A Versatile Synthesis of Unsymmetrical 3,3'-Bioxindoles: Stereoselective Mukaiyama Aldol Reactions of 2-Siloxyindoles with Isatins

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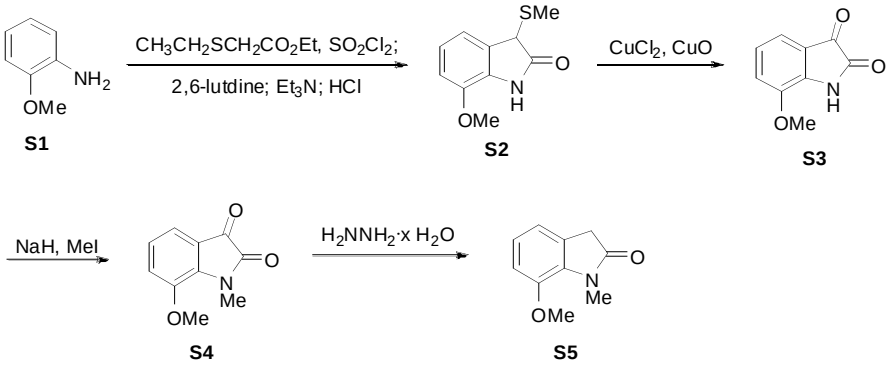
Supporting Information – Table of Contents

Materials and Methods. Unless stated otherwise, all reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. Elevated reaction temperatures were regulated using a temperature modulator, while prolonged low temperature reactions were carried out using a cryobath. Unless otherwise noted, reactions were performed at room temperature (rt, approximately 23 ^{o}C). Thin layer chromatography (TLC) was conducted with pre-coated silica gel plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, iodine on silica, and potassium permanganate staining. Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H NMR spectra were recorded on spectrometers (at 400 and 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on spectrometers (at 100 and 125 MHz) and are reported in terms of chemical shift. Hydrogen multiplicity assignments were made using DEPT and HMQC two-deminsional NMR. HRMS data were recorded via positive ion electrospray mass spectrometry using a time of flight analyzer. IR spectra were recorded on a REACT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Concentrations were carried out at reduced pressure using a rotary evaporator.

Oxindoles **S5**,[1] **S7**,[2] and **S9**[3] were prepared by Wolf–Kishner reduction of the corresponding isatins. Isatins **S7**[4] and **S8**[5] were made by standard protection of isatin (**S6**). Isatin **S12** was synthesized by protection of commercially available 7-fluoroisatin (**S11**). Vinyl- and aryl-substituted isatins **10**, **S15**, and **S18** were most conveniently prepared via Suzuki–Miyaura coupling of the *N*-protected haloisatins and the corresponding organotrifluoroborate.[6,7]

Experimental Procedures.



7-Methoxy-3-(methylthio)oxindole (S2). The general procedure of Gassman was followed.[8] To a solution of ethyl(methylthio)acetate (28.5 mL, 222 mmol, 1.0 equiv) and dichloromethane (205 mL) at –78 °C was added a solution of freshly distilled sulfuryl chloride (17.8 mL, 222 mmol, 1.0 equiv) and dichloromethane (225 mL) via a wide-bored cannula over 10 min. After stirring for 1 h at –78 °C, a solution of *o*-anisidine (**S1**) (26.0 mL, 222 mmol, distilled over $CaSO_4$, 1.0 equiv), 2,6-lutidine (26.0 mL, 222 mmol, 1.0 equiv), and dichloromethane (370 mL) was added dropwise over 45 min via a cannula resulting in a bright orange reaction mixture. The reaction was maintained at –78 °C for 1 h. After this time, triethylamine (30.9 mL, 222 mmol, 1.0 equiv) was added and the reaction mixture was allowed

(1) Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1981**, *29*, 128.
(2) Wang, J.-J.; Hu, W.-P. *J. Org. Chem.* **1999**, *64*, 5725–5727.
(3) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505–11515.
(4) Trost, B. M.; Frederiksen, M. U. *Angew. Chem. Int. Ed.* **2005**, *44*, 308–310.
(5) Overman, L. E.; Peterson, E. A. *Tetrahedron* **2003**, *59*, 6905–6919.
(6) (a) Negishi, E. A. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002. (b) Miyaura, N. *Cross-Coupling Reactions: A Practical Guide*; Springer: New York, 2002. (c) Suzuki, A.; Brown, H. C. *Organic Synthesis via Boranes*; Aldrich Chemical Co.: Milwaukee, WI, 2002; Vol. 3. (d) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286.
(7) The previously reported Suzuki cross-coupling conditions between boronic acids and isatins provided significantly lower yields of the desired product: Gérard, A. L.; Lisowski, V.; Rault, S. *Tetrahedron* **2005**, *61*, 6082–6087.
(8) Gassman, P. G.; Van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5508–5512.

to warm to rt. After 3 h, the reaction mixture was concentrated, the resultant solid was dissolved in a mixture of diethyl ether (450 mL) and 1 N HCl (450 mL), and this mixture was stirred vigorously for 16 h to afford an off-white precipitate. The solid was then collected by vacuum filtration and further washed with hexanes and air-dried. The solid was further dried under reduced pressure to afford oxindole **S2** (35.6 g, 77%) as an off-white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.03 (t, *J* = 7.7, 1H), 6.98 (d, *J* = 7.5, 1H), 6.82 (d, *J* = 8.1, 1H), 4.27 (s, 1H), 3.86 (s, 3H), 1.99 (s, 3H)); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{10}H_{11}NO_2SNa$, 232.0408, found, 232.0411.

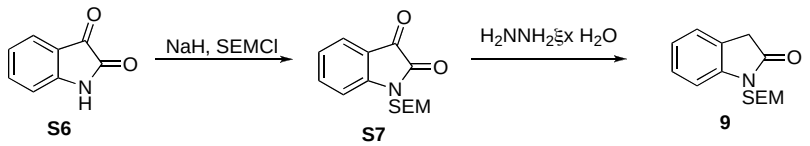
7-Methoxyindoline-2,3-dione (S3). The general procedure of Caubere was followed.[9] To a suspension of 7-methoxy-3-(methylthio)oxindole (**S2**) (10.6 g, 50.7 mmol, 1.0 equiv) and acetone:water (1:1, 150:150 mL) was added sequentially copper (II) chloride dihydrate (17.3 g, 101 mmol, 2.0 equiv) and copper (II) oxide (16.1 g, 203 mmol, 4.0 equiv). The resulting dark brown suspension was stirred at rt for 30 min. Celite (21 g) and dichloromethane (500 mL) were added, and the resulting mixture was stirred vigorously for 20 min. The slurry was then filtered under vacuum and the filter cake was washed with additional dichloromethane (500 mL). The aqueous layer was separated and extracted with dichloromethane (2×120 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield isatin **S3** (7.60 g, 84%) as a dark red solid showing ^{1}H NMR and melting point data consistent to previously reported values [10]: mp 235–236 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$). δ 7.25 (dd, *J* = 7.5, 1.0, 1H), 7.15 (dd, *J* = 8.2, 1.0, 1H), 7.09 (dd, *J* = 8.2, 7.5, 1H), 3.95 (s, 3H); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_9H_7NO_3Na$, 200.0324, found, 200.0327.

***N*-Methyl-7-methoxyindoline-2,3-dione (S4).** To a solution of 7-methoxyindoline-2,3-dione (**S3**) (16.7 g, 94.3 mmol, 1.0 equiv) and *N*,*N*-dimethylformamide (205 mL) was added sodium hydride (4.41 g, 104 mmol, 60% dispersion in mineral oil, 1.1 equiv) at rt. After 10 min, iodomethane (6.45 mL, 104 mmol, 1.1 equiv) was added, and the reaction mixture was maintained at rt for 4 h. The reaction mixture was then poured into ice water (800 mL) and the resulting dark red precipitate was collected by vacuum filtration. The solid was washed with water (2×300 mL), redissolved in dichloromethane (700 mL), dried over $MgSO_4$, and concentrated to provide isatin **S4** (16.1 g, 90%) as a dark red solid: ^{1}H NMR (500 MHz, $CDCl_3$)

(9) Carre, M. C.; Caubere, P. *Tetrahedron Letters* **1985**, *26*, 3103–3106.
(10) (a) Deady, L. W.; Desneves, J.; Kaye, A. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *Bioorg. Med. Chem.* **2001**, *9*, 445–452. (b) Stearns, B. A. Ph. D. Dissertation, University of California, Irvine, 2000.

