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Synthesis of bis-4*H*-furo[3,4-*b*]indoles

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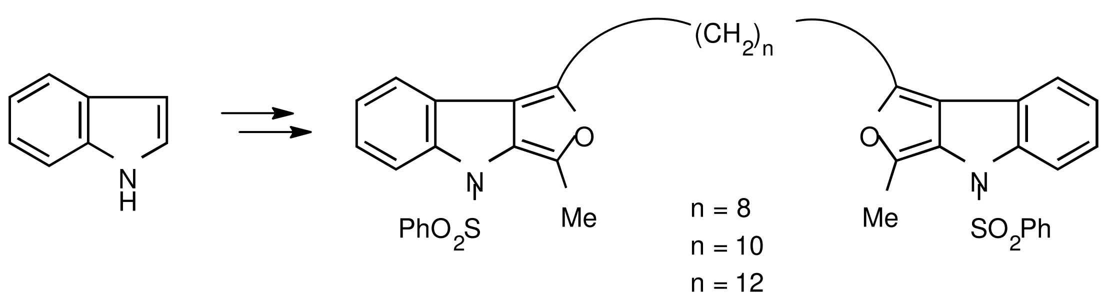
Abstract

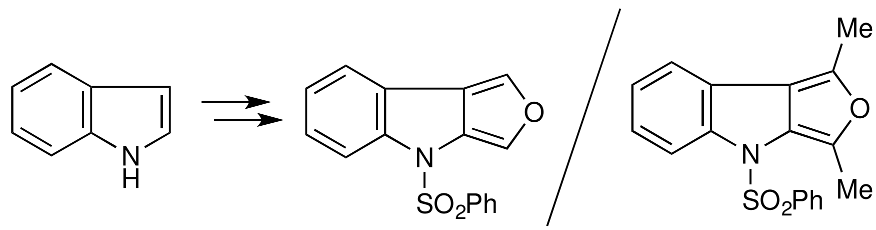
We describe the synthesis of two novel bis-4*H*-furo[3,4-*b*]indoles from indole. Several alternative pathways to these potential DNA bis-intercalator precursors are discussed, and the synthesis of a novel semi-rigid tether is reported.



Keywords: Indole, furo[3,4-*b*]indole, furan, acylation, acid chloride

Introduction

We have had a long interest in the synthesis and Diels–Alder cycloaddition reactions of 4*H*-furo[3,4-*b*]indoles,[1–8] particularly as a novel route to the synthesis of ellipticine alkaloids.[3–5] Following our inaugural synthesis of the 4*H*-furo[3,4-*b*]indole (**2**, **3**) ring system (Figure 1),[1,2] we greatly improved the efficiency and the overall yield of this ring system from indole.[7,8] For example, our original synthesis[1] of 1,3-dimethyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**3**) from indole (**1**) proceeded in 21% yield, whereas our shortened synthesis of **3** from indole gives an overall yield of 45%.[8]

