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Synthesis of an azide-tethered 4*H*-furo[3,4-b]indole

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This paper is dedicated to the memory of Robert J. Milligan

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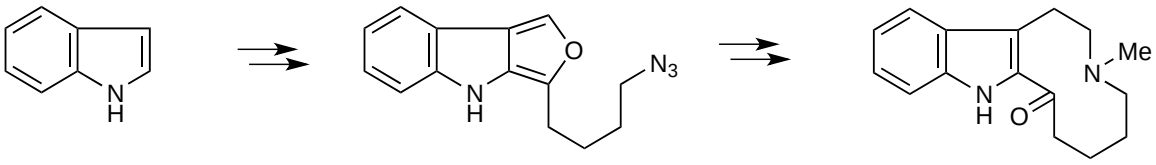
Abstract

We describe the synthesis of a novel azide-tethered 4*H*-furo[3,4-*b*]indole as a putative intermediate for a projected route to the 2-acylindole class of indole alkaloids.



Keywords: Indole, 4*H*-furo[3,4-*b*]indole, azide, lithiation

Introduction

Synthetic routes to the family of 2-acylindole alkaloids (e.g., burnamicine (**1**), vobasine (**2**), dregamine (**3**), and tabernaemontanine (**4**)) (Figure 1), are relatively few.[1,2] In contrast, the biogenetically related sarpagine, macroline, and ajmaline collection of alkaloids has received intense interest over many decades.[3–6]

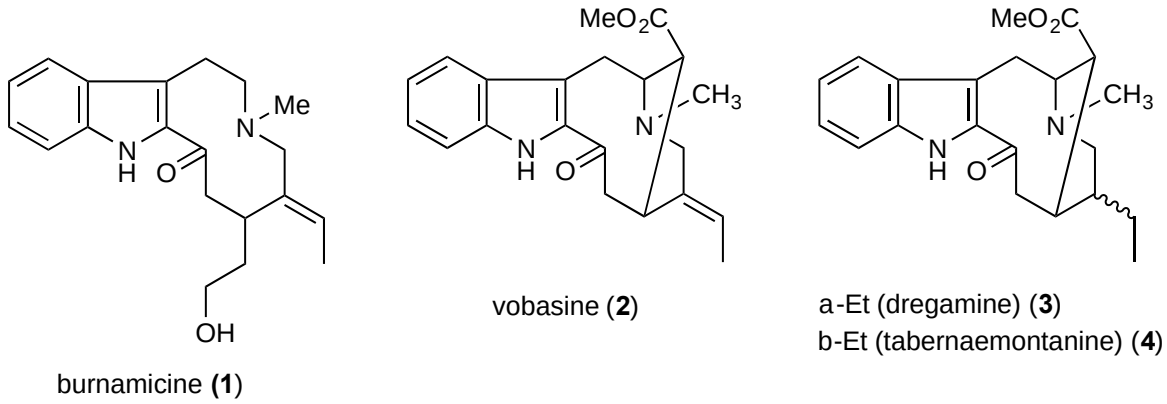
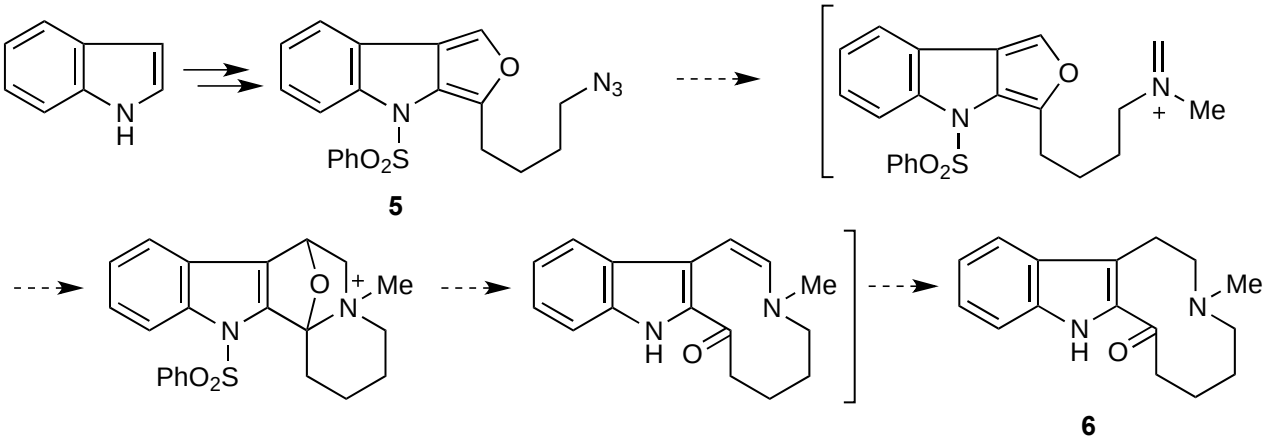


