Supporting Information

Exploring an Anomaly: The Synthesis of 7,7’-Diazaindirubin through a 7-Azaindoxyl Intermediate

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1. General Methods and Safety

All starting materials were commercially available and used without additional purification from TCI, Aldrich, Fisher Scientific and Alfa Aesar. All NMR spectra were determined in d6-DMSO at 300 MHz (1H NMR) on a Bruker Avance™ spectrometer. The chemical shifts are expressed in δ values relative to the appropriate solvent. For reaction mixtures, NMR integration was used to assess approximate relative values using high scan number to optimize accuracy.
2. Synthetic Details.

7,7’-Diaza-indirubin (6)

**Method 1:** To a round bottomed flask, 0.591 g (5 mmol) of 7-azaindole, 0.066 g (0.25 mmol) of Mo\((\text{CO})_6\), 1.63 mL (11 mmol) of an 80% solution of cumyl hydroperoxide in cumene, 0.015 mL (0.25 mmol) of acetic acid and 10.9 mL of tert-butanol were added. The round bottomed flask was then placed in an oil bath set to 86°C. After 24 hours the product was put in an ice bath for 20 minutes, vacuum filtered, washed with cold methanol and placed on a high vacuum pump for 3 hours to afford a brick red solid (0.580 g, 2.19 mmol, 87.8% yield).

**Method 2:** To a round bottomed flask 0.176 g (1 mmol) of 7-azaindoxyl acetate (6), 0.012 g (0.02 mmol) of ytterbium (III) triflate, 4 mL of DMSO and 1 mL of hexanol were added. The round bottomed flask was then placed in an oil bath set to 150°C. After 24 hours the product was put in an ice bath and 15 mL of water was added to force precipitation. The product was then vacuum filtered, washed with a 1:1 solution of cold methanol and water and placed on the high vacuum pump for 3 hours to afford a brick red solid (0.045 g, 0.170 mmol, 34.1% yield).

**Spectroscopy:** $^1$H NMR of 6 was previously published

$^1$H NMR (300 MHz, $d_6$-DMSO) $\delta$: 11.60 (1H, s); 10.76 (1H, s); 8.86 (1H, d, $J = 7.5$ Hz); 8.52 (1H, dd, $J = 5.1$ Hz and 1.5 Hz); 8.13-8.18 (2H, m); 7.16 (1H, dd, $J = 7.5$ Hz and 5.1 Hz); 7.11 (1H, dd, $J = 7.2$ Hz and 5.4 Hz).

Indirubin (1)

To a round bottomed flask 0.588 g (5 mmol) of indole, 0.736 g (5 mmol) of isatin, 0.006 g (0.025 mmol) of Mo\((\text{CO})_6\), 0.813 mL (5.5 mmol) of an 80% solution of cumyl hydroperoxide in cumene, 0.015 mL (0.25 mmol) of acetic acid and 10.9 mL of tert-butanol were added. The round bottomed flask was then placed in an oil bath set to 55°C. After 24 hours the product was put in an ice bath for 20 minutes, vacuum filtered, washed with cold methanol and placed on a high vacuum pump for 3 hours to afford 0.673 g (2.57 mmol) of a dark purple solid. This was a 51.3% recovery with an indirubin to indigo product ratio of 8:1 as determined by an $^1$H NMR.

**Spectroscopy:** $^1$H NMR of 1 was previously published

$^1$H NMR (300 MHz, $d_6$-DMSO) $\delta$: 11.03 (1H, s); 10.91 (1H, s); 8.78 (1H, d, $J = 7.5$ Hz); 7.66 (1H, dd, $J = 5.1$ Hz and 1.5 Hz); 7.59 (1H, t, $J = 7.5$ Hz); 7.43 (1H, d, 8.1 Hz); 7.27 (1H, t, $J = 7.4$Hz); 7.01-7.07 (2H, m); 6.91 (1H, d, $J = 7.8$ Hz).

