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A PRACTICAL SYNTHESIS OF 2-SUBSTITUTED 5-BROMOINDOLES

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Abstract – This paper describes a non-cryogenic synthetic procedure for a variety of 2-substituted 5-bromoindoles. The direct magnesiation of 5-bromo-1-(4-toluenesulfonyl)indole with a mixture of *i*-PrMgCl/LiCl and diisopropylamine allows for the preparation of various 2-substituted indoles. The advantages of this procedure include the non-cryogenic conditions, simple operations and inexpensive Grignard reagents. In addition, this procedure is especially advantageous for the preparation of 2,5-dibromoindole with reduced synthetic steps, low production cost and good overall yields.

Indoles are important structural moieties frequently found in natural products, materials and therapeutic agents.[1] Especially, many brominated indole derivatives are very useful as the starting materials or building blocks for synthesis of a large number of products.[2] In addition, 2-substituted indoles also prevail in various biologically active compounds.[3]

It is well-known that the nucleophilic addition of 2-metalated indoles to electrophiles is a straightforward method for the construction of 2-substituted indole analogues (Figure 1).[4] Generally, *N*-tosyl or *N*-Boc indole derivatives are treated with a lithiating reagent at -70 ºC.[5] The resulting 2-lithioindole species are quenched with an electrophile to produce 2-substituted indole analogues. Since 2-lithioindole species are very unstable, these reactions are always conducted at very low temperature, resulting in an inconvenience on large scale reactions. Although Wu *et al.* reported that bis(*N*,*N*'-dimethylaminoethyl) ether,[6] a chelating reagent, could effectively stabilize these lithiated intermediates at an elevated temperature (-25 °C), this temperature was still quite low. Other metallation methods involve the

magnesiation of indoles with magnesium amide bases. Kondo *et al.* reported a non-cryogenic magnesiation procedure for the synthesis of 2-substituted indoles.[7] In this protocol, the magnesium amide bases were prepared from dibutylmagnesium, that was not cheap.

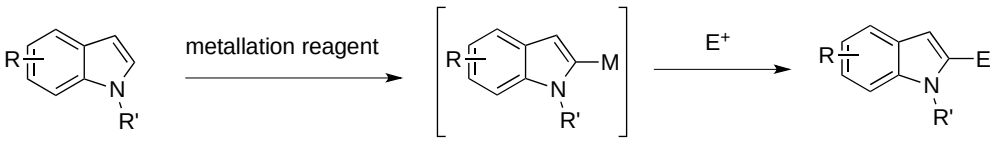


Figure 1. Synthesis of 2-substituted indoles via metallation

Recently, we required a procedure for the large scale preparation of 2,5-dibromoindole (**1**), which could serve as a useful building block. However, the reported methods for this compound always needed time-consuming, laborious and costly procedures (Figue 2, A).[8] Our initial attempt was the direct brominating of 5-bromo-2-oxindole with phosphorus oxybromide,[9] but failed to afford the desired compound (Figue 2, B). Thus, we had to develop other synthetic procedures. Naturally, it was occurred to us that the 2-position bromide could also be introduced via the metallation of 5-bromoindole and subsequent quenching the reactive species with carbon tetrabromide. Nevertheless, our procedure should be practical, operationally simple and cost effective.