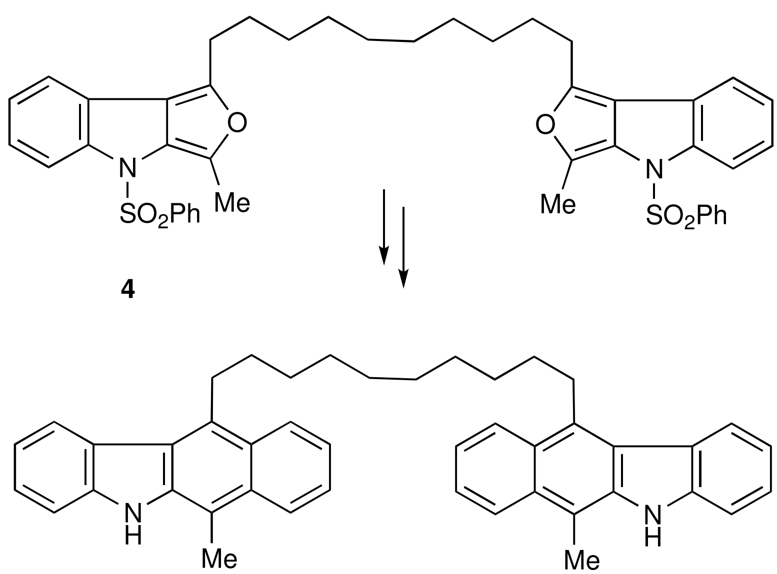


1 **2** **3**

Figure 1

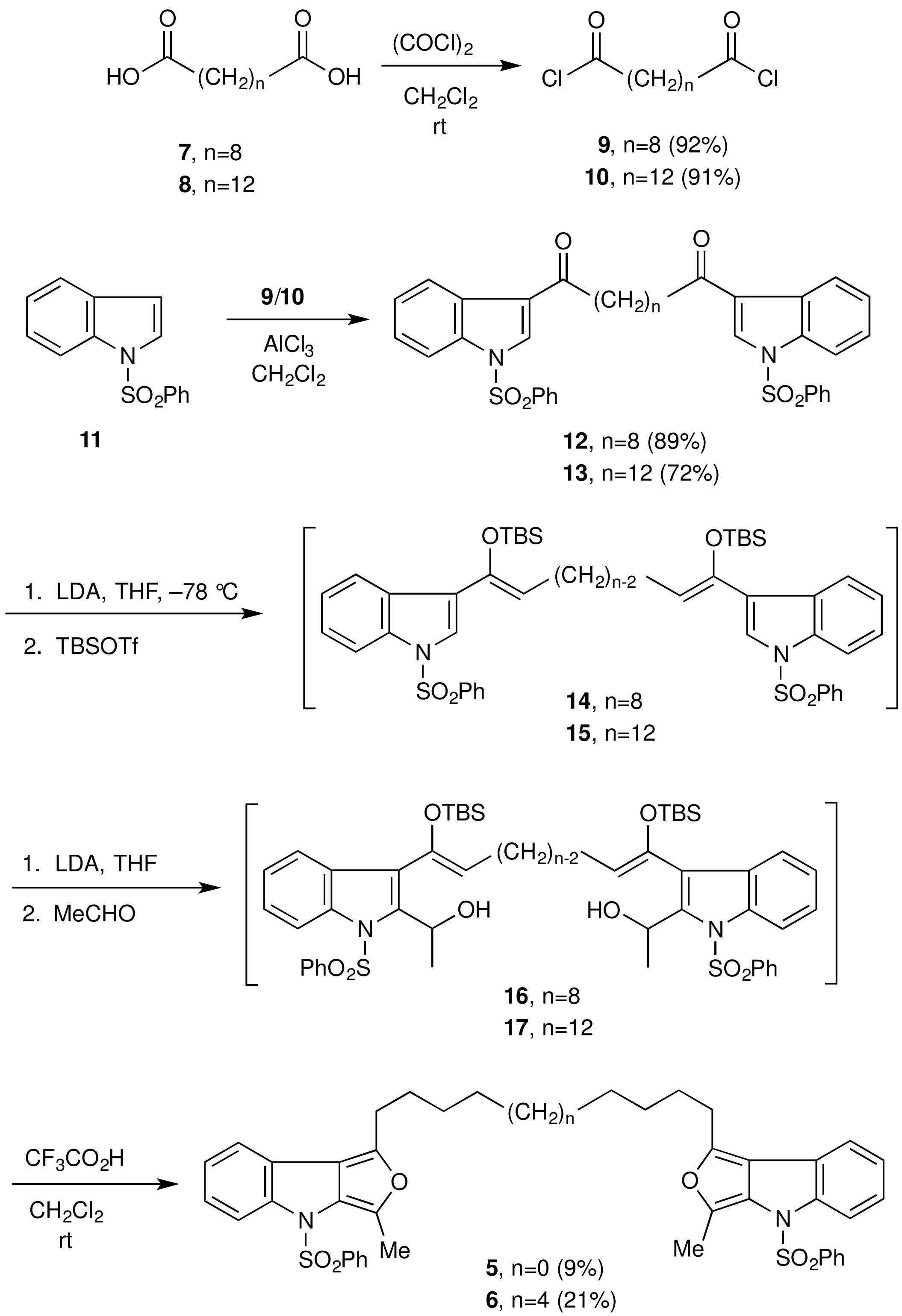
Results and Discussion

In connection with our interest in the synthesis and antitumor activity of potential bis-DNA intercalators,[2,9,10] we utilized bis-furoindole **4** for the synthesis of 1,10-bis(6-methyl-5*H*-benzo[*b*]carbazol-11-yl)decane (Figure 2).[2] Although successful, our early synthesis of **4** was less efficient than we desired. We now describe syntheses of bis-furo[3,4-*b*]indoles **5** and **6** using our improved methodology[8] (Scheme 1). Our newer method avoids an extra reduction step featured earlier[1,2] and relies on an initial indole acylation protocol.



