# Preparation and Reactions of 4-, 5-, and 6-Methoxy Substituted 3-Lithioindoles and 3-Indolylzinc Derivatives

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**Abstract:** The preparation of 4-, 5-, and 6-methoxy substituted 3-lithio-1-(trialkylsilyl)indoles **4b**–**d** by metalation of the corresponding 3-bromoindoles, and their reactions with iodomethane, DMF, ethylene oxide and aziridines are reported. Transmetalation of 3-lithioindoles **4b**–**d** with $ZnCl_2$ afforded 3-indolylzinc chlorides **11b**–**d**, which underwent Pd(0)-catalyzed cross-coupling reactions with 2-halopyridines to give 4-, 5-, and 6-methoxy substituted 3-(2-pyridyl)indoles.

**Key words:** indoles, lithium, zinc, cross-coupling, pyridylindoles, silyl protecting groups

In 1994 we reported that 3-lithio-1-(trialkylsilyl)indoles, prepared by halogen-metal exchange from the corresponding 3-bromo derivatives, are stable species that efficiently react with a variety of electrophiles to regioselectively give 3-substituted indoles.[1] Due to its steric requirements and non-coordinating abilities,[2] a bulky trialkylsilyl group prevents the undesired migration of the lithium atom from the 3 to the 2 position of the indole ring, which occurs in 3-lithioindoles bearing the more usual *N*-benzenesulfonyl protecting group.[3] 3-Lithio-1-(trialkylsilyl)indoles have proven to be versatile synthetic intermediates with a variety of applications,[4] including the preparation of valuable 3-indolylboronic acids[5] and 3-indolylzinc derivatives,[6] which can undergo Pd(0)-catalyzed cross coupling reactions. In particular, 3-indolylzinc halides react in excellent yields with diversely substituted 2-halopyridines to give 3-(2-pyridyl)indoles, from which we have accomplished the formal total synthesis of several alkaloids of the *Strychnos* and uleine groups.[6b]

In this paper we describe the preparation of 4-, 5-, and 6-methoxy substituted 3-lithio-1-(trialkylsilyl)indoles, their reactions with electrophiles, and their conversion to the corresponding 4-, 5-, and 6-methoxy-3-indolylzinc halides. To our knowledge, 1-(benzenesulfonyl)-5-methoxy-3-lithioindole was the only methoxy substituted 3-lithioindole reported at the begining of our studies,[7,8] and their generation and manipulation require temperatures as low as −100 °C to avoid the rearrangement to the more stable 2-lithio isomer.[7] Hydroxyindoles and their methyl or benzyl ethers have acquired great importance as synthetic precursors of physiologically active hydroxytryptamines, such as serotonin and the pineal hormone melatonin, as well as of the naturally occurring hallucinogens psilocin, bufotenine, and psilocybin (Figure). Hydroxy- and methoxyindoles are also important intermediates in the synthesis of biologically active indole alkaloids, such as physostigmine and harmaline, and the more complex monoterpenoid indole alkaloids reserpine, sarpagine, mitragynine, ibogaine and vindoline.[9]

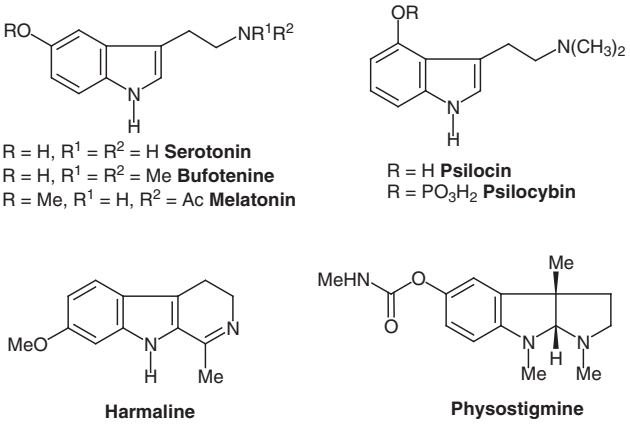
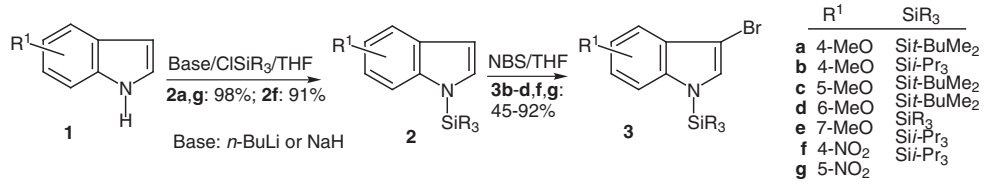



**Figure** Structures of some naturally occurring indoles

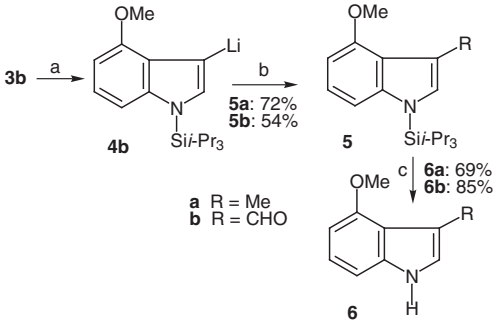
The required 3-bromo-1-(trialkylsilyl)methoxyindoles were prepared in excellent yield by silylation of the lithium salt of the corresponding 4-, 5-, and 6-methoxyindoles **1**, followed by addition of NBS at −78 °C in a one-pot reaction. The use of *t*-$BuMe_2SiCl$ gave satisfactory results in the preparation of bromoindoles **3c** and **3d** (5- and 6-methoxy series), but the bromo derivative **3a** proved to be unstable and decomposed during column chromatography (Scheme 1). For this reason, we prepared the 1-triisopropylsilyl derivative **3b**, since in a previous work[4b] we had observed that *N*-(triisopropylsilyl)indoles are more stable towards hydrolysis than the *N*-(*tert*-butyldimethylsilyl) analogs. In contrast, all attempts to prepare 7-methoxy-1-(trialkylsilyl)indoles **2e** by treatment of the lithium or the sodium salt of 7-methoxyindole with *tert*-butyldimethyl-silyl chloride or the less bulky trimethylsilyl chloride were unsuccessful, due to the steric hindrance of the 7-methoxy substituent which lies in the space near to the nitrogen atom.

Treatment of a THF solution of 3-bromoindoles **3b**–**d** with 2.2 equivalents of *t*-BuLi at −78 °C for 10 minutes, followed by addition of a THF solution of iodomethane at −78 °C afforded the respective 3-methylindoles **5a**, **7a**, and **9a**, which were desilylated by treatment with $Bu_4NF$ to give the unprotected 3-methylindoles **6a** (Scheme 2),




**Scheme 1**

**8a** (Scheme 3), and **10a** (Scheme 4) in 50%, 87%, and 89% overall yields, respectively, from the corresponding 3-bromoindoles **3**. Minor amounts of the respective 3-unsubstituted indoles **2b**–**d** were also isolated, but not the starting 3-bromoindoles **3b**–**d**, thus indicating that the lithio derivatives **4b**–**d** are generated in an essentially quantitative manner. 4-, 5-, and 6-methoxy substituted 1-(trialkylsilyl)-3-lithioindoles **4b**–**d** proved to be stable species, which do not undergo rearrangement of the lithium atom to the indole 2-position or the *ortho*-position[10] with respect to the methoxy substituent, even upon warming to room temperature. Thus, when a solution of 3-lithio-5-methoxyindole **4c** was allowed to reach 25 °C, before the addition of iodomethane, the yield of the protected 3-methylindole **7a** was similar to that obtained at −78 °C.