Figure 1

In continuation of our interest in the synthesis and utility of the 4*H*-furo[3,4-*b*]indole ring system for the construction of carbazoles, pyridocarbazoles, and related ring systems,[7] we now report the synthesis of azide-tethered 4*H*-furo[3,4*b*]indole **5** for a projected synthesis of the 2-acylindole alkaloid skeleton **6** (Scheme 1).

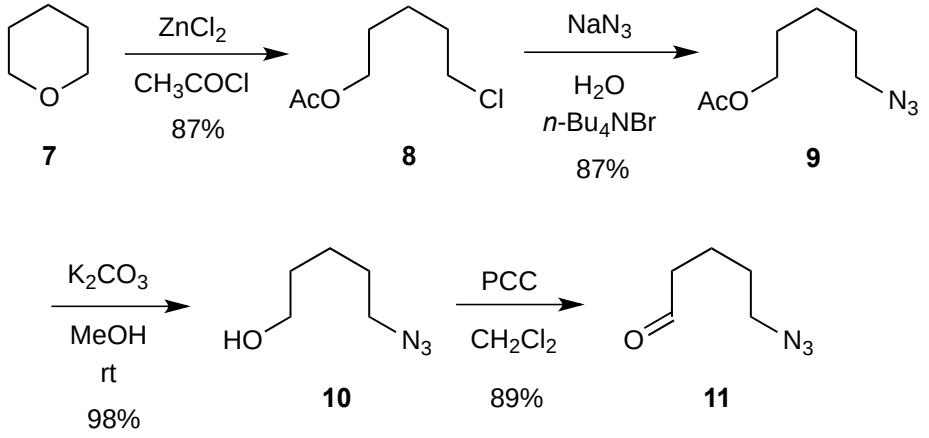


Scheme 1

Results and Discussion

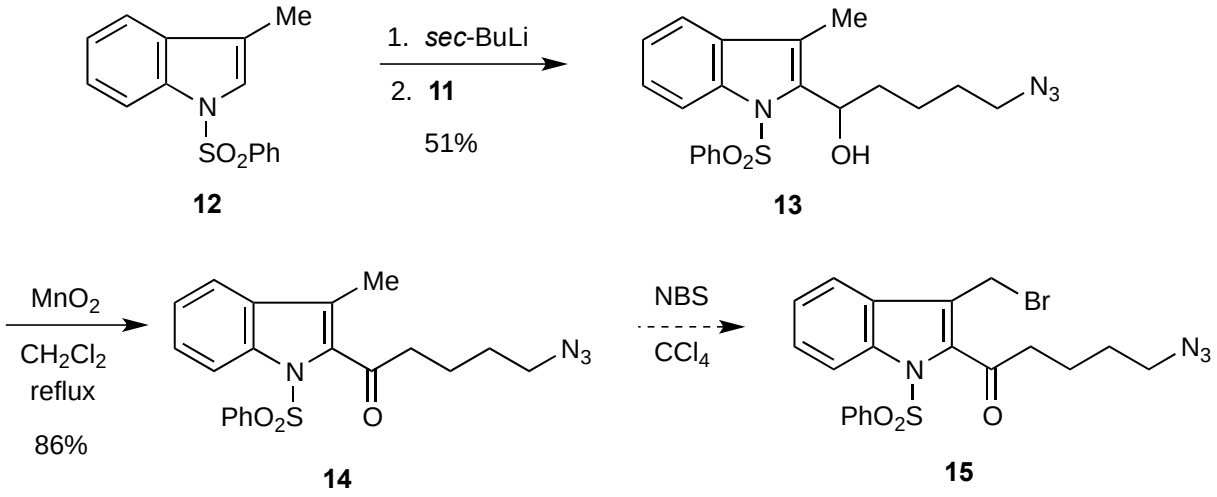
Our synthesis of azido furo[3,4-*b*]indole **5** began with an improved preparation of 5-azidopentanol (**11**) (Scheme 2). Treatment of tetrahydropyran (**7**) with freshly fused $ZnCl_2$ and acetyl chloride gave 5-chloropentyl acetate (**8**) in excellent yield.[9] Displacement of the chloride with sodium azide under phase transfer conditions