7’-Azaindirubin (9)

To a round bottomed flask 0.591 g (5 mmol) of 7-azaindole, 0.736 g (5 mmol) of isatin, 0.006 g (0.025 mmol) of molybdenumhexacarbonyl, 1.63 mL (11 mmol) of an 80% solution of cumyl hydroperoxide in cumene, 0.015 mL (0.25 mmol) of acetic acid and 10.9 mL of tert-butanol were added. The round bottomed flask was then placed in an oil bath set to 86°C. After 24 hours the product was put in an ice bath for 20 minutes, vacuum filtered, washed with cold methanol and placed on a high vacuum pump for 3 hours to afford a brick red solid (0.138 g, 0.522 mmol, 10.5% yield).

**Spectroscopy:** $^1$H NMR of 9 was previously published

$^1$H NMR (300 MHz, $d_6$-DMSO) $\delta$: 11.05 (1H, s); 10.81 (1H, s); 8.71 (1H, d, $J = 7.5$ Hz); 8.51 (1H, d, $J = 4.8$ Hz); 8.13 (1H, d, $J = 6.9$ Hz); 7.32 (1H, t, $J = 7.2$ Hz); 7.05-7.15 (2H, m); 6.96 (1H, d, $J = 7.8$ Hz).

Indigo (2)

To a round bottomed flask 0.588 g (5 mmol) of indole, 0.0660 g (0.25 mmol) of Mo\((\text{CO})_6\), 1.63 mL (11 mmol) of an 80% solution of cumyl hydroperoxide in cumene, 0.0143 mL (0.25 mmol) of acetic acid and 10.9 mL of tert-butanol were added. The round bottomed flask was then placed in an oil bath set to 86°C. After 24 hours the product was put in an ice bath for 20 minutes, vacuum filtered, washed with cold
methanol and placed on a high vacuum pump for 3 hours to afford 0.517 g (1.97 mmol) of a dark blue/black solid in a 79% yield as affirmed by $^1$H NMR.

**Spectroscopy:** $^1$H NMR was consistent with widely available spectra.$^3$ $^1$H NMR (300 MHz, d$_6$-DMSO) δ-10.51 (2H, s); 7.62 (2H, d, $J = 7.5$ Hz); 7.52 (2H, t, $J = 7.2$ Hz); 7.34 (2H, d, $J = 8.1$ Hz); 6.96 (2H, t, $J = 8.4$ Hz).

**6,6′-dinitroindirubin (10) and 6,6′-dinitroindigo (11)**

**Method 1:** To a round bottomed flask 0.811 g (5 mmol) of 6-nitroindole, 0.0660 g (0.25 mmol) of Mo(CO)$_6$, 1.63 mL (11 mmol) of an 80% solution of cumyl hydroperoxide in cumene, 0.0143 mL (0.25 mmol) of acetic acid and 10.9 mL of tert-butanol were added. The round bottomed flask was then placed in an oil bath set to 86 °C. After 24 hours the product was put in an ice bath for 20 minutes, vacuum filtered, washed with cold methanol and placed on a high vacuum pump for 3 hours to afford 0.592 g (1.68 mmol) of a blue solid. This was a 67% recovery with a 10:11 ratio of 2:9 as determined by $^1$H NMR.

**Method 2:** To a round bottomed flask 0.811 g (5 mmol) of 6-nitroindole, 0.0264 g (0.1 mmol) of molybdenumhexacarbonyl, 1.63 mL (11 mmol) of an 80% solution of cumyl hydroperoxide in cumene, 0.0620 g (0.1 mmol) of ytterbium (III) triflate and 10.9 mL of tert-butanol were added. The round bottomed flask was then placed in an oil bath set to 86 °C. After 24 hours the product was put in an ice bath for 20 minutes, vacuum filtered, washed with cold methanol and placed on a high vacuum pump for 3 hours to afford 0.159 g (0.451 mmol) of a dark purple solid. This was a 18% recovery with a 10:11 ratio of 3:1 as determined by an $^1$H NMR spectra recorded on a Bruker 300 MHz spectrometer.