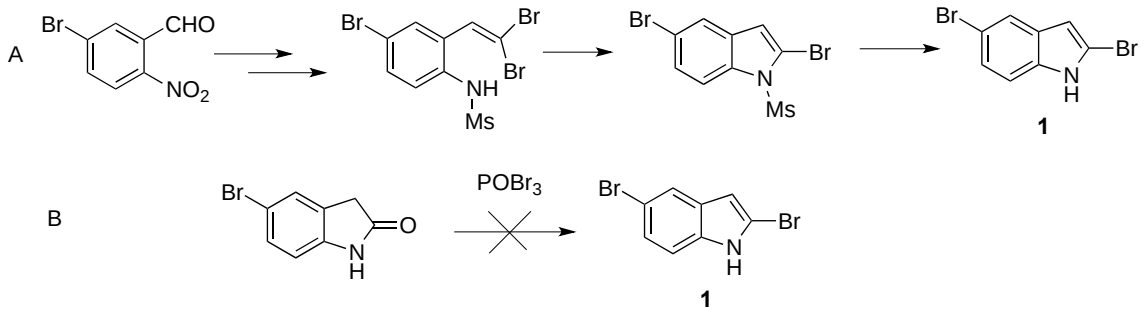
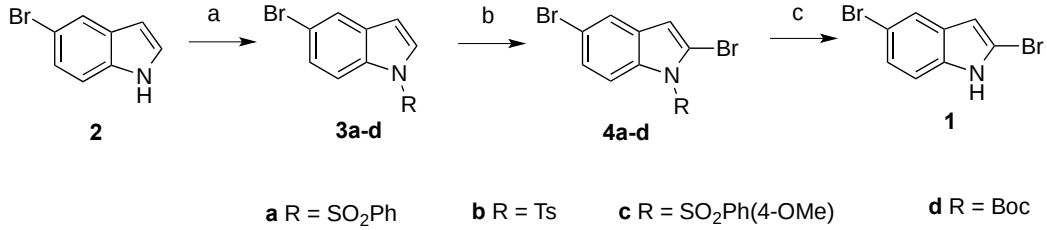


Figure 2. The reported synthetic methods (A) and our initial attempt (B)

Nxumalo *et al.* reported a direct magnesiation of various *N*-heterocyclic compounds with *i*-PrMgCl/LiCl and catalytic $(i\text{-Pr})_2$NH at room temperature.[10] Using this protocol, some 2-substituted heterocyclic compounds could be effectively prepared in moderate to good yields. However, but it should be pointed out that no brominated heterocyclic compounds were tested against this protocol in their article. Thus, it is a question whether or not the bromine-magnesium exchange will occur as a side reaction, since *i*-PrMgCl is often used to effect this exchange. Furthermore, we also anticipated to study the influence of *N*-protecting groups on the magnesiation reaction and optimise the reaction conditions.

Our synthesis of 2,5-dibromoindole was outlined in Scheme 1. The commercially available starting material 5-bromoindole (**2**) was directly condensed with three sulfonyl chlorides or Boc_2O according to

the reported methods.[11] The desired compounds **3a-d** were obtained in good yields. Then **3a-d** were subjected to this proton-magnesium exchange reaction (Table 1). It was found that the *N*-Ts indole **3b** gave the best yield (Table 1, enrty 2), while the *N*-Boc indole **3d** did not yield the desired 2,5-dibromoindole **4d** (Table 1, entry 4). In addition, hexamethyldisilazane (HMDS) and 2,2,6,6-tetramethylpiperidine (HTMP) were investigated and compared with $(i\text{-Pr})_2$NH. However, these two amines could not affect the 2-position magnesiation and gave no desired products (Table 1, entries 8 and 9). The yields were further optimized by increasing the amounts of $(i\text{-Pr})_2$NH from 0.1 equivalent to 1.0 equivalent (Table 1, entries 2 and 5). Besides, it was noticed that no obvious bromine-magnesium exchange occurred and corresponding by-products were not obtained. At last, **4b** was obtained in a 72% yield, which was deprotected by TBAF to afford the target molecular 2,5-dibromoindole (**1**) in a good yield.



Scheme 1. Reagents and conditions: a) (i) arylsulfonyl chloride, NaH, DMF, 86% for **3a**, 91% for **3b**, 87% for **3c**; (ii) Boc_2O, Py, 84% for **3d**; b) *i*-PrMgCl, LiCl, $(i\text{-Pr})_2$NH, dry THF, CBr_4, 72% for **4b**; c) THF, TBAF, 75% from **4b**.