1,10-bis(6-methyl-5*H*-benzo[*b*]carbazol-11-yl)decane

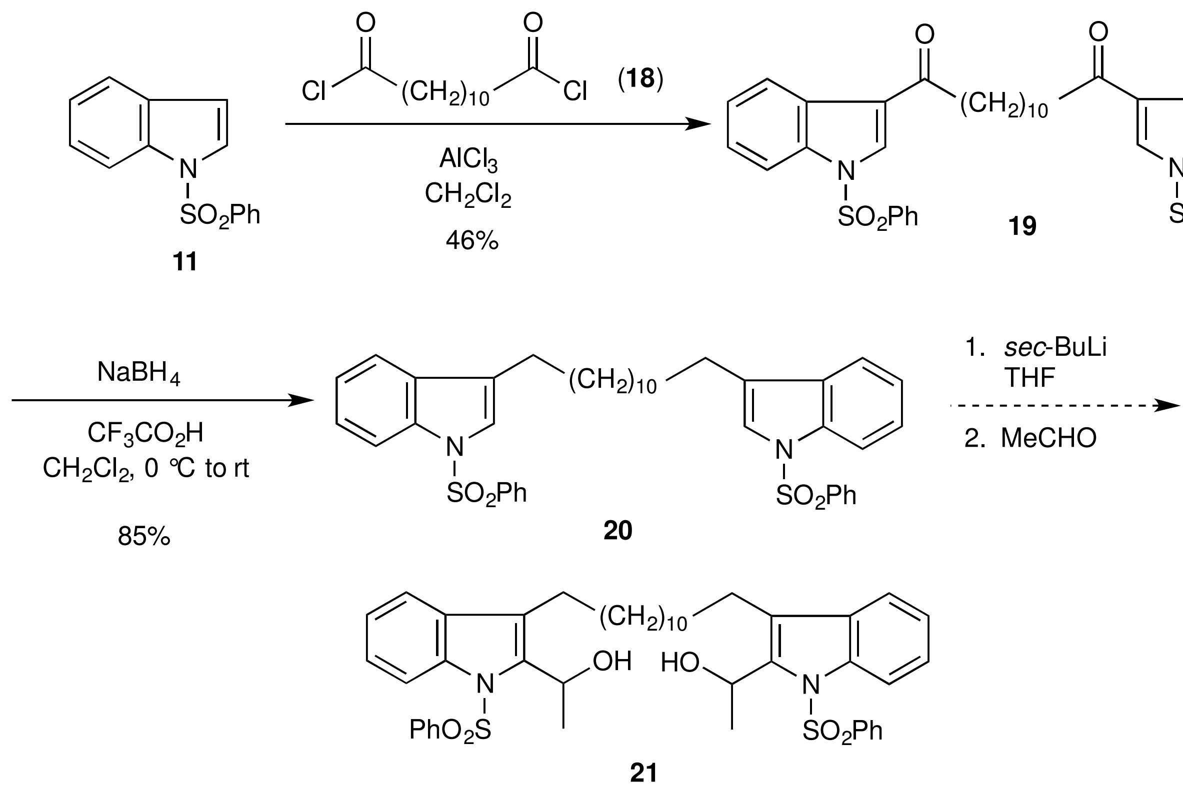
Figure 2



Scheme 1

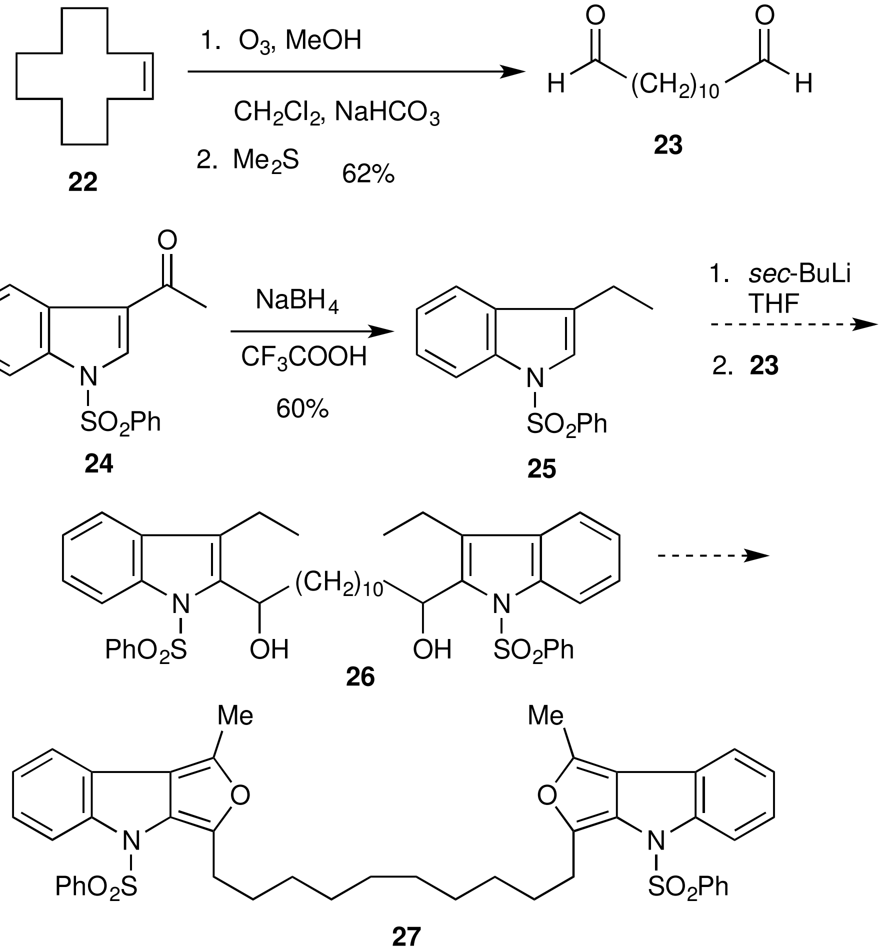
Commercially available decanedioic acid (**7**) and tetradecanedioic acid (**8**) were converted into the respective diacid chlorides **9** and **10** in high yields (Scheme 1). Friedel–Crafts acylation[11] of 1-(phenylsulfonyl)indole (**11**)[12] with **9** and **10** afforded the respective 3-acylindoles **12** and **13** in good yields. In a one-pot operation, ketones **12** and **13** were transformed into the desired bis-furo[3,4-*b*]indoles **5** and **6** by a sequence of carbonyl protection as the bis-enol ethers **14** and **15**, C-2 lithiation and quenching with acetaldehyde to generate intermediates **16** and **17**, followed by trifluoroacetic acid–induced twin cyclodehydration to give the desired furoindoles **5** and **6**. Although the final yields of these new bis-furoindoles **5** and **6** are low, the method is relatively short and should be amenable to the preparation of analogues and the subsequent synthesis of Diels–Alder cycloadducts.[2]

We explored an alternative approach to these bis-furo[3,4-*b*]indoles by removing the carbonyl groups at an early stage as shown in Scheme 2. Thus, bis-acylation of 1-(phenylsulfonyl)indole (**11**) with dodecanedioic acid chloride (**18**), prepared from dodecanedioic acid and thionyl chloride, gave diketone **19**. Reduction[11] of **19** with $NaBH_4$/TFA gave **20** in 85% yield. Unfortunately, attempts to effect bis-lithiation of **20** with *sec*-BuLi and quenching with acetaldehyde failed to afford a clean mixture of diastereomeric diols **21**, and this alternative route was not further pursued.



Scheme 2

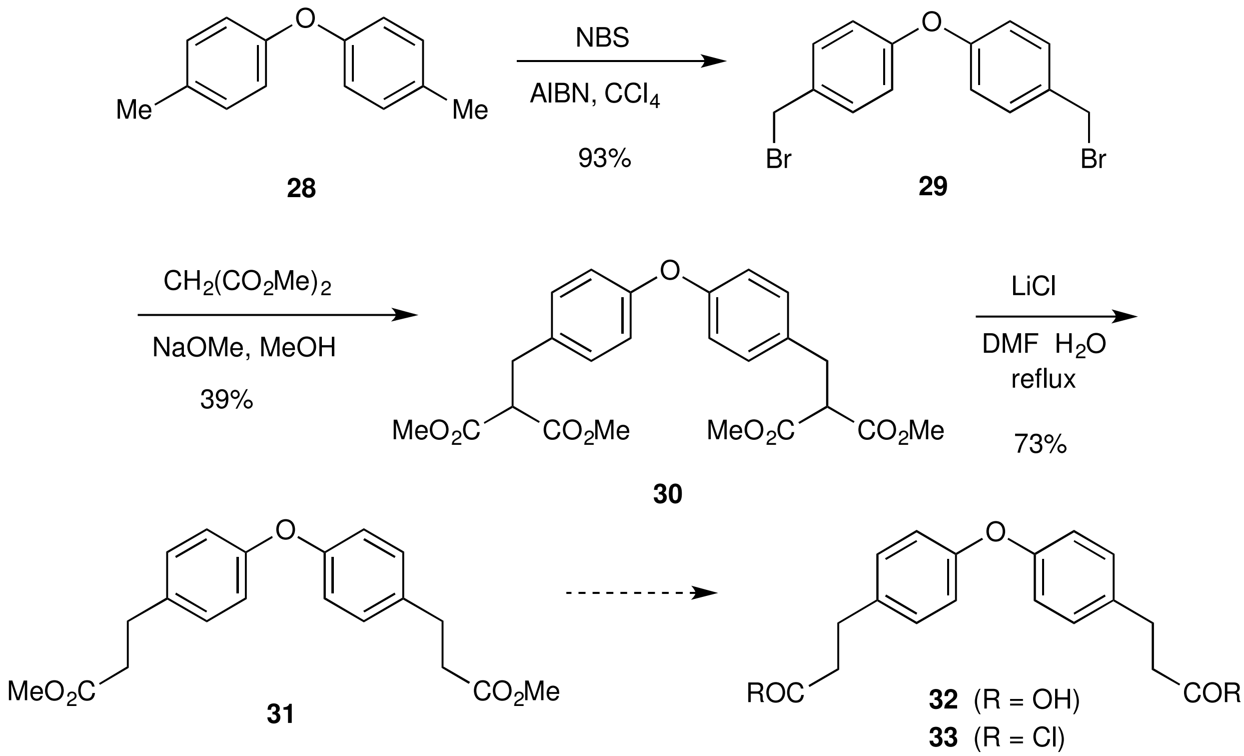
In an approach to the isomeric bis-furo[3,4-*b*]indole **27**, we prepared dodecanedial (**23**) via the ozonolysis of cyclododecene (**22**).[13,14] Other attempts to prepare **23** via the reduction of 1,10-dodecanedioic acid[15,16] were unsatisfactory. Lithiation of 3-ethyl-1-(phenylsulfonyl)indole (**25**),[11] prepared by reduction of 3-acetyl-1-(phenylsulfonyl)indole (**24**),[11] and condensation with dialdehyde **23** gave a mixture of diols **26** in modest yield, along with other products (Scheme 3). Therefore, we deemed that this route was not worth further investigation.