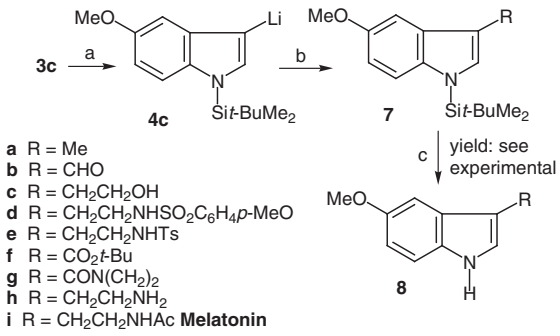



*Reagents and conditions*: a) *t*-BuLi/THF, −78 °C; b) Methylation: MeI/THF, −78 °C to r.t., Formylation: DMF/THF, −78 °C (reverse addition), 15 min; c) $Bu_4NF$/THF, r.t., 10 min

**Scheme 2**

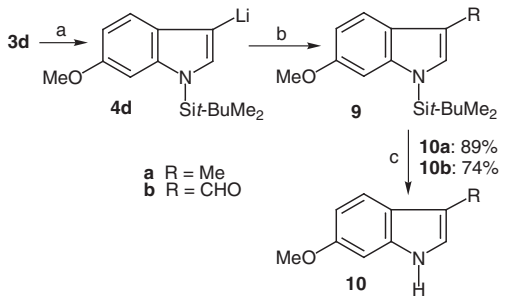
When a THF solution of 3-lithioindoles **4b**-**d** was added to a solution of DMF at −78 °C (reverse addition), 3-formyl-1-(trisopropylsilyl)indole **5b** and the desilylated 3-formylindoles **8b** and **10b** were isolated in 54%, 80%, and 74% yields, respectively (Schemes 3 and 4). This result corroborates that the triisopropylsilyl group is more stable towards hydrolysis than the *tert*-butyldimethylsilyl group, thus allowing the isolation of the *N*-silylated derivatives in 3-acylindoles.[4b] In these reactions, small amounts of the corresponding 3-unsubstituted indoles **2b**–**d** were also formed. A subsequent treatment of **5b** with $Bu_4NF$ afforded the deprotected 3-formylindole **6b**.

Since 5-methoxytryptamine and 5-methoxytryptophol are important intermediates in the synthesis of natural products, we decided to study the reaction of the 3-lithioindole **4c** with ethylene oxide and aziridines. Ring opening of aziridines with indoles requires the presence of an electron-withdrawing group on the aziridine nitrogen. Thus, *N*-acylaziridines undergo ring opening upon treatment with indoles in the presence of Lewis acids.[11] On the other hand, the reaction of indolyllithium with *N*-sulfonyl (tosyl or mesyl) or *N*-acylaziridines affords tryptamines along with the corresponding *N*-substituted indoles,[12] whereas indolylmagnesium bromide derivatives in the presence of $CuBr{\bullet}SMe_2$ afford regioselectively 3-substituted indoles.[13] As expected, the addition of a saturated THF solution of ethylene oxide to **4c** afforded the silylated 5-methoxytryptophol **7c** in 56% yield, which was desilylated to the known[14] tryptophol **8c** (Scheme 3). Similarly,




*Reagents and conditions*: a) *t*-BuLi/THF, −78 °C; b) **7a**–**i**: see experimental; c) Desilylation: $Bu_4NF$/THF, r.t., 10 min, Conversion of **8e** to **8i**: i. $NH_3$(liq)/Na/THF, −78 °C, ii. $Ac_2O/Et_3N$/THF, r.t., 3 h

**Scheme 3**




*Reagents and conditions*: a) *t*-BuLi/THF, −78 °C; b) Methylation: MeI/THF, −78 °C to r.t., Formylation: DMF/THF, −78 °C (reverse addition), 15 min; c) $Bu_4NF$/THF, r.t., 10 min

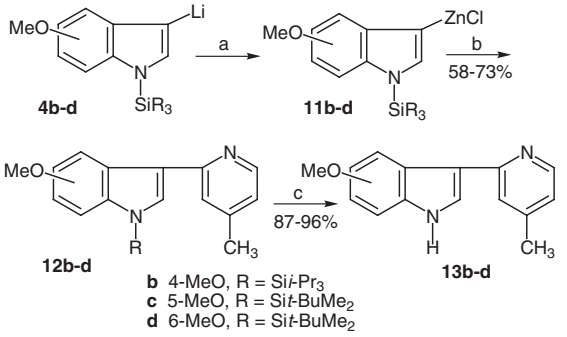
**Scheme 4**

3-lithioindole **4c** satisfactorily reacted with *N*-sulfonyl (*p*-methoxybenzenesulfonyl or tosyl) aziridines in the presence of $CuBr•SMe_2$ and $BF_3•OEt_2$[15] to give tryptamines **7d** (61%) and **7e** (50%). However, in the absence of the Lewis acid the reaction failed from both the 3-lithioindole **4c** and the corresponding cuprate. Also unsuccessful were the attempts to prepare tryptamine derivatives bearing a *N*-substituent easier to remove than sulfonyl. Thus, treatment of *N*-(*tert*-butoxycarbonyl)aziridine[16] or *N*-(benzyloxycarbonyl)aziridine[17] with 3-lithioindole **4c** under the above conditions gave a complex mixture, whereas in the absence of Cu salt and Lewis acid the 3-acylindoles **8f** (43%) or **8g** (38%), respectively, were obtained.[18] Desilylation of **7e** with $Bu_4NF$, followed by removal of the tosyl group from the resulting known[19] $N_b$-sulfonyltryptamine **8e** with sodium in liquid ammonia, afforded 5-methoxytryptamine **8h** (58% overall yield), which was then acetylated to give the pineal hormone melatonin (**8i**).

In order to explore the viability of our method for the synthesis of indole derivatives bearing an amino group on the benzene ring, we also prepared the *N*-silylated 4- and 5-nitro-3-bromoindoles **3f** and **3g**, by treatment of 4- and 5-nitroindole (**1f** and **1g**, respectively) with NaH, followed by silylation with triisopropylsilyl chloride and subsequent halogenation of the resulting silylnitroindoles **2f** and **2g** with NBS (Scheme 1). The use of BuLi, instead of NaH, to generate the indolyl anion of 4-nitroindole **1f** was not satisfactory as a consequence of the concomitant addition of the organometallic reagent to the benzene ring of indole.[20] Unfortunately, treatment of 4-, and 5-nitro substituted 3-bromoindoles **3f** and **3g** with *t*-BuLi, followed by addition of iodomethane afforded complex mixtures from which the corresponding 3-methylindoles could not be isolated.[21]

As has been mentioned before, 3-(2-pyridyl)indoles can be prepared by Pd(0)-catalyzed heteroarylation of 3-indolylzinc derivatives with 2-halopyridines. In order to extend the scope of the method to the synthesis of methoxy substituted 3-(2-pyridyl)indoles, we generated the 3-indolylzinc chlorides **11b–d** by transmetalation of the corresponding methoxy-3-lithioindoles **4b–d**,[22] and then allowed them to react with 2-bromo-4-methylpyridine in the presence of Pd(0) in refluxing THF (Scheme 5). The best conditions were found to be the use of 0.1 equivalent of $Pd(PPh_3)_4$ with respect to the 2-halopyridine. In this manner, methoxy-3-(2-pyridyl)indoles **12b–d** were obtained in 73%, 58%, and 61% yield, respectively. The corresponding 3-unsubstituted indoles **2b–d** were isolated as byproducts, but the formation of 3,3'-biindoles was not observed. Finally, the deprotected methoxy-3-(2-pyridyl)indoles **13b–d** were obtained in good yields by treatment of **12b–d** with $Bu_4NF$.

The new organometal methoxyindoles reported here, namely 3-lithioindoles **4b–d** and 3-indolylzinc chlorides **11b–d**, are useful and versatile intermediates for the synthesis of indole derivatives.




*Reagents and conditions*: a) $ZnCl_2$/THF, r.t., 30 min; b) 2-bromo-4-methylpyridine/$(Ph_3P)_4Pd$/THF, reflux, 4 h, c) $Bu_4NF$/THF, r.t., 10 min

**Scheme 5**

Mps were determined on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded on either a Varian Gemini 200 operating at 200 MHz for $^1H$ and 50.3 MHz for $^{13}C$, or a Varian Gemini 300 operating at 300 MHz for $^1H$ and 75.5 MHz for $^{13}C$. Chemical shifts are reported in values ppm relative to TMS as internal reference. Abbreviations used in NMR analyses are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, m = multiplet, br = broad. IR spectra were recorded on a FTIR Perkin-Elmer 1600 spectrometer with samples prepared as either KBr pellets or thin films on NaCl salt plates and only noteworthy absorptions are listed. TLC was done on $SiO_2$ (silica gel 60 $F_{254}$, Merck), and the spots were located with aq $KMnO_4$ solution. Column chromatography was carried out on $SiO_2$ (silica gel 60, SDS, 70–200 microns). Flash chromatography was carried out on $SiO_2$ (silica gel 60, SDS, 35–70 microns). All reagents were purchased from Aldrich or Fluka and were used without further purification. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried using standard procedures. Drying of the organic extracts during the workup of reactions was performed over $Na_2SO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HRMS were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona.