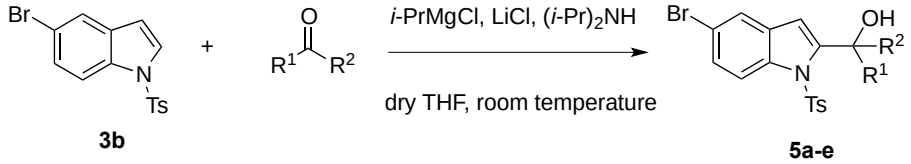
Table 1. Magnesiation of 1-substituted indoles[a]

Entry	Starting materials	*i*-PrMgCl (equiv.)	LiCl (equiv.)	Amine (equiv.)	Products	Yield[b] (%)
1	**3a**	1.6	1.6	$(i\text{-Pr})_2$NH (1.0)	**4a**	62%
2	**3b**	1.6	1.6	$(i\text{-Pr})_2$NH (1.0)	**4b**	72%
3	**3c**	1.6	1.6	$(i\text{-Pr})_2$NH (1.0)	**4c**	58%
4	**3d**	1.6	1.6	$(i\text{-Pr})_2$NH (1.0)	**4d**	-[c]
5	**3b**	1.6	1.6	$(i\text{-Pr})_2$NH (0.1)	**4b**	55%
6	**3b**	1.6	1.6	$(i\text{-Pr})_2$NH (0.5)	**4b**	60%
7	**3b**	2.0	2.0	$(i\text{-Pr})_2$NH (1.0)	**4b**	65%
8	**3b**	1.6	1.6	HMDS (1.0)	**4b**	-[c]
9	**3b**	1.6	1.6	HTMP (1.0)	**4b**	-[c]

[a] Reagents and conditions: A mixture of *i*-PrMgCl (for entries 1-6, 8, 9: 4.8 mmol; for entry 7: 6.0 mmol), LiCl (for entries 1-6, 8, 9: 4.8 mmol; for entry 7: 6.0 mmol), amines (for entries 1-4 and 7-9: 3.0 mmol; for entry 5: 0.3 mmol; for entry 6: 1.5 mmol) in dry THF was stirred at 0 ºC for 10 min under nitrogen. Then starting materials (3.0 mmol) were added and stirred at 0 ºC for 3.5 h. At last, electrophiles (6.0 mmol) were added to the mixture.
[b] Isolated yield.
[c] No products obtained.

Further experiments focused on the coupling of **3b** with different aldehyde or ketone electrophiles, as shown in Table 2. The coupling of **3b** with a variety of aldehydes proceeded smoothly to afford the compounds **5a-g** in moderate to good yields (Table 2, entries 1-7). Unfortunately, **3b** could not couple with more sterically hindered ketones (Table 2, entries 8 and 9). Besides, the coupling of **3b** with acetic anhydride also failed to afford the desired 2-acetylindole compound. These results suggest that 2-magnesioindoles are less nucleophilic and reactive than 2-lithioindoles.

Table 2. Magnesiation of **3b** and subsequent reaction with a variety of electrophiles[a]



Entry	Aldehyde or ketone	Product	R^1, R^2	Yield[b] (%)
1	benzaldehyde	**5a**	phenyl, H	82
2	4-chlorobenzaldehyde	**5b**	4-chlorophenyl, H	86
3	4-methoxybenzaldehyde	**5c**	4-methoxyphenyl, H	78
4	6-bromopyridine-2-carbaldehyde	**5d**	6-bromopyridin-2-yl, H	81
5	6-bromopyridine-3-carbaldehyde	**5e**	6-bromopyridin-3-yl, H	75
6	pentaldehyde	**5f**	pentyl, H	66
7	heptaldehyde	**5g**	heptyl, H	61
8	acetone	**5h**	methyl, methyl	-[c]
9	cyclohexanone	**5i**	$-(CH_2)_5-$	-[c]

[a] Reagents and conditions: A mixture of *i*-PrMgCl (4.6 mmol), LiCl (4.6 mmol), $(i\text{-Pr})_2NH$ (2.9 mmol) in dry THF was stirred at 0 ºC for 10 min under nitrogen. Then **3b** (2.9 mmol) was added and stirred at 0 ºC for 3.5 h. At last, electrophiles (5.7 mmol) were added to the mixture.
[b] Isolated yield.
[c] No products obtained.

