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REGIOSELECTIVE *ORTHO*-DIRECTED METALATION AND ELECTROPHILIC SUBSTITUTION OF INDOLE- AND INDOLINE-5-(*N*-PHENYL)CARBOXAMIDES

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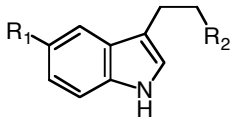
Abstract - Treatment of 1-(*N,N*-dimethylsulfamoyl)-1*H*-indole-5-(*N*-phenyl)carboxamide (**1**) with *s*-butyllithium at -80°C in THF followed by addition of an electrophile gave exclusively the product of C-2 substitution. A second metalation-substitution cycle on this product led to incorporation of the electrophile exclusively at C-4. In the case of the analogous indoline derivative (**2**), the first *o*-metalation occurred at C-4 while C-6 was the site of the second *o*-metalation.

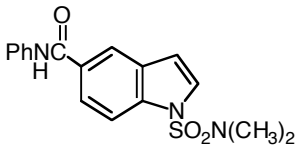
The ubiquity of substituted indoles as constituents of natural products and medicinally important compounds justifies the development of methodologies for their preparation. One of the most efficient techniques described over the last few years for the regioselective introduction of substituents on the indole nucleus is that of directed lithiation followed by electrophilic substitution. Thus, the reaction of N-protected indole with a lithiated base generally leads to exclusive lithiation at the C-2 position where the most acidic hydrogen atom is found.[1,2] However, it has been recently shown that lithiation can be directed mainly to the C-7 position by using an appropriate N-protecting group (e.g. the 2,2-diethylbutanoyl group), in which case the anion-stabilizing carbonyl group is, for kinetic and steric reasons, in closer proximity to the C-7 than the C-2 position.[3] Lithiation at other positions of the indole nucleus can be favored by incorporating anion-stabilizing substituents at an *ortho* position. Thus, the presence of a carboxylic acid[4] or a *N,N*-diethylcarboxamide group[5] at C-2 leads to C-3 lithiated products in the presence of *s*-butyllithium. Using

the *N,N*-diethylcarbamate of 5-hydroxyindole, Snieckus was able to achieve *o*-directed lithiation (followed by electrophilic substitution) at the C-4 position.[6] A second substituent, this time at the C-6 position, could be introduced by resubjecting the product to the same *o*-metalation conditions. In all cases, lithiation at the more labile C-2 position was prevented by the presence of a bulky trialkylsilyl N-1 blocking group.

The metalation of indoline derivatives, which can be easily oxidized to the corresponding indoles, has also been studied, though to a lesser extent. For instance, while N-Boc protected indoline affords the C-7-lithiated species when treated with *s*-butyllithium,[7] the closely related *t*-butylamidine-protected indoline leads to only C-2 metalation under similar reaction conditions.[8]



Sumatriptan: $R_1=CH_2SO_2NHCH_3$
$R_2=N(CH_3)_2$
5-CT: $R_1=CONH_2$
$R_2=NH_2$



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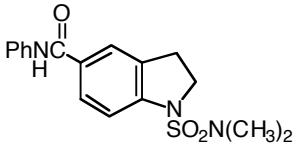

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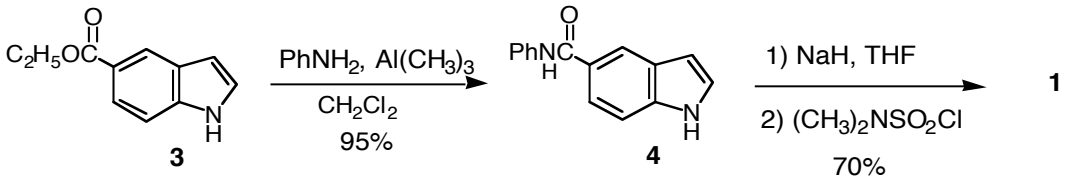
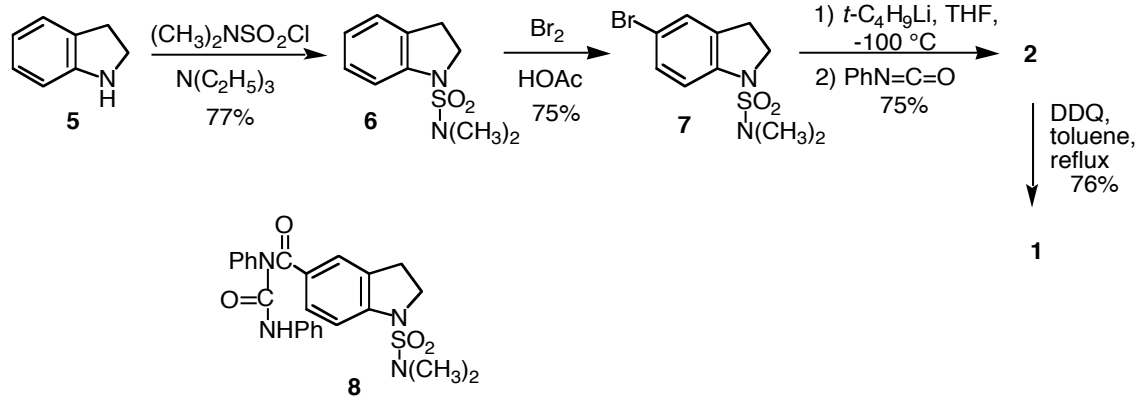
As part of a program aimed at the development of new CNS agents related to the selective serotoninergic ligands sumatriptan (3-[2-(dimethylamino)ethyl]-*N*-methyl-1*H*-indole-5-methanesulfonamide) and 5-CT (5-carboxamidotryptamine),[9] we decided to study *ortho* metalation reactions of 5-carboxamide derivatives of indole and indoline as a first step to accessing 4- and 6-substituted analogues of these compounds. By analogy with our work in the area of *o*-metalation of β-carboline-3-carboxamides,[10] the *N*-phenylcarboxamide group was chosen as the *o*-directing group[11] and the *N,N*-dimethylsulfamoyl moiety as the indolic NH protecting group. This protecting group, as we[10] and others[12,13] have shown, is highly stable to the strongly basic conditions of the *o*-metalation reaction, enhances the proton abstraction process by virtue of its electron-withdrawing properties and can be removed by a variety of means including acid treatment[10a,12], magnesium in methanol,[13b] tetra-*n*-butylammonium fluoride[13] or samarium diodide.[10a] We have also recently shown that so-protected indole derivatives, including the indole-5-carboxamide (**1**), can be very efficiently deprotected by electrolysis.[14] We thus report herein our results concerning the metalation reactions of the *N,N*-dimethylsulfamoyl-protected indole and indoline 5-(*N*-phenyl)carboxamides (**1**) and (**2**), respectively.