**1-(*tert*-Butyldimethylsilyl)-4-methoxyindole (2a)**

A solution of BuLi (0.7 mL of a 1.6 M solution in hexane, 1.1 mmol) was added dropwise to a solution of 4-methoxyindole[23] (**1a**; 100 mg, 0.68 mmol) in anhyd THF (3 mL) cooled to −78 °C, and the temperature was raised to −10 °C. After 15 min the reaction mixture was cooled to −50 °C, and TBDMSCl (164 mg, 1.1 mmol) was added. The solution was warmed to 0 °C, stirred for 3 h, and poured into $H_2O$ (10 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), and the combined organic extracts were dried, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$) affording pure **2a** as a white solid. Mp 40 – 41 °C; yield: 176 mg (98%).

IR (film): υ = 1260, 1136 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 0.63 (s, 6 H, $SiCH_3$), 0.96 [s, 9 H, $C(CH_3)_3$], 3.98 (s, 3 H, $OCH_3$), 6.58 (d, *J* = 8.0 Hz, 1 H, H-7), 6.77 (m, 1 H, H-3), 7.00–7.21 (m, 3 H, H-2, H-5, and H-6).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = −4.1 ($SiCH_3$), 19.4 [$C(CH_3)_3$], 26.2 [$C(CH_3)_3$], 55.1 ($OCH_3$), 99.6 (C-3), 101.8 (C-5), 107.4 (C-7), 121.8 (C-3a), 121.9 (C-6), 129.4 (C-2), 142.4 (C-7a), 153.2 (C-4).

HRMS: *m/z* calcd for $C_{15}H_{23}NOSi$ ($M^+$) 261.1549. Found: 261.1539.

**4-, 5-, and 6-Methoxy Substituted 3-Bromo-1-(trialkylsilyl)indoles 3b–d; General Procedure**

A 250 mL three-necked round bottom flask equipped with a magnetic stirrer was charged with a solution of methoxyindole **1b**,[23] **1c**[24] or **1d**[25] (3.0 g, 20.4 mmol) in anhyd THF (84 mL) and flushed with argon. The flask was submerged in a dry ice/acetone bath, and a solution of BuLi (16.6 mL of a 1.6 M solution in hexane, 26.5 mmol) was added dropwise. The mixture was warmed to −10 °C, stirred for 15 min, and cooled to −50 °C. Then, a solution of the trialkylsilyl chloride (*t*-$BuMe_2SiCl$ or *i*-$Pr_3SiCl$, 26.5 mmol) in anhyd THF (20 mL) was added dropwise, and the mixture was stirred at 0 °C for 3 h. The solution was cooled to −78 °C, and freshly crystallized *N*-bromosuccinimide (4.7 g, 26.5 mmol) was added. After stirring for 2 h, the mixture was warmed to 25 °C, and hexane (60 mL) and pyridine (0.6 mL) were added. The resulting suspension was filtered through a Celite pad, the filtrate was concentrated in vacuo, and the crude residue was immediately purified by flash chromatography on alumina ($CH_2Cl_2$/hexane, 1:1).

**3-Bromo-4-methoxy-1-(triisopropylsilyl)indole (3b)**

Yield: 6.8g (87%). White solid, mp 64 – 65 °C.

IR (film): υ = 1259, 1133, 736 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 1.13 (d, *J* = 7.5 Hz, 18 H, $CH_3$), 1.65 (m, 3 H, SiCH), 3.94 (s, 3 H, $OCH_3$), 6.56 (dd, *J* = 6.2, 2.3 Hz, 1 H, H-5), 7.05−7.13 (m, 3 H, H-2, H-6, and H-7).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 12.7 (SiCH), 18.0 ($CH_3$), 55.4 ($OCH_3$), 90.3 (C-3), 100.8 (C-5), 107.4 (C-7), 118.9 (C-3a), 122.9 (C-6), 129.3 (C-2), 141.9 (C-7a), 153.6 (C-4).

Anal. calcd for $C_{18}H_{28}BrNOSi$ (382.4): C, 56.53; H, 7.38; N, 3.66. Found: C, 56.67; H, 7.61; N, 3.62.

**3-Bromo-1-(*tert*-butyldimethylsilyl)-5-methoxyindole (3c)**

Yield: 5.4 g (78%). White solid, mp 65 – 67 °C.

IR (film): υ = 1261, 1211, 1167, 1028, 791 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 0.58 (s, 6 H, $SiCH_3$), 0.92 [s, 9 H, $C(CH_3)_3$], 3.89 (s, 3 H, $OCH_3$), 6.85 (dd, *J* = 9.0, 2.5 Hz, 1 H, H-6), 6.98 (d, *J* = 2.5 Hz, 1 H, H-4), 7.14 (s, 1 H, H-2), 7,35 (d, *J* = 9.0 Hz, 1 H, H-7).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = −4.1 ($SiCH_3$), 19.3 [$C(CH_3)_3$], 29.2 [$C(CH_3)_3$], 55.7 ($OCH_3$), 93.2 (C-3), 100.2 (C-4), 113.0 (C-6), 114.9 (C-7), 130.2 (C-2 and C-3a), 135.0 (C-7a), 154.7 (C-5).

Anal. calcd for $C_{15}H_{22}BrNOSi$ (340.3): C, 52.90; H, 6.52; N, 4.12. Found: C, 52.60; H, 6.44; N, 4.28.

**3-Bromo-1-(*tert*-butyldimethylsilyl)-6-methoxyindole (3d)**

Yield: 6.4 g (92%). White solid, mp 50 – 52 °C.

IR (film): υ = 1300, 1210, 1171, 1130, 1025, 798 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 0.58 (s, 6 H, $SiCH_3$), 0.94 [s, 9 H, $C(CH_3)_3$], 3.84 (s, 3 H, $OCH_3$), 6.86 (dd, *J* = 8.6, 2.0 Hz, 1 H, H-5), 6.97 (d, *J* = 2.0 Hz, 1 H, H-7), 7.05 (s, 1 H, H-2), 7.43 (d, *J* = 8.6 Hz, 1 H, H-4).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = −4.1 ($SiCH_3$), 19.4 [$C(CH_3)_3$], 26.2 [$C(CH_3)_3$], 55.6 ($OCH_3$), 93.4 (C-3), 98.3 (C-7), 109.9 (C-5), 119.5 (C-4), 124.3 (C-3a), 128.3 (C-2), 141.0 (C-7a), 156.6 (C-6).

Anal. calcd for $C_{15}H_{22}BrNOSi$ (340.3): C, 52.94; H, 6.52; N, 4.12. Found: C, 52.94; H, 6.65; N, 4.03.

**4- and 5-Nitro Substituted 3-Bromo-1-(triisopropylsilyl)indoles 3f and 3g; General Procedure**

A 100 mL three-necked round bottom flask equipped with a magnetic stirrer was charged with a solution of nitroindole **1f**[26] or **1g** (1.0 g, 6.2 mmol) in anhyd THF (16 mL), flushed with $N_2$, and the solution was cooled to −78 °C. Then, NaH (368 mg of a 55% dispersion in mineral oil, 8.4 mmol) was added and the temperature was raised to 25 °C. After stirring for 1 h, the mixture was cooled to −50 °C, and TIPSCl (1.5 g, 11.7 mmol) was added. The stirring was continued for 3 h at 0 °C and the reaction mixture was poured into $H_2O$ (15 mL). The aqueous phase was extracted with $CH_2Cl_2$ (3 × 15 mL) and the combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo to give crude silylindoles **2f** or **2g**, which were purified by flash chromatography ($CH_2Cl_2$) on silica gel. Freshly crystallized *N*-bromosuccinimide (290 mg, 1.60 mmol) was added to a cooled (−78 °C) solution of **2f** or **2g** (400 mg, 1.26 mmol) in anhyd THF (5 mL), and the resulting mixture was stirred at this temperature for 2 h and warmed to r.t. Hexane (4 mL) and pyridine (0.05 mL) were added, the resulting suspension was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The crude residue was immediately purified by flash chromatography on alumina ($CH_2Cl_2$/hexane, 7:3).

**4-Nitro-1-(triisopropylsilyl)indole (2f)**

Yield: 1.8 g (91%). Yellow solid, mp 58 – 59 °C.

IR (film): υ = 1513, 1322, 1281 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 1.15 (d, *J* = 7.5 Hz, 18 H, $CH_3$), 1.69 (m, 3 H, SiCH), 7.28 (t, *J* = 8.0 Hz, 1 H, H-6), 7.41 (dd, *J* = 3.2, 0.8 Hz, 1 H, H-3), 7.51 (d, *J* = 3.2 Hz, 1 H, H-2), 7,81 (d, *J* = 8.0 Hz, 1 H, H-7), 8.14 (d, *J* = 8.1 Hz, 1 H, H-5).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 12.8 (SiCH), 17.9 ($CH_3$), 105.2 (C-3), 117.7 (C-5), 120.2 (C-6 and C-7), 125.8 (C-3a), 135.9 (C-2), 140.4 (C-7a), 143.0 (C-4).