δ 7.22 (dd, *J* = 7.4, 1.1, 1H), 7.16 (dd, *J* = 8.3, 1.0, 1H), 7.04 (dd, *J* = 8.3, 7.4, 1H), 3.90 (s, 3H), 3.50 (s, 3H), .95 (s, 3H); HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{10}H_9NO_3Na$, 214.0480, found, 21.0482.

***N*-Methyl-7-methoxyindolin-2-one (S5).** A suspension of isatin **S4** (16.1 g, 83.9 mmol, 1.0 equiv) and hydrazine·hydrate (160 mL, 2.52 mol, 51% solution, 30.0 equiv) was heated to 130 °C for 3 h. After this time, the reaction mixture was allowed to cool to rt and then was partitioned between brine (160 mL) and ethyl acetate (200 mL). The aqueous layer was separated and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with 1 M aqueous $NaHSO_4$ (2×300 mL), dried over $MgSO_4$ and concentrated to afford oxindole **S5** (14.8 g, 99%) as a beige solid showing ^{1}H NMR and melting point data consistent with previously reported values:[11] mp 95–97 ^{o}C; R_f 0.50 (1:1 EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 8.0, 8.0 1H), 6.84 (m, 2H), 3.84 (s, 3H), 3.48 (s, 2H), 3.47 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) d 175.4, 145.4, 133.2, 126.1, 122.9 (CH), 117.3 (CH), 111.9 (CH), 56.1 (CH_3), 36.2 (CH_2), 29.6 (CH_3); IR (film) 2948, 1706, 1615 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{10}H_{11}NO_2Na$, 200.0687, found, 200.0690.

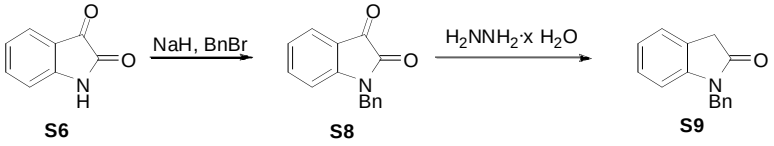


***N*-((2-(Trimethylsilyl)ethoxy)methyl)indoline-2,3-dione (S7).** To a rapidly stirring suspension of isatin (**S6**) (22.0 g, 150 mmol, 1.0 equiv) and *N*,*N*-dimethylformamide (237 mL) was added sodium hydride (7.18 g, 179.4 mmol, 60% dispersion in mineral oil, 1.2 equiv) at rt. The suspension was stirred for 20 min, cooled to 0 °C, and 2-(trimethylsilyl)ethoxymethyl chloride (32.3 mL, 178 mmol, 1.19 equiv) was added dropwise. The solution was then allowed to warm to rt. After 2 h, the reaction mixture was quenched by pouring into brine (200 mL) and the resulting mixture was cooled to 0 °C. The aqueous layer was separated and extracted with EtOAc (4×200 mL). The combined organic layers were washed with saturated aqueous lithium chloride (400 mL), then dried over $MgSO_4$ and concentrated to yield a brown solid. This solid was further purified by silica gel flash column chromatography (gradient: 1:8 Et_2O-hexanes to 1:2 Et_2O-

(11) Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1981**, *29*, 128–136.

hexanes) to afford isatin **S7**[12] (30.4 g , 74%) as an orange solid: mp 61–62 °C; R_f 0.57 (1:1 EtOAc-hexanes); ^{1}H NMR (500 MHz. $CDCl_3$) δ 7.65 (t, *J* = 7.6, 1H), 7.63 (td, *J* = 7.6, 1.4, 1H), 7.18 (td, *J* = 7.6, 0.8, 1H), 7.14 (t, *J* = 8.1, 1H), 5.17 (s, 2H), 3.60 (d, *J* = 8.3, 2H), 0.94 (d, *J* = 8.3, 2H), –0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) d 183.1 (C), 158.3 (C), 150.4 (C), 138.7 (CH), 125.4 (CH), 124.3 (CH), 117.5 (C), 111.7 (CH), 69.8 (CH_2), 66.8 (CH_2), 17.9 (CH_2), –1.4 (CH_3); IR (film) 2954, 1742, 1611 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{14}H_{19}NO_3SiNa$, 300.1032, found, 300.1038.

***N*-((2-(Trimethylsilyl)ethoxy)methyl)indolin-2-one (9).** A suspension of isatin **S7** (5.78 g, 20.8 mmol, 1.0 equiv) and hydrazine·hydrate (40.0 mL, 625 mol, 51% solution, 30.0 equiv) was heated to 130 °C for 3 h. After this time, the reaction mixture was allowed to cool to rt and partitioned between brine (30 mL) and EtOAc (40 mL). The aqueous layer was separated and extracted with EtOAc (4×40 mL). The combined organic layers were washed with 1 M aqueous $NaHSO_4$ (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield a yellow oil. This oil was further purified by silica gel flash column chromatography (gradient: 1:5 Et_2O-hexanes to 1:4 Et_2O-hexanes) to afford oxindole **9**, (4.95 g , 90%) as a yellow oil showing NMR data consistent to previously reported values:[13] R_f 0.44 (1:4 EtOAc-hexanes); ^{1}H NMR (500 MHz. $CDCl_3$) δ 7.31–7.24 (m, 2H), 7.05 (d, *J* = 7.6, 1H), 7.02, (d, *J* = 8.1, 1H), 5.13 (s, 2H), 3.58–3.55 (m, 4H), 0.94 (d, *J* = 8.3, 2H), –0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) d 175.5 (C), 143.7 (C), 128.0 (CH), 124.4 (CH), 124.0 (C), 122.8 (CH), 109.7 (CH), 69.5 (CH_2), 66.2 (CH_2), 36.0 CH_2), 17.9 (CH_2), –1.4 (CH_3); IR (film) 2954, 1725, 1615, cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{14}H_{21}NO_2SiNa$, 286.1239, found, 286.1238.



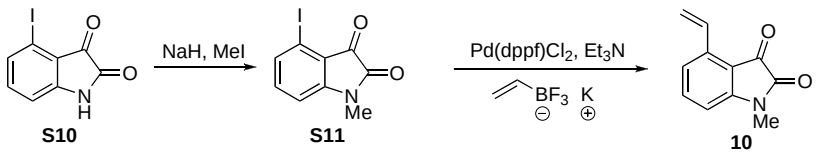
S6 **S8** **S9**

***N*-Benzylindoline-2,3-dione (S8).** Isatin (**S6**) (10.0 g, 68.0 mmol, 1.0 equiv) was dissolved in *N*,*N*-dimethylformamide (125 mL), and the resultant solution was cooled to 0 °C. Sodium hydride (2.85 g, 71.4 mmol, 60% dispersion in mineral oil, 1.05 equiv) was added in

(12) Trost, B. M.; Frederiksen, M. U. *Angew. Chem. Int. Ed.* **2005**, *44*, 308–310.
(13) Wang, J.-J.; Hu, W.-P. *J. Org. Chem.* **1999**, *64*, 5725–5727.

three portions resulting in a purple suspension. The mixture was maintained at 0 °C for 15 min. Benzyl bromide (9.43 mL, 78.8 mmol, 1.16 equiv) was added dropwise, and the brown solution was maintained at 0 °C for 15 min. Ice-cooled water (600 mL) was added to the mixture, and a precipitate formed. The precipitate was filtered, washed with water (60 mL) and hexanes (30 mL). This solid was recrystallized from hot ethanol (240 mL), filtered and dried under reduced pressure to afford isatin **S8** (15.1 g, 94%) as red-needlelike crystals. Melting point and ^{1}H NMR data were consistent with previously reported values:[14] mp 131–132 °C; R_f 0.61 (2:3 EtOAc-hexanes) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.4, 1H), 7.45 (t, *J* = 7.8, 1H), 7.33–7.24 (m, 5H), 7.04 (t, *J* = 7.5, 1H), 6.77 (d, *J* = 8.0, 1H), 4.89 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.3 (C), 158.3 (C), 150.7 (C), 138.5 (CH), 134.6 (C), 129.1 (CH), 128.2 (C), 127.5 (CH), 125.3 (CH), 123.9 (CH), 117.7 (C), 111.1 (CH), 44.0 (CH_2); IR (film): 1729, 1609, cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{15}H_{11}NO_2Na$, 260.0688, found, 260.0692.