Indole (**1**) was prepared from ethyl indole-5-carboxylate (**3**) (itself prepared by Fischer esterification of commercial indole-5-carboxylic acid) as shown in Scheme 1. Thus, using the Weinreb amidation procedure,[10a,15,16] a 1:1 mixture of aniline and trimethylaluminum in dichloromethane was treated with compound (**3**) to give the phenylcarboxamide (**4**). The latter, in the presence of sodium hydride and *N,N*-dimethylsulfamoyl chloride, afforded the desired indole substrate (**1**) in 70% yield.



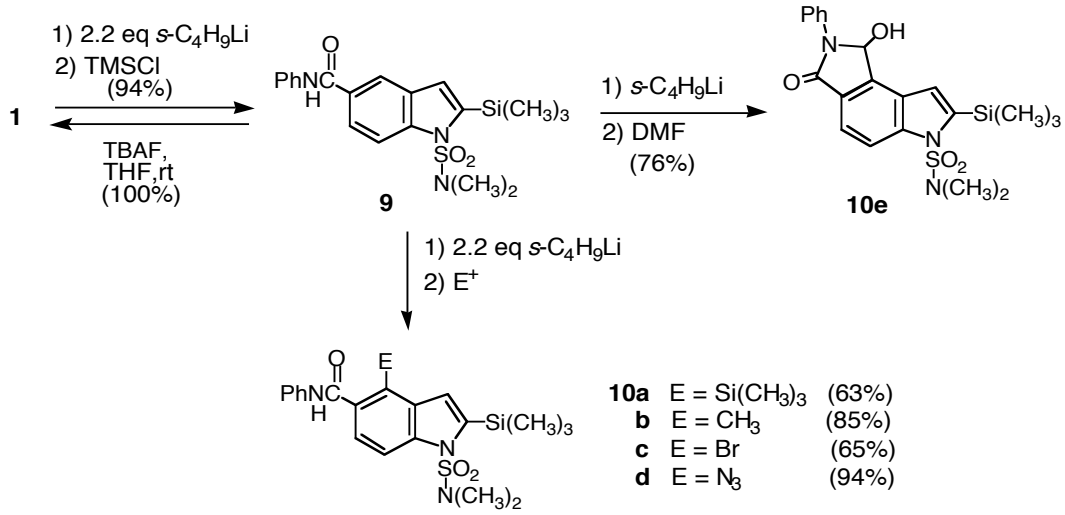
Scheme 1

The indoline substrate (**2**) was prepared by first protecting the amine function of commercial indoline (**5**) with the dimethylsulfamoyl group (using triethylamine rather than sodium hydride as base) to give **6** followed by bromination of the latter in acetic acid (**7**, Scheme 2).[17] Halogen-lithium exchange was effected by treatment of **7** with *t*-butyllithium in THF at -100°C and the resulting anion was reacted *in situ* with 1 equiv of phenyl isocyanate[18] to afford **2** in 75% yield. Use of higher reaction temperatures (e.g., -78°C), of *n*-butyllithium or of more than 1 equiv of phenyl isocyanate led to considerable formation of bis-addition product (**8**). Compound (**2**) could be transformed into indole (**1**) by reaction with DDQ in toluene at reflux.



Scheme 2

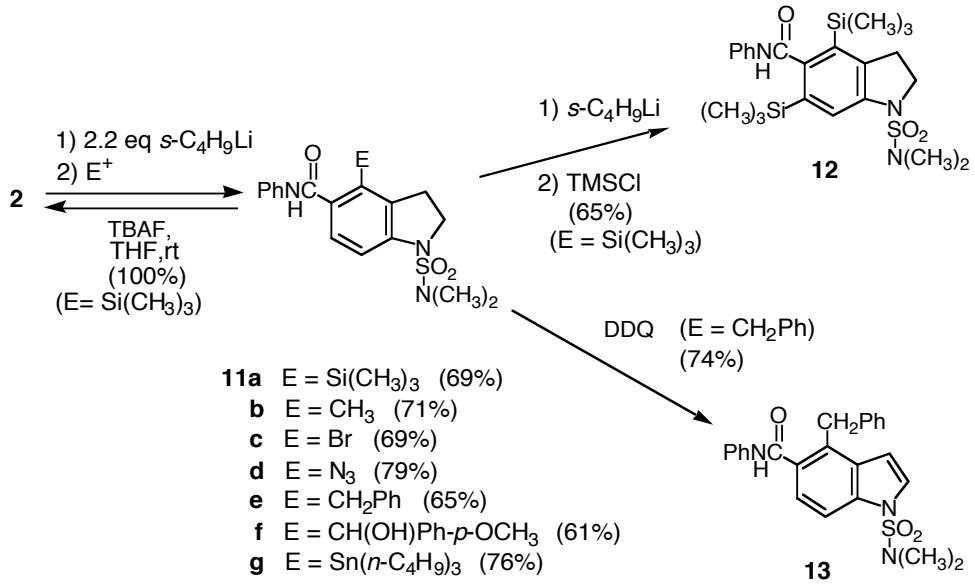
Treatment of indole (**1**) with 2.2 equiv of *s*-butyllithium in THF at -80°C for 45 min followed by addition of an electrophile (trimethylsilyl chloride, 2.2 equiv) gave the product of C-2 metalation/substitution, compound (**9**) in 94% yield (Scheme 3). Thus, despite the high *o*-metalating efficiency of the phenylcarboxamide group, the proton at C-2 is, as in other indole derivatives,[1,2] the most easily abstracted. This effect may be exacerbated by the electron-withdrawing capacity of the sulfonamide group as well as its *o*-metalating capacity.[12,19] Be that as it may, the trimethylsilyl group may be considered as an excellent protecting group for the C-2 position since, in addition to being incorporated in high yield, it can also be removed quantitatively by the action of TBAF, as shown by the complete regeneration of the starting material (**1**) from **9**. When silylated derivative (**9**) was subjected to a second metalation with *s*-butyllithium and the resulting anion reacted with a variety of electrophiles (trimethylsilyl chloride, methyl iodide, bromine, trisyl azide) the products of C-4 substitution (**10a-d**, respectively) were obtained in good to excellent yields. When DMF was used as the electrophile, the product of C-4 formylation was isolated as the lactam (**10e**).