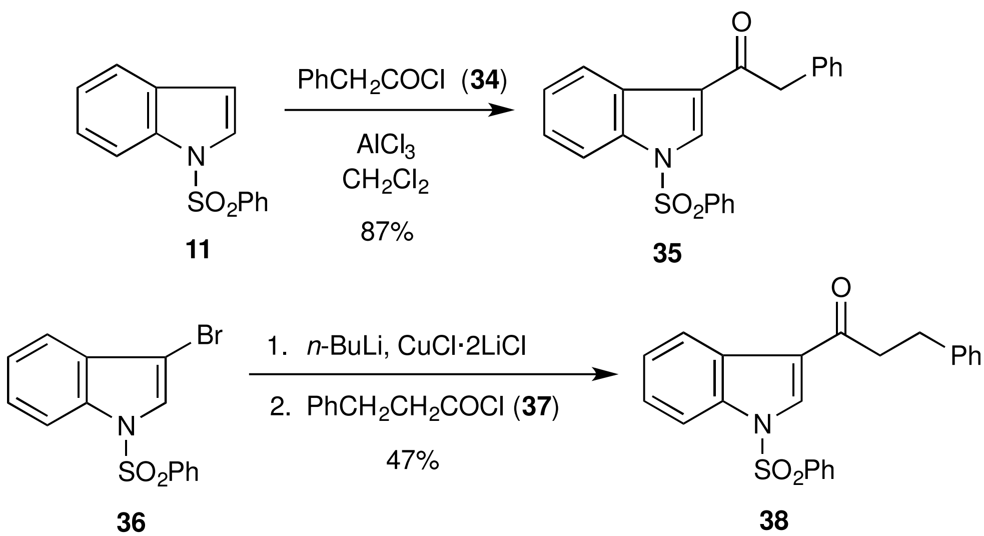
Scheme 3

DNA-bis intercalators possessing semi-rigid tethers typically exhibit improved antitumor activity over those with flexible tethers.[17–20] In this regard, we targeted the potential semi-rigid tethers embodied in diacid **32** and diacid chloride **33** (Scheme 4) for study. Bis-bromination of diphenyl ether **28** gave dibromide **29**, and subsequent alkylation with dimethyl malonate gave the new tetraester **30**. Double Krapcho decarbomethoxylation[21-23] led to the corresponding diester **31**. Future work will involve the conversion of **31** into acid **32** and then acid chloride **33**, which will serve in an indole acylation protocol.

Our planned indole acylation using diacid chloride **33** is modeled with the syntheses of 3-acylindoles **35** and **38** (Scheme 5). Interestingly, whereas 1-(phenylsulfonyl)indole (**11**) undergoes smooth acylation with phenylacetyl chloride (**34**) to give ketone **35** in high yield, an acylation attempt of **11** with 3-phenylpropionyl chloride (**37**) yielded mainly indanone (not shown). However, the desired ketone **38** could be synthesized from 3-bromo-1-(phenylsulfonyl)indole[24] (**36**) via the corresponding indolyl bromo cuprate as according to the method of Dieter.[25]



Scheme 4



Scheme 5

An attractive target for our future work on this project is bis-ellipticine **40** (Figure 3). The diphenyl ether tether imparts significant anticancer activity when tethered to two 9-aminoacridines.[9] Accordingly, tethers such as **31-33** can be envisaged to forge **39** and, subsequently, bis-ellipticine **40**.

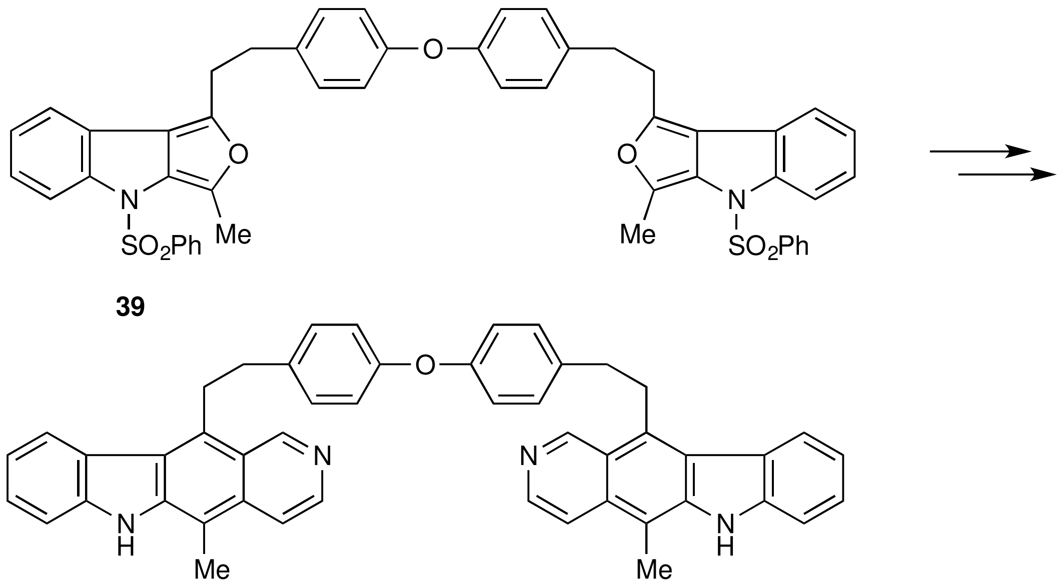


Figure 3

Conclusions

We have synthesized the novel bis-4*H*-furo[3,4-*b*]indoles **5** and **6**, which now join the first member, **4**, of this family. These bis-dienes are suitable for double Diels–Alder cycloaddition reactions leading to potential DNA bis-intercalators.[2] Furthermore, we prepared the bifunctional tether **31**, which can be envisioned as leading to the semi-rigid bis-4*H*-furo[3,4-*b*]indole **39** and thence to bis-ellipticine **40.**

Experimental Section

General. Thin layer chromatography was performed on precoated (0.2 mm) silica gel 60 F_{254} plastic sheets with spots 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 Varian XL-300 and XL-500 Fourier transform spectrometers as noted. The chemical shifts noted from these spectra are reported in parts per million (ppm, δ) using the signal of chloroform-d_1 (δ 7.27) or acetone-d_6 (δ 1.94) or Me_4Si as an internal standard. In a few cases a Varian EM 360A NMR Spectrometer measuringat 60 MHz was used. Infrared spectra were recorded with a Perkin Elmer 1600 FTIR or 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 Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois at Urbana Champaign, 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. (Norcross, GA). Tetrahydrofuran (THF) was distilled from sodium/benzophenone and the alkyl lithium reagents were standardized by titration against diphenylacetic acid.