**3-Bromo-4-nitro-1-(triisopropylsilyl)indole (3f)**

Yield: 225 mg (45%). Yellow solid, mp 69 – 70 °C.

IR (film): υ = 1517, 1351, 884, 733 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 1.15 (d, *J* = 7.5 Hz, 18 H, $CH_3$), 1.69 (m, 3 H, SiCH), 7.24 (t, *J* = 8.0 Hz, 1 H, H-6), 7.45 (br s, 1 H, H-2), 7.71 (d, *J* = 8.0 Hz, 1H , H-7), 7.72 (d, *J* = 8.0 Hz, 1 H, H-5).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 12.7 (SiCH), 17.9 ($CH_3$), 117.3 (C-6), 118.7 (C-7), 121.0 (C-5), 121.1 (C-3a), 135.3 (C-2), 142.4 (C-7a), 142.5 (C-4).

Anal. calcd for $C_{17}H_{25}BrN_2O_2Si$ (397.4): C, 51.38; H, 6.34; N, 7.05. Found: C, 51.54; H, 6.63; N, 6.93.

**5-Nitro-1-(triisopropylsilyl)indole (2g)**

Yield: 1.9 g (98%). Yellow solid, mp 50 – 51 °C.

IR (film): υ = 1508, 1343, 1285 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 1.15 (d, *J* = 7.5 Hz, 18 H, $CH_3$), 1.71 (m, 3 H, SiCH), 6.79 (d, *J* = 3.2 Hz, 1 H, H-3), 7.40 (d, *J* = 3.2 Hz, 1 H, H-2), 7.52 (d, *J* = 9.3 Hz, 1 H, H-7), 8.06 (dd, *J* = 9.3, 2.5 Hz, 1 H, H-6), 8.57 (d, *J* = 2.5 Hz, 1 H, H-4).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 12.7 (SiCH), 17.9 ($CH_3$), 106.8 (C-3), 113.4 (C-7), 116.8 (C-6), 117.3 (C-4), 130.8 (C-3a), 134.3 (C-2), 141.6 (C-7a), 144.1 (C-5).

**3-Bromo-5-nitro-1-(triisopropylsilyl)indole (3g)**

Yield: 364 mg (73%). Yellow solid, mp 65 – 66 °C.

IR (film): υ = 1510, 1344, 732 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 1.15 (d, *J* = 7.5 Hz, 18 H, $CH_3$), 1.70 (m, 3 H, SiCH), 7.38 (s, 1 H, H-2), 7.52 (d, *J* = 9.3 Hz, 1 H, H-7), 8.10 (dd, *J* = 9.3, 2.5 Hz, 1 H, H-6), 8.53 (d, *J* = 2.5 Hz, 1 H, H-4).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 12.7 (SiCH), 17.8 ($CH_3$), 95.5 (C-3), 114.1 (C-7), 116.3 (C-6), 117.8 (C-4), 129.7 (C-3a), 132.9 (C-2), 142.3 (C-7a), 143.4 (C-5).

Anal. calcd for $C_{17}H_{25}BrN_2O_2Si$ (397.4): C, 51.38; H, 6.34; N, 7.05. Found: C, 51.33; H, 6.43; N, 6.98.

**3-Lithioindoles 4b-d; General Procedure**
A solution of *t*-BuLi (2.2 equiv of a 1.7 M solution in pentane) was added to a 0.33 M solution of the bromoindole **3b**, **3c** or **3d** in anhyd THF cooled to −78 °C, and the mixture was stirred under argon for 10 min.

**Methylation of 3-Lithioindoles 4b−d; General Procedure**
A 3.5 M solution of MeI (2.7 equiv) in anhyd THF was added to a solution of the 3-lithioindole **4b−d**, prepared from the corresponding 3-bromoindole **3b−d** (500 mg) as described above, and the mixture was stirred at −78 °C for 15 min. The mixture was allowed to warm up to r.t. and poured into sat aq $Na_2CO_3$ (10 mL). The aqueous layer was extracted with $Et_2O$ (3 × 10 mL), and the combined organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo to give a mixture of the 3-methylindole and the respective 3-unsubstituted indole.

**Deprotection of Silylindoles; General Procedure**
A 1.0 M solution of $Bu_4NF$(1.1 equiv) in THF was added to a 0.2 M solution of the silylindole in anhyd THF, and the mixture was stirred at r.t. for 10 min. After quenching with sat aq $Na_2CO_3$, the mixture was extracted with $CH_2Cl_2$, the combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo, and the residue was chromatographed (flash, $SiO_2$).

**4-Methoxy Series**
Indoles **5a** (oil, 300 mg, 72% yield) and **2b** (white solid, 100 mg) were obtained after flash chromatography ($SiO_2$, $CH_2Cl_2$/hexane, 1:1). Compound **6a** (140 mg, 69% yield) was obtained from pure **5a** (400 mg) following the general procedure for desilylation. Eluent for chromatography: $CH_2Cl_2$/hexane (1:1).

**4-Methoxy-3-methyl-1-(triisopropylsilyl)indole (5a)**

IR (film): υ = 1259, 1150 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 300 MHz): δ = 1.12 (d, *J* = 7.5 Hz, 18 H, $CH_3$), 1.65 (m, 3 H, SiCH), 2.46 (s, 3 H, $CH_3$), 3.89 (s, 3 H, $OCH_3$), 6.47 (d, *J* = 7.5 Hz, 1 H, H-5), 6.82 (br s, 1 H, H-2), 6.99 (t, *J* = 7.5 Hz, 1 H, H-6), 7.05 (d, *J* = 7.5 Hz, 1 H, H-7).

$^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ = 12.5 ($CH_3$), 12.7 (SiCH), 18.2 ($CH_3$), 55.0 ($OCH_3$), 99.4 (C-5), 107.4 (C-7), 113.7 (C-3), 120.9 (C-3a), 121.8 (C-6), 127.1 (C-2), 143.0 (C-7a), 154.9 (C-4).

**4-Methoxy-1-(triisopropylsilyl)indole (2b)**

IR (film): υ = 1488, 1259, 1133 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 300 MHz): δ = 1.12 (d, *J* = 7.5 Hz, 18 H, $CH_3$), 1.68 (m, 3 H, SiCH), 3.94 (s, 3 H, $OCH_3$), 6.52 (d, *J* = 7.8 Hz, 1 H, H-5), 6.72 (d, *J* = 3.2 Hz, 1 H, H-3), 7.05 (t, *J* = 7.8 Hz, 1 H, H-6), 7.13 (d, *J* = 7.8 Hz, 1 H, H-7), 7.14 (d, *J* = 3.2 Hz, 1 H, H-2).

$^{13}$C NMR ($CDCl_3$, 75.5 MHz):δ = 12.8 (SiCH), 18.0 ($CH_3$), 55.1 ($OCH_3$), 99.5 (C-3), 101.7 (C-5), 107.0 (C-3a), 107.3 (C-7), 121.9 (C-6), 129.5 (C-2), 142.1 (C-7a), 153.1 (C-4).

HRMS: *m*/*z* calcd for $C_{18}H_{29}NOSi$ ($M^+$) 303.2018. Found: 303.2007.

**4-Methoxy-3-methylindole (6a)**

White solid, mp 50 °C.
IR (film): υ = 3389, 1506, 1259 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 300 MHz): δ = 2.47 (s, 3 H, $CH_3$), 3.89 (s, 3 H, $OCH_3$), 6.45 (d, *J* = 8.0 Hz, 1 H, H-5), 6.76 (m, 1 H, H-2), 6.89 (dd, *J* = 8.0, 0.7 Hz, 1 H, H-7), 7.05 (t, *J* = 8.0 Hz, 1 H, H-6), 7.70 (br s, 1 H, NH).

$^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ = 12.2 ($CH_3$), 55.1 ($OCH_3$), 99.2 (C-5), 104.4 (C-7), 112.1 (C-3), 117.9 (C-3a), 120.2 (C-6), 122.6 (C-2), 138.0 (C-7a), 155.2 (C-4).

HRMS: *m*/*z* calcd for $C_{10}H_{11}NO$ ($M^+$) 161.0841. Found: 161.0823.

