed with water and dried to give **17** (525 mg, 83%) as a cream solid. HRMS calcd for $C_{20}H_{16}N_2O_2$ 316.1212, found 316.1196. Mp >250°C (decomp.). IR (KBr) 3386, 1613, 1509, 1462, 1431, 1272, 1227, 1122, 1075, 1008, 984, 748 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.39 (2H, s), 8.24 (2H, d, J=7.6 Hz), 7.67 (2H, d, J=8.0 Hz), 7.47 (2H, dd, J=7.3, 8.0 Hz), 7.24 (2H, dd, J=7.3, 7.6 Hz), 6.40 (2H, t, J=6.9 Hz, OH), 5.89 (4H, d, J=6.9 Hz, CH_2); ^{13}C NMR (DMSO-d_6) δ 140.89 (s), 135.44 (s), 125.64 (d), 122.81 (s), 122.47 (s), 120.08 (d), 118.75 (d), 109.55 (d), 99.96 (d), 65.50 (t).

3.1.26. 5-*t*-Butyloxycarbonylindolo[3,2-*b*]carbazole (18). Compound **19** (3.77 g, 8.26 mmol) was dissolved in THF (140 mL), cooled to 0°C under Ar flow and then *n*-BuLi (25 mL, 1.6 M in pentane, 40 mmol) was added in portions during 40 min. The reaction was monitored by TLC (hexane–EtOAc 5:1). When the starting material was consumed the reaction mixture was quenched with saturated NH_4Cl (2 mL) and diluted with $CHCl_3$ (350 mL). The organic layer was washed with water (5×300 mL) to pH 7, dried and evaporated in vacuo. The crude product was suspended in acetone, filtered and washed with small

amounts of acetone to give **18** as a light coloured powder (2.12 g, 72%). The analytically pure sample was obtained by crystallisation from dioxane. HRMS calcd for $C_{23}H_{20}N_2O_2$ 356.1525, found 356.1519. At heating over 250°C to measure melting point undergoes Boc-deprotection. IR (KBr) 3416, 3385, 1723, 1442, 1358, 1311, 1157, 746 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.34 (1H, s, NH), 8.94 (1H, s, H-6), 8.29 (1H, d, J=7.1 Hz), 8.24 (1H, d, J=7.1 Hz), 8.17 (1H, s, H-11), 8.15 (1H, d, J=7.7 Hz), 7.55 (2H, m), 7.41 (2H, m), 7.19 (1H, dd, J=7.3, 7.5 Hz), 1.83 (9H, s, Boc); ^{13}C NMR (DMSO-d_6) δ 150.69 (s), 141.17 (s), 138.50 (s), 136.96 (s), 131.99 (s), 127.11 (d), 126.02 (d), 125.78 (s), 124.51 (s), 123.04 (d), 122.91 (s), 122.67 (s), 120.15 (d), 119.99 (d), 118.50 (d), 115.90 (d), 110.97 (d), 106.61 (d), 100.99 (d), 83.74 (s), 27.97 (q).