1,10-Decanedioyl dichloride (9). To a stirred solution of 1,10-decanedioic acid (**7**) (2.0 g, 10 mmol, 1 eq.) in anhydrous CH_2Cl_2 (165 mL) under nitrogen was added oxalyl chloride (16.5 mL, 190 mmol, 10 eq.) rapidly via syringe. The reaction was stirred for 24 h, after which the solvent and unreacted oxalyl chloride were distilled off under reduced pressure. The resulting yellow liquid was concentrated via azeotrope with benzene (3 x 50 mL) *in vacuo*, following which it was redissolved in CH_2Cl_2 and filtered to remove unreacted **7**. The solvent was removed *in vacuo* and the product dried under a vacuum to yield (**9**) (2.21 g, 92%) as a yellow liquid; ^{1}H NMR ($CDCl_3$): δ 2.89 (t, 4H), 1.78–1.68 (m, 4H), 1.31–1.25 (b, 8H). This was used directly in the next step with **11**.

1,14-Tetradecanedioyl dichloride (10). To a stirred solution of 1,14-tetradecanedioic acid (**8**) (2.6 g, 10 mmol, 1 eq.) in anhydrous CH_2Cl_2 (165 mL) under nitrogen was added oxalyl chloride (16.5 mL, 190 mmol, 10 eq.) rapidly via syringe. The reaction was stirred for 24 h, after which the solvent and unreacted oxalyl chloride were removed by distillation under reduced pressure. The resulting yellow liquid was concentrated via azeotrope with benzene (3 x 50 mL) *in vacuo*, following which it was redissolved in CH_2Cl_2 and filtered to remove unreacted **8**. The solvent was removed *in vacuo* and the product was dried under a vacuum to yield (**10**) (2.68 g, 91%) as a yellow liquid, which was used directly in the next step with **11**.

1,10-Bis(1-(phenylsulfonyl)-1*H*-indol-3-yl)decane-1,10-dione) (12). To a stirred solution of $AlCl_3$ (2.24 g, 16.8 mmol, 4 eq.) in CH_2Cl_2 (90 mL) at 0 °C was added after 15 min a solution of 1,10-decanedioyl dichloride (**9**) (1.01 g, 4.2 mmol, 1 eq.) in CH_2Cl_2 (3 mL) dropwise via an addition funnel. The solution was stirred 30 min, after which a solution of 1-(phenylsulfonyl)indole (**11**) (2.15 g, 8.41 mmol, 2 eq.) in CH_2Cl_2 (20 mL) was added over 30 min via addition funnel. During this time the solution turned from light yellow to dark orange. The solution was allowed to come to rt and stirred for 2.5 h, during which the solution appeared dark red. The reaction was quenched with ice (150 g) in a 400 mL beaker and covered with a watch glass until the ice melted. The aqueous layer was then extracted with CH_2Cl_2 (4 x 75 mL) and the combined organic extracts were washed with brine (2 x 50 mL), aqueous sodium carbonate (50 mL), and brine (2 x 50 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield (**12**) as a white solid (2.54 g, 89%). The solid was washed with 4:1 hexane:EtOAc and recrystallized in CH_2Cl_2/hexane to yield white solid product (**12**): mp 194–197 °C; ^{1}H NMR ($CDCl_3$): δ 8.37–8.34 (m, 2H), 8.23 (s, 2H), 7.98–7.93 (m, 6H), 7.64–7.58 (m, 2H), 7.54–7.40 (m, 4H), 7.39–7.35 (m, 4H), 2.91 (t, 4H), 1.82–1.75 (m, 4H), 1.61–1.48 (b, 2H), 1.39 (m, 10H). ^{13}C NMR ($CDCl_3$): 196.6, 134.8, 131.7, 129.9, 127.9, 127.3, 126.0, 125.1, 123.4, 113.2, 40.3, 29.5, 29.5, 24.7; IR (KBr): 3089, 3067, 2920, 2850, 1661 (C=O), 1540, 1444, 1381, 1287, 1180, 1134, 980, 934, 754, 683, 594. MS (EI): 680.4 (M^+), 539.2, 446.2, 399.2, 327.1, 299.1, 257.1, 144.0, 116.1, 77.0 (100%). *Anal*. Calcd for $C_{38}H_{36}N_2O_6S_2$: C, 67.04; H, 5.33; N, 4.11; S, 9.42. Found: C, 66.18; H, 5.33; N, 4.03; S, 8.97.

1,14-Bis(1-(phenylsulfonyl)-1*H*-indol-3-yl)tetradecane-1,14-dione) (13). To a stirred solution of $AlCl_3$ (4.85 g, 36.4 mmol, 4 eq.) in CH_2Cl_2 (180 mL) at 0 °C was added after 15 min a solution of 1,14-tetradecanedioyl dichloride (**10**) (2.67 g, 9.1 mmol, 1 eq.) in CH_2Cl_2 (6 mL) dropwise via an addition funnel. [note: some of the acid was spilt during addition] The solution was stirred for 30 min, after which a solution of 1-(phenylsulfonyl)indole (**11**) (4.65 g, 18.2 mmol, 2 eq.) in CH_2Cl_2 (40 mL) was added over 30 min via addition funnel. During this time the solution turned from light yellow to dark orange-red. The solution was allowed to come to rt and stirred for 2.5 h, during which the solution appeared dark red. The reaction was quenched with ice (300 g) in a 600 mL beaker and allowed to stand overnight covered with a watch glass. The aqueous layer was extracted with CH_2Cl_2 (4 x 125 mL) and the combined organic extracts were washed with brine (2 x 100 mL), aqueous sodium carbonate (100 mL), and brine (2 x 100 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield (**13**) as a beige solid (4.81 g, 72%). The solid was washed with 4:1 hexane:EtOAc and recrystallized from EtOAc/hexane to yield the **13** as a light beige solid: mp 155–156 °C. ^{1}H NMR ($CDCl_3$): 8.40–8.36 (m, 2H), 8.25 (s, 2H), 8.02–7.92 (m, 6H), 7.64–7.60 (t, 2H), 7.57–7.45 (m, 4H), 7.42–7.32 (m, 4H), 2.95 (t, 4H), 1.82–1.75 (m, 4H), 1.63–1.55 (b, 2H), 1.45–1.24 (m, 12H). ^{13}C NMR ($CDCl_3$): 196.7, 141.7, 134.8, 131.7, 129.8, 127.3, 126.0, 125.1, 123.4, 113.2, 40.4, 29.8, 29.7, 29.6, 24.8. IR (KBr): 3111, 3066, 2924, 2847, 1669 (C=O), 1541, 1444, 1386, 1290, 1172, 1134, 1097, 990, 755, 683 cm^{-1}; MS (EI): 736.3 (M^+), 595.3, 539.0, 446.2, 398.2, 327.1 (100%), 267.1, 141.0, 88.1. *Anal*. Calcd for $C_{42}H_{44}N_2O_6S_2$: C, 68.45; H, 6.02; N, 3.80; S, 8.70. Found: C, 67.04; H, 5.93; N, 3.79; S, 8.49.