**Spectroscopy:** $^1$H NMR was previously published for 10 and 11.$^4$ $^1$H NMR for 10, (300 MHz, d$_6$-DMSO) δ-11.75 (1H, s); 11.36 (1H, s); 8.89 (1H, d, $J = 8.7$ Hz); 8.30 (1H, d, $J = 2.1$ Hz); 7.98 (1H, dd, $J = 8.7$ Hz and 2.1 Hz); 7.92-7.87 (2H, m); 7.64 (1H, d, $J = 2.1$ Hz). For 11 $^1$H NMR (300 MHz, d$_6$-DMSO) δ- 11.20 (2H, s); 8.18 (2H, d, $J = 1.8$ Hz); 7.91 (2H, d, $J = 8.1$ Hz); 7.75 (2H, dd, $J = 8.1$Hz and 1.8Hz).

**Indirubin- 5,5′-dicarbonitrile (12) and Indigo-5,5′-dicarbonitrile (13)**

To a round bottomed flask 0.711 g (5 mmol) of 5-cyanoindole, 0.0660 g (0.25 mmol) of Mo(CO)$_6$, 1.63 mL (11 mmol) of an 80% solution of cumyl hydroperoxide in cumene, 0.0143 mL (0.25 mmol) of acetic acid and 10.9 mL of tert-butanol were added. The round bottomed flask was then placed in an oil bath set to 86 °C. After 24 hours the product was put in an ice bath for 20 minutes, vacuum filtered, washed with cold methanol and placed on a high vacuum pump for 3 hours to afford 0.483 g (1.55 mmol) of a purple solid. This was a 62% recovery with a 12:13 ratio of 2:3 as determined by an $^1$H NMR spectra recorded on a Bruker 300 MHz spectrometer.

**Spectroscopy:** $^1$H NMR was previously published for 12 and 13.$^3$ $^1$H NMR for 12, (300 MHz, d$_6$-DMSO) δ- 11.57 (1H, s); 11.36 (1H, s); 9.05 (1H, d, $J = 1.7$ Hz); 8.21 (1H, d, $J = 0.9$ Hz); 8.01 (1H, dd, $J = 8.4$ Hz and 1.8 Hz); 7.75 (1H, dd, $J = 8.4$ Hz and 1.8 Hz) 7.60 (1H, d, $J = 8.4$ Hz). 7.08 (1H, d, $J = 8.1$ Hz). For 13 $^1$H NMR (300 MHz, d$_6$-DMSO) δ- 11.20 (2H, s); 8.14 (2H, d, $J = 1.2$ Hz); 7.91 (2H, dd, $J = 8.4$ Hz and 1.5 Hz); 7.48 (2H, d, $J = 8.1$Hz ).

**Indirubin- 5,5′-dicarboxylic acid (14) and Indigo-5,5′-dicarboxylic acid (15)**

To a round bottomed flask 0.711 g (5 mmol) of indole-5-carboxylic acid, 0.0660 g (0.25 mmol) of Mo(CO)$_6$, 1.63 mL (11 mmol) of an 80% solution of cumyl hydroperoxide in cumene, 0.0143 mL (0.25 mmol) of acetic acid and 10.9 mL of tert-butanol were added. The round bottomed flask was then placed in an oil bath set to 86 °C. After 24 hours the product was put in an ice bath for 20 minutes, vacuum filtered, washed with cold methanol and placed on a high vacuum pump for 3 hours to afford 0.512 g (1.46 mmol) of a purple solid. This was a 59% recovery with a 14:15 ratio of 1:2 as determined by an $^1$H NMR. A small quantity of an unidentified impurity, likely an indigoid, was also present.
Spectroscopy: $^1$H NMR was previously published for 14 and 15. For 14, numerous peaks were obscured by the larger peaks for 15. For 15 $^1$H NMR (300 MHz, d$_6$-DMSO) δ- 12.82 (2H, s); 11.03 (2H, s); 8.13 (2H, d, J = 1.5 Hz); 8.10 (2H, dd, J = 8.4 Hz and 1.5 Hz); 7.40 (2H, d, J = 8.4 Hz).