**5-Methoxy Series**
A mixture (9:1, 390 mg) of indoles **7a** and **2c**, which could not be completely separated, was obtained after flash chromatography ($SiO_2$, $CH_2Cl_2$/hexane). Compound **8a** (206 mg, 87% overall yield from bromoindole **3c**) was obtained from the above mixture of **7a** and **2c** (390 mg) following the general procedure for desilylation. Eluent for chromatography: $CH_2Cl_2$/hexane (7:3).

**1-(*tert*-Butyldimethylsilyl)-5-methoxy-3-methylindole (7a)**
Yellow oil.

IR (film): υ = 1258, 1230, 1190 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 300 MHz): δ = 0.59 (s, 6 H, $SiCH_3$), 0.96 [s, 9 H, $C(CH_3)_3$], 2.34 (s, 3 H, $CH_3$), 3.92 (s, 3 H, $OCH_3$), 6.86 (dd, *J* = 8.9, 2.2 Hz, 1 H, H-6), 6.96 (br s, 1 H, H-2), 7.03 (d, *J* = 2.2 Hz, 1 H, H-4), 7.40 (d, *J* = 8.9 Hz, 1 H, H-7).

$^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ = −4.2 ($SiCH_3$), 9.6 ($CH_3$), 19.3 [$C(CH_3)_3$], 26.1 [$C(CH_3)_3$], 55.4 ($OCH_3$), 100.4 (C-4), 111.0 (C-6), 113.0 (C-3), 114.2 (C-7), 128.8 (C-2), 132.1 (C-3a), 136.2 (C-7a), 153.7 (C-5).

**3-Methyl-5-methoxyindole (8a)[27]**
$^1$H NMR ($CDCl_3$, 300 MHz): δ = 2.30 (s, 3 H, $CH_3$), 3.87 (s, 3 H, $OCH_3$), 6.85 (dd, *J* = 8.7, 2.5 Hz, 1 H, H-6), 6.95 (m, 1 H, H-2), 7.01 (d, *J* = 2.5 Hz, 1 H, H-4), 7.23 (d, *J* = 8.7 Hz, 1 H, H-7), 7.8 (br s, 1 H, NH).

$^{13}$C NMR ($CDCl_3$-$CD_3OD$, 75.5 MHz): δ = 9.5 ($CH_3$), 55.8 ($OCH_3$), 100.5 (C-4), 111.0 (C-3), 111.6 (C-6 and C-7), 122.6 (C-2), 128.3 (C-3a), 131.4 (C-7a), 153.4 (C-5).

**6-Methoxy Series**
A mixture (93:7, 402 mg) of indoles **9a** and **2d**, which could not be completely separated, was obtained after flash chromatography ($SiO_2$, $CH_2Cl_2$/hexane). Compound **10a** (211 mg, 89% overall yield from bromoindole **3d**) was obtained from the above mixture of **9a** and **2d** (402 mg) following the general procedure for desilylation. Eluent for chromatography: $CH_2Cl_2$/hexane (9:1).

**1-(*tert*-Butyldimethylsilyl)-6-methoxy-3-methylindole (9a)**

Yellow oil.
IR (film): υ = 1619, 1484, 1202, 1130 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 300 MHz): δ = 0.56 (s, 6 H, $SiCH_3$), 0.94 [s, 9 H, $C(CH_3)_3$], 2.28 (s, 3 H, $CH_3$), 3.84 (s, 3 H, $OCH_3$), 6.80 (dd, *J* = 8.7, 2.2 Hz, 1 H, H-5), 6.82 (s, 1 H, H-2), 6.98 (d, *J* = 2.2 Hz, 1 H, H-7), 7.41 (d, *J* = 8.7 Hz, 1 H, H-4).

$^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ = −4.1 ($SiCH_3$), 19.5 [$C(CH_3)_3$], 26.3 [$C(CH_3)_3$], 55.6 ($OCH_3$), 98.3 (C-7), 108.2 (C-5), 113.3 (C-3), 118.9 (C-4), 125.7 (C-3a), 126.9 (C-2), 125.7 (C-3a), 142.0 (C-7a), 155.8 (C-6).

**6-Methoxy-3-methylindole (10a)[28]**
$^1$H NMR ($CDCl_3$, 300 MHz): δ = 2.30 (s, 3 H, $CH_3$), 3.84 (s, 3 H, $OCH_3$), 6.79 (dd, *J* = 8.5, 2.3 Hz, 1 H, H-5), 6.83 (d, *J* = 2.3 Hz, 1 H, H-7), 6.85 (m, 1 H, H-2), 7.45 (d, *J* = 8.5 Hz, 1 H, H-4), 7.73 (br s, 1 H, NH).

$^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ = 9.7 ($CH_3$), 55.6 ($OCH_3$), 94.5 (C-7), 108.9 (C-5), 111.5 (C-3), 119.4 (C-4), 120.3 (C-2), 122.7 (C-3a), 136.9 (C-7a), 156.3 (C-6).

**Formylation of 3-Lithioindoles 4b−d; General Procedure**
A solution of 3-lithioindole **4b−d**, prepared from 500 mg of the corresponding 3-bromoindole **3b−d** as described above, was added via canula to a 3.5 M solution of DMF (3.0 equiv) in anhyd THF, and the mixture was stirred at −78 °C for 15 min. Aqueous workup was carried out as described in the above general procedure for methylation to give a mixture of the 3-formylindole and the respective 3-unsubstituted indole, which were separated by flash chromatography ($SiO_2$).

**4-Methoxy Series**
Indoles **5b** (235 mg, 54% yield) and **2b** (155 mg) were obtained. Eluent for chromatography: $CH_2Cl_2$/hexane (8:2).

**3-Formyl-4-methoxy-1-(triisopropylsilyl)indole (5b)**

White solid, mp 130 – 131 °C.
IR (film) 1650, 1508 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 1.14 (d, *J* = 7.5 Hz, 18 H, $CH_3$), 1.71 (m, 3 H, SiCH), 3.98 (s, 3 H, $OCH_3$), 6.72 (dd, *J* = 5.2, 3.5 Hz, 1 H, H-5), 7.15 (m, 2 H, H-6 and H-7), 7.97 (s, 1 H, H-2), 10.11 (s, 1 H, CHO).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 12.6 (SiCH), 17.9 ($CH_3$), 55.3 ($OCH_3$), 102.4 (C-5), 107.8 (C-7), 111.4 (C-3a), 121.4 (C-7a), 123.4 (C-6), 135.5 (C-2), 143.0 (C-3), 154.5 (C-4), 188.6 (s, 1H, CHO).

**3-Formyl-4-methoxyindole (6b)[29]**
Compound **6b** (190 mg, 85% yield) was obtained as a white solid from pure **5b** (424 mg) following the general procedure for desilylation. Eluent for chromatography: $CH_2Cl_2$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 4.06 (s, 3 H, $OCH_3$), 6.73 (d, *J* = 8.0 Hz, 1 H, H-5), 7.09 (d, *J* = 8.0 Hz, 1 H, H-7), 7.22 (t, *J* = 8.0 Hz, 1 H, H-6), 7.93 (d, *J* = 3.2 Hz, 1 H, H-2), 9.2 (br s, 1 H, NH), 10.5 (s, 1 H, CHO).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 55.3 ($OCH_3$), 102.5 (C-5), 105.4 (C-7), 119.3 (C-3), 124.2 (C-6), 128.9 (C-2), 137.8 (C-7a), 154.4 (C-4), 188.8 (CHO).

**5-Methoxy Series**
Indoles **8b** (205 mg, 80% yield) and **2c** (20 mg), were obtained. Eluent for chromatography: $CH_2Cl_2$.

**3-Formyl-5-methoxyindole (8b)[30]**
$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 3.89 (s, 3 H, $OCH_3$), 6.33 (dd, *J* = 9.0, 2.5 Hz, 1 H, H-6), 7.33 (d, *J* = 9.0 Hz, 1 H, H-7), 7.81 (m, 2 H, H-2 and H-4), 8.75 (br s, 1 H, N-H), 10.0 (s, 1 H, CHO).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 55.8 ($OCH_3$), 103.1 (C-4), 112.4 (C-6), 115.0 (C-7), 119.6 (C-3), 125.2 (C-3a), 131.4 (C-7a), 135.6 (C-2), 156.6 (C-5), 185.2 (CHO).