afforded 5-azidopentyl acetate (**9**) in high yield. Saponification with K_2CO_3 MeOH yielded 5-azidopentanol (**10**). Both azides **9** and **10** were distilled (not to dryness) and fully characterized. A Swern oxidation of **10** to 5-azidopentanol (**11**) proceeded in 48% yield. However, PCC oxidation of **10** afforded **11** in 89% yield. This aldehyde is relatively unstable but could be distilled without incident.



Scheme 2

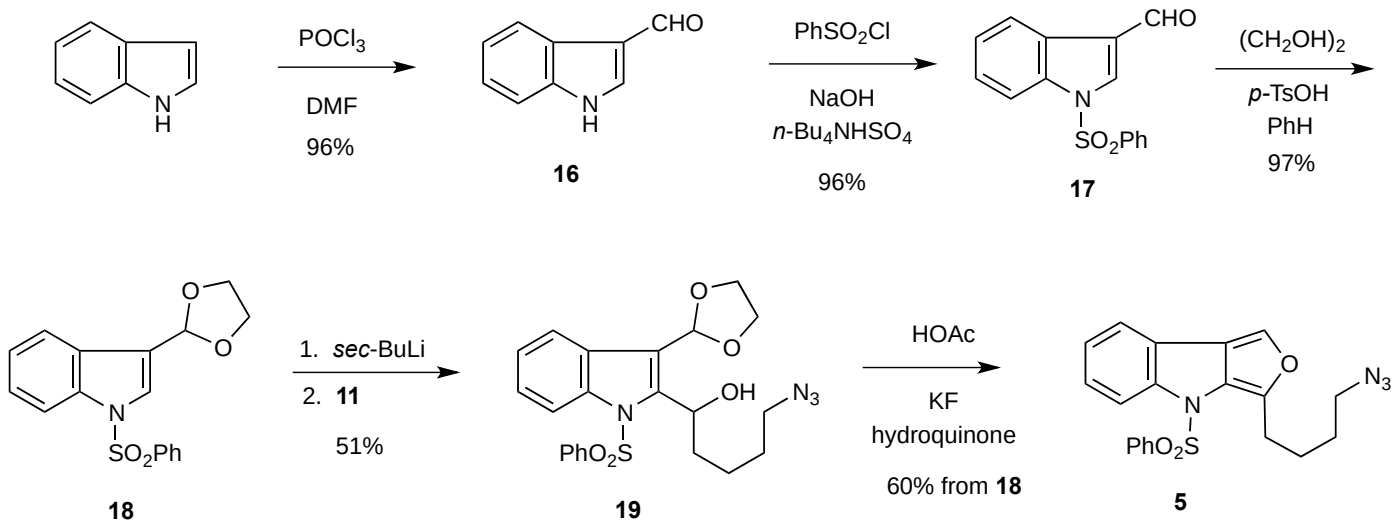
Our first approach to the target furo[2,4-*b*]indole **5** is shown in Scheme 3. Lithiation of 3-methyl-1-(phenylsulfonyl)indole (**12**) with *sec*-BuLi and quenching with 5-azidopentanal (**11**) gave **13** in 51% yield (80% based on recovered starting material). Oxidation of **13** with activated MnO_2 afforded ketone **14** in high yield. However, subsequent attempts to brominate selectively the C-3 methyl group with NBS proceeded in low yield at best, and often afforded mixtures of at least two other bromine-containing 2-acylindoles.



Scheme 3

Our successful synthesis of furo[2,4-*b*]indole **5** is shown in Scheme 4. Indole was converted in standard fashion to 1-(phenylsulfonyl)indole-3-carbaldehyde (**17**) in excellent yield. Protection of the formyl group with

ethylene glycol gave ketal **18**. Lithiation of **18** and quenching with aldehyde **11** gave alcohol **19**, which was directly transformed into the desired azido-furo[3,4-*b*]indole **5** in 60% yield for the two steps.