3.1.27. 5-*t*-Butyloxycarbonyl-11-ethyloxycarbonylindolo[3,2-*b*]carbazole (21). To a vigorously stirred suspension of **18** (356 mg, 1.00 mmol) in CH_2Cl_2 (12 mL), 50% aqueous solution of NaOH (1 mL), n-Bu_4NHSO_4 (67.8 mg, 0.20 mmol) and ClCOOEt (0.122 mL, 1.25 mmol) were all added. After 30 min of stirring the reaction was complete (as judged by TLC in hexane–EtOAc 5:1). The mixture was diluted with CH_2Cl_2 (25 mL) and decanted. The NaOH layer was washed with CH_2Cl_2 (2×5 mL). The combined organic phases were carefully washed with water to pH 7, dried over Na_2SO_4, evaporated in vacuo and purified by flash chromatography on a short column (hexane–EtOAc 5:1) to give **21** (180 mg, 84%). This material was crystallised from CH_3CN to give white crystals. Mp 167–168°C (decomp.). Anal. calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.94; H, 5.60; N, 6.61. IR (KBr) 3553, 3476, 3413, 1722, 1637, 1616, 1478, 1436, 1379, 1308, 1291, 1243, 1223, 1165, 1152, 1052, 759, 743, 620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.93 (1H, s), 8.91 (1H, s), 8.28 (3H, m), 8.21 (1H, d, J=8.2 Hz), 7.57 (2H, m), 7.45 (2H, m), 4.63 (2H, q, J=7.1 Hz, CH_2), 1.79 (9H, s, Boc), 1.56 (3H, t, J=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 152.83 (s), 151.50 (s), 139.48 (s), 139.25 (s), 135.60 (s), 135.21 (s), 127.46 (d), 127.42 (d), 126.72 (s), 126.48 (s), 126.16 (s), 126.13 (s), 123.51 (d), 123.27 (d), 119.92 (2C, d), 116.58 (d), 116.55 (d), 107.16 (d), 107.02 (d), 84.19 (s), 63.35 (t), 28.69 (q), 14.79 (q).

3.1.28. 5-Ethoxycarbonylindolo[3,2-*b*]carbazole (23). A solution of **21** (270 mg, 0.63 mmol) in dry CH_2Cl_2 (26 mL) was cooled to 0°C under Ar flow, and then TFA (2.70 mL) was added in portions. The reaction mixture was stirred for 15 min at 0°C before the ice bath was removed and stirring continued for 2.5 h to complete the reaction (TLC in hexane–EtOAc 5:1). The reaction mixture was evaporated and re-evaporated in vacuo with CH_2Cl_2. The residue was crystallised from CH_3CN to give **23** (171 mg, 83%) as cream crystals. Mp 253–254°C. Anal. calcd for $C_{21}H_{16}N_2O_2$: C, 76.71; H, 4.91; N, 8.53. Found: C, 76.56; H, 4.89; N, 8.42. IR (KBr) 3477, 3411, 1731, 1638, 1616, 1444, 1372, 1294, 1182, 1048, 750, 623 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.38 (1H, s, NH), 8.96 (1H, s, H-6), 8.29 (1H, d, J=7.3 Hz), 8.27 (1H, d, J=8.2 Hz), 8.21 (1H, d, J=8.0 Hz), 8.18 (1H, s, H-12), 7.52 (2H, m), 7.43 (2H, m), 7.19 (1H, dd, J=7.3, 7.7 Hz), 4.62 (2H, q, J=7.1 Hz, CH_2), 1.56 (3H, t, J=7.1 Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 151.99 (s), 141.14 (s), 138.35 (s), 137.03 (s), 131.81 (s), 127.18 (d), 126.05 (d), 125.88 (s), 124.57 (s), 123.23 (d), 122.92 (s), 122.62 (s), 120.23 (d), 120.15 (d), 118.48 (d), 115.91 (d), 110.96 (d), 106.65 (d), 101.09 (d), 63.03 (t), 14.33 (q).

