Supplementary Material (ESI) for Chemical Communications

Supplementary Information for

Synthesis of reaction-ready 6,6′-biindole and 6,6′-biisatin via palladium(II)-catalysed intramolecular C-H functionalisation

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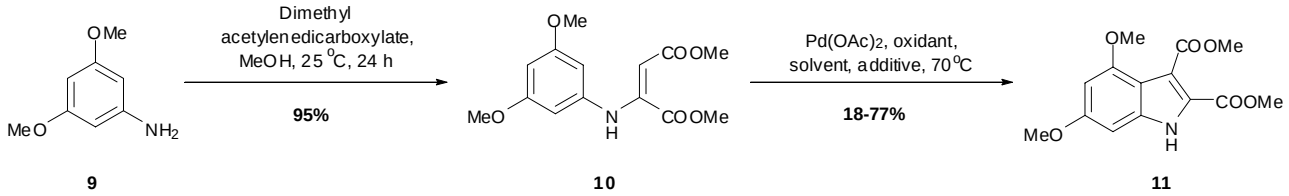
Table 1. Investigation into the Pd(II)-catalysed C-H activation of enamine **10**, affording 2,3-disubstituted indole **11**.



9 **10** **11**

Entry	$Pd(OAc)_2$ (mol%)	Oxidant (mol%) Additive (mol%)	Solvent	Time (h)	Yield (%)[a,b]
1	200	Air	DMA	24	0, 54[c]
2	10	Air	DMA	24	38 (38)
3	10	$Cu(OAc)_2.H_2O$ (100)	DMA	18	43
4	10	$Cu(OAc)_2.H_2O$ (50)	DMA	10	61
5	10	$Cu(OAc)_2.H_2O$ (25)	DMA	10	57
6	10	$Cu(OAc)_2.H_2O$ (25)	MeCN	18	18 (49)[d]
7	10	$Cu(OAc)_2.H_2O$ (20) NaOAc (20)	MeCN	48	18 (30)[e]
8	10	$Cu(OAc)_2.H_2O$ (10)	DMA	18	77
9	10	$Cu(OAc)_2.H_2O$ (100) DPPP (20)	DMA	18	28
10	10	$Cu(OTf)_2$ (15)	DMA	24	70
11	10	Benzoquinone (100)	DMA	24	22 (50)
12	10	Benzoquinone (300)	DMA	24	22 (48)[f]

[a]Isolated yield of indole **11**.

[b]Values in parentheses denotes amount of unreacted enamine **10** recovered after column chromatography. No value indicates complete consumption of **10**.

[c]Yield of dimethyl 7-acetoxy-4,6-dimethoxyindole-2,3-dicarboxylate isolated.

[d]Dimethyl 2-acetoxy-3-(3,5-dimethoxyphenylamino)maleate isolated in 11% yield.

[e]Dimethyl 2-acetoxy-3-(3,5-dimethoxyphenylamino)maleate isolated in 25% yield.

[f]Reaction performed under $N_{2(g)}$.

DMA = *N*,*N*-dimethylacetamide, MeCN = acetonitrile, DPPP = 1,3-*bis*(diphenylphosphino)propane

Initial attempts at the synthesis of indole **11** involved air as the sole source of oxidant, with an excess of $Pd(OAc)_2$, analogous to the previously reported syntheses (Table 1, entry 1).[14] Intramolecular cyclisation was observed, however, only the 7-acetoxy functionalised indole could be identified, indicating that the excess acetate source can prove problematic in the presence of a highly activated arene. In addition the high catalyst loading was expected to prove problematic for arenes carrying a halide substituent in which reductive dehalgenation is possible. The catalyst loading was subsequently dropped to 10 mol%, with the desired product observed in 38% yield. Various loadings of $Cu(OAc)_2.H_2O$ with 10 mol% $Pd(OAc)_2$ in DMA were investigated (Table 1, entries 3-5), and intriguingly, as the amount of $Cu(OAc)_2.H_2O$ was

reduced, the yield of indole **11** increased. Concurrently, the solvent was changed to acetonitrile, resulting in a much lower yield of the desired indole **11**, and a previously unseen by-product identified as dimethyl 2-acetoxy-3-(3,5-dimethoxyphenylamino)maleate in 11% yield (Table 1, entry 6). Addition of a base (NaOAc) did not help facilitate the reaction in acetonitrile (Table 1, entry 7), resulting in further acetoxylation of enaminone **10** (25%).[1] Promisingly, reducing the oxidant loading to 10 mol% in DMA, provided **11** in 77% yield (Table 1, entry 8). Further experiments with a stabilising phosphine ligand (Table 1, entire 9) and different oxidants (Table 1, entries 10-12) did not improve the yield of **11**.