In summary, we have demonstrated that the magnesiation of *N*-Ts indoles with a mixture of *i*-PrMgCl, LiCl and diisopropylamine can produce 2-magnesiated species under non-cryogenic conditions. After quenching with a variety of electrophiles, 2-substituted indoles can be produced in moderate to good yields. Using this protocol, 2,5-dibromoindole (**1**) can be easily prepared in three steps with a 49% overall yield. This synthetic route to 2,5-dibromoindole (**1**) is more convenient than the reported methods and is amenable to large scale preparations.

EXPERIMENTAL

Starting materials, reagents and chemicals were purchased from commercial suppliers and used without further purification. The progress of reactions was monitored by silica gel thin layer chromatography (TLC) plates, visualized under UV. Flash column chromatography was performed using Qingdao Haiyang silica gel (200 - 300) with distilled solvents. ^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz) or DRX-400 (400 MHz) spectrometer. ^{13}C NMR spectra were obtained on a JNM-EX400 (100 MHz) spectrometer. High-resolution mass data were obtained on a MicrOTOF II spectrometer. Melting points were measured on a SGW X-4 (INESA) temperature apparatus and were uncorrected. IR spectra were obtained using KBr disks on the FTIR Bruker Tensor 27.

General procedure for the synthesis of 2-substituted 5-bromo-1-tosyl-1*H*-indole.

All substitution reactions were run on the same scale, using the following general procedure.

2,5-Dibromo-1-tosyl-1*H*-indole (4b). Under a nitrogen atmosphere, dry lithium chloride (0.19 g, 4.6 mmol) and diisopropylamine (0.29 g, 2.9 mmol) were added to a mixture of 2.0 M isopropylmagnesium chloride (2.3 mL, 4.6 mmol) and dry THF (4.0 mL). The mixture was stirred at 0 ºC for 10 min. To the mixture was added **3b** (1.00 g, 2.9 mmol) in dry THF (4.0 mL) and stirred at 0 ºC for 3.5 h. Then, carbon tetrabromide (1.90 g, 5.7 mmol) was added and the mixture was stirred at room temperature for 0.5 h. The reaction was quenched with aqueous NH_4Cl and extracted with EtOAc (3 × 20 mL). The organic layer was washed with 1M hydrochloric acid, dried over Na_2SO_4, and concentrated. The crude material was purified by flash column chromatography eluting with 5-10% EtOAc/petroleum ether to provide **4b** as a white solid (0.88 g, 72%). mp 91-93 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 8.07 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 1.4 Hz, 1H), 7.31-7.35 (m, 1H), 7.13-7.18 (m, 2H), 6.57 (s, 1H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 145.7, 136.2, 135.0, 131.2, 129.9, 127.7, 127.1, 122.5, 117.5, 116.7, 114.0, 111.5, 21.7; IR (KBr) 3123, 1594, 1433, 1380 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{11}Br_2NNaO_2S$: [M (^{79}Br, ^{79}Br) + Na]$^{+}$: 449.8775; [M (^{79}Br, ^{81}Br) + Na]$^{+}$: 451.8775; [M (^{81}Br, ^{81}Br) + Na]$^{+}$: 453.8734; found: *m/z* = 449.8773; 451.8754; 453.8738.

[(5-Bromo-1-tosyl-1*H*-indol-2-yl)phenyl]methanol (5a). General procedure was followed (2.9 mmol scale), but benzaldehyde (0.60 g, 5.7 mmol) was used as the electrophile. The product was purified by flash column chromatography eluting with 10-15% EtOAc/petroleum ether to provide **5a** as an oil (1.07 g, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.88 (d, *J* = 8.9 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 1.5 Hz, 1H), 7.28-7.31 (m, 6H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.30 (s, 1H), 6.06 (s, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 145.4, 145.2, 140.5, 136.0, 135.3, 130.7, 130.0, 128.4, 128.2, 127.9, 127.1, 126.5, 123.9, 117.2, 116.2, 111.1, 69.3, 21.6; IR (KBr) 3422, 3061, 1722, 1591, 1487, 869 cm^{-1}; HRMS (ESI):

m/z calcd for $C_{22}H_{18}BrNNaO_3S$: [M (^{79}Br) + Na]$^+$: 478.0088; [M (^{81}Br) + Na]$^+$: 480.0068; found: *m/z* = 478.0089; 480.0042.