**1-(*tert*-Butyldimethylsilyl)-5-methoxyindole (2c)[4a]**
$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 0.57 (s, 6 H, $SiCH_3$), 0.91 [s, 9 H, $C(CH_3)_3$], 3.84 (s, 3 H, $OCH_3$), 6.53 (dd, *J* = 3.3, 0.7 Hz, 1 H, H-3), 6.80 (dd, *J* = 9.0, 2.5 Hz, 1 H, H-6), 7.08 (d, *J* = 2.5 Hz, 1 H, H-4), 7.14 (d, *J* = 3.3 Hz, 1 H, H-2), 7.38 (d, *J* = 9.0 Hz, 1 H, H-7).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = −4.05 ($SiCH_3$), 19.4 [$C(CH_3)_3$], 26.3 [$C(CH_3)_3$], 55.7 ($OCH_3$), 112.2 (C-3), 104.5 (C-4), 11.3 (C-6), 114.4 (C-7), 131.7 (C-2), 131.8 (C-3a), 135.9 (C-7a), 154.0 (C-5).

**6-Methoxy Series**
Indoles **10b** (190 mg, 74% yield) and **2d** (40 mg) were obtained. Eluent for chromatography: $CH_2Cl_2$/hexane (8:2).

**3-Formyl-6-methoxyindole (10b)[31]**
$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 3.86 (s, 3 H, $OCH_3$), 6.91 (d, *J* = 2.0 Hz, 1 H, H-7), 6.97 (dd, *J* = 8.6, 2.0 Hz, 1 H, H-5), 7.75 (d, *J* = 3.0 Hz, 1 H, H-2), 8.19 (d, *J* = 8.6 Hz, 1 H, H-4), 8.7 (br s, 1 H, NH), 10.0 (s, 1 H, CHO).

$^{13}C$ NMR ($CDCl_3$/$CD_3OD$, 75.5 MHz): δ = 55.5 ($OCH_3$), 95.4 (C-7), 112.0 (C-5), 118.4 (C-3), 118.9 (C-3a), 122.1 (C-4), 136.3 (C-2), 138.0 (C-7a), 157.4 (C-6), 185.5 (CHO).

**1-(*tert*-Butyldimethylsilyl)-6-methoxyindole (2d)[5b]**
$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 0.62 (s, 6 H, $SiCH_3$), 0.97 [s, 9 H, $C(CH_3)_3$], 3.87 (s, 3 H, $OCH_3$), 6.56 (dd, *J* = 3.2, 0.8 Hz, 1 H, H-3), 6.83 (dd, *J* = 8.7, 2.2 Hz, 1 H, H-5), 7.05 (d, *J* = 2.2 Hz, 1 H, H-7), 7.09 (d, *J* = 3.2 Hz, 1 H, H-2), 7.52 (d, *J* = 8.7 Hz, 1 H, H-4).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = −4.1 ($SiCH_3$), 19.6 [$C(CH_3)_3$], 26.3 [$C(CH_3)_3$], 55.6 ($OCH_3$), 98.3 (C-7), 104.5 (C-3), 108.9 (C-5), 120.8 (C-4), 125.6 (C-3a), 129.8 (C-2), 141.7 (C-7a), 155.7 (C-6).

**1-(tert-Butyldimethylsilyl)-3-(2-hydroxyethyl)-5-methoxyindole (7c)**
A saturated solution of ethylene oxide in anhyd THF (2 mL) was added via canula to a solution of 3-lithioindole **4c**, prepared from 3-bromoindole **3c** (500 mg) as described above, and the mixture was stirred at −78 °C for 15 min. The resulting mixture was poured into aq sat $Na_2CO_3$ (10 mL), and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo. The residue was chromatographed (flash, $SiO_2$, $CH_2Cl_2$/AcOEt, 9:1) to give **7c** (250 mg, 56% yield) as a colorless oil and **2c** (150 mg).

IR (film): υ = 3425, 1478, 1220, 1036 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 0.60 (s, 6 H, $SiCH_3$), 0.92 [s, 9 H, $C(CH_3)_3$], 3.0 (t, *J* = 6.6 Hz, 2 H, $CH_2$), 3.87 (s, 3 H, $OCH_3$), 3.89 (t, *J* = 6.6 Hz, 2 H, $CH_2OH$), 6.82 (dd, *J* = 8.9, 2.5 Hz, 1 H, H-6), 7.01 (s, 1 H, H-2), 7.03 (d, *J* = 2.5 Hz, 1 H, H-4), 7.37 (d, *J* = 8.9 Hz, 1 H, H-7).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = −4.1 ($SiCH_3$), 19.4 (SiC), 26.2 ($CH_3$), 28.7 ($CH_2$), 55.7 ($OCH_3$), 62.4 ($CH_2OH$), 100.5 (C-4), 111.4 (C-6), 113.7 (C-3), 114.6 (C-7), 129.9 (C-2), 131.2 (C-3a), 136.5 (C-7a), 153.8 (C-5).

**3-(2-Hydroxyethyl)-5-methoxyindole (8c)[14]**
Compound **8c** (142 mg, 84%) was obtained from **7c** (270 mg) following the general procedure for desilylation. Eluent for chromatography (flash, $SiO_2$): $CH_2Cl_2$/EtOAc (8:2).

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 2.96 (t, *J* = 6.6 Hz, 2 H, H-1'), 3.83 (s, 3 H, $OCH_3$), 3.86 (t, *J* = 6.6 Hz, 2 H, H-2'), 6.84 (dd, *J* = 8.7, 2.4 Hz, 1 H, H-6), 6.95 (d, *J* = 2.4 Hz, 1 H, H-2), 7.03 (d, *J* = 2.4 Hz, 1 H, H-4), 7.18 (d, *J* = 8.7 Hz, 1 H, H-7), 8.15 (br s, 1 H, NH).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 28.5 (C-1'), 55.8 ($OCH_3$), 62.4 (C-2'), 100.4 (C-4), 111.4 (C-6), 111.9 (C-3), 123.3 (C-2), 127.5 (C-3a), 131.4 (C-7a), 153.5 (C-5).

**1-(*tert*-Butyldimethylsilyl)-5-methoxy-*N*-(4-methoxybenzenesulfonyl)tryptamine (7d)**
A solution of *t*-BuLi (1.14 mL of a 1.7 M solution in pentane, 1.94 mmol) was added dropwise to a solution of 3-bromoindole **3c** (300 mg, 0.88 mmol) in anhyd $Et_2O$ (3.0 mL) cooled to −78 °C, and the mixture was stirred under argon for 10 min. $CuBr•SMe_2$ (96 mg, 0.46 mmol) was added, and the stirring was continued for 15 min at the same temperature. Then, a solution of 1-(4-methoxybenzenesulfonyl)aziridine[32] (375 mg, 1.76 mmol) and $BF_3•OEt_2$ (265 μL, 2.1 mmol) in anhyd $Et_2O$ (6 mL) was added via canula to the above mixture. After stirring at −78 °C for 4 h, the reaction was quenched with sat aq $Na_2CO_3$ (10 mL). The mixture was extracted with $CH_2Cl_2$ (3 × 15 mL), and the combined organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo to give a residue. Flash chromatography ($SiO_2$, hexane/EtOAc, 8:2) afforded pure **7d** (257 mg, 61% yield) as a white solid, mp 85 – 86 °C.

IR (KBr): υ = 3480, 1550, 1317, 1162 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 0.56 (s, 6 H, $SiCH_3$), 0.90 [s, 9 H, $C(CH_3)_3$], 2.89 (t, *J* = 6.6 Hz, 2 H, $CH_2$), 3.25 (m, 2 H, $CH_2N$), 3.80 (s, 3 H, $OCH_3$), 3.85 (s, 3 H, $OCH_3$), 4.30 (t, *J* = 6.3 Hz, 1 H, NH), 6.80 (m, 2 H, H-4 and H-6), 6.87 (dm, *J* = 9.0 Hz, 2 H, *m*-H), 6.90 (s, 1 H, H-2), 7.35 (d, *J* = 9.6 Hz, 1 H, H-7), 7.66 (dm, *J* = 9.0 Hz, 2 H, *o*-H).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = −4.1 ($SiCH_3$), 19.4 [$C(CH_3)_3$], 25.5 ($CH_2$), 26.3 [$C(CH_3)_3$], 42.7 ($NCH_2$), 55.5 ($OCH_3$), 55.7 ($OCH_3$), 100.3 (C-4), 111.6 (C-6), 113.1 (C-3), 114.1 (2 *m*-C),

114.7 (C-7), 129.1 (2 *o*-C), 130.0 (C-2), 130.7 (*i*-C), 131.3 (C-3a), 136.5 (C-7a), 153.9 (C-5), 162.7 (*p*-C).