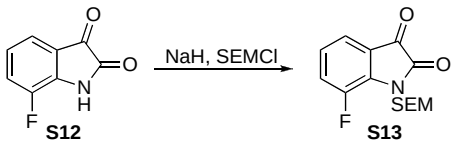
***N*-Benzylindolin-2-one (S9).** A suspension of isatin **S8** (1.51 g, 6.36 mmol, 1.0 equiv) and hydrazine·hydrate (12.0 mL, 191 mol, 51% solution, 30.0 equiv) was heated to 130 °C for 3 h. After this time, the reaction mixture was allowed to cool to rt and was partitioned between brine (20 mL) and EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (3×20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL), then dried over Na_2SO_4 and concentrated to yield a yellow oil. This oil was further purified by silica gel flash column chromatography (1:4 EtOAc-hexanes) to afford oxindole **S9**, (1.31 g , 92%) as a yellow oil. ^{1}H NMR data was consistent with previously reported values:[14b] R_f 0.61 (2:3 EtOAc-hexanes); ^{1}H NMR (500 MHz. $CDCl_3$) δ 7.33–7.26 (m, 4H), 7.22 (m, 2H), 7.14 (t, *J* = 7.7, 1H), 6.97 (t, *J* = 7.5, 1H), 6.71 (d, *J* = 7.8, 1H), 4.88 (s, 2H), 3.55 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) d 174.9 (C), 144.2 (C), 135.9 (C), 128.6 (CH), 127.7 (CH), 127.5 (CH), 127.3 (CH), 124.4 (C), 124.3 (CH), 122.2 (CH), 108.9 (CH), 43.5 (CH_2), 35.6 (CH_2); IR (film) 1702, 1613 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{15}H_{13}NONa$, 246.0895, found, 246.0896.



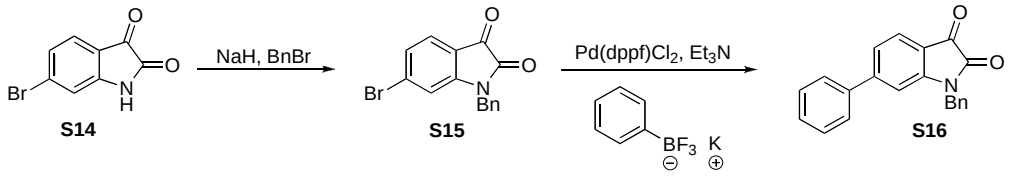
(14) (a) Overman, L. E.; Peterson, E. A. *Tetrahedron* **2003**, *59*, 6905–6919. (b) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505–11515.

4-Iodo-*N*-Methyl-1*H*-indole-2,3-dione (3) To a solution of 4-iodoisatin (**S10**) (11.7 g, 42.8 mmol, 1.0 equiv) and *N*,*N*-dimethylformamide (70 mL) at rt was added sodium hydride (2.57 g, 64.2 mmol, 60% dispersion in mineral oil, 1.5 equiv) resulting in an exotherm and a dark purple solution. After 5 min, methyl iodide (3.20 mL, 51.4 mmol, filtered through basic alumina, 1.2 equiv) was added rapidly using a syringe. The resulting dark brown solution was maintained at rt for 20 min and then poured into brine at 0 °C. The resulting mixture was allowed to stand at 0 °C for 2 h forming a dark brown precipitate. This precipitate was collected by vacuum filtration, and was washed with H_2O (300 mL) and hexanes (200 mL) to provide 12.3 g (100%) of isatin **S11**. ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.55 (d, *J* = 7.9, 1H), 7.36 (t, *J* = 7.9, 1H), 7.16 (d, *J* = 7.8, 1H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 182.0, 158.0, 153.4, 133.7, 118.0, 110.2, 92.8, 25.8; IR (film) 1731, 1592 cm^{-1}; HRMS-ESI calcd for $C_9H_6INO_2$ (M^+) 286.9443, found 286.9447.

***N*-Methyl-4-vinyl-1*H*-indole-2,3-dione (10).** The general procedure of Molander was followed.[6d] Prior to carrying out this reaction all liquids (isopropanol, water and triethylamine) were degassed by bubbling argon thought stock solutions for 30 min. To a suspension of aryl iodide **S11** (1.86 g, 6.48 mmol, 1.0 equiv), potassium vinyltrifluoroborate (955 mg g, 7.12 mmol, 1.1 equiv), [1,1'-bis(diphenylphosphino)ferrocene]palladium (II)] dichloromethane complex (95 mg, 0.13 mmol, 0.02 equiv), and *i*-PrOH:H_2O (2:1, 43.5:21.25 mL) was added triethylamine (2.71, 19.4 mmol, 3.0 equiv). The resulting suspension was heated to reflux (oil bath at 98 °C) for 2 h. After this time, the reaction mixture was diluted with water (60 mL) and EtOAc (60 mL). The aqueous layer was separated and extracted with EtOAc (4×75 mL). The combined organic layers were washed with 1 M aqueous $NaHSO_4$ (250 mL) then dried over $MgSO_4$ and concentrated to yield a red solid. This solid was further purified by silica gel flash column chromatography (100% CH_2Cl_2)) to afford isatin **10** (913 mg , 75%) as a red solid: mp 129–132 ^{o}C; R_f 0.61 (1:5 (Et_2O-CH_2Cl_2); ^{1}H NMR (500 MHz. $CDCl_3$) d 7.59 (dd, *J* = 17.6, 11.0, 1H), 7.50 (t, *J* = 8.0, 1H), 7.37 (d, *J* = 8.0, 1H), 6.75 (d, *J* = 8.0, 1H), 6.03 (t, *J* = 7.7, 1H), 5.58 (d, *J* = 17.6 Hz, 1H), 3.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) d 183.6 (C), 158.0 (C), 151.3 (C), 138.6 (C), 137.6 (CH), 131.0 (CH), 120.7 (CH_2), 119.9 (CH), 113.6 (C), 108.5 (CH), 26.3 (CH_3); IR (film) 1733, 1578 cm^{-1}; HRMS (ES) (*m/z*) [M + Na]$^+$ calcd for $C_{11}H_9NO_2Na$, 219.0531, found, 210.0527.