[(5-Bromo-1-tosyl-1*H*-indol-2-yl)]-(4-chlorophenyl)methanol (5b). General procedure was followed (2.9 mmol scale), but 4-chlorobenzaldehyde (0.80 g, 5.7 mmol) was used as the electrophile. The product was purified by flash column chromatography eluting with 10-15% EtOAc/petroleum ether to provide **5b** as an oil (1.20 g, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.88 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 1.6 Hz, 1H), 7.29-7.32 (m, 1H), 7.21-7.25 (m, 5H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.26 (s, 1H), 6.07 (s, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 145.5, 144.6, 139.0, 136.1, 135.3, 130.5, 130.0, 128.6, 128.4, 128.3, 128.1, 126.4, 123.9, 117.3, 116.2, 111.1, 68.7, 21.6; IR (KBr) 3370, 2917, 1784, 1599, 1492, 865 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{17}BrClNNaO_3S$: [M (^{35}Cl, ^{79}Br) + Na]$^+$: 511.9699; [M (^{35}Cl, ^{81}Br) + Na]$^+$: 513.9678; [M (^{37}Cl, ^{79}Br) + Na]$^+$: 513.9678; [M (^{37}Cl, ^{81}Br) + Na]$^+$: 515.9636; found: *m/z* = 511.9692, 513.9700, 513.9700, 515.9622.

[(5-Bromo-1-tosyl-1*H*-indol-2-yl)]-(4-methoxyphenyl)methanol (5c). General procedure was followed (2.9 mmol scale), but 4-methoxybenzaldehyde (0.78 g, 5.7 mmol) was used as the electrophile. The product was purified by flash column chromatography eluting with 10-15% EtOAc/petroleum ether to provide **5c** as an oil (1.08 g, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.88 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 1.5 Hz, 1H), 7.18-7.30 (m, 4H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.25 (s, 1H), 6.12 (s, 1H), 3.75 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 159.5, 145.6, 145.3, 136.1, 135.4, 132.7, 130.7, 130.0, 128.3, 127.8, 126.5, 123.8, 117.2, 116.2, 113.8, 110.8, 69.0, 55.3, 21.6; IR (KBr) 3514, 2825, 2546, 2058, 1879, 1725 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}BrNNaO_4S$: [M (^{79}Br) + Na]$^+$: 508.0194; [M (^{81}Br) + Na]$^+$: 510.0174; found: *m/z* = 508.0167; 510.0142.

[(6-Bromopyridin-2-yl)]-(5-bromo-1-tosyl-1*H*-indol-2-yl)methanol (5d). General procedure was followed (2.9 mmol scale), but 6-bromopyridine-2-carbaldehyde (1.05 g, 5.7 mmol) was used as the electrophile. The product was purified by flash column chromatography eluting with 10-15% EtOAc/petroleum ether to provide **5d** as a white solid (1.24 g, 81%). mp 147-149 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.88 (d, *J* = 8.9 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.36-7.53 (m, 4H), 7.29 (d, *J* = 8.9 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.48 (s, 1H), 6.17 (s, 1H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 159.7, 144.4, 142.6, 139.9, 138.3, 134.8, 133.9, 129.8, 128.9, 126.9, 126.5, 125.8, 122.8, 119.6, 166.2, 115.3, 109.8, 67.4, 20.6; IR (KBr) 3223, 2669, 1984, 1878, 1753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{16}Br_2N_2NaO_3S$: [M ($^{79}Br$, ^{79}Br) + Na]$^+$: 556.9146; [M (^{79}Br, ^{81}Br) + Na]$^+$: 558.9126; [M (^{81}Br, ^{81}Br) + Na]$^+$: 560.9105; found: *m/z* = 556.9149; 558.9123; 560.9115.