Scheme 3

Application of the same reaction conditions to indoline (**2**) gave uniquely the products of C-4 substitution (**11a-g**, Scheme 4) with a variety of electrophiles (trimethylsilyl chloride, methyl iodide, bromine, trisyl azide, benzyl bromide, *p*-anisaldehyde, tri-*n*-butylstannyl chloride, respectively). No products of C-2 or C-

7 substitution, as observed by others in metalation studies of certain indolines,[7,8] were formed. Thus, for derivative (**11a**), an nOe of 2% was observed between the methyl protons of the trimethylsilyl group at C-4 and the protons at C-3 while the two protons at C-2, coupled to the two protons at C-3, were clearly observed in the ^{1}H NMR spectrum.[20] The trimethylsilyl group of compound (**11a**) then served as a blocking group for the C-4 position[6] since, as in the case of **9**, it could be efficiently removed by the action of TBAF to give **2**. With the C-4 position occupied by the protecting trimethylsilyl group, a second *o*-metalation reaction led to lithiation at C-6 to afford, after quenching with trimethylsilyl chloride, the 4,6-bis-trimethylsilylindoline (**12**). Finally, the C-4 substituted indolines were easily transformed into the corresponding indoles by treatment with DDQ as exemplified by the preparation of the 4-benzyl derivative (**13**) from **11e**.



Scheme 4

In conclusion, successive *o*-metalation reactions of 1-(*N*,*N*-dimethylsulfamoyl)indole-5-(*N*-phenyl)carboxamide (**1**) allow efficient regioselective substitution of first the C-2 then the C-4 positions. On the other hand, when the analogous indoline derivative (**2**) is subjected to the same reaction conditions, the C-4 position is preferentially substituted followed by the C-6 position, with no trace of C-2 substitution.[21] Both substrates (**1**) and (**2**) can be prepared on a large scale from inexpensive commercial starting materials. Moreover, since the indolines can be conveniently transformed into the corresponding indoles, this methodology now permits preparation of a vast array of substituted indole-5-carboxamides of potential pharmacological interest.

EXPERIMENTAL

General. Melting points are uncorrected. IR spectra of samples were obtained as films (i.e., by application of a $CHCl_3$ solution to an NaCl plate followed by evaporation of the solvent) or as KBr pellets. ^1H and ^{13}C NMR chemical shifts are given as δ values with reference to Me_4Si as internal standard. Thin-layer chromatography was performed on Merck silica gel 60 plates with a fluorescent indicator. The plates were visualized with UV light (254 nm) and with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230-240 mesh) at medium pressure (200 mbar). All solvents were distilled and stored over 4 Å molecular sieves before use. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

1*H*-Indole-5-(*N*-phenyl)carboxamide (4) - To a solution of trimethylaluminum (31.7 mL of a 2.0 M solution in toluene, 63.4 mmol) in anhydrous dichloromethane (100 mL) held at -20°C under argon was added dropwise aniline (2.9 mL, 31.7 mmol). The solution was stirred at -20°C for 15 min and then at rt for 1.5 h. A solution of ethyl indole-5-carboxylate (**3**, 2.0 g, 10.6 mmol) in dichloromethane (10 mL) was then added and the reaction mixture was stirred for 1 h. Saturated aqueous ammonium chloride (100 mL) was added, the organic phase was separated and the aqueous phase was extracted with dichloromethane (4 x 200 mL). The combined organic extracts were washed with water (200 mL), dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35), affording compound (**4**) as a white powder (2.37 g, 95%) : mp 183-184°C (ethyl acetate-heptane) ; IR (KBr) 3419, 3205, 1634 cm^{-1} ; CIMS m/z 344 $(MH)^+$; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.66 (1H, d, J = 3.6 Hz), 7.15 (1H, t, J = 7.4 Hz), 7.29 (1H, d, J = 3.6 Hz), 7.39 (2H, t, J = 7.9 Hz), 7.45 (1H, d, J = 8.7 Hz), 7.68 (2H, d, J = 7.7 Hz), 7.74 (1H, dd, J = 1.7 and 8.7 Hz), 7.93 (1H, br s), 8.21 (1H, d, J = 1.6 Hz), 8.57 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 103.8, 111.4, 120.2, 120.4, 121.3, 124.3, 125.9, 127.0, 127.8, 129.2, 137.9, 138.5, 166.9. Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25 ; H, 5.12 ; N, 11.86. Found : C, 76.03 ; H, 5.48 ; N, 11.91.

1-(*N,N*-Dimethylsulfamoyl)-1*H*-indole-5-(*N*-phenyl)carboxamide (1) - A solution of compound (**4**) (2.0 g, 8.7 mmol) in anhydrous THF (100 mL) was treated at 0°C under argon with sodium hydride (1.13 g of a 60% dispersion in oil, 28 mmol) and, after 45 min, with *N,N*-dimethylsulfamoyl chloride (2.8 mL, 26.0 mmol). The reaction mixture was stirred for 50 min and aqueous saturated

ammonium chloride (100 mL) was added. The mixture was extracted with dichloromethane (3 x 100 mL) and the combined organic extracts were washed with saturated aqueous sodium chloride (100 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35) affording compound (**1**) as transparent crystals (2.07 g, 70%) : mp 177-178°C (ethyl acetate-heptane) ; IR (KBr) 3200, 1650, 1385 cm^{-1} ; CIMS m/z 344 $(MH)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.82 (6H, s), 6.94 (1H, d, J = 3.6 Hz), 7.17 (1H, t, J = 7.4 Hz), 7.39 (2H, t, J = 7.9 Hz), 7.54 (1H, d, J = 3.6 Hz), 7.67 (2H, d, J = 7.7 Hz), 7.81 (1H, dd, J = 1.4 and 8.7 Hz), 7.91 (1H, br s), 8.03 (1H, d, J = 8.7 Hz), 8.16 (1H, d, J = 1.7 Hz) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.4, 107.1, 113.8, 120.3, 120.9, 122.9, 124.4, 128.4, 128.5, 129.1, 129.9, 137.1, 138.2, 166.1. Anal. Calcd for $C_{17}H_{17}N_3O_3S$: C, 59.46 ; H, 4.99 ; N, 12.24 ; S, 9.34. Found : C, 59.43 ; H, 4.96 ; N, 12.07 ; S, 9.11.