3.1.29. 5-Hydroxymethylindolo[3,2-*b*]carbazole (24). Compound **23** (40 mg, 0.12 mmol) was dissolved in THF (5 mL) and cooled to 0°C under Ar flow. $LiAlH_4$ (46 mg, 12.2 mmol) was then added in several portions, after which, the temperature was allowed to reach rt. After 15 min at rt the reaction was completed, as judged by TLC (hexane–EtOAc 2.5:1). The reaction mixture was quenched with a solution of saturated NH_4Cl (0.5 mL), diluted with EtOAc (25 mL) and washed with water (4×30 mL). The organic phase was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column flash chtomatography (hexane–EtOAc 2.5:1) to give **24** (31 mg, 90%) as light coloured plates. Mp 128°C (decomp.). HRMS calcd for $C_{19}H_{14}N_2O$ 286.1106, found 286.1116; IR (KBr) 3399, 1515, 1458, 1322, 1250, 1226, 989, 847, 745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.09 (1H, s), 8.34 (1H, s), 8.23 (1H, d, J=7.7 Hz), 8.19 (1H, d, J=8.0 Hz), 8.14 (1H, s), 7.64 (1H, d, J=8.2 Hz), 7.47 (2H, m), 7.39 (1H, dd, J=8.2, 7.3 Hz), 7.19 (1H, dd, J=7.7, 7.3 Hz), 7.15 (1H, dd, J=7.3, 7.3 Hz), 6.36 (1H, t, J=7.0 Hz, OH), 5.87 (2H, d, J=7.0 Hz, CH_2); ^{13}C NMR (DMSO-d_6) δ 141.10 (s), 140.87 (s), 135.41 (s), 135.07 (s), 125.53 (2C, d), 122.78 (s), 122.61 (s), 122.58 (s), 122.50 (s), 120.21 (d), 120.07 (d), 118.55 (d), 117.83 (d), 110.60 (d), 109.40 (d), 100.64 (d), 99 (d), 65.47 (t).

3.1.30. 5-*t*-Butyloxycarbonyl-11-hydroxymethylindolo[3,2-*b*]carbazole (25). To a solution of **18** (295 mg, 0.647 mmol) in 95% EtOH (45 mL) a 37% aqueous solution of H_2CO (0.96 mL, 12.94 mmol) was added, followed by the slow addition of a solution of K_2CO_3 (357 mg, 2.59 mmol) in water (2 mL). The reaction mixture was stirred at room temperature for 1.5 h, before it was concentrated in vacuo to 6–7 mL. The residue was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, evaporated in vacuo and purified by column chromatography with a gradient system from $CHCl_3$–hexane 2:1 to $CHCl_3$. After chromatography some **18** (45 mg) was recovered and **25** was isolated (178 mg, 88% yield based on recovered **18**). Washing **25** with a hot solution of 10% EtOH/n-heptane gave analytically pure **25** as a pinkish crystals. Mp 170°C (decomp.). Anal. calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.47; H, 5.66; N, 7.16. IR (KBr) 3436, 2974, 1720, 1512, 1482, 1448, 1379, 1311, 1226, 1155, 986, 763, 743 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.96 (1H, s), 8.44 (1H, s), 8.27 (2H, m), 8.20 (1H, d, J=7.5 Hz), 7.70 (1H, d, J=8.0 Hz), 7.51 (2H, m), 7.44 (1H, dd, J=7.5, 7.3 Hz), 7.26 (1H, dd, J=7.1, 7.0 Hz), 6.47 (1H, t, J=6.6 Hz, OH), 5.90 (2H, d, J=6.6 Hz, CH_2), 1.79 (9H, s, Boc); ^{13}C NMR (DMSO-d_6) δ 150.60 (s), 140.91 (s), 138.48 (s), 137.03 (s), 132.41 (s), 127.20 (d), 126.08 (d), 125.72 (s), 124.46 (s), 123.14 (d), 122.86 (s), 122.78 (s), 120.00 (2C, d), 119.34 (d), 115.93 (d), 109.93 (d), 106.59 (d), 100.33 (d), 83.85 (s), 65.52 (t), 27.91 (q).