1,8-Bis(3-methyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indol-1-yl)octane (5). To a –78 °C stirred solution of 1,10-bis(1-(phenylsulfonyl)-1*H*-indol-3-yl)decane-1,10-dione) (**12**) (680 mg, 1 mmol, 1 eq.) in dry THF (50 mL) under nitrogen was added lithium diisopropylamide (LDA) (1 mL of 2.0 M in THF/heptane, 2 mmol, 2 eq.) dropwise via syringe. The reaction was stirred for 15 min, after which *tert*-butyldimethylsilyl triflate (TBSOTf) (0.46 mL, 2 mmol, 2 eq.) was added dropwise via syringe. The reaction was stirred 1 h at –78 °C, after which lithium diisopropylamide (1 mL of 2.0 M in THF/heptane, 2 mmol, 2 eq.) was added dropwise. The solution turned from yellow to orange. The mixture was stirred for 10 min, after which freshly distilled acetaldehyde (0.24 mL, 4 mmol, 4 eq.) was quickly added in one portion, after which the solution turned rapidly from orange to yellow. The mixture was stirred for 1 h before it was quenched in aqueous ammonium chloride (50 mL). The THF was removed under reduced pressure and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were treated with TFA (0.25 mL, 3.4 mmol, 3.4 eq.) and the mixture was stirred for 2 h under nitrogen. The reaction was then neutralized with saturated sodium bicarbonate (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to yield a dark yellow oil. Purification by flash chromatography (20% EtOAc in hexane) afforded **5** as a light yellow oil (66 mg, 9%). Further purification on activity III neutral alumina (20% EtOAc in hexane) afforded the analytical sample of **5** as a colorless oil; ^{1}H NMR (acetone-d_6): δ 8.07–7.78 (m, 6H), 7.68–7.11 (m, 12H), 2.71 (s, 6H), 2.68 (t, 4H), 1.69–1.57 (m, 4H), 1.39–1.05 (m, 8H); HRMS (ESI): 733.2 $(M + H)^+$, 722.3, 721.3, 708.2, 707.2. Calcd for $C_{42}H_{40}N_2O_6S_2$: 732.2328 (M), $C_{42}H_{41}N_2O_6S_2$: 733.2406 (M + H). Found: 733.2410 $(M + H)^+$.

1,12-Bis(3-methyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indol-1-yl)dodecane (6). To a –78 °C stirred solution of 1,14-bis(1-(phenylsulfonyl)-1*H*-indol-3-yl)tetradecane-1,14-dione) (**13**) (740 mg, 1 mmol, 1 eq.) in dry THF (50 mL) under nitrogen was added lithium diisopropylamide (LDA) (1 mL of 2.0 M in THF/heptane, 2 mmol, 2 eq.) dropwise via syringe. The reaction was stirred for 15 min, after which *tert*-butyldimethylsilyl triflate (TBSOTf) (0.46 mL, 2 mmol, 2 eq.) was added dropwise via syringe. The reaction was stirred for 1 h at –78 °C, after which lithium diisopropylamide (1 mL of 2.0 M in THF/heptane, 2 mmol, 2 eq.) was added dropwise. The mixture was stirred for 10 min, after which freshly distilled acetaldehyde (0.24 mL, 4 mmol, 4 eq.) was quickly added in one portion. The mixture was stirred for 1 h before it was quenched in aqueous ammonium chloride (50 mL). The THF was removed under reduced pressure and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were treated with TFA (0.25 mL, 3.4 mmol, 3.4 eq.) and the mixture was stirred for 2 h under nitrogen. The reaction was then neutralized with saturated sodium bicarbonate (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo* to yield a dark yellow oil. Purification by flash chromatography (20% EtOAc in hexane) afforded the crude product as a light yellow oil (169 mg, 21%). Further purification on activity III neutral alumina (20% EtOAc in hexane), followed by purification by preparative TLC (20% EtOAc in hexane) afforded the analytical sample of **6** as a faint yellow oil; ^{1}H NMR ($CDCl_3$): δ 8.03 (m, 2H), 7.63 (m, 4H), 7.45–7.18 (m, 12H), 2.75 (t, 4H), 2.69 (s, 6H), 1.71–1.60 (m, 4H), 1.28–1.19 (m, 16H). MS (ESI): 789.3 ($M^+ + H^+$), 787.3, 777.4, 773.3, 761.2. Calcd for $C_{46}H_{49}N_2O_6S_2$: 789.3032 (M + H). Found: 789.3015 $(M + H)^+$.

1,12-Dodecanedioyl dichloride (18). A solution of 1,12-dodecanedioic acid (2.0 g, 8.68 mmol) in thionyl chloride (25 mL) was magnetically stirred under reflux at 40 °C for 2 h resulting in a dark brown liquid. Excess thionyl chloride was removed with gentle warming under vacuum. Unreacted thionyl chloride was distilled away affording 2.32 g of crude **18**, which could be used directly in the next step.

1,12-Di-(1-(phenylsulfonyl)-3-indolyl)-1,12-dioxododecane (19). To a magnetically stirred suspension of $AlCl_3$ (13.9 g, 0.104 mol) in CH_2Cl_2 (180 mL) at 0 °C was added dropwise the crude 1,12-dodecanedioyl dichloride (**18**) (2.21 g, 8.27 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 30 min, at which time a solution of (**11**) (4.52 g, 0.018 mol) in CH_2Cl_2 (40 mL) was added dropwise. The mixture was allowed to reach rt and stirred an additional 2 h. The resulting dark red-brown reaction mixture was poured over crushed ice (300 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The organic layer was washed with brine (2 x 75 mL), $NaHCO_3$ (75 mL), made basic with dilute NaOH and washed with brine (2 x 75 mL). The product was then dried over K_2CO_3 and concentrated *in vacuo*. The crude powder (5.34 g) was purified by flash chromatography over silica gel with gradient elution of EtOAc/hexane (0:1, 1:9, 3:7, 1:1, 7:3, 1:0). Final yields were not calculated due to the difficulty of removing all the diketone before other products eluted off the column. Fine white crystals were obtained from fractions containing the diketone, in EtOAc/hexane approximately (3:7): mp 134 °C and 160–161 °C. Recrystallization attempts were unsuccessful and this crude material was used in the next step. IR ($CHCl_3$) 2930, 2870, 1660, 1530, 1450, 1380, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.4–7.25 (m, 10H), 2.9 (t, 2H), 1.8 (t, 2H), 1.37 (t, 6H); ^{13}C NMR ($CDCl_3$) δ 196.5, 137.5, 134.9, 134.5, 131.5, 129.6, 127.7, 127.0, 125.7, 124.9, 123.2, 121.5, 113.0, 40.1, 29.4, 29.3, 24.5; Mass spectrum, *m/e* 708 (M^+), 567, 310, 299, 284, 159, 144, 141, 130, 77 (100).