2,3-Dihydro-1-(*N*,*N*-dimethylsulfamoyl)-1*H*-indole (6) - To a solution of indoline (**5**) (10.6 g, 88.3 mmol) and triethylamine (24.5 mL, 176.6 mmol) in anhydrous dichloromethane (100 mL) was added dropwise at rt under argon *N*,*N*-dimethylsulfamoyl chloride (14.5 mL, 132.4 mmol). The solution was stirred for 15 h and hydrochloric acid (200 mL of a 0.5 M solution) was added. The organic phase was separated and the aqueous phase was washed with dichloromethane (2 x 150 mL). The combined organic extracts were washed with water (200 mL) and then with saturated aqueous NaCl solution (200 mL). The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure affording compound (**6**) as an oil (15.5 g, 77%) which was used without further purification in the following steps : IR (film) 2962, 1603, 1479 cm^{-1} ; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.84 (6H, s), 3.10 (2H, t, J = 8.6 Hz), 3.97 (2H, t, J = 8.6 Hz), 6.92 (1H, t, J = 7.1 Hz), 7.11 (2H, q, J = 7.6 Hz), 7.28 (1H, d, J = 7.6 Hz) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.8, 38.0, 50.5, 113.5, 122.6, 124.9, 127.3, 130.5, 142.7. HRCIMS calcd for $C_{10}H_{15}N_2O_2S$ $(MH)^+$ m/z 227.0854, found m/z 227.0841.

5-Bromo-2,3-dihydro-1-(*N*,*N*-dimethylsulfamoyl)-1*H*-indole (7) - To a solution of compound (**6**) (18 g, 79.6 mmol) in acetic acid (200 mL) held at 10°C under argon was added bromine (3.7 mL, 71.7 mmol) over a period of 20 min. The reaction mixture was stirred for 5 min and then poured into ice water (400 mL). Saturated aqueous sodium hydrogen sulfite was added until the bromine color disappeared and the mixture was extracted with dichloromethane (3 x 300 mL). The organic extracts were combined,

washed with saturated aqueous sodium hydrogen carbonate (200 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was crystallized in heptane-ethyl acetate (4:1) to afford compound (**7**) (16.4 g, 75%) : mp 61°C ; IR (KBr) 2897, 1468 cm^{-1} ; CIMS m/z 307 (MH^+ with ^{81}Br) and m/z 305 (MH^+ with ^{79}Br) ; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.85 (6H, s), 3.1 (2H, t, J = 8.6 Hz), 3.97 (2H, t, J = 8.6 Hz), 7.21 (3H, m) ; ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 27.7, 38.2, 50.8, 115.0, 115.1, 128.1, 130.4, 132.9, 142.2. Anal. Calcd for $C_{10}H_{13}N_2O_2BrS$: C, 39.36 ; H, 4.29 ; N, 9.18 ; S, 10.50 ; Br, 26.18. Found : C, 39.12 ; H, 4.22 ; N, 8.98 ; S, 10.72 ; Br 26.14.

2,3-Dihydro-1-(*N*,*N*-dimethylsulfamoyl)-1*H*-indole-5-(*N*-phenyl)carboxamide (2) - To a solution of the 5-bromoindoline (**7**) (6.0 g, 19.7 mmol) in anhydrous THF (200 mL) held at -100°C under argon was added dropwise a solution of *t*-butyllithium in pentane (23 mL of a 1.7 M solution, 39.1 mmol). The solution was stirred for 30 min and phenyl isocyanate (2.18 mL, 19.7 mmol) was added. The reaction mixture was stirred for 1 h and a solution of saturated aqueous ammonium chloride was added. The mixture was extracted with dichloromethane (3x, 200 mL), the organic extracts were combined, washed with water and dried over sodium sulfate. Removal of the solvents under reduced pressure left crude **2** which was purified by crystallization in ethanol (5.1 g, 75%) : mp 144-145°C ; IR (KBr) 1648, 1155 cm^{-1} ; CIMS m/z 346 $(MH)^+$, 239 $(MH\text{-}SO_2NMe_2)^+$; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.86 (6H, s), 3.08 (2H, t, J = 8.6 Hz), 3.98 (2H, t, J = 8.6 Hz), 7.11 (1H, t, J = 7.2 Hz), 7.29 (3H, m), 7.64 (4H, m), 8.30 (1H, br s) ;^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 27.6, 38.2, 51.0, 112.7, 120.4, 124.4, 124.7, 127.2, 129.0, 129.3, 131.1, 138.3, 146.0, 165.6. Anal. Calcd for $C_{17}H_{19}N_3O_3S$: C, 59.11 ; H, 5.54 ; N, 12.16 ; S, 9.28. Found : C, 59.17 ; H, 5.39 ; N, 12.02 ; S, 9.25. When the reaction was conducted at higher temperatures (e.g., -78°C) or in the presence of excess phenyl isocyanate, the product of bis-addition, compound (**8**), could be isolated in varying yields : mp 139-140°C (hexane) ; IR (KBr) 3226, 1720, 1592 cm^{-1}; CIMS m/z 345 $(MH\text{-}CONHPh)^+$; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.81 (6H, s), 2.99 (2H, t, J = 8.6 Hz), 3.94 (2H, t, J = 8.6 Hz), 7.29 (11H, m), 7.64 (2H, m), 11.33 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 27.4, 38.2, 50.8, 112.2, 120.3, 124.6, 125.6, 128.2, 128.8, 128.9, 129.2, 129.6, 130.0, 130.1, 137.7, 138.9, 145.1, 152.2, 173.5. Anal. Calcd for $C_{24}H_{24}N_4O_4S$. 0.2 H_2O : C, 61.58 ; H, 5.25 ; N, 11.97 ; S, 6.85. Found : C, 61.43 ; H, 5.32 ; N, 11.82 ; S, 6.76.