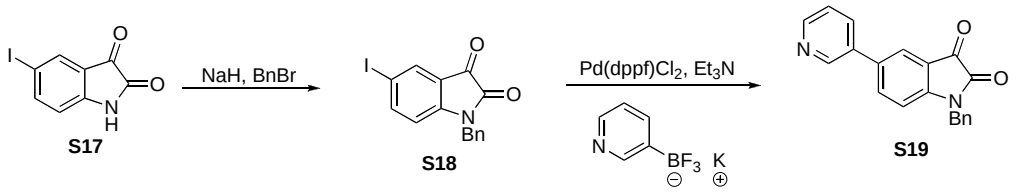
7-Fluoro-*N*-((2-(trimethylsilyl)ethoxy)methyl)indoline-2,3-dione (S13). 7-Fluoroisatin (**S12**) (1.50 g, 9.08 mmol, 1.0 equiv) was dissolved in *N*,*N*-dimethylformamide (30 mL), and the resultant red solution was cooled to 0 °C. Sodium hydride (436 mg, 10.9 mmol, 60% dispersion in mineral oil, 1.2 equiv) was added in two portions resulting in a purple suspension. The mixture was allowed to warm to rt for 20 min with vigorous stirring, then cooled to 0 °C. 2-(Trimethylsilyl)ethoxymethyl chloride (1.91 mL, 10.8 mmol, 1.2 equiv) was added dropwise, and the dark brown solution was maintained at 0 °C for 1.5 h, then poured into brine (10 mL) at 0 °C. The resulting mixture was extracted with Et_2O (4×20 mL), and the combined organic extracts were dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel flash column chromatography (1:4 EtOAc-hexanes) gave isatin **S13** (2.44 g, 91%) as an orange solid: mp 55–56 °C; R_f 0.51 (1:3 EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.5, 1H), 7.34 (dd *J* = 11.1, 8.4, 1H), 7.09 (td, *J* = 11.6, 3.9, 1H), 5.19 (s, 2H), 3.56 (t, *J* = 7.7, 2H), 0.87 (t, *J* = 7.7, 2H), –0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.8 (d, *J* = 1.9, C), 158.1 (C), 148.5 (d, *J* = 249.2, C), 136.5 (d, *J* = 9.6, C), 126.6 (d, *J* = 19.6, CH), 125.2 (d, *J* = 5.8, CH), 121.4 (d, *J* = 3.4, CH), 120.6, (d, *J* = 2.5, C), 71.2, (d, *J* = 4.9, CH_2), 66.9 (CH_2), 17.8 (CH_2), –1.5 (CH_3); IR (film): 1746, 1627 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{14}H_{18}FNO_3SiNa$, 318.0938, found, 318.0935.



***N*-Benzyl-6-bromoindoline-2,3-dione (S15).** 6-Bromoisatin (**S14**) (984 mg, 4.35 mmol, 1.0 equiv) was dissolved in *N*,*N*-dimethylformamide (8.70 mL), and the orange solution was cooled to 0 °C. Sodium hydride (183 mg, 4.57 mmol, 60% dispersion in mineral oil, 1.05 equiv) was added in two portions, and the resulting purple suspension was maintained at 0 °C for 15

min. Benzyl bromide (604 μL, 5.05 mmol, 1.16 mmol) was added dropwise, and the resultant orange solution was maintained at 0 °C for 30 min. Water (30 mL) was added, and the biphasic mixture was extracted with EtOAc (4×50 mL). The combined organics were dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel flash column chromatography (gradient 1:3 EtOAc-hexanes to 100% EtOAc) gave isatin **S15** (1.31 g, 95%) as an orange solid: mp 190–192 °C; R_f 0.69 (3:7 EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.9 Hz, 1H), 7.41–7.36 (m, 2H), 7.36–7.31 (m, 3H), 7.28–7.24 (m, 1H), 6.96 (d, *J* = 1.4, 1H), 4.91 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.1 (C), 158.3 (C), 151.6 (C), 134.2 (C), 133.7 (C), 129.4 (CH), 128.6 (CH), 127.6 (CH), 127.3 (CH), 126.5 (CH), 116.5 (C), 114.7 (CH), 44.4 (CH_2); IR (film): 1733, 1603 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{15}H_{10}NO_2BrNa$, 337.9792, found, 337.9786.

***N*-Benzyl-6-phenylindoline-2,3-dione (S16).** Prior to use, all liquids (isopropanol, water, and triethylamine) were degassed by bubbling argon through stock solutions for 30 min. Isatin **S15** (626 mg, 1.98 mmol, 1.0 equiv) was suspended in a mixture of isopropanol (13.2 mL) and water (6.6 mL). Potassium phenyltrifluoroborate (401 mg, 2.18 mmol, 1.1 equiv) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane complex (29 mg, 39.6 μmol, 0.02 equiv) were added, followed by triethylamine (828 μL, 5.94 mmol, 3.0 equiv). The orange suspension was heated to reflux (oil bath at 98 °C) for 2 h, resulting in a red solution, which ultimately became a brown solution. After allowing to cool to rt, water (10 mL) was added, and the mixture was extracted with EtOAc (4×40 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel flash column chromatography (3:17 EtOAc-hexanes) gave isatin **S16** (615 mg, 99%) as an orange solid: mp 135–137 °C; R_f 0.57 (3:7 EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.8, 1H), 7.51–7.42 (m, 5H), 7.41–7.36 (m, 4H), 7.35–7.27 (m, 2H), 6.98 (s, 1H), 4.99 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.7 (C), 159.0 (C), 151.7 (C), 151.5 (C), 139.6 (C), 134.8 (C), 129.5 (CH), 129.30 (CH), 129.26 (CH), 128.4 (CH), 127.6 (CH), 127.4 (CH), 126.0 (CH), 122.9 (CH), 116.6 (C), 109.7 (CH), 44.2 (CH_2); IR (film): 1733, 1613 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{15}NO_2Na$, 336.1000, found, 336.1005.

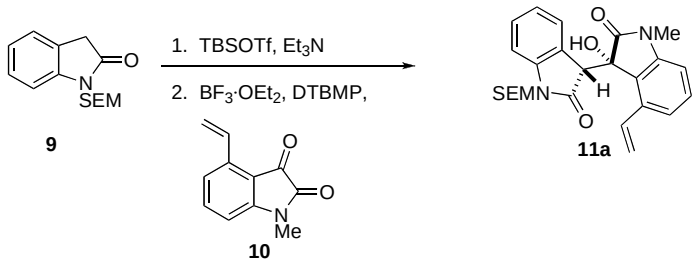


***N*-Benzyl-5-iodoindoline-2,3-dione (S18).** 5-Iodoisatin (**S17**) (871 mg, 3.19 mmol, 1.0 equiv) was dissolved in *N*,*N*-dimethylformamide (6.40 mL), and the red solution was cooled to 0 °C. Sodium hydride (134 mg, 3.35 mmol, 60% dispersion in mineral oil, 1.05 equiv) was added in two portions, and the resulting purple suspension was maintained at 0 °C for 15 min. Benzyl bromide (443 μL, 3.70 mmol, 1.16 mmol) was added dropwise, and the resultant red solution was maintained at 0 °C for 30 min. Water (20 mL) was added, and the biphasic mixture was extracted with EtOAc (4×50 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. Purification via silica gel flash column chromatography (3:7 EtOAc-hexanes) gave isatin **S18** (1.29 g, 88%) as a red solid with melting point and ^{1}H NMR data consistent with previously reported:[15] mp 150–152 °C; R_f 0.32 (1:3 EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 1.6, 1H), 7.76 (dd, *J* = 8.3, 1.7, 1H), 7.37–7.28 (m, 5H), 6.59 (d, *J* = 8.3, 1H), 4.92 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.0 (C), 157.4 (C), 150.1 (C), 146.5 (CH), 134.2 (C), 133.9 (CH), 129.3 (CH), 128.5 (CH), 127.5 (CH), 119.3 (C), 113.3 (CH), 86.4 (C), 44.2 (CH_2); IR (film): 1733, 1603 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{15}H_{10}INO_2Na$, 385.9654, found, 385.9659.

***N*-Benzyl-5-(pyridin-3-yl)indoline-2,3-dione (S19).** Prior to use, all liquids (isopropanol, water, and triethylamine) were degassed by bubbling argon through stock solutions for 30 min. Isatin **S18** (910 mg, 2.51 mmol, 1.0 equiv) was suspended in isopropanol (16 mL) and water (8 mL). Potassium 3-pyridyltrifluoroborate (510 mg, 2.76 mmol, 1.1 equiv) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane complex (47 mg, 50.1 μmol, 0.02 equiv) were added, followed by triethylamine (1.05 mL, 7.52 mmol, 3.0 equiv). The red suspension was heated to reflux (oil bath at 98 °C) for 2 h, resulting in a brown solution. After allowing this solution to cool to rt, water (20 mL) was added, and the mixture was extracted with EtOAc (4×50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel flash column chromatography (gradient 1:1

(15) Zhou, L.; Liu, Y.; Zhang, W.; Wei, P.; Huang, C.; Pei, J.; Yuan, Y.; Lai, L. *J. Med. Chem.* **2006**, 49, 3440–3443.