Scheme 4

Conclusion

We have synthesized an azido-tethered furo[3,4-*b*]indole (**5**) preparatory for future efforts to effect the proposed Scheme 1 as an entry into the 2-acylindole family of alkaloids.

Experimental Section

General. Thin layer chromatography was performed on precoated (0.2 mm) silica gel 60 F_{254} plastic sheets visualized using a 254 nm UV lamp. Flash chromatography was performed with 230–400 mesh Silicycle gel 60. Melting points were taken on a Laboratory Devices Mel Temp or a Buchi 510 melting point apparatus in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian EM-300A Fourier transform spectrometer. The chemical shifts noted from these spectra are reported in parts per million (ppm, δ) using the signal of chloroform-d1 (δ 7.27) or acetone-d_6 (δ 1.94) or Me_4Si as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 599 spectrophotometer and were obtained either neat or using solid potassium bromide pellets. Both low-resolution and high-resolution mass spectra (MS and HRMS) were performed at the National Institutes Regional Facility at Rockefeller University, New York, NY., or were measured at 35 eV and 70 eV on a Finnigan EI-CI 4023 gas chromatograph-mass spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, or Desert Analytics, Tucson, AZ.

5-Chloropentyl acetate (8). Tetrahydropyran **7** (105 g, 1.22 mol) was treated with acetyl chloride (87.4 g, 1.12 mol) and freshly fused[8] (60 Torr) $ZnCl_2$ (17.55 g, 0.129 mol) according to the method of Synerholm.[9] An exothermic reaction ensued and the mixture was heated on a steam bath for 1.25 h. The mixture was cooled

to room temperature, diluted with benzene (200 mL), washed with water (2 x 400 mL), saturated sodium bicarbonate (400 mL), and saturated brine (400 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Distillation at reduced pressure provided 161 g (87%) of **8** as a colorless liquid: bp 117–122 °C (29 Torr) (lit.[9] bp 104 °C (18 Torr)); ^{1}H NMR ($CDCl_3$) δ 4.05 (t, 2H, *J* 6.6 Hz), 3.55 (t, 2H, *J* 6.5 Hz), 2.05 (s, 3H), 1.85-1.45 (m, 6H); IR (neat) 2954, 2868, 1739, 1453, 1387, 1364, 1233, 1043, 735, 648 cm^{-1}.

5-Azidopentyl acetate (9). A magnetically stirred solution of sodium azide (47.9 g, 737 mmol) in water (150 mL) was treated at reflux with tetra-*n*-butylammonium bromide (8.27 g, 25.6 mmol) and **8** (59.8 g, 352 mmol). The mixture was heated at reflux for 1 h and a second portion of sodium azide (54.2 g, 806 mmol) was added. The mixture was heated at reflux for 12 h, cooled to room temperature, diluted with water (100 mL), and separated the layers. The aqueous layer was extracted with fresh CH_2Cl_2 (3 x 150 mL), the combined organic extracts were washed with saturated brine (300 mL), dried (K_2CO_3), filtered, and concentrated in vacuo to provide a colorless liquid. Distillation at reduced pressure provided 34.1 g (87%) of **9** as a colorless liquid (bp 129–137 °C (29 Torr)). Redistillation at reduced pressure provided the analytical sample: bp 133–135 °C (29 Torr): ^{1}H NMR ($CDCl_3$) δ 4.12 (t, *J* 6.0 Hz, 2H), 3.34 (t, *J* 6.0 Hz, 2H), 2.04 (s, 3H), 1.81–1.37 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 170.3, 63.7, 50.8, 28.1, 27.8, 22.8, 20.4; IR (neat) 2944, 2868, 2099, 1739, 1456, 1388, 1363, 1239, 1066, 1044 cm^{-1}. *Anal*. Calcd for $C_7H_{13}N_3O_2$: C, 49.11; H, 7.65; N, 24.54. Found: C, 49.18; H, 7.67; N, 24.56. Azide **9** appears to be a new compound.