Preparation of compound (1) by dehydrogenation of compound (2) - A solution of compound (**2**) (1.0 g, 2.9 mmol) and DDQ (3.3 g, 14.5 mmol) in toluene (50 mL) was refluxed for 15 h. The reaction mixture was cooled and filtered through a pad of alumina. The pad was washed with heptane-ethyl acetate (1:1) and the filtrates were combined and evaporated under reduced pressure. The residue was crystallized in ethyl acetate-heptane, providing compound (**1**) (0.76 g, 76%) identical in all respects with that prepared from compound (**4**).

General procedure for the metalation and electrophilic substitution of indole- and indoline-5-(*N*-phenyl)carboxamides (1) and (2) - A solution of the indole (**1** or **9**) or indoline (**2** or **11a**) in anhydrous THF (10 mL/100 mg of substrate) was treated dropwise at -80°C under argon with *s*-butyllithium (2.1 eq of a 1.2 M solution in cyclohexane). The orange colored reaction mixture was stirred for 40 min and the electrophile (2.1 eq), either neat (liquids) or dissolved in THF (1 mL, solids) was added dropwise. The reaction mixture was stirred for 40 min more at -80°C (indoline) or rt (indole) and then quenched with saturated aqueous ammonium chloride (20 mL). The mixture was extracted with dichloromethane (3 x 100 mL), the combined organic extracts were washed with water (100 mL), dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was purified as described below for each different compound. The following compounds were prepared in this manner :

1-(*N*,*N*-Dimethylsulfamoyl)-2-trimethylsilyl-1*H*-indole-5-(*N*-phenyl)carboxamide (9) - Following the same procedure as described above, compound (**9**) was prepared from compound (**1**) (178 mg, 0.52 mmol) and trimethylsilyl chloride (138 µL, 1.09 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 4:1), affording compound (**9**) (202 mg, 94%) as transparent crystals after crystallization in heptane-ethyl acetate : mp 147°C ; IR (KBr) 3206, 1659 cm^{-1} ; CIMS m/z 416 $(MH)^+$; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.43 (9H, s), 2.82 (6H, s), 6.94 (1H, s), 7.17 (1H, t, J = 7.4 Hz), 7.39 (2H, t, J = 7.9 Hz), 7.67 (2H, d, J = 7.7 Hz), 7.82 (1H, dd, J = 1.7 and 8.7 Hz), 7.87 (1H, br s), 7.92 (1H, d, J = 8.7 Hz), 8.12 (1H, d, J = 1.7 Hz) ; ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 0.0, 38.4, 114.0, 119.6, 120.3, 120.4, 123.3, 124.5, 129.2, 129.8, 130.5, 138.2, 139.9, 146.2, 166.2. Anal. Calcd for $C_{20}H_{25}N_3O_3SSi$. 0.4 H_2O : C, 56.82 ; H, 6.15 ; N, 9.94 ; S, 7.58. Found : C, 56.83 ; H, 6.29 ; N, 9.78 ; S, 7.43.

1-(*N*,*N*-Dimethylsulfamoyl)-2,4-bis-trimethylsilyl-1*H*-indole-5-(*N*-phenyl)carboxamide (10a) - Following the same procedure as described above, compound (**10a**) was prepared from compound (**9**) (100 mg, 0.24 mmol) and trimethylsilyl chloride (67 µL, 0.53 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35) to afford compound (**10a**) (74 mg, 63%) as a white solid : mp 184°C (ethyl acetate-heptane) ; IR (KBr) 3283, 1656 cm^{-1} ; CIMS m/z 488 $(MH)^+$; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.44 (9H, s), 0.45 (9H, s), 2.80 (6H, s), 7.10 (1H, s), 7.15 (1H, t, J = 7.4 Hz), 7.39 (3H, m), 7.61 (2H, d, J = 7.7 Hz), 7.81 (1H, d, J = 8.5 Hz), 7.83 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 0.2, 1.3, 38.2, 114.6, 119.7, 121.0, 122.9, 124.6, 129.2, 130.5, 135.7, 137.7, 138.2, 138.4, 145.0, 170.0. Anal. Calcd for $C_{23}H_{33}N_3O_3SSi_2$. 0.5 $CH_3CO_2C_2H_5$: C, 56.46 ; H, 7.01 ; N, 7.90 ; S, 6.03. Found : C, 56.42 ; H, 6.71 ; N, 8.21 ; S, 5.93.

1-(*N*,*N*-Dimethylsulfamoyl)-4-methyl-2-trimethylsilyl-1*H*-indole-5-(*N*-phenyl)-carboxamide (10b) - Following the same procedure as described above, compound (**10b**) was prepared from compound (**9**) (100 mg, 0.24 mmol) and methyl iodide (33 µL, 0.53 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35) affording compound (**10b**) (88 mg, 85%) as a pale yellow powder : mp 164°C (ethyl acetate-heptane) ; IR (KBr) : 3282, 1656 cm^{-1} ; CIMS m/z 430 $(MH)^+$; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.43 (9H, s), 2.67 (3H, s), 2.82 (6H, s), 6.93 (1H, s), 7.16 (1H, t, J = 7.4 Hz), 7.38 (3H, m), 7.69 (3H, m) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.6, 16.0, 38.2, 111.7, 118.1, 119.9, 123.4, 124.5, 129.2, 129.8, 130.6, 131.2, 138.2, 138.5, 145.1, 168.2. Anal. Calcd for $C_{21}H_{27}N_3O_3SSi$. 0.35 H_2O : C, 57.86 ; H, 6.41 ; N, 9.64 ; S, 7.35. Found : C, 58.22 ; H, 6.47 ; N, 9.47 ; S, 6.96.