EtOAc-hexanes to 100% EtOAc) gave isatin **S19** (570 mg, 72%) as an orange-red solid: mp 168–169 °C; R_f 0.43 (100% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.62 (d, *J* = 4.1, 1H), 7.84 (s, 1H), 7.79 (d, *J* = 7.9, 1H), 7.71 (d, *J* = 8.2, 1H), 7.40–7.33 (m, 6H), 6.91 (d, *J* = 8.2, 1H), 4.99 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.2 (C), 158.4 (C), 150.6 (C), 149.3 (CH), 147.9 (CH), 136.9 (CH), 134.8 (C), 134.5 (C), 134.2 (C), 134.0 (CH), 129.4 (CH), 128.5 (CH), 127.7 (CH), 124.1 (CH), 123.9 (CH), 118.5 (C), 111.9 (CH), 44.5 (CH_2); IR (film): 1737, 1619 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{20}H_{15}N_2O_2$, 315.1133, found, 315.1129.



Generation of 2-Siloxyindoles and Their Mukaiyama Aldol Reactions with Isatins. 3-Hydroxy-*N*-methyl-*N*'-((2-(trimethylsilyl)ethoxy)methyl)-4-vinyl-3,3'-biindoline-2,2'-dione (11a). Following the general procedure described for the synthesis of **11b**, oxindole **9** (150 mg, 0.569 mmol, 1.0 equiv) and isatin **10** (215 mg, 0.569 mmol, 1.01 equiv) were converted to tertiary alcohol **11a** (197 mg, 77%), which was purified by silica gel flash column chromatography (1:4 EtOAc-hexanes) and isolated as a yellow oil: R_f 0.30 (1:3 EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 17.6, 11.0, 1H), 7.42 (t, *J* = 7.9, 1H), 7.37 (d, *J* = 7.9, 1H), 7.19 (t, *J* = 7.7, 1H), 7.05 (d, *J* = 7.9, 1H), 6.72 (t, *J* = 7.5, 1H), 6.68 (d, *J* = 9.4, 1H), 6.14 (s, 1H), 5.92 (d, *J* = 17.8, 1H), 5.79 (d, *J* = 7.5, 1H), 5.48 (d, *J* = 11.1, 1H), 5.26 (d, *J* = 11.1, 1H), 5.22 (d, *J* = 11.1, 1H), 4.24 (s, 1H), 3.80 (dd, *J* = 16.7, 8.4, 1H), 3.66 (dd, *J* = 17.4, 9.2, 1H), 2.82 (s, 3H), 0.96 (t, *J* = 8.1, 2H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.9 (C), 174.4 (C), 144.7 (C), 143.5 (C), 136.7 (C), 132.2 (CH), 130.9 (CH), 129.2 (CH), 123.9 (CH), 123.7 (C), 122.9 (CH), 122.4 (C), 120.4 (CH), 118.4 (CH_2), 110.4 (CH), 107.7 (CH), 78.2 (C), 70.0 (CH_2), 66.6 (CH_2), 48.8 (CH), 26.0 (CH_3), 18.1 (CH_2), –1.2 (CH_3); IR (film): 3400, 2952, 1727, 1698, 1613, 1588 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{25}H_{30}N_2O_4SiNa$, 473.1873, found, 473.1876.

***N*-Benzyl-3-hydroxy-7'-methoxy-*N*'-methyl-3,3'-biindoline-2,2'-dione (11c).** Following the general procedure described for the preparation of **11b**, oxindole **S5** (50 mg, 0.28 mmol, 1.04 equiv) and *N*-benzylindoline-2,3-dione (**S8**) (64 mg, 0.27 mmol, 1.0 equiv) were converted to tertiary alcohol **11c** (93 mg, 80%), , which was purified by silica gel flash column chromatography (gradient: 1:9 EtOAc-hexanes to 1:2 EtOAc-hexanes) and isolated as a yellow solid. Recrystallization from EtOAc-hexanes gave single crystals that were suitable for X-ray analysis: mp 161–163 °C; R_f 0.15 (1:2 EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.3, 1H), 7.27–7.25 (m, 1H), 7.16 (d, *J* = 7.6, 1H) 7.13 (d, *J* = 7.3, 1H), 7.09 (t, *J* = 7.6, 2H), 6.83 (d, *J* = 8.4, 1H), 6.64–6.60 (m, 3H), 6.54 (d, *J* = 7.8, 1H), 6.48 (s, 1H), 5.52 (d, *J* = 7.4, 1H), 4.93 (d, *J* = 15.9, 1H), 4.29 (d, *J* = 16.0, 1H), 3.93 (s, 1H), 3.81 (s, 3H), 3.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) d 176.4 (C), 175.2 (C), 145.9 (C), 143.8 (C), 135.2 (C), 133.3 (C), 130.8 (CH), 128.8 (CH), 128.1 (C), 127.5 (CH), 126.9 (CH), 124.7 (CH), 124.2 (C), 123.7 (CH), 123.4 (CH), 117.2 (CH), 113.0 (CH), 109.8 (CH), 77.4 (C), 56.2 (CH_3), 49.6 (CH), 43.9 (CH_2), 30.0 (CH_3); IR (film) 3369, 2950, 1719, 1684, 1615 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{25}H_{22}N_2O_4Na$, 437.1477, found, 437.1482.

***N*-Benzyl-3-hydroxy-*N*'-((2-(trimethylsilyl)ethoxy)methyl)-3,3'-biindoline-2,2'-dione (11d).** Following the general procedure described for the preparation of **11b**, oxindole **9** (147 mg, 0.558 mmol, 1.0 equiv) and *N*-benzylindoline-2,3-dione (**S8**) (134 mg, 0.564 mmol, 1.01 equiv) were converted to tertiary alcohol **11d** (211 mg, 76%), which was purified by silica gel flash column chromatography (1:4 EtOAc-hexanes) and isolated as a yellow oil: R_f 0.33 (1:3 EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, *J* = 2.2, 1H), 7.30–7.27 (m, 2H), 7.20–7.08 (m, 5H), 6.73 (t, *J* = 7.6, 1H), 6.66, (d, *J* = 7.4, 2H), 6.61 (d, *J* = 7.8, 1H), 6.0 (br s, 1H), 5.98 (br d, *J* = 6.9, 1H), 5.27 (d, *J* = 11.1, 1H), 5.23 (d, *J* = 11.1, 1H), 4.95 (d, *J* = 5.8, 1H), 4.31 (d, *J* = 5.8, 1H), 4.09 (s, 1H), 3.78 (dd, *J* = 17.1, 8.7, 1H), 3.66 (dd, *J* = 16.5, 8.2, 1H), 0.93 (t, *J* = 8.2, 2H), –0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.4 (C), 175.1 (C), 143.8 (C), 143.7 (C), 135.1 (C), 130.9 (CH), 129.4 (CH), 128.8 (CH), 127.9 (CH), 127.5 (CH), 126.9 (CH), 124.7 (CH), 123.6 (CH), 123.2 (CH), 122.4 (C), 110.6 (CH), 109.8 (CH), 77.3 (C), 70.0 (CH_2), 66.5 (CH_2), 50.2 (CH), 43.9 (CH_2), 18.1 (CH_2), –1.2 (CH_3); IR (film): 3400, 2952, 1725, 1615 cm^{-1}; HRMS-ESI (*m/z*) [M + Na]$^+$ calcd for $C_{29}H_{32}N_2O_4SiNa$, 523.2029, found, 523.2040.