1,12-Di-(1-(phenylsulfonyl)-3-indolyl)dodecane (20). To magnetically stirred trifluoroacetic acid (80 mL) at 0 °C under argon, equipped with a reflux condenser and drying tube, was added sodium borohydride (30 pellets, 0.214 mol) over 1.5 h. To this mixture at 0 °C was added dropwise over 1 h a solution of (**19**) (1.5 g, 2.12 mmol) in CH_2Cl_2 (80 mL). The mixture was allowed to come to rt and stirred under argon with a reflux condenser overnight. The resulting mixture was poured over crushed ice (225 mL) and made basic with NaOH pellets at 0 °C. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL), and the organic layer was washed with brine (3 x 50 mL), dried over K_2CO_3, and concentrated *in vacuo* to give a crude light brown powder 1.22 g (85%). The sample was purified by flash chromatography over silica gel with gradient elution of Et_2O/hexane (1:1, 1:9, 1:1, 1:0) and finally ether/ CH_2Cl_2 (9:1, 1:1, 0:1). The purest fractions were combined, filtered, and concentrated *in vacuo* to give **20** as a fine off-white powder: mp 121 °C; IR ($CHCl_3$) 2930, 2850, 1450, 1360, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.2–7.15 (m, 10H), 2.65 (t, 2H), 1.65 (t, 2H), 1.25 (t, 8H); ^{13}C NMR ($CDCl_3$) δ 138.3, 135.4, 133.5, 131.2, 129.1, 126.7, 124.6, 123.9, 123.0, 122.5, 119.5, 113.8, 77.0, 76.9, 76.6, 29.3, 29.4, 28.8, 24.9; Mass spectrum, *m/e* 680 (M^+), 271, 270, 170, 156, 141, 131, 130, 77 (100).

Ozonolysis of cyclododecene (22). Preparation of 1,12-dodecanedial (23). In a 250 mL three-neck round bottom flask fitted with a glass stopper, an ozone inlet, a low-temperature thermometer, a $CaSO_4$ drying tube, and a magnetic stirrer was charged cyclododecene (6.24 g, 0.0375 mol), CH_2Cl_2 (125 mL), MeOH (25 mL), and $NaHCO_3$ (2.15 g, 0.0256 mol) as a buffer. The flask was cooled to –78 °C (isopropanol/dry ice) and ozone was bubbled through with stirring (6.5 lbs/in^2 at 1.6 L/min). The solution turned blue, and ozone was allowed to bubble through for 0.5 h more. Ozone addition was stopped, and nitrogen was passed through to discharge the blue color. The cold bath was then removed, and dimethyl sulfide (5.07 g, 0.075 mol) was added via syringe. The reaction mixture was stirred overnight at rt, then filtered to remove the $NaHCO_3$, and concentrated to a white slurry by rotary evaporation. CH_2Cl_2 (50 mL) was added and the mixture was washed with H_2O (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic extract was washed with H_2O (50 mL). The aqueous layer was extracted again with CH_2Cl_2 (50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude product. Short path distillation yielded 4.58 g (62%) of 1,12-dodecanedial (**23**) as a white solid. mp 28–38 °C; (lit.[26] mp 65-66 °C); bp 123–131 °C at 0.4 Torr; IR ($CHCl_3$) 3510, 3430, 2940, 2740, 1725, 1465, 1400, 1230, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.7 (t, 2H, *J* 1.8 Hz), 2.4 (m, 4H), 1.4 (m, 16H) (lit.[27] ^1H NMR ($CDCl_3$) δ 9.78 (t, *J* 1.65

Hz), 2.57-2.33 (td), 1.88-1.31 (m); (lit.[28] ^{1}H NMR ($CDCl_3$) δ 9.76-9.77 (t, 2H, *J* 1.83), 2.40-2.44 (4H), 1.61-1.64 (4H), 1.29 (m, 12H)); ^{13}C NMR ($CDCl_3$) δ 203.0, 179.7, 43.8, 33.9, 29.1, 24.6, 22.0) (Lit.[28] ^{13}C NMR ($CDCl_3$) δ 201.89, 29.29, 29.11, 22.04).

4,4'-Oxybis((bromomethyl)benzene) (29). Prior to use, NBS was recrystallized from water and the carbon tetrachloride was bubbled with nitrogen, stirred for 45 min with sodium sulfate, and checked by ^{1}H-NMR spectroscopy. To a stirred solution of 4,4'-oxybis(methylbenzene) (**28**) (5.0 g, 25.2 mmol, 1 eq.) and NBS (8.98 g, 50.4 mmol, 2 eq.) in carbon tetrachloride (125 mL) under nitrogen was added a catalytic amount of AIBN. The reaction mixture was heated to 80–90 °C (reflux) and stirred for 6.5 h. The solution was then cooled and the succinimide was removed on a sintered glass filter funnel. The solvent was removed *in vacuo* to yield the desired product **29** as beige crystals (8.3 g, 93%). A portion (1.82 g) was purified by flash chromatography (10:1 hexane:EtOAc) to yield **29** as white crystals: mp 85–86 °C (lit.[29] mp 93–95 °C). ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 4H), 6.98 (d, 4H), 4.52 (s, 4H).

Tetramethyl 2,2'-((oxybis(4,1-phenylene))bis(methylene))dimalonate (30). To a freshly prepared 5% weight solution of NaOMe in anhydrous MeOH (2 mL) was added dimethyl malonate (0.12 mL, 1.13 mmol, 2 eq.) dropwise via syringe. The solution was cooled to 0 °C and a solution of 4,4'-oxybis((bromomethyl)benzene) (**29**) (crude, 0.2 g, 0.56 mmol, 1 eq.) in anhydrous benzene (0.6 mL) was added dropwise via syringe. The solution was stirred for 0.5 h before allowing it to warm to rt, after which it was stirred for 15 h. The solvent was removed *in vacuo*, and the resulting oil was resuspended in water (5 mL) and extracted with chloroform (3 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and filtered. The solvent was removed *in vacuo* to yield crude **30** as a yellow oil (100 mg, 39%). Preparative TLC was used to purify 20 mg of the oil to confirm product identification by NMR spectroscopy. Column chromatography (3:2 hexane:EtOAc) gave **30** (30 mg, 12%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.14 (d, 4H), 6.88 (d, 4H), 3.71 (s, 12H), 3.65 (t, 2H), 3.19 (d, 4H). MS (EI): 458.2 (M+), 427.2, 398.2, 357.2, 327.2 (100%), 267.1, 227.1, 197.1, 91.1. HRMS (EI): Calcd for $C_{24}H_{26}O_9$: 458.1577 (M). Found: 458.1585 (M^+).