Anal. calcd for $C_{24}H_{34}N_2O_4SSi$ (474.7): C, 60.73; H, 7.22; N, 5.90. Found: C, 60.85; H, 7.31; N, 5.94.

**1-(*tert*-Butyldimethylsilyl)-5-methoxy-*N*-(4-methylbenzenesulfonyl)tryptamine (7e)**

Operating as described for **7d**, from 3-bromoindole **3c** (250 mg, 0.74 mmol) and 1-(4-methylbenzenesulfonyl)aziridine[33] (292 mg, 1.48 mmol), pure compound **7e** (169 mg, 50% yield) was obtained as a white solid, (mp 92 – 93 °C) after flash chromatography ($SiO_2$, hexane/EtOAc, 7:3).

IR (film): υ = 3450, 1699, 1479, 1216, 1148 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 0.56 (s, 6 H, $SiCH_3$), 0.90 [s, 9 H, $C(CH_3)_3$], 2.39 (s, 3H, Ar$CH_3$), 2.89 (t, *J* = 6.6 Hz, 2 H, $CH_2$), 3.25 (m, 2 H, $CH_2N$), 3.80 (s, 3 H, $OCH_3$), 4.42 (t, *J* = 6.0 Hz, 1 H, NH), 6.80 (m, 2 H, H-4 and H-6), 6.90 (s, 1 H, H-2), 7.20 (d, *J* = 8.0 Hz, 2 H, *m*-H), 7.34 (d, *J* = 9.6 Hz, 1 H, H-7), 7.62 (d, *J* = 8.0 Hz, 2 H, *o*-H).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = −4.1 ($SiCH_3$), 19.4 [$C(CH_3)_3$], 21.4 (Ar$CH_3$), 25.5 ($CH_2$), 26.3 [$C(CH_3)_3$], 42.8 ($CH_2N$), 55.6 ($OCH_3$), 100.2 (C-4), 111.6 (C-6), 113.1 (C-3), 114.7 (C-7), 126.9 (2 *m*-C), 129.5 (2 *o*-C), 130.0 (C-2), 130.7 (C-3a), 136.5 (C-7a), 136.7 (*i*-C), 143.2 (*p*-C), 153.9 (C-5).

***N*-[2-(5-Methoxyindol-3-yl)ethyl]4-methylbenzenesulfonamide (8e)[19]**

Compound **8e** (113 mg, 89%) was obtained from **7e** (168 mg, 0.36 mmol) following the general procedure for desilylation. Eluent for chromatography (flash, $SiO_2$): $CH_2Cl_2$/EtOAc (7:3).

$^1H$ NMR ($CDCl_3$, 300 MHz): δ = 2.39 (s, 3 H, Ar$CH_3$), 2.74 (s, 1 H, NH), 2.89 (t, *J* = 6.6 Hz, 2 H, $CH_2$), 3.21 (t, *J* = 6.6 Hz, 2 H, $CH_2N$), 3.80 (s, 3 H, $OCH_3$), 6.82 (m, 2 H, H-4 and H-6), 6.95 (s, 1 H, H-2), 7.22 (m, 3 H, H-7 and *m*-H), 7.61 (dm, *J* = 8.0 Hz, 2 H, *o*-H).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 21.2 (Ar$CH_3$), 25.3 ($CH_2$), 42.7 ($CH_2N$), 55.7 ($OCH_3$), 100.0 (C-4), 110.8 (C-3), 111.9 (C-6*), 112.0 (C-7*), 123.2 (C-2), 126.7 (2 *m*-C), 127.0 (C-3a), 129.4 (2 *o*-C), 131.4 (C-7a), 136.4 (*i*-C), 143.2 (*p*-C), 153.6 (C-5) (*assignments excahngeable).

**Melatonin (8i)**

Liquid ammonia (100 mL) was distilled into a solution of sulfonamide **8e** (100 mg, 0.29 mmol) in anhyd THF (8 mL) kept at −78 °C under argon. Then, Na was added in small pieces, resulting in a deep blue solution which was stirred for 15 min and quenched with solid $NH_4Cl$. The ammonia was allowed to evaporate, the mixture was diluted with $H_2O$ and extracted with $Et_2O$ (3 × 15 mL), and the combined organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo. The residue was chromatographed (flash, $CH_2Cl_2/Et_3N$, 9:1) to give pure 3-(2-aminoethyl)-5-methoxyindole (**8h**) (36 mg, 65%). The identity of **8h** was established by comparison of its spectroscopic data with those of a commercial sample. A solution of **8h** (40 mg, 0.21 mmol), $Ac_2O$ (30 μL, 0.32 mmol), and $Et_3N$ (47 μL, 0.34 mmol) in THF (2 mL) was stirred at r.t. for 3 h. The resulting mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc. The organic solution was washed with sat aq $Na_2CO_3$ (2 × 10 mL), dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed ($CH_2Cl_2$/EtOH, 99:1) to give melatonin **8i** (27 mg, 55%). The identity of melatonin was established by comparison of its spectroscopic data with those of a commercial sample.

**3-Indolylzinc Chlorides 11b–d and Pd(0)-Catalyzed Cross-Coupling Reactions; General Procedure**

A 0.35 M solution of anhyd $ZnCl_2$ (1.1 equiv, fused by flame-drying under reduced pressure) in anhyd THF was added to a solution of 3-lithioindoles **4b–d** in THF prepared as described above, and the mixture was stirred at r.t. for 30 min. A 0.1 M solution of $Pd(PPh_3)_4$ (0.1 equiv) in anhyd THF was added to a 0.5 M solution of 2-bromo-4-methylpyridine[34] (1 equiv) in anhyd THF. The mixture was stirred at r.t. for 10 min and then transferred via canula to a solution of indolylzinc chloride **11b–d** (1.5 equiv) prepared as described above. The resulting mixture was heated at reflux for 4 h, cooled, and poured into sat aq $Na_2CO_3$. The combined aqueous layers were extracted with $Et_2O$, and the organic extracts were dried ($Na_2SO_4$) and concentrated to give a mixture of the 3-(2-pyridyl)indole **12b–d** and the corresponding 3-unsubstituted indoles **2b–d**, which were separated by flash chromatography ($SiO_2$).

**4-Methoxy Series**

From 2-bromo-4-methylpyridine (180 mg, 1.05 mmol) and 3-bromoindole **3b** (600 mg, 1.57 mmol) were obtained pyridylindole **12b** (300 mg, 73% yield) and 4-methoxyindole **2b** (224 mg). Eluent for chromatography: $CH_2Cl_2$/EtOH (98:2).

**4-Methoxy-3-(4-methyl-2-pyridyl)-1-(triisopropylsilyl)indole (12b)**

Solid, mp 57 – 58 °C.
IR (film): υ = 1603, 1226, 1269, 1105 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz, assignments aided by $^1H$-$^{13}C$ HETCOR): δ = 1.18 (d, *J* = 7.4 Hz, 18 H, $CH_3$), 1.75 (m, 3 H, CH), 2.40 (s, 3 H, $CH_3$), 3.87 (s, 3 H, $OCH_3$), 6.62 (dd, *J* = 7.8, 1.0 Hz, 1 H, H-5), 6.95 (dm, *J* = 5.0 Hz, 1 H, H-5'), 7.11 (t, *J* = 7.8 Hz, 1 H, H-6), 7.18 (dd, *J* = 7.8, 1.0 Hz, 1 H, H-7), 7.60 (s, 1 H, H-2), 7.66 (m, 1 H, H-3'), 8.46 (d, *J* = 5.0 Hz, 1 H, H-6').

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 12.8 (SiCH), 18.2 [SiCH($CH_3$)$_2$], 21.2 ($CH_3$), 55.1 ($OCH_3$), 101.2 (C-5), 107.7 (C-7), 118.5 (C-3a), 120.3 (C-3), 121.3 (C-5'), 122.1 (C-6), 125.9 (C-3'), 131.7 (C-2), 143.4 (C-7a), 145.8 (C-4'), 148.3 (C-6'), 154.0 (C-4), 154.8 (C-2').

**4-Methoxy-3-(4-methyl-2-pyridyl)indole (13b)**

Compound **13b** (117 mg, 91% yield) was obtained from pyridylindole **12b** (213 mg, 0.54 mmol) following the general procedure for desilylation. Eluent for chromatography: $CH_2Cl_2$/EtOH (99:1).