***N*'-Benzyl-7-fluoro-3-hydroxy-*N*-((2-(trimethylsilyl)ethoxy)methyl)-3,3'-biindoline-2,2'-dione (11e).** Following the general procedure described for the preparation of **11b**, oxindole **S9** (173 mg, 0.775 mmol, 1.0 equiv) and isatin **S13** (231 mg, 0.783 mmol, 1.01 equiv) were converted to tertiary alcohol **11e** (333 mg, 83%), whcih was purified by silica gel flash column chromatography (gradient: 1:4 EtOAc-hexanes to 3:7 EtOAc-hexanes) and isolated as a purple foam that contained a small amount of an inseparable impurity that we speculate is the minor diastereomer: R_f 0.21 (1:3 EtOAc-hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.22 (m, 5H), 7.21–7.09 (m, 4H), 6.83 (t, *J* = 7.6, 1H), 6.66 (d, *J* = 7.9, 1H), 6.34 (br s, 1H), 6.01 (br m, 1H), 5.05 (s, 2H), 5.04 (d, *J* = 15.7, 1H), 4.84 (d, *J* = 15.7, 1H), 4.12 (s, 1H), 3.19 (dd, *J* = 16.3, 8.5, 1H), 3.11 (dd, *J* = 16.3, 8.5, 1H), 0.73 (t, *J* = 8.4, 2H), –0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.7 (C), 175.2 (C), 148.2 (d, *J* = 246.1, C), 144.2 (C), 135.3, (C), 130.44 (d, *J* = 2.9, C), 129.8 (d, *J* = 9.5, C), 129.4 (CH), 128.9 (CH), 127.8 (CH), 127.5 (CH), 124.7 (d, *J* = 6.3, CH), 124.6 (CH), 122.9 (CH), 122.7 (C), 120.6 (d, *J* = 3.3, CH), 119.0 (d, *J* = 19.3, CH), 110.0 (CH), 77.3 (C), 70.7 (d, *J* = 4.8, CH_2), 66.2 (CH_2), 50.0 (CH), 44.2 (CH_2), 17.8 (CH_2), –1.3 (CH_3); IR (film): 3375, 2952, 1740, 1713, 1630, 1613 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{29}H_{31}FN_2O_4SiNa$, 541.1935, found, 541.1927.

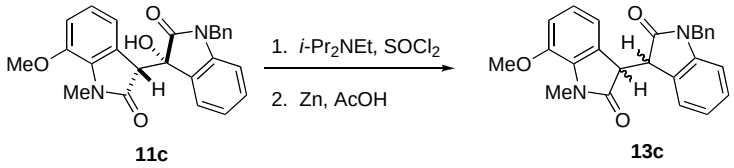
***N*-Benzyl-3-hydroxy-6-phenyl-*N*'-((2-(trimethylsilyl)ethoxy)methyl)-3,3'-biindoline-2,2'-dione (11f).** Following the general procedure described for the preparation of **11b**, oxindole **9** (132 mg, 0.501 mmol, 1.0 equiv) and isatin **S16** (159 mg, 0.506 mmol, 1.01 equiv) were converted to tertiary alcohol **11f** (243 mg, 84%), which was purified by silica gel flash column chromatography (3:17 EtOAc-hexanes) and isolated as a purple oil: R_f 0.23 (1:3 EtOAc-hexanes);^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (br d, *J* = 7.3, 1H), 7.52 (d, *J* = 7.4, 2H), 7.47–7.36 (m, 4H), 7.34 (t, *J* = 7.8, 1H), 7.21–7.11 (m, 4H), 6.85 (s, 1H), 6.78 (t, *J* = 7.5, 1H), 6.75 (d, *J* = 7.3, 2H), 6.20 (br m, 1H), 6.09 (br s, 1H), 5.30 (d, *J* = 11.1, 1H), 5.24 (d, *J* = 11.1, 1H), 5.01 (d, *J* = 15.7, 1H), 4.42 (d, *J* = 15.9, 1H), 4.16 (s, 1H), 3.80 (dd, *J* = 17.2, 8.8, 1H), 3.67 (dd, *J* = 16.8, 7.9, 1H), 0.95 (t, *J* = 8.1, 2H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3 (C), 175.3 (C), 144.3 (C), 144.0 (C), 143.8 (C), 140.5 (C), 135.1 (C), 129.4 (CH), 129.0 (CH), 128.8 (CH), 128.1 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.7 (C), 124.9 (CH), 124.7 (CH), 123.2 (CH), 122.4 (CH), 122.4 (CH), 110.5 (CH), 108.5 (CH), 77.1 (C), 70.0 (CH_2), 66.5 (CH_2), 50.2

(CH), 43.9 (CH_2), 18.0 (CH_2), –1.2 (CH_3); IR (film): 3392, 3062, 2952, 1725, 1702, 1621 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{35}H_{36}N_2O_4SiNa$, 599.2342, found, 599.2357.

***N*-Benzyl-3-hydroxy-5-(pyridin-3-yl)-*N*'-((2-(trimethylsilyl)ethoxy)methyl)-3,3'-biindoline-2,2'-dione (11g).** The general procedure described for the preparation of **11b** was followed with a modification of the workup to use saturated aqueous sodium bicarbonate (10 mL) to quench the reaction instead of water. In this way, oxindole **9** (152 mg, 0.577 mmol, 1.0 equiv) and isatin **S19** (183 mg, 0.583 mmol, 1.01 equiv) were converted to tertiary alcohol **11g** (199 mg, 60%), which was purified by silica gel flash column chromatography (1:1 EtOAc-hexanes) and isolated as a purple foam: R_f 0.46 (3:1 EtOAc-hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.55 (d, *J* = 4.8, 1H), 7.80 (d, *J* = 7.8, 1H), 7.60 (br s, 1H), 7.47 (d, *J* = 8.1, 1H), 7.34 (t, *J* = 7.7, 2H), 7.21–7.10 (m, 4H), 6.80 (t, *J* = 7.5, 1H), 6.75 (d, *J* = 7.0, 2H), 6.70 (d, *J* = 8.8, 1H), 6.35 (br s, 1H), 6.26 (br s, 1H), 5.25 (d, *J* = 11.1, 1H), 5.19 (d, *J* = 11.1, 1H), 4.98 (d, *J* = 15.8, 1H), 4.42 (d, *J* = 15.9, 1H), 4.17 (s, 1H), 3.68 (m, 1H), 3.58 (dd, *J* = 16.4, 8.2, 1H), 0.88 (t, *J* = 8.2, 2H), –0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.0 (C), 175.2 (C), 148.5 (CH), 148.0 (CH), 143.9 (C), 143.8 (C), 136.0 (C), 135.0 (C), 134.1 (CH), 133.3 (C), 129.6 (CH), 129.5 (CH), 128.9 (CH), 127.6 (CH), 127.0 (CH), 124.9 (C), 123.8 (CH), 123.4 (CH), 123.3 (CH), 122.4 (C), 110.6 (CH), 110.4 (CH), 77.2 (C), 70.0 (CH_2), 66.5 (CH_2), 50.4 (CH), 44.1 (CH_2), 18.0 (CH_2), –1.2 (CH_3); IR (film): 3402, 2952, 1725, 1613 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{34}H_{35}N_3O_4SiNa$, 600.2294, found, 600.2285.

3-Hydroxy-7'-methoxy-*N*,*N*'-dimethyl-4-vinyl-3,3'-biindoline-2,2'-dione (11h). Following the general procedure described for the preparation of **11b**, oxindole **S5** (95 mg, 0.536 mmol, 1.0 equiv) and isatin **10** (101 mg, 0.541 mmol, 1.01 equiv) were converted to tertiary alcohol **11h** (102 mg, 52%), which was purified by silica gel flash column chromatography (gradient: 1:4 EtOAc-hexanes to 3:7 EtOAc-hexanes) and isolated as a reddish-brown oil: R_f 0.14 (1:3 EtOAc-hexanes); ^1H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 17.6, 11.0, 1H), 7.40 (t, *J* = 7.9, 1H), 7.35 (d, *J* = 7.7, 1H), 6.74 (d, *J* = 8.4, 1H), 6.66 (d, *J* = 7.5, 1H), 6.61 (t, *J* = 7.7, 1H), 6.57 (br s, 1H), 5.90 (d, *J* = 17.6, 1H), 5.46 (d, *J* = 11.0, 1H), 5.40 (d, *J* = 7.5, 1H), 4.12 (s, 1H), 3.80 (s, 3H), 3.57 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.4 (C), 174.5 (C), 145.6 (C), 144.6 (C), 136.5 (C), 132.7 (C), 132.1 (CH), 130.6 (CH), 124.2 (C), 123.7 (C),

122.9 (CH), 120.3 (CH), 118.1 (CH_2), 116.2 (CH), 112.7 (CH), 107.5 (CH), 78.2 (C), 55.8 (CH_3), 48.1 (CH), 29.8 (CH_3), 25.9 (CH_3); IR (film): 3344, 2943, 1721, 1684, 1613, 1588 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{21}H_{20}N_2O_4Na$, 387.1321, found, 387.1318.