[(6-Bromopyridin-3-yl)]-(5-bromo-1-tosyl-1*H*-indol-2-yl)methanol (5e). General procedure was followed (2.9 mmol scale), but 6-bromopyridine-3-carbaldehyde (1.05 g, 5.7 mmol) was used as the electrophile. The product was purified by flash column chromatography eluting with 10-15%

EtOAc/petroleum ether to provide **5e** as a white solid (1.15 g, 75%). mp 96-98 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 8.26 (d, *J* = 1.5 Hz, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.43-7.58 (m, 4H), 7.30-7.42 (m, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.31 (s, 1H), 6.11 (s, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 149.1, 145.8, 143.5, 141.7, 137.3, 136.1, 135.6, 135.2, 130.3, 130.2, 128.4, 127.9, 126.2, 124.1, 117.5, 116.2, 111.3, 66.8, 21.7; IR (KBr) 3167, 2924, 1934, 1758, 1585 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{16}Br_2N_2NaO_3S$: [M (^{79}Br, ^{79}Br) + Na]$^+$: 556.9146; [M (^{79}Br, ^{81}Br) + Na]$^+$: 558.9126; [M (^{81}Br, ^{81}Br) + Na]$^+$: 560.9105; found: *m/z* = 556.9122; 558.9101; 560.9109.

[1-(5-Bromo-1-tosyl-1*H*-indol-2-yl)]pentan-1-ol (5f). General procedure was followed (2.9 mmol scale), but pentaldehyde (0.49 g, 5.7 mmol) was used as the electrophile. The product was purified by flash column chromatography eluting with 10-15% EtOAc/petroleum ether to provide **5f** as an oil (0.82 g, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz), δ 7.89 (d, *J* = 8.9 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.22-7.32 (m, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.51 (s, 1H), 5.05 (m, 1H), 2.26 (s, 3H), 1.79-1.94 (m, 2H), 1.21-1.43 (m, 4H), 0.83 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 144.6, 144.3, 134.9, 134.3, 130.0, 129.0, 126.6, 125.3, 122.7, 116.2, 115.2, 107.2, 65.7, 34.4, 27.2, 21.5, 20.6, 13.0; IR (KBr) 3560, 2942, 2855, 1915, 1715, 1598, 868 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{22}BrNNaO_3S$: [M (^{79}Br) + Na]$^+$: 458.0401; [M (^{81}Br) + Na]$^+$: 460.0381; found: *m/z* = 458.0402; 460.0382.

[1-(5-Bromo-1-tosyl-1*H*-indol-2-yl)]heptan-1-ol (5g). General procedure was followed (2.9 mmol scale), but hentaldehyde (0.65 g, 5.7 mmol) was used as the electrophile. The product was purified by flash column chromatography eluting with 10-15% EtOAc/petroleum ether to provide **5g** as an oil (0.80 g, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.90 (d, *J* = 8.9 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 1.9 Hz, 1H), 7.28-7.32 (m, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.53 (s, 1H), 5.04-5.10 (m, 1H), 2.28 (s, 1H), 1.82-1.93 (m, 2H), 1.15-1.31 (m, 8H), 0.82 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 144.6, 144.3, 134.9, 134.4, 130.0, 129.0, 126.6, 125.3, 122.7, 116.2, 115.2, 107.2, 65.7, 34.7, 30.7, 28.1, 25.1, 21.6, 20.6, 13.1; IR (KBr) 3341, 2930, 2837, 1704, 1591, 1435 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{26}BrNNaO_3S$: [M (^{79}Br) + Na]$^+$: 486.0714; [M (^{81}Br) + Na]$^+$: 488.0694; found: *m/z* = 486.0706; 488.0686.

2,5-Dibromo-1*H*-indole (1). The compound **4b** (1.00 g, 2.3 mmol) was stirred in THF (4.0 mL), a solution of tetrabutylammonium fluoride (1.22 g, 4.6 mmol) in THF (4.0 mL) was added and the mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure. The residue was extracted with EtOAc (20 mL), washed with water (3 × 10 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash column chromatography eluting with 5-10% EtOAc/petroleum ether to provide **1** as a white solid (0.48 g, 75%). mp 74 ºC (decomposed); ^{1}H NMR ($CDCl_3$, 400 MHz), δ 8.04 (s, 1H), 7.58 (s, 1H), 7.17 (d, *J* = 4.8 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ 134.0, 129.3, 124.1, 121.1, 112.8, 110.7, 109.0, 103.5.

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