4-Bromo-1-(*N*,*N*-dimethylsulfamoyl)-2-trimethylsilyl-1*H*-indole-5-(*N*-phenyl)-carboxamide (10c) - Following the same procedure as described above, compound (**10c**) was prepared from compound (**9**) (100 mg, 0.24 mmol) and bromine (27 µL, 0.53 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35) affording compound (**10c**) as a brown solid (77 mg, 65%) : mp 94°C (ethyl acetate-heptane) ; IR (KBr) 3283, 2955, 1646 cm^{-1} ; CIMS m/z 496 (MH^+ with ^{81}Br), 494 (MH^+ with ^{79}Br) ; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.44 (9H, s), 2.80 (6H, s), 6.94 (1H, s), 7.16 (1H, t, J = 7.4 Hz), 7.35 (2H, t, J = 7.9 Hz), 7.53 (1H, d, J = 8.7 Hz), 7.66 (2H, d, J = 7.7 Hz), 7.80 (1H, d, J = 8.7 Hz), 8.00 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 75

MHz) δ 0.4, 38.2, 113.4, 119.5, 120.3, 124.5, 124.7, 125.5, 129.2, 131.6, 138.0, 140.0, 146.1, 146.8, 166.0.

4-Azido-1-(*N,N*-dimethylsulfamoyl)-2-trimethylsilyl-1*H*-indole-5-(*N*-phenyl)-carboxamide (10d) - Following the same procedure as described above, compound (**10d**) was prepared from compound (**9**) (100 mg, 0.24 mmol) and trisyl azide (164 mg, 0.53 mmol) as the electrophile. At the end of the reaction period, acetic acid (0.5 mL), sodium acetate (160 mg) and methanol (1.6 mL) were added successively and work up was continued as before. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35) affording compound (**10d**) as a brown solid (103 mg, 94%) : mp 103°C (ethyl acetate-heptane) ; IR (KBr) 2960, 2119, 1661 cm^{-1} ; CIMS m/z 429 $(MH-N_2)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.43 (9H, s), 2.82 (6H, s), 7.16 (1H, s), 7.17 (1H, t, J = 7.4 Hz), 7.33 (2H, t, J = 7.9 Hz), 7.59 (1H, d, J = 8.7 Hz), 7.67 (2H, d, J = 7.7 Hz), 7.89 (1H, d, J = 8.7 Hz), 9.26 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.0, 38.1, 111.2, 114.5, 120.4, 123.6, 124.5, 127.2, 129.2, 129.8, 138.0, 140.5, 145.8, 149.1, 163.8. Anal. Calcd for $C_{20}H_{24}N_6O_3SSi$: C, 52.61 ; H, 5.30 ; N, 18.41 ; S, 7.02. Found : C, 52.94 ; N, 5.54 ; N, 18.31 ; S, 6.95.

(*RS*)-1,2-Dihydro-6-(*N,N*-dimethylsulfamoyl)-9-hydroxy-2-*N*-phenyl-7-trimethylsilyl-pyrrolo[4,3-*c*]indol-3(2*H*)-one (10e) - Following the same procedure as described above, compound (**10e**) was prepared from compound (**9**) (100 mg, 0.24 mmol) and *N,N*-dimethylformamide (41 μL, 0.53 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35) to afford compound (**10e**) (81 mg, 76%) as a white powder : mp 215-220°C (ethyl acetate-heptane) ; IR (KBr) 3283, 2900, 1656 cm^{-1} ; CIMS m/z 444 $(MH)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.43 (9H, s), 2.82 (6H, s), 3.70 (1H, br s), 6.54 (1H, s), 7.12 (1H, s), 7.18 (1H, t, J = 7.4 Hz), 7.36 (2H, t, J = 7.9 Hz), 7.53 (1H, d, J = 8.7 Hz), 7.70 (2H, d, J = 7.7 Hz), 7.87 (1H, d, J = 8.7 Hz), 9.26 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.6, 38.2, 115.9, 116.3, 119.1, 121.6, 125.1, 125.3, 126.1, 129.2, 135.8, 137.4, 141.1, 147.9, 167.1. Anal. Calcd for $C_{21}H_{25}N_3O_4SSi$. 0.4 H_2O : C, 55.95 ; H, 5.77 ; N, 9.32. Found : C, 56.11 ; H, 5.67 ; N, 9.21.

2,3-Dihydro-1-(*N,N*-dimethylsulfamoyl)-4-trimethyl-1*H*-indole-5-(*N*-phenyl)-carboxamide (11a) - Following the same procedure as described above, compound (**11a**) was prepared

from compound (**2**) (1.0 g, 2.9 mmol) and trimethylsilyl chloride (0.77 mL, 6.1 mmol) as the electrophile. The crude product was crystallized in ethyl acetate-heptane to afford compound (**11a**) as a white powder (521 mg, 41%). Chromatography of the mother liquor on silica gel (dichloromethane) allowed isolation of a second lot of pure **11a** (330 mg, 28%) (total yield of 69%) : mp 225°C (ethyl acetate-heptane) ; IR (KBr) 3348, 2954, 1659 cm^{-1} ; CIMS m/z 418 $(MH)^+$; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.34 (9H, s), 2.86 (6H, s), 3.08 (2H, t, J = 8.6 Hz), 3.98 (2H, t, J = 8.6 Hz), 7.15 (1H, t), 7.39 (4H, m), 7.62 (2H, d), 7.76 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 1.3, 30.4, 38.3, 50.7, 113.5, 119.9, 124.5, 126.6, 129.2, 135.7, 137.6, 138.3, 138.6, 143.6, 169.8. Anal. Calcd for $C_{20}H_{27}N_3O_3SSi$. 0.1 C_7H_{16} : C, 58.14 ; H, 6.74 ; N, 9.83 ; S, 7.50 ; Si, 6.23. Found : C, 57.91 ; H, 6.76 ; N, 9.63 ; S, 7.71 ; Si, 6.57.