Dimethyl 3,3'-(oxybis(4,1-phenylene))dipropionate (31). To a stirred solution of LiCl (5.14 mg, 0.12 mmol, 2 eq.) in DMF (4.5 mL) and water (1 drop) was added tetramethyl 2,2'-((oxybis(4,1-phenylene))bis(methylene))dimalonate (**30**) (27 mg, 0.06 mmol, 1 eq.). The reaction mixture was heated in an oil bath to reflux (140 °C) for 1 h. The reaction mixture was then cooled to rt and poured into H_2O (10 mL). The aqueous layer was extracted with Et_2O (4 x 8 mL), and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield the crude product as a colorless oil. To remove any residual DMF the oil was then rewashed with H_2O (10 mL), extracted with Et_2O (4 x 8 mL), and the combined organic layers were washed again with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield **31** as a colorless oil (15 mg, 73%); ^{1}H NMR ($CDCl_3$): δ 7.15 (d, 4H), 6.92 (d, 4H), 3.73 (s, 6H), 2.95 (t, 4H), 2.62 (t, 4H). MS (EI): 458.2 (compound [**30**]), 400.2, 342.2 (M+), 327.2, 269.1, 219.2, 177.1, 153.1, 133.1, 104.1, 84.0 (100%). HRMS (EI): Calcd for $C_{20}H_{22}O_5$: 342.1467 (M). Found: 342.1463 (M^+).

2-Phenyl-1-(1-(phenylsulfonyl)-1*H*-indol-3-yl)ethan-1-one [35]. To a stirred solution of phenylacetyl chloride (**34**) (1.11 mL, 8.43 mmol, 1 eq.) in dichloromethane (50 mL) at 0 °C was added $AlCl_3$ (1.30 g, 16.9 mmol, 2 eq.). After the solution was stirred for 15 min a solution of 1-(phenylsulfonyl)indole (**11**) (2.17 g, 8.43 mmol, 1 eq.) in CH_2Cl_2 (17.5 mL) was added over 20 min via an addition funnel. During this time the solution turned from light yellow to dark orange-yellow. The solution was allowed to come to rt and stirred for 2.5 h, during which the solution appeared dark orange-red. The reaction was quenched with ice in a 300 mL beaker and allowed to stand overnight covered with a watch glass, during which the solution turned yellow-green. The solution was extracted with CH_2Cl_2 (6 x 30 mL) and the combined organic extracts were washed with brine (50 mL), aqueous sodium carbonate (50 mL), and brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield (**35**) as light peach crystals (2.76 g, 87%). The product was recrystallized from Et_2O to give **35** with mp 121–123 °C; ^1H NMR ($CDCl_3$): δ 8.25 (s, 1H), 7.94–7.85 (m, 2H), 7.63–7.56 (m, 1H), 7.50–7.26 (m, 6H), 4.21 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 193.62, 137.70, 135.15, 134.99, 134.82, 132.66, 129.88, 129.66, 129.08, 127.30, 126.21, 127.29, 123.53, 113.31, 47.61. IR (KBr): 3313, 3140, 2911, 1678 (C=O), 1602, 1529, 1475, 1451, 1232 cm^{-1}. MS (EI): 375.1 (M^+), 284.1 (100%), 264.1, 237.0, 223.0, 185.1, 157.1, 143.1, 129.1, 115.1, 91.1, 77.0. *Anal*. Calcd for $C_{22}H_{17}NO_3S$: C, 70.38; H, 4.56; N, 3.73; S, 8.54. Found: C, 70.36; H, 4.58; N, 3.62; S, 8.54.

3-Phenylpropanoyl chloride (37). To a stirred solution of 3-phenylpropanoic acid (3.0 g, 20 mmol, 1 eq.) in anhydrous CH_2Cl_2 (165 mL) under nitrogen was added oxalyl chloride (16.5 mL 190 mmol, 10 eq.) rapidly via syringe. The reaction mixture was stirred for 24 h, after which the solvent and unreacted oxalyl chloride were Removed by distillation under reduced pressure. The resulting yellow liquid was concentrated via azeotrope with benzene (3 x 50 mL) *in vacuo* and dried under a vacuum to yield **37** (3.4 g, ~100%) as a yellow liquid, which was used directly in the next step.

3-Phenyl-1-(1-(phenylsulfonyl)-1*H*-indol-3-yl)propan-1-one (38). To a dark, stirred solution of CuCl (50 mg, 0.5 mmol, 1 eq.), LiCl (42 mg, 1 mmol, 2 eq.), and 3-bromo-1-(phenylsulfonyl)indole (**36**)[24] (162 mg, 0.5 mmol, 1 eq.) in THF (4 mL) at –100 °C (Et_2O and dry ice) after 15 min was added *n*-BuLi (0.19 mL, 0.5 mmol, 1 eq.) slowly via syringe. The reaction mixture was stirred 15 min, after which 3-phenylpropanoyl chloride (**37**) (80 uL, 0.53 mmol, 1.1 eq.) was added rapidly via syringe. The reaction mixture was stirred for an additional 15 min at –100 °C, after which it was warmed rapidly to rt and quenched in aqueous $NaHCO_3$ (5 mL). The green aqueous layer was extracted with Et_2O (3 x 15 mL), after which the peach-colored organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to yield a pink oil (210 mg). The crude product was further purified by preparative TLC (3:1 hexane:EtOAc) to yield the desired product (**38**) as a yellow oil (88 mg, 47%). ^1H NMR (acetone-d_6): δ 8.56 (s, 1H), 8.20 (d, 1H), 8.02 (d, 2H), 7.92 (d, 1H), 7.60 (t, 2H), 7.53 (t, 2H), 7.35–7.05 (m, 6H), 3.28 (t, 2H), 2.94 (t, 2H). MS (EI): 389.2 (M+), 284.1, 262.2, 248.1, 220.1, 206.1, 191.2, 173.1, 144.1, 115.1, 84.0 (100%).

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