11c **13c**

Elimination and Reduction of 3-Hydroxy-3,3'-bioxindoles. Preparation of *N*'-Benzyl-7-methoxy-*N*-methyl-3,3'-biindoline-2,2'-dione (13b). To a solution of aldol adduct **11c** (88 mg, 0.21 mmol, 1.0 equiv) and dichloromethane (2 mL) at 0 °C was added diisopropylethylamine (110 μL, 0.64 mmol, 3.0 equiv) and thionyl chloride (20 μL, 0.25 mmol, 1.2 equiv) over 5 min. The resulting solution was maintained for 15 min at 0 °C before allowing it to warm to rt. After 15 min, the reaction mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate (5 mL), and the aqueous layer was separated and extracted with dichloromethane (3×5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield a brown solid that was used without further purification in the next reaction.

This unpurified solid was dissolved in THF (2.1 mL) and cooled to 0 °C. To this solution was added zinc dust (420 mg, 6.4 mmol, 30 equiv) and glacial acetic acid (0.21 mL, 3.7 mmol, 18 equiv). The resulting suspension was vigorously stirred for 1 h at 0 °C and then allowed to warm to rt for 2 h. After this time, the reaction mixture was filtered through a pad of Celite, eluting with EtOAc (20 mL). The organic solution was washed with saturated aqueous sodium hydrogen carbonate (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield an orange oil. This oil was further purified by silica gel flash column chromatography (1:2 EtOAc-hexanes) to afford 3,3'-bioxindole **13b** (75 mg, 89% yield), a 1.3:1 mixture of epimers, as a light yellow foam: R_f 0.15 and 0.19 (1:2 EtOAc:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 5.2H), 7.24–7.16 (m, 5.1H), 7.07–6.97 (m, 6.2H), 6.94 (d, *J* = 7.3, 1.1H), 6.88 (d, *J* = 8.4, 1.5H), 6.84–6.79 (m, 2.6H), 6.68–6.60 (m, 4.5H), 6.44 (d, *J* = 7.3, 0.9H), 6.21 (d, *J* = 7.4, 1.1H), 5.04–4.93 (m, 3.4H), 4.63 (d, *J* = 15.8, 1.3H), 4.37–4.30 (m, 3.1H), 4.16 (d, *J* = 3.4, 1.3H), 3.85 (s, 4.1H), 3.76 (s, 3H), 3.57 (s, 3H) 3.49 (s, 3.9H); ^{13}C NMR (125 MHz, $CDCl_3$) 176.3 (C),

176.2 (C), 175.4 (C), 174.9 (C), 145.6 (C), 145.2 (C), 144.3 (C), 143.7 (C), 135.8 (C), 135.7 (C), 133.3 (C), 132.2 (C), 128.93 (CH), 128.85 (CH), 128.8 (CH), 128.5 (CH), 127.9 (CH), 127.5 (CH), 127.4 (CH), 127.2 (C), 126.5 (C), 126.4 (C). 125.1 (C), 123.9 (CH), 123.7 (CH), 123.3 (CH), 123.09 (CH), 123.06 (CH), 122.7 (CH), 116.8 (CH), 116.5 (CH), 112.8 (CH), 112.5 (CH), 109.6 (CH), 109.2 (CH), 56.1 (CH_3), 56.0 (CH_3), 46.8 (CH), 46.6 (CH), 46.5 (CH), 46.4 (CH), 44.2 (CH_2), 44.0 (CH_2), 29.0 (CH_3); IR (film) 3062, 3033, 2941, 1708, 1613, 1490, 1466, 1366, 1254, 1121 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{25}H_{22}N_2O_3Na$, 421.1528, found, 421.1526.

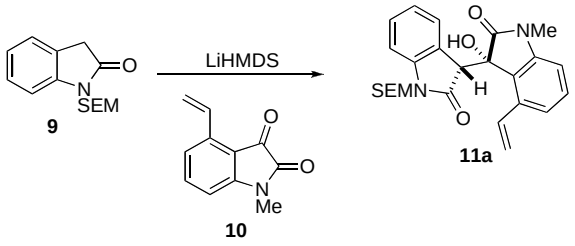
***N*-Benzyl-*N′*-((2-(trimethylsilyl)ethoxy)methyl)-3,3'-biindoline-2,2'-dione (13c).** Following the procedure described for the preparation of **13b**, 3-hydroxy-3,3'-bioxindole **11d** (112 mg, 0.224 mmol) was converted to 3,3'-bioxindole **13c** (92 mg, 85%), which was purified by silica gel flash column chromatography (3:17 EtOAc-hexanes), and isolated as a 3.7:1 mixture of epimers as a yellow oil: R_f 0.31 (1:4 EtOAc-hexanes);^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.14 (m, 9.6H), 7.14–7.09 (m, 1.4H), 7.08–7.01 (m, 2.0H), 6.99–6.88 (m, 3.0H), 6.82–6.68 (m, 1.3H), 6.65 (t, *J* = 8.2, 1.8H), 5.26 (d, *J* = 10.6, 0.3H), 5.22 (d, *J* = 10.9, 0.3H), 5.18 (d, *J* =11.1, 0.8H), 5.13 (d, *J* = 0.8H), 5.03–4.95 (m, 1.3H), 4.63 (d, *J* = 15.7, 0.8H), 4.43 (d, *J* = 3.9, 0.2H), 4.40 (d, *J* = 3.8, 0.2H), 4.35 (d, *J* = 3.5, 0.8H), 4.29 (d, *J* = 3.1, 1.0H), 3.69 (t, *J* = 8.7, 0.5H), 3.56 (dd, *J* = 17.5, 8.4, 0.8H), 3.48 (dd, *J* = 16.6, 8.5, 0.9H), 0.99 (m, 0.4H), 0.88 (t, *J* = 8.0, 1.9H), 0.02 (s, 2.1H), –0.1 (s, 7.9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.4 (C), 175.8 (C), 175.3 (C), 174.4 (C), 148.5 (C), 144.1 (C), 143.6 (C), 143.5 (C), 142.7 (C), 135.5 (C), 135.4 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 127.74 (CH), 127.69 (CH), 127.3 (CH), 127.1 (CH), 126.5 (CH), 125.8 (C), 125.1 (C), 123.62 (CH), 123.57 (CH), 123.5 (CH), 123.4 (CH), 122.8 (CH), 122.4 (CH), 110.0 (CH), 109.43 (CH), 109.37 (CH), 109.0 (CH), 69.8 (CH_2), 69.6 (CH_2), 66.5 (CH_2), 66.0 (CH_2), 46.35 (CH), 46.30 (CH), 46.0 (CH), 45.9 (CH), 44.0 (CH_2), 43.8 (CH_2), 17.9 (CH_2), 17.8 (CH_2), –1.4 (CH_3), –1.5 (CH_3); IR (film): 2951, 1721, 1612 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{29}H_{32}N_2O_3SiNa$, 507.2080, found, 507.2082.