5-Azidopentan-1-ol (10). A solution of **9** (115 g, 669 mmol) in 95% methanol (225 mL) was treated with 5.90 g (42.7 mmol) of K_2CO_3 and magnetically stirred for 24 h. The suspension was treated with an additional 3.94 g (28.5 mmol) of K_2CO_3 and stirred for 24 h. The mixture was then poured into saturated sodium chloride solution (350 mL), extracted with Et_2O (6 x 200 mL), and the combined extracts were dried (K_2CO_3), filtered, and concentrated in vacuo. Distillation at reduced pressure provided 84.8 g (98%) of **10** as a colorless liquid: bp 127–129 °C (28 Torr); ^{1}H NMR ($CDCl_3$) δ 3.63 (bs, 3H), 3.34 (t, *J* 5.1 Hz, 2H), 1.87–1.54 (m, 6H); ^{13}C NMR ($CDCl_3$) □ 61.6, 50.9, 31.6, 28.2, 22.6; IR (neat) 3335, 2935, 2864, 2092, 1456, 1349, 1261, 1051, 906, 877 cm^{-1}. *Anal*. Calcd for $C_5H_{11}N_3O$: C, 46.50; H, 8.58; N, 32.53. Found: C, 46.30; H, 8.51; N, 32.39. This alcohol is known but has not been previously characterized.[10-12]

5-Azidopentanal (11) (Swern). A mechanically stirred solution of oxalyl chloride (4.0 mL, 46 mmol) in CH_2Cl_2 (100 mL) at -60 °C under argon was treated dropwise with a solution of dimethyl sulfoxide (7.4 g, 95 mmol) in CH_2Cl_2 (18 mL). The solution was stirred for 2 min and treated with a solution of **10** (5.2 g, 40 mmol) in CH_2Cl_2 (40 mL) over 4 min. The solution was stirred for 15 min, and treated with triethylamine (28.0 ml, 201 mmol) via syringe, and allowed to warm to room temperature (1 h). The solution was stirred for 1 h at room temperature, treated with water (200 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 75 mL). The combined organic extracts were washed with water (6 x 500 mL) and brine (3 x 500 mL), dried (K_2CO_3), filtered, and concentrated in vacuo to give **11** as a yellow liquid. Distillation afforded 2.5 g (48%) of **11** as a colorless liquid: bp 108–114 °C (25 Torr) (Lit.[13] bp 60 °C (2 Torr)); ^{1}H NMR ($CDCl_3$) □ 9.79 (t, *J* 2.7 Hz, 1H), 3.30 (t, *J* 6.4 Hz, 2H), 2.67–2.35 (m, 2H), 1.80–1.55 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 201.3, 50.8, 43.0, 28.1, 19.0; IR (neat) 2940, 2868, 2722, 2095, 1724, 1455, 1411, 1390, 1350, 1268 cm^{-1}. Spectral data agreed with **11** as prepared below and with that reported in the literature.[13,14]

5-Azidopentanal (11) (PCC). To a suspension of pyridinium chlorochromate (12.5 g, 0.0581 mol) in methylene chloride (130 mL) was added dropwise a solution of 5-azidopentanol (**10**) (5.00 g, 0.0387 mol) in methylene chloride (20 mL). The mixture was stirred at room temperature for 10 min and diluted with ethyl ether (100

mL). The solids were removed by filtration and the filtrate was subjected to flash chromatography (ethyl acetate/hexane 20/80) to give **11** as an oil (4.39 g, 89%), which was used directly as described below.

6-Azido-1-hydroxyl-1-[3-methyl-1-(phenylsulfonyl)indol-2-yl]pentane (13). A magnetically stirred solution of **12** (15.00 g, 55.18 mmol) in dry THF (250 mL) at -70 °C under argon was treated with *sec*-butyllithium (1.11 M in cyclohexane, 59.7 mL, 66.3 mmol) via syringe. The solution was stirred for 0.5 h, allowed to slowly warm to room temperature (1 h), stirred for 3 h, recooled to -70 °C, and treated with aldehyde **11** (9.06 g, 71.3 mmol). The solution was allowed to warm to room temperature (1 h), stirred for 12 h, treated with saturated NH_4Cl (100 mL), poured into saturated NH_4Cl (300 mL), and extracted with CH_2Cl_2 (4 x 500 mL). The combined organic extracts were washed with water (500 mL), brine (500 mL), dried (K_2CO_3), filtered, and concentrated in vacuo. Flash chromatography (CH_2Cl_2 elution) gave **13** (11.28 g, 51%; 80% based on recovered starting material) as a colorless oil: IR (neat) 3538, 2928, 2860, 2086, 1448, 1357, 1170, 956, 744, 722, 682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H) 7.47–7.19 (m, 6H), 5.22 (q, J = 8.1 Hz, 1H), 3.75 (d, J = 8.8 Hz, 1H), 3.22 (t, J = 6.6 Hz, 2H), 2.30 (s, 3H), 2.21–2.09 (m, 1H), 2.08–1.96 (m, 1H), 1.65–1.54 (m, 2H), 1.54–1.44 (m, 1H), 1.35–1.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 137.8, 137.76, 136.7, 133.6, 131.1, 128.9, 126.3, 125.2, 123.8, 120.4, 119.2, 115.1, 67.3, 51.1, 36.5, 28.4, 23.3, 9.6. *Anal*. Calcd for $C_{20}H_{22}N_4O_3S$: C, 60.28; H, 5.57; N, 14.06; S, 8.05. Found: C, 59.96; H, 5.60; N, 14.14; S, 7.70.