3.1.31. 5-*t*-Butyloxycarbonyl-11-(2-dimethylaminoethyl)indolo[3,2-*b*]carbazole (26). To a solution of **18** (700 mg, 1.97 mmol) in DMF (24 mL) under Ar flow, was added

t-BuOK (551 mg, 4.82 mmol) during 5 min. The resulting solution was stirred for 10 min at room temperature. Freshly prepared 2-dimethylamino-1-chloroethane as a free base[25] (ca 3 eq.) was then added, followed by KI (981 mg, 5.91 mmol). The reaction mixture was stirred at 21°C for 1 h, before the temperature was increased to 50°C, and stirring was continued for 2.5 h further. The solvent was evaporated in vacuo, and the residue was diluted with CH_2Cl_2 (250 mL) and water (120 mL). The aqueous phase was washed with CH_2Cl_2, the combined organic phases were washed with water, dried, evaporated and purified by gradient flash chromatography (CH_2Cl_2→CH_2Cl_2–MeOH 9:1) to give **26** (505 mg, 56%). Crystallisation from acetonitrile gave **26** as brownish crystals. Mp 91°C. HRMS calcd for $C_{27}H_{29}N_3O_2$ 427.2260, found 427.2260; IR (KBr) 2971, 2765, 1718, 1510, 1443, 1368, 1308, 1226, 1153, 1044, 835, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.95 (1H, s), 8.37 (1H, s), 8.32 (1H, d, J=7.5 Hz), 8.25 (1H, d, J=8.1 Hz), 8.19 (1H, d, J=7.6 Hz), 7.61 (1H, d, J=8.1 Hz), 7.52 (2H, m), 7.40 (1H, dd, J=7.4, 7.4 Hz), 7.23 (1H, dd, J=7.4, 7.5 Hz), 4.58 (2H, t, J=6.8 Hz, CH_2), 2.70 (2H, t, J=6.8 Hz, CH_2), 2.25 (6H, s, Me), 1.78 (9H, s, Boc); ^{13}C NMR (DMSO-d_6) δ 150.64 (s), 141.29 (s), 138.49 (s), 137.43 (s), 132.05 (s), 127.22 (d), 126.16 (d), 125.80 (s), 124.60 (s), 123.06 (d), 122.42 (s), 122.34 (s), 120.28 (d), 120.09 (d), 118.70 (d), 115.92 (d), 109.32 (d), 106.71 (d), 99.68 (d), 83.81 (s), 57.12 (t), 45.58 (q), 41.00 (t), 27.93 (q).

3.1.32. 5-(2-Dimethylaminoethyl)indolo[3,2-*b*]carbazole (15b). To a precooled (0°C) solution of **26** (220 mg, 0.515 mmol) in MeOH (8 mL) under Ar flow, was added freshly prepared 2 M solution of MeONa in methanol (16 mL) during 30 min. After 10 min the cooling bath was removed and the reaction mixture was stirred at 21°C under Ar for 72 h, after which time the starting material had been consumed (as judged by TLC in $CHCl_3$–MeOH, 9:1). The solvent was evaporated, and the residue was partitioned in CH_2Cl_2 and water. The water phase was extracted twice with CH_2Cl_2. The combined organic phases were then washed with water to pH 7, dried by Na_2SO_4, evaporated in vacuo and suspended in acetone (3 mL). The light yellow precipitate obtained was collected and washed with acetone (2 mL) to give pure **15b** (125 mg, 74%). Mp 225–226°C. HRMS calcd for $C_{22}H_{21}N_3$ 327.1735, found 327.1722; IR (KBr) 3406, 3046, 2919, 2826, 1614, 1516, 1470, 1447, 1325, 1234, 1163, 1033, 739 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.09 (1H, s, NH), 8.27 (1H, s), 8.25 (1H, d, J=7.5 Hz), 8.22 (1H, d, J=7.0 Hz), 8.15 (1H, s), 7.54 (1H, d, J=8.1 Hz), 7.48 (1H, d, J=8.0 Hz), 7.39 (2H, m), 7.15 (2H, m), 4.55 (2H, t, J=6.9 Hz, CH_2), 2.69 (2H, t, J=6.9 Hz, CH_2), 2.26 (6H, s, Me); ^{13}C NMR (DMSO-d_6) δ 141.18 (s), 141.08 (s), 135.48 (s), 135.08 (s), 125.58 (d), 125.52 (d), 122.64 (s), 122.60 (s), 122.24 (s), 122.17 (s), 120.28 (d), 120.24 (d), 117.77 (d), 117.68 (d), 110.54 (d), 108.67 (d), 100.73 (d), 98.96 (d), 57.04 (t), 45.60 (q), 40.96 (t).