2,3-Dihydro-1-(*N*,*N*-dimethylsulfamoyl)-4-methyl-1*H*-indole-5-(*N*-phenyl)carboxamide (11b) - Following the same procedure as described above, compound (**11b**) was prepared from compound (**2**) (250 mg, 0.725 mmol) and methyl iodide (100 µL, 1.52 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35) affording compound (**11b**) as transparent crystals (184 mg, 71%) : mp 162°C (ethyl acetate-heptane) ; IR (KBr) 3308, 1658 cm^{-1} ; CIMS m/z 360 $(MH)^+$; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.38 (3H, s), 2.89 (6H, s), 3.09 (2H, t, J = 8.6 Hz), 4.05 (2H, t, J = 8.6 Hz), 7.17 (2H, t, J = 7.5 Hz), 7.36 (3H, m), 7.62 (2H, d, J = 7.2 Hz), 7.66 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 16.4, 27.1, 38.3, 50.7, 110.5, 119.9, 124.5, 127.2, 129.1, 130.8, 134.5, 138.2, 138.6, 144.5, 169.8. Anal. Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.15 ; H, 5.89 ; N, 11.69 ; S, 8.92. Found : C, 59.85 ; H, 5.76 ; N, 11.54 ; S, 8.77.

4-Bromo-2,3-dihydro-1-(*N*,*N*-dimethylsulfamoyl)-1*H*-indole-5-(*N*-phenyl)carboxamide (11c) - Following the same procedure as described above, compound (**11c**) was prepared from compound (**2**) (250 mg, 0.725 mmol) and bromine (78 µL, 1.52 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel (dichloromethane) to afford compound (**11c**) as a pale yellow powder (211 mg, 69%) : mp 165-170°C (decomp) (dichloromethane) ; IR (KBr) 2964, 1654 cm^{-1} ; CIMS m/z 426 (MH^+ with ^{81}Br), 424 (MH^+ with ^{79}Br) ; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.88 (6H, s), 3.13 (2H, t, J = 8.6 Hz), 4.03 (2H, t, J = 8.6 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.25 (1H, d, J = 8.3 Hz), 7.36 (3H, m), 7.63 (2H, d, J = 7.2 Hz), 8.06 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.0, 38.3, 50.2, 111.9, 120.0, 124.6, 129.1, 129.7, 131.6, 131.9, 132.5, 137.8, 145.3, 165.4. Anal. Calcd for

$C_{17}H_{18}N_3O_3BrS$. 0.1 H_2O : C, 47.92 ; H, 4.31 ; N, 9.86 ; S, 7.52. Found : C, 47.72 ; H, 4.23 ; N, 9.78 ; S, 7.43.

4-Azido-2,3-dihydro-1-(*N,N*-dimethylsulfamoyl)-1*H*-indole-5-(*N*-phenyl)carboxamide (11d) - Following the same procedure as described above, compound (**11d**) was prepared from compound (**2**) (200 mg, 0.58 mmol) and trisyl azide (376 mg, 1.22 mmol) as the electrophile. At the end of the reaction period, acetic acid (0.5 mL), sodium acetate (160 mg) and methanol (1.6 mL) were added successively and work up was continued as before. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35) affording compound (**11d**) as a white powder (177 mg, 79%) after crystallization in heptane-ethyl acetate : mp 170°C ; IR (KBr) 2115, 1664 cm^{-1} ; CIMS m/z 387 $(MH)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.91 (6H, s), 3.35 (2H, t, J = 8.6 Hz), 4.12 (2H, t, J = 8.6 Hz), 7.17 (2H, t, J = 7.5 Hz), 7.21 (1H, d, J = 8.6 Hz), 7.36 (2H, t), 7.64 (2H, d, J = 7.2 Hz), 7.92 (1H, d, J = 8.6 Hz), 8.96 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.5, 38.3, 51.3, 110.8, 120.5, 123.2, 124.7, 129.1, 132.5, 132.7, 137.8, 140.0, 142.4, 165.4. Anal. Calcd for $C_{17}H_{18}N_6O_3S$. 0.35 $CH_3CO_2C_2H_5$: C, 52.96 ; H, 5.02 ; N, 20.14 ; S, 7.68. Found : C, 53.03 ; H, 4.82 ; N, 19.91 ; S, 7.81.

4-Benzyl-2,3-dihydro-1-(*N,N*-dimethylsulfamoyl)-1*H*-indole-5-(*N*-phenyl)-carboxamide (11e) - Following the same procedure as described above, compound (**11e**) was prepared from compound (**2**) (250 mg, 0.725 mmol) and benzyl bromide (176 µL, 1.45 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35), affording compound (**11e**) (205 mg, 65%) as a white powder after crystallization in heptane-ethyl acetate : mp 140°C ; IR (KBr) 3316, 1659 cm^{-1} ; CIMS m/z 436 $(MH)^+$; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.90 (6H, s), 3.00 (2H, t, J = 8.6 Hz), 4.00 (2H, t, J = 8.6 Hz), 4.19 (2H, s), 7.10 (3H, dt, J = 7.2 and 8.3 Hz), 7.27 (8H, m), 7.43 (1H, d, J = 8.3 Hz), 7.51 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 27.1, 35.9, 38.1, 50.8, 111.6, 119.9, 124.4, 126.5, 128.2, 128.4, 128.8, 129.0, 131.5, 131.7, 135.4, 137.9, 139.2, 144.7, 167.6. Anal. Calcd for $C_{24}H_{25}N_3O_3S$. 0.2 $CH_3CO_2C_2H_5$: C, 65.73 : H, 5.92 ; N, 9.27 ; S, 7.07. Found : C, 65.97 ; H, 6.06 ; N, 9.19 ; S, 7.06.

(*RS*)-2,3-Dihydro-1-(*N,N*-dimethylsulfamoyl)-4-(1-hydroxy-*p*-methoxybenzyl)-1*H*-indole-5-(*N*-phenyl)carboxamide (11f) - Following the same procedure as described above,

compound (**11f**) was prepared from compound (**2**) (250 mg, 0.725 mmol) and *p*-anisaldehyde (180 µL, 1.45 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 65:35) affording compound (**11f**) (213 mg, 61%) as transparent crystals after crystallization in ethyl acetate-heptane : mp 146°C ; IR (KBr) 3280, 1660 cm^{-1} ; CIMS m/z 482 $(MH)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.90 (6H, s), 3.15 (2H, t, J = 8.6 Hz), 3.69 (3H, s), 4.03 (2H,t, J = 8.6 Hz), 5.44 (1H, br s), 5.89 (1H, br s), 6.71 (2H, d, J = 8.6 Hz), 7.10 (3H, dt, J = 7.2 and 8.3 Hz), 7.63 (5H, m), 7.38 (1H, d, J = 8.3 Hz), 7.67 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 27.1, 38.4, 50.8, 55.3, 71.8, 111.9, 113.5, 120.9, 125.1, 126.0, 127.2, 128.9, 129.2, 131.1, 134.8, 137.2, 140.3, 145.1, 158.8, 168.8. Anal. Calcd for $C_{25}H_{27}N_3O_5S$. 0.15 H_2O : C, 62.01 ; H, 5.68 ; N, 8.68 ; S, 6.62. Found : C, 62.01 ; H, 5.57 ; N, 8.58 ; S, 6.59.