***N*-Benzyl-6-phenyl-*N′*-((2-(trimethylsilyl)ethoxy)methyl)-3,3'-biindoline-2,2'-dione (13d).** Following the general procedure described for the preparation of **13b**, 3-hydroxy-3,3'-bioxindole **11e** (118 mg, 0.228 mmol) was converted to 3,3'-bioxindole **13d** (90 mg, 79%), purified via

silica gel flash column chromatography (3:17 EtOAc-hexanes), and isolated as a 3.8:1 mixture of epimers as a pale yellow oil: R_f 035 (1:4 EtOAc-hexanes);^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.29 (m, 1.6H), 7.26–7.20 (m, 2.0H), 7.19 (t, *J* = 7.5, 0.8H), 7.11–6.93 (m, 4.1H), 6.88–6.81 (m, 1.3H), 6.72 (d, *J* = 7.8, 0.4H), 6.67 (d, *J* = 7.9, 0.7H), 6.62 (td, *J* = 7.8, 4.5, 0.3H), 6.55 (d, *J* = 7.4, 0.3H), 6.46 (d, *J* = 7.4, 0.6H), 5.33 (s, 0.6H), 5.25 (s, 1.3H), 5.04–4.92 (m, 1.4H), 4.66 (d, *J* = 15.7, 0.6H), 4.43 (d, *J* = 3.5, 0.3H), 4.39 (d, *J* = 3.6, 0.3H), 4.34 (d, *J* = 3.3, 0.7H), 4.32 (d, *J* = 3.3, 0.6H), 3.72 (ddd, *J* = 9.8, 6.8, 2.9, 0.6H), 3.56 (dd, *J* = 17.6, 8.5, 0.7H), 3.52 (dd, *J* = 16.7, 8.4, 0.7H), 1.01 (m, 0.6H), 0.90 (t, *J* = 8.1, 1.4H), 0.01 (s, 2.9H), –0.05 (s, 5.9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2 (C), 175.5 (C), 175.0 (C), 174.3 (C), 147.9 (d, *J* = 245.1, C), 147.6 (d, *J* = 245.0, C), 144.1 (C), 143.4 (C), 135.5 (C), 135.4 (C), 130.4 (d, *J* = 9.3, C), 129.5 (d, *J* = 9.3, C), 128.9 (CH), 128.8 (CH), 128.61 (CH), 128.57 (CH), 128.5 (CH), 128.2 (d, *J* = 3.0, C), 127.82 (CH), 127.78 (CH), 127.4 (CH), 127.2 (CH), 125.5 (C), 124.5 (C), 123.8 (CH), 123.5 (CH), 123.4 (CH), 122.64 (CH), 122.58 (CH), 119.7 (d, *J* = 3.4, CH), 119.4 (d, *J* = 3.4, CH), 117.0 (d, *J* = 19.3, CH), 116.6 (d, *J* = 19.3, CH), 109.5 (CH), 109.0 (CH), 70.9 (d, *J* = 4.9, CH_2), 70.6 (d, *J* = 4.9, CH_2), 66.7 (CH_2), 66.3 (CH_2), 46.5 (CH), 46.4 (CH), 46.3 (CH), 46.2 (CH), 44.1 (CH_2), 43.8 (CH_2), 18.0 (CH_2), 17.8 (CH_2), –1.4 (CH_3), –1.5 (CH_3); IR (film): 2952, 1724, 1614 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{29}H_{31}FN_2O_3SiNa$, 525.1985, found, 525.1983.

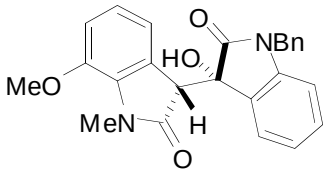
***N'*-Benzyl-7-fluoro-*N*-((2-(trimethylsilyl)ethoxy)methyl)-3,3'-biindoline-2,2'-dione (13e).** Following the general procedure described for the preparation of **13b**, 3-hydroxy-3,3'-bioxindole **11f** (81 mg, 0.14 mmol) was converted to 3,3'-bioxindole **13e** (71 mg, 90%), which was purified by silica gel flash column chromatography (3:17 EtOAc-hexanes) and isolated as a 2.2:1 mixture of epimers as a pale orange oil: R_f 0.33 (1:4 EtOAc-hexanes);^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48–7.30 (m, 7.3H), 7.28–7.17 (m, 3.1H), 7.11 (d, *J* = 7.9, 1.1H), 7.10–7.07 (m, 1.6H), 7.04–7.00 (m, 1.2H), 6.93 (t, *J* = 7.9, 1.2H), 6.83 (d, *J* = 7.3, 0.3H), 6.83 (d, *J* = 7.3, 1.0H) 5.28 (d, *J* = 10.9, 0.2H), 5.23 (d, *J* = 11.0, 0.2H), 5.18 (d, *J* = 7.1, 0.8H), 5.16 (d, *J* = 7.1, 0.8H), 5.11–4.97 (m, 0.5H), 5.03 (d, *J* = 15.6, 0.7H), 4.70 (d, *J* = 15.8, 0.7H), 4.46 (s, 0.4H), 4.40 (d, *J* = 3.4, 0.7H), 4.33 (d, *J* = 3.4, 0.7H), 3.71 (t, *J* = 7.6, 0.4H), 3.58 (dd, *J* = 17.6, 8.6, 0.8H), 3.52 (dd, *J* = 17.6, 9.2, 0.7H), 1.01 (m, 0.4H), 0.87 (t, *J* = 8.1, 1.5H), 0.03 (s, 2.1H), –0.06 (s, 6.4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.4 (C), 176.0 (C), 175.3 (C), 174.7 (C), 144.7 (C), 144.1 (C), 143.6 (C), 142.8 (C), 142.1 (C), 141.8 (C), 140.6 (C), 135.5 (C), 135.4 (C), 128.9 (CH), 128.8 (CH), 128.7

(CH), 128.6 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 126.9 (CH), 125.1 (C), 124.9 (C), 124.3 (C), 124.0 (CH), 123.9 (CH), 123.82 (C), 123.75 (CH), 123.6 (CH), 122.9 (CH), 122.8 (CH), 121.5 (CH), 121.4 (CH), 110.0 (CH), 109.5 (CH), 108.1 (CH), 107.8 (CH), 69.9 (CH_2), 69.6 (CH_2), 66.6 (CH_2), 66.0 (CH_2), 46.4 (CH), 46.2 (CH), 45.9 (CH), 44.1 (CH_2), 43.8 (CH_2), 17.9 (CH_2), 17.7 (CH_2), –1.40 (CH_3), –1.44 (CH_3); IR (film): 2952, 1722, 1618 cm^{-1}; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{35}H_{36}N_2O_3SiNa$, 583.2393, found, 583.2388.



Preparation of 3'-hydroxy-*N*'-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)-4'-vinyl-3,3'-biindoline-2,2'-dione (11a) by Aldol Reaction of the Lithium Enolate of Oxindole 9. To a solution of hexamethyldisilazane (120 μL, 0.58 mmol, 2.2 equiv) in THF (1.3 mL) at 0 °C was added *n*-butyllithium (240 μL, 0.58 mmol, 2.4 M in hexanes, 2.2 equiv). The resulting solution was maintained at 0 °C for 10 min, before cooling to –40 °C. A solution of oxindole **9** (70 mg, 0.26 mmol, 1.0 equiv) in THF (0.55 mL) was then added dropwise and the reaction was maintained at –40 °C for 1 h. A solution of isatin **10** (50 mg, 0.26 mmol, 1.0 equiv) in THF (0.8 mL) was then added dropwise, and the solution was maintained at –40 °C for 2 h before being allowed to warm to –20 °C over 1 h. The reaction was allowed to warm to rt, and after 2 h was quenched by the addition of saturated ammonium chloride (10 mL) and diluted with EtOAc (20 mL). The aqueous layer was separated and extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with brine (100 mL) then dried over $MgSO_4$ and concentrated under reduced pressure to yield an orange solid. The solid was further purified by silica gel flash column chromatography (gradient 1:5 EtOAc-hexanes to 1:4 EtOAc-hexanes) to afford tertiary alcohol **11a**, as a 2.8:1.0 mixture of diastereomers (57 mg, 48% based on conversion, 75% based on consumed starting material) as an orange oil: R_f 0.19 (1:4 EtOAc-hexanes). Isatin **10**, (18 mg, 36%), R_f 0.06 (1:4 EtOAc-hexanes) was also isolated as an orange solid .

ORTEP Diagram of Mukaiyama Aldol Adduct 11c



11c