3.1.33. 5-*t*-Butyloxycarbonyl-11-methylindolo[3,2-*b*]carbazole (20). To a vigorously stirred suspension of **18** (168 mg, 0.47 mmol) in CH_2Cl_2 (7.5 mL), 50% aqueous solution of NaOH (1 mL), *n*-Bu_4NBr (30 mg, 94 mmol) and MeI (0.18 mL, 2.82 mmol) were added. After stirring for 1 h 40 min the reaction was complete (as judged by TLC in hexane–EtOAc 5:1) and the mixture was diluted with CH_2Cl_2 (20 mL) and decanted. The basic layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic extracts were carefully washed with water to pH 7, dried over Na_2SO_4 and evaporated in vacuo. The product was crystallised from CH_3CN to give analytically pure pale crystals (106 mg) of **20**. Flash chromatography of the evaporated mother liquid (hexane–EtOAc 4:1) gave an additional quantity of **20** (43 mg, total yield 86%). Mp 164–165°C. HRMS calcd for $C_{24}H_{22}N_2O_2$ 370.1681, found 370.1697; IR (KBr) 3428, 2925, 1727, 1510, 1474, 1440, 1368, 1312, 1292, 1255, 1148, 829, 739, 682 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.97 (1H, s, H-6), 8.37 (1H, s, H-12), 8.30 (1H, d, J=7.3 Hz), 8.25 (1H, d, J=8.2 Hz), 8.20 (1H, d, J=7.7 Hz), 7.62 (1H, d, J=8.2 Hz), 7.51 (2H, m), 7.43 (1H, dd, J=7.5, 7.0 Hz), 7.23 (1H, dd, J=7.3, 7.7 Hz), 3.99 (3H, s, Me), 1.79 (9H, s, Boc); ^{13}C NMR (DMSO-d_6) δ 150.60 (s), 141.82 (s), 138.46 (s), 138.06 (s), 131.99 (s), 127.15 (d), 126.11 (d), 125.78 (s), 124.54 (s), 123.06 (d), 122.24 (s), 122.17 (s), 120.05 (d), 119.99 (d), 118.61 (d), 115.90 (d), 109.04 (d), 106.63 (d), 99.48 (d), 83.77 (s), 29.22 (q), 27.90 (q).

3.1.34. 5-Methylindolo[3,2-*b*]carbazole (22). Compound **20** was deprotected by sublimation at 200°C for 4 h in quantitative yield to give the product **22** as greenish-yellow crystals. Mp 309–310°C. Anal. calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.34; H, 5.14; N, 10.42. IR (KBr) 3400, 1613, 1514, 1477, 1450, 1447, 1429, 1321, 1282, 1265, 1240, 1104, 1002, 874, 745, 688, 565 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.07 (1H, s, NH), 8.25 (1H, s), 8.23 (1H, d), 8.21 (1H, d, J=7.6 Hz), 8.16 (1H, s), 7.55 (1H, d, J=8.1 Hz), 7.46 (2H, m), 7.39 (1H, dd, J=7.2, 7.8 Hz), 7.16 (2H, m), 3.95 (3H, s, Me); ^{13}C NMR (DMSO-d_6) δ 141.74 (s), 141.06 (s), 136.27 (s), 135.07 (s), 125.58 (d), 125.49 (d), 122.63 (2C, s), 122.10 (s), 122.02 (s), 120.20 (d), 120.13 (d), 117.73 (2C, d), 110.60 (d), 108.50 (d), 100.72 (d), 98.88 (d), 29.16 (q).