6-Azido-1-oxo-1-[3-methyl-1-(phenylsulfonyl)indol-2-yl)]pentane (14). A magnetically stirred suspension of **13** (10.89 g, 27.3 mmol) and manganese (IV) oxide (60.88 g, 700.2 mmol) in CH_2Cl_2 (300 mL) was heated at reflux for 22 h under argon. The suspension was then cooled to room temperature, filtered, and the filtrate concentrated in vacuo to give 9.34 g (86%) of a pale yellow oil that was homogeneous by TLC (CH_2Cl_2). Flash chromatography (CH_2Cl_2 elution) gave 7.95 g (73%) of **14** as a colorless oil: ^1H NMR ($CDCl_3$) δ 8.04 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 7.9 Hz, 2H), 7.44–7.36 (m, 3H), 7.31–7.22 (m, 3H), 3.32 (t, J = 6.8 Hz, 2H), 3.05 (t, J = 7.3 Hz, 2H), 2.20 (s, 3H), 1.89–1.78 (m, 2H), 1.76–1.65 (m, 2H); IR (neat) 2090, 1693, 1600, 1578, 1454, 1375, 1191, 960, 759, 731 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 197.8, 137.1, 136.0, 135.1, 133.8, 131.7, 128.6, 127.3, 127.1, 126.4, 124.8, 120.7, 116.0, 51.2, 43.9, 28.2, 21.6, 9.3. *Anal*. Calcd for $C_{20}H_{20}N_4O_3S$: C, 60.59; H, 5.08; N, 14.13; S, 8.09. Found: C, 60.20; H, 4.82; N, 14.00; S, 7.98.

Indole-3-carbaldehyde (16). To ice cooled DMF (200 mL) was added phosphorus oxychloride (187.5 g, 1.22 mol) via an additional funnel. The resulting yellow-orange solution was stirred for 20 min and then a solution of indole (100.0 g, 0.854 mol) in DMF (150 mL0 was added via an additional funnel. The reaction was stirred at room temperature for 2 days, then poured into ice. An aqueous sodium hydroxide (230 g, 5.75 mol) solution was added slowly frequently along with ice to keep the reaction cool. The resulting precipitate was collected by filtration and washed thoroughly with water to afford **16** as a white solid (119.5 g, 96%) after drying; mp 190–192 °C (Lit.[15] mp 196–197 °C); ^1H NMR (DMSO-d_6) δ 11.80 (br, s, 1H), 9.94 (s, 1H), 8.18 (m, 1H), 7.95 (s, 1H), 7.48 (m, 1H), 7.23 (m, 2H).

1-(Phenylsulfonyl)indole-3-carbaldehyde (17). A mixture of 3-formylindole (**16**) (11.95 g, 0.0823 mol), crushed sodium hydroxide (9.65 g, 0.241 mol) and tetra-*n*-butylammonium hydrogen sulfate (1.09 g, 3.21 mmol) in methylene chloride (100 mL) was stirred in an ice bath. Benzenesulfonyl chloride (17.16 g, 0.0972 mol) was added via an additional funnel over 10 min. The resulting mixture was stirred at room temperature for 2 h. Water was added and the organic layer was washed several times with water and dried over magnesium sulfate to afford **17** as a white solid (22.6 g, 96%) after removal of solvent; mp 156–157 °C (lit.[16] mp 158–158.5 °C). ^1H NMR ($CDCl_3$) δ 10.06 (s, 1H), 8.22–8.17 (m, 2H), 7.95–7.89 (m, 3H), 7.58–7.32 (m, 5H).