Mp 93 – 94 °C.
IR (film): υ = 3500, 1610, 1541, 1339, 1246, 1093 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300MHz): δ = 2.40 (s, 3 H, $CH_3$), 3.90 (s, 3 H, $OCH_3$), 6.61 (dd, *J* = 8.0, 1.0 Hz, 1 H, H-5), 6.97 (dm, *J* = 5.0 Hz, 1 H, H-5'), 7.04 (dd, *J* = 8.0, 1.0 Hz, 1 H, H-7), 7.16 (t, *J* = 8.0 Hz, 1 H, H-6), 7.60 (d, *J* = 2.7 Hz, 1 H, H-2), 7.77 (m, 1 H, H-3'), 8.45 (d, *J* = 5.0 Hz, 1 H, H-6'), 8.90 (br s, 1 H, N-H).

$^{13}C$ NMR ($CDCl_3$, 75.5 MHz): δ = 21.3 ($CH_3$), 55.2 ($OCH_3$), 101.0 (C-5), 105.0 (C-7), 115.2 (C-3), 118.5 (C-3a), 121.5 (C-5'), 123.0 (C-6), 124.8 (C-2), 125.8 (C-3'), 138.5 (C-7a), 146.2 (C-4'), 148.3 (C-6'), 154.2 (C-4), 154.5 (C-2').

Anal. calcd for $C_{15}H_{14}N_2O$ (238.3): C, 75.61; H, 5.92; N, 11.76. Found: C, 75.67; H, 5.92; N, 11.75.

**5-Methoxy Series**

From 2-bromo-4-methylpyridine (336 mg, 1.95 mmol) and 3-bromoindole **3c** (1.0 g, 2.94 mmol) were obtained pyridylindole **12c** (oil, 396 mg, 58% yield) and 5-methoxyindole **2c** (465 mg). Eluent for chromatography: $CH_2Cl_2$.

**1-(*tert*-Butyldimethylsilyl)-5-methoxy-3-(4-methyl-2-pyridyl)indole (12c)**

IR (film): υ = 1603, 1465, 1209, 1171, 1035 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 300 MHz, assignments aided by $^1H$-$^{13}C$ HETCOR): δ = 0.64 (s, 6 H, $SiCH_3$), 0.95 [s, 9 H, $C(CH_3)_3$], 2.40 (s, 3 H, $CH_3$), 3.91 (s, 3 H, $OCH_3$), 6.86 (dd, *J* = 9.0, 2.5 Hz, 1 H, H-6), 6.94 (dm, *J* = 5.0 Hz, 1 H, H-5'), 7.42 (d, *J* = 9.0 Hz, 1 H, H-7), 7.48 (m, 1 H, H-3'), 7.67 (s, 1 H, H-2), 7.84 (d, *J* = 2.5 Hz, 1 H, H-4), 8.52 (d, *J* = 5.0 Hz, 1 H, H-6').

$^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ = −3.96 ($SiCH_3$), 19.3 [$C(CH_3)_3$], 21.2 ($CH_3$), 26.3 [$C(CH_3)_3$], 55.8 ($OCH_3$), 103.2 (C-4), 111.5 (C-6), 114.6 (C-7), 119.1 (C-3), 121.1 (C-3'), 121.2 (C-5'), 129.4 (C-3a), 131.6 (C-2), 137.1 (C-7a), 146.9 (C-4'), 149.3 (C-6'), 154.7 (C-5), 154.9 (C-2').

**5-Methoxy-3-(4-methyl-2-pyridyl)indole (13c)**
Compound **13c** (237 mg, 96% yield) was obtained from pyridylindole **12c** (363 mg, 1.03 mmol) following the general procedure for desilylation. Eluent for chromatography: $CH_2Cl_2$/EtOH (99:1); mp 135 °C.

IR (film): υ = 3450, 1606, 1469, 1216, 800 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 300MHz): δ = 2.40 (s, 3 H, $CH_3$), 3.92 (s, 3 H, $OCH_3$), 6.90 (dd, *J* = 8.8, 2.7 Hz, 1 H, H-6), 6.94 (dm, *J* = 5.2 Hz, 1 H, H-5'), 7.31 (d, *J* = 8.8 Hz, 1 H, H-7), 7.48 (m, 1 H, H-3'), 7.72 (d, *J* = 2.8 Hz, 1 H, H-2), 7.87 (d, *J* = 2.5 Hz, 1 H, H-4), 8.36 (br s, 1 H, N-H), 8.52 (d, *J* = 5.2 Hz, 1 H, H-6').

$^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ = 21.2 ($CH_3$), 56.0 ($OCH_3$), 103.1 (C-4), 112.1 (C-7), 112.4 (C-6), 116.5 (C-3), 121.1 (C-3'), 121.3 (C-5'), 125.0 (C-2), 126.0 (C-3a), 132.0 (C-7a), 147.2 (C-4'), 149.1 (C-6'), 154.9 (C-5), 155.0 (C-2').

Anal. calcd for $C_{15}H_{14}N_2O$ (238.3): C, 75.61; H, 5.92; N, 11.76. Found: C, 75.26; H, 5.83; N, 11.43.

**6-Methoxy Series**
From 2-bromo-4-methylpyridine (336 mg, 1.95 mmol) and 3-bromoindole **3d** (1.0 g, 2.94 mmol) were obtained pyridylindole **12d** (oil, 420 mg, 61% yield) and 6-methoxyindole **2d** (453 mg). Eluent for chromatography: $CH_2Cl_2$.

**1-(*tert*-Butyldimethylsilyl-)-6-methoxy-3-(4-methyl-2-pyridyl)indole (12d)**
$^1$H NMR ($CDCl_3$, 300 MHz, assignments aided by $^1$H-$^{13}$C HETCOR): δ = 0.65 (s, 3 H, $SiCH_3$), 0.97 [s, 9 H, $C(CH_3)_3$], 2.40 (s, 3 H, $CH_3$), 3.87 (s, 3 H, $OCH_3$), 6.90 (dd, *J* = 8.8, 2.3 Hz, 1 H, H-5), 6.93 (dm, *J* = 5.0 Hz, 1 H, H-5'), 7.05 (d, *J* = 2.3 Hz, 1 H, H-7), 7.50 (m, 1 H, H-3'), 7.62 (s, 1 H, H-2), 8.17 (d, *J* = 8.8 Hz, 1 H, H-4), 8.51 (d, *J* = 5.0 Hz, 1 H, H-6').

$^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ = −3.9 ($SiCH_3$), 19.5 [$C(CH_3)_3$], 21.2 ($CH_3$), 26.4 [$C(CH_3)_3$], 55.6 ($OCH_3$), 98.5 (C-7), 109.6 (C-5), 119.2 (C-3), 121.2 (C-4), 121.3 (C-3'), 121.4 (C-5'), 123.2 (C-3a), 129.9 (C-2), 142.9 (C-7a), 146.9 (C-4'), 149.3 (C-6'), 154.7 (C-2'), 155.8 (C-6).

**6-Methoxy-3-(4-methyl-2-pyridyl)indole (13d)**
Compound **13d** (134 mg, 87% yield) was obtained from pyridylindole **12d** (227 mg, 0.65 mmol) following the general procedure for desilylation. Eluent for chromatography: $CH_2Cl_2$/EtOH (98:2); mp 120 °C.

IR (film): υ = 3400, 1625, 1549, 1460, 1199, 1164, 803 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 300 MHz): δ = 2.40 (s, 3 H, $CH_3$), 3.83 (s, 3 H, $OCH_3$), 6.88 (d, *J* = 2.0 Hz, 1 H, H-7), 6.90 (dd, *J* = 8.5, 2.0 Hz, 1 H, H-5), 6.94 (dm, *J* = 5.0 Hz, 1 H, H-5'), 7.51 (m, 1 H, H-3'), 7.64 (d, *J* = 2.6 Hz, 1 H, H-2), 8.20 (d, *J* = 8.5 Hz, 1 H, H-4), 8.38 (br s, 1 H, NH), 8.51 (d, *J* = 5.0 Hz, 1 H, H-6').

$^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ = 21.0 ($CH_3$), 55.3 ($OCH_3$), 94.8 (C-7), 110.2 (C-5), 115.9 (C-3), 119.4 (C-3a), 120.5 (C-4), 121.2 (C-3'), 121.7 (C-5'), 123.8 (C-2), 137.6 (C-7a), 147.9 (C-4'), 148.4 (C-6'), 154.5 (C-2'), 156.0 (C-6).

Anal. calcd for $C_{15}H_{14}N_2O$ (238.3): C, 75.61; H, 5.92; N, 11.76. Found: C, 75.87; H, 5.85; N, 11.62.

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