5,5'-Dimethoxyindigo (16)
To a round bottomed flask 0.736 g (5 mmol) of 5-methoxyindole, 0.0660 g (0.25 mmol) of Mo(CO)$_6$, 1.63 mL (11 mmol) of an 80% solution of cumyl hydroperoxide in cumene, 0.0143 mL (0.25 mmol) of acetic acid and 10.9 mL of tert-butanol were added. The round bottomed flask was then placed in an oil bath set to 86 °C. After 24 hours the product was put in an ice bath for 20 minutes, vacuum filtered, washed with cold methanol and placed on a high vacuum pump for 3 hours to afford 0.521 g (1.62 mmol) of a blue solid in a 65% yield.

Spectroscopy: $^1$H NMR was not previously published for 16, though it has been made on multiple occasions. A clean $^1$H NMR and $^{13}$C NMR (40,000 scans) were obtained for characterization. For 14 $^1$H NMR (300 MHz, d$_6$-DMSO) δ- 10.27 (2H, s); 7.28 (2H, d, J = 9.0 Hz); 7.16 (2H, dd, J = 9.0 Hz and 2.7 Hz); 7.09 (2H, d, J = 2.4 Hz); 3.78 (6H, s). $^{13}$C NMR (75 MHz, d$_6$-DMSO) δ- 188.04; 154.21; 148.13; 125.26; 122.04; 119.55; 115.03; 105.27; 56.09.

7-azaindoxyl acetate (17)
In a modified synthetic procedure, to a round bottomed flask 2.363 g (20 mmol) of 7-azaindole, 9.663 g (30 mmol) of diacetoxyiodobenzene, 2.244 g (40 mmol) of potassium hydroxide and 100 mL of acetonitrile were added. The round bottomed flask was then placed in an oil bath set to 50°C. After 24 hours the product was placed into a separatory funnel with 600 mL of water and 150 mL of dichloromethane. Once separated, the water layer was washed twice more with 150 mL of dichloromethane. The organic layer was then washed twice with 300 mL of water and finally with 300 mL of brine solution. Magnesium sulfate was added to the dichloromethane solution for to dry, the product was then vacuum filtered and placed on the rotary evaporator. A column was run using 1:1 hexane to ethyl acetate as the eluent. The product was then collected, placed on the rotary evaporator and the high vacuum pump for 3 hours to afford a light pink solid (1.163 g, 6.61 mmol, 33% yield).

Spectroscopy: The $^1$H NMR did not match with the original published procedure, which looks to be incorrectly assigned or transcribed. An independent study using thallium acetate, aligned with our NMR data. $^1$H NMR (300 MHz, d$_6$-DMSO) δ- 11.57 (1H, s); 8.26 (1H, d, J = 3.3 Hz); 7.84 (1H, d, J = 7.5 Hz); 7.44 (1H, d, J = 2.4 Hz); 7.09 (1H, dd, J = 7.8 and 4.8 Hz); 2.33 (3H, s).
3. NMR

$^1\text{H NMR of } 6$ (Method 1)
$^1$H NMR of 6 (Method 2)
$^1$H NMR of 1 (with indole).
$^1$H NMR of 9.
$^1$H NMR of 2.
$^{1}H$ NMR of 10 and 11 no Yb(OTf)$_3$
$^1$H NMR of 10 and 11 with Yb(OTf)$_3$
$^1$H NMR of 12 and 13.
$^1$H NMR of 12 and 13.
$^1$H NMR of 16
$^{13}$C NMR of 17
NMR of 15.
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