1-(Phenylsulfonyl)-3-formaldehyde ethylene glycol acetal (18).[17] A mixture of 1-(phenylsulfonyl)-3-formylindole (**17**) (20.0 g, 70.1 mmol), ethylene glycol (50.0 g, 80.6 mmol) and *p*-toluenesulfonic acid (1.00 g, 5.26 mmol) in 200 mL of benzene was refluxed under nitrogen with a Dean-Stark trap for overnight. The mixture was cooled and washed with water. The organic layer was dried over magnesium sulfate. A dark yellow solid was obtained after removal of solvent. A white solid (19.6 g, 85%) was obtained after treatment of the crude product with a mixture of ether and hexane, mp 87–90 °C; ^{1}H NMR ($CDCl_3$) δ 7.95–7.83 (m, 3H), 7.63–7.17 (m, 7H), 6.03 (s, 1H), 4.11–3.98 (m, 4H). A sample for elemental analysis was prepared by recrystallization from ether and hexane, mp 95–97 °C. *Anal.* Calcd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25; S, 9.74. Found: C, 61.75; H, 4.63; N, 4.36; S, 9.85.

1-(Phenylsulfonyl)-2-(5'-azido-1'-hydroxypentyl)-3-formylindole ethylene glycol acetal (19). A solution of 1-(phenylsulfonyl)-3-formylindole ethylene glycol (**18**) (2.20 g, 6.69 mmol) in 15 mL of THF was cooled to –78 °C. *sec*-BuLi (6.2 mL, 1.3 M solution in hexane) was added dropwise, the resulting solution was stirred for an additional 10 min. A solution of 5-azidopentanal (**11**) (1.02 g, 8.03 mmol) in THF (10 mL) was then added and the mixture was stirred at –78 °C for 2 h and then allowed to warm to room temperature. The residue after removal of solvent was purified by flash chromatography (30/70 EtOAc/Hexane) to obtain **19** as an oil (2.05 g, 67%), which was used directly in the next step; ^{1}H NMR (acetone-d_6) δ 8.17 (d, 1H, J = 8.4 Hz), 7.90 (m, 2H), 7.76–7.54 (m, 4H), 7.32–7.18 (m, 2H), 6.61 (s, 1H), 5.80–5.76 (m, 1H), 4.88 (d, 1H, J = 5.2 Hz), 4.23–4.19 (m, 2H), 4.07–3.98 (m, 2H), 3.36 (t, 2H, J = 6.6 Hz), 1.90–1.85 (m, 2H), 1.70–1.60 (m, 4H).

4-(Phenylsulfonyl)-3-(4'-azidobutyl)-furo[3,4-*b*]indole (5). A mixture of **19** (100 mg, 0.219 mmol), potassium fluoride (5.2 mg, 0.090 mmol) and hydroquinone (1.7 mg, 0.016 mmol) in 7.0 mL of acetic acid was heated in a 90 °C oil bath for 30 min. The mixture was allowed to cool and poured slowly into a saturated solution of sodium bicarbonate, and then extracted with methylene chloride. The organic layer was dried over magnesium sulfate. The residue after removal of solvent was purified by flash chromatography (30/70 EtOAc/Hexane) to give **5** as a white solid (53 mg, 61%); mp 95–96.5 °C; ^{1}H NMR (acetone-d_6) δ 8.02 (d, 1H, *J* 8.4 Hz), 7.71 (s, 1H), 7.67 (m, 2H), 7.60–7.53 (m, 2H), 7.44–7.35 (m, 3H), 7.26–7.21 (m, 1H), 3.41–3.34 (t, 2H, *J* 6.6 Hz), 3.21–3.17 (t, 2H, *J* 7.3 Hz), 1.89–1.80 (m, 2H), 1.72–1.63 (m, 2H). HRMS MS *m/z* Calcd for $C_{20}H_{18}N_4O_3S$: 394.1100 (M^+). Found: 394.1096. *Anal.* Calcd for $C_{20}H_{18}N_4O_3S$: C, 60.91; H, 4.56; N, 14.21; S, 8.12. Found: C, 60.95; H, 4.71; N, 14.11; S, 8.01.

Acknowledgements

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