2,3-Dihydro-1-(*N*,*N*-dimethylsulfamoyl)-4-tri-*n*-butylstannyl-1*H*-indole-5-(*N*-phenyl)-carboxamide (11g) - Following the same procedure as described above, compound (**11g**) was prepared from compound (**2**) (200 mg, 0.58 mmol) and tri-*n*-butylstannyl chloride (343 µL, 1.22 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel by first eluting the column with heptane (100 mL) and then with heptane-ethyl acetate (4:1). Compound (**11g**) was obtained as a powder (281 mg, 76%) which was crystallized in ethyl acetate-heptane to give transparent crystals : mp 120-125°C ; IR (KBr) 3100, 1664 cm^{-1} ; CIMS m/z 636 $(MH)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80-1.50 (27H, m), 2.88 (6H, s), 3.13 (2H, t, J = 8.6 Hz), 4.03 (2H, t, J = 8.6 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.36 (3H, m), 7.49 (1H, d, J = 8.3 Hz), 7.63 (2H, d, J = 7.2 Hz), 7.80 (1H, br s) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.1, 13.8, 27.6, 29.4, 31.0, 38.3, 50.5, 112.6, 120.0, 124.4, 125.6, 129.1, 137.0, 138.6, 139.7, 142.4, 143.9, 168.9. Anal. Calcd for $C_{29}H_{46}N_3O_3SSn$. 0.35 $(C_4H_9)_3SnCl$: C, 53.21 ; H, 7.46 ; N, 5.61 ; S, 4.29 ; Sn, 21.38. Found : C, 53.29 ; H, 7.22 ; N, 5.61 ; S, 3.97 ; Sn, 21.69.

2,3-Dihydro-1-(*N*,*N*-dimethylsulfamoyl)-4,6-bis-trimethylsilyl-1*H*-indole-5-(*N*-phenyl)carboxamide (12) - Following the same procedure as described above, compound (**12**) was prepared from compound (**11a**) (150 mg, 0.36 mmol) and trimethylsilyl chloride (100 µL, 0.79 mmol) as the electrophile. The crude product was purified by column chromatography on silica gel (heptane-ethyl acetate 7:3). Compound (**12**) (114 mg, 65%) was first eluted followed by the unreacted starting material (**11a**) (40 mg) : mp 180°C (ethyl acetate-heptane) ; IR (KBr) 3350, 2955, 1676 cm^{-1} ; CIMS m/z 490

$(MH)^+$; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.29 (9H, s), 0.34 (9H, s), 2.89 (6H, s), 3.21 (2H, t, J = 8.6 Hz), 3.98 (2H, t, J = 8.6 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.36 (3H, m), 7.63 (2H, d, J = 7.2 Hz) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.2, 1.2, 30.4, 38.3, 50.7, 119.0, 120.1, 124.4, 129.4, 133.5, 137.0, 137.7, 138.2, 142.2, 144.2, 170.4. Anal. Calcd for $C_{23}H_{35}N_3O_3SSi_2$: C, 56.40 ; H, 7.20 ; N, 8.58. Found : C, 56.34 ; H, 7.26 ; N, 8.29.

Preparation of compound (1) *via* desilylation of compound (9) - A solution of 2-trimethylsilylindole (**9**) (10 mg, 0.024 mmol) in THF (5 mL) was treated dropwise at rt under argon with a solution of tetra-*n*-butylammonium fluoride (100 μL of a 1 M solution in THF ; 0.1 mmol). The reaction mixture was stirred for 15 min and saturated aqueous ammonium chloride (10 mL) was added. The mixture was extracted with dichloromethane (3 x 20 mL), the organic extracts were combined, washed with water (30 mL) and dried over sodium sulfate. Removal of the solvents under reduced pressure afforded compound (**1**) (8 mg, 100%) identical in all respects with the compound prepared from **4**.

Preparation of compound (2) *via* desilylation of compound (11a) - Following the same procedure as for the desilylation of compound (**9**), the 4-trimethylsilylindoline derivative (**11a**) (50 mg, 0.12 mmol) in THF (10 mL) was treated with TBAF (240 μL of a 1 M solution in THF ; 0.24 mmol) for 15 min. Work up afforded compound (**2**) (41 mg, 100%), identical in all respects with the compound prepared from **7**.

4-Benzyl-1-(*N*,*N*-dimethylsulfamoyl)-1*H*-indole-5-(*N*-phenyl)carboxamide (13) - A solution of compound (**11e**) (150 mg, 0.35 mmol) in anhydrous toluene (15 mL) was treated with DDQ (391 mg, 1.72 mmol) at reflux for 15 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on alumina (heptane-ethyl acetate 1:1) affording compound (**13**) as a faintly pink solid (110 mg, 74%) : mp 225°C (ethyl acetate-heptane) ; IR (KBr) 3307, 1650 cm^{-1} ; CIMS m/z 434 $(MH)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.90 (6H, s), 4.49 (2H, s), 6.69 (1H, d, J = 2.8 Hz), 7.00-7.27 (12H, m), 7.89 (1H, d, J = 8.3 Hz) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.9, 38.6, 106.0, 112.4, 119.9, 124.2, 124.5, 126.5, 128.3, 128.5, 128.9, 129.0, 130.8, 131.1, 131.7, 136.0, 137.4, 140.2, 168.1. Anal. Calcd for $C_{24}H_{23}N_3O_3S$. 1.5 H_2O : C, 62.59 ; H, 5.69 ; N, 9.12 ; S, 6.84. Found : C, 62.84 ; H, 5.61 ; N, 8.76 ; S, 6.96.

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20. This structural assignment was confirmed by an X-Ray diffraction study of **11a**.
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