References

1. Bergman, J.; Janosik, T.; Wahlström, N. *Adv. Heterocycl. Chem.* **2001**, *80*, 1–71.
2. Bjeldanes, L.; Kim, J.; Grose, K.; Bartholomew, J.; Bradfield, C. *Proc. Natl Acad. Sci. USA* **1991**, *88*, 9543–9547.
3. Rannug, U.; Rannug, A.; Sjöberg, U.; Li, H.; Westerholm, R.; Bergman, *J. Chem. Biol.* **1995**, *2*, 841–845.
4. Wei, Y.; Helleberg, H.; Rannug, U.; Rannug, A. *Chem. Biol. Interact.* **1998**, *110*, 39–55.
5. Gonzalez, F. J.; Fernandez-Salguero, P.; Ward, J. M. *J. Toxicol. Sci.* **1996**, *21*, 273–277.
6. Bergman, J. *Tetrahedron* **1970**, *26*, 3353–3355.
7. Tholander, J.; Bergman, J. *Tetrahedron* **1999**, *55*, 12577–12594.
8. Robinson, B. *J. Chem. Soc., Perkin Trans. 1* **1963**, 3097–3099.
9. (a) Teuber, H.; Vogel, L. *Chem. Ber.* **1970**, *103*, 3302–3318. (b) Teuber, H.; Vogel, L. *Chem. Ber.* **1970**, *103*, 3319–3342.
10. Kistenmacher, A.; Müllen, K. *J. Heterocycl. Chem.* **1992**, *29*, 1237–1239.

11. Bergman, J.; Janosik, T.; Yudina, L.; Desarbre, E.; Lidgren, G.; Venemaln, L. *Tetrahedron* **2000**, *56*, 1911–1916.
12. Wei, Y.-D.; Bergander, L.; Rannug, U.; Rannug, A. *Arch. Biochem. Biophys.* **2000**, *383*, 99–107.
13. Chen, Y.-H.; Riby, J.; Srivastava, P.; Bartholomew, J.; Denison, M.; Bjeldanes, L. *J. Biol. Chem.* **1995**, *270*, 22548–22555.
14. Formisyn, P.; Tran-Minh, C.; Bourgois, J. *Fr. Lett. Appl. Microbiol.* **1994**, *19*, 244–246.
15. Bergman, J.; Pelcman, B. *J. Org. Chem.* **1989**, *54*, 824–828.
16. Bergman, J.; Norrby, P.-O.; Sand, P. *Tetrahedron* **1990**, *46*, 6113–6124.
17. Gillner, M.; Bergman, J.; Cambillau, C.; Alexandersson, M.; Fernström, B. *Mol. Pharmacol.* **1993**, *44*, 336–345.
18. (a) Zegar, I.; Gräslund, A.; Bergman, J.; Nordèn, B.; Eriksson, M. *Chem. Biol. Interact.* **1989**, *72*, 277–293. (b) Sehlstedt, U.; Aich, P.; Bergman, J.; Vallberg, H.; Norden, B.; Gräslund, A. *J. Mol. Biol.* **1998**, *278*, 31–56.
19. Tholander, J.; Bergman, J. *Tetrahedron* **1999**, *55*, 6243–6260.
20. Gardner, H.; Haynes, R.; Brandon, A. *J. Org. Chem.* **1957**, *22*, 1206–1210.
21. Fuerst, B. *Chem. Ber.* **1951**, *84*, 83–86.
22. Grandberg, I. I.; Bobrova, N. I. *Chem. Heterocycl. Compd* **1973**, *9*, 196–199.
23. Mitchell, J.; Pausacker, K. H. *J. Chem. Soc.* **1954**, 4502–4504.
24. Miles, P.; Suschitzky, H. *Tetrahedron* **1963**, *19*, 385–390.
25. Hickmott, P. W.; Wood, S.; Murray-Rust, *J. Chem. Soc., Perkin Trans. 1* **1985**, 2033–2038.