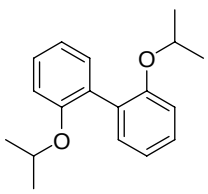
General Remarks

Sonication reactions were performed in an Elma Transsonic T460 ultrasonic cleaning bath at a frequency of 35 kHz and a nominal power of 85 W with all reactions exposed to air in standard glassware or glass sample vials, with the temperature maintained at 30 °C

Infrared spectra (IR) were recorded on a Nicolet Avatar 360 FTIR spectrometer in percentage transmittance method, with peak values given in wavenumbers (cm^{-1}), and intensities described as strong (s), medium (m), or weak (w). Proton nuclear magnetic resonance spectra (^1H NMR) were acquired with Varian Unity-300 or -500 spectrometers at 300 and 500 MHz respectively. Spectra were recorded using solutions of dueterated solvents obtained from Cambridge Isotope Laboratories, Inc., including chloroform (δ 7.26 ppm), acetone (δ 2.05 ppm), methanol (δ 3.31 ppm), and DMSO (δ 2.50 ppm), with internal standards shown in brackets. Carbon nuclear magnetic resonance spectra were acquired with Varian Unity-300 or -500 spectrometers at 75 and 126 MHz respectively, with solutions of deuterated chloroform (δ 77.16 ppm), acetone (δ 29.84 ppm), methanol (δ 49.00 ppm), and DMSO (δ 39.52 ppm). Chemical shifts (δ) are expressed in ppm and coupling constants (*J*) are expressed in Hertz (Hz), both relative to the internal standard. Multiplicities are denoted as singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), triplet of triplets (tt), quartet (q), septet (sep), and multiplet (m). Low resolution Electron impact (EI) mass spectra were recorded on a Shimadzu QP-5000 spectrometer, and low resolution Electrospray ionisation was recorded on a Micromass platform LCZ spectrometer. Principle ion peaks *m/z* values are stated with their respective intensities as a percentage.

Synthetic Procedures

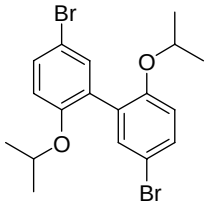
2,2'-Diisopropoxy-1,1'-biphenyl (4)



To a solution of 2,2'-biphenol **3** (0.997 g, 5.36 mmol) in DMF (20 mL) was added K_2CO_3 (6.86 g, 49.6 mmol) and 2-bromopropane (4.62 mL, 49.2 mmol) and the resulting solution was heated at 100 °C for 48 h. TLC analysis revealed that the starting material had reacted but a large amount of mono-isopropoxy compound still remained. Additional 2-bromopropane (2.50 mL) was added and stirring continued for a further 24 h. TLC analysis still identified the presence of mono-isopropoxy, therefore stirring was continued for a final 48 h at room temperature after which time only diisopropoxy compound remained. The reaction was diluted with water (40 mL) and extracted with diethyl ether (3 x 40 mL), and DCM (1 x 40 mL). The organic extracts were washed with 2M KOH (2 x 50 mL), brine

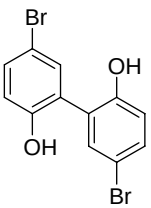
(100 mL) and water (2 x 100 mL), dried ($MgSO_4$), and concentrated to give the di-isopropoxy compound **4** as a light yellow liquid (1.336 g, 92%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25, m, 4H, ArH4, ArH6, ArH4' and ArH6'; 6.97, m, 4H, ArH3, ArH5, ArH3' and ArH5'; 4.33, septet, *J* = 6.3 Hz, 2H, 2 x O<u>C</u>H$(CH_3)_2$; 1.16, d, *J* = 6.3 Hz, 12H, 2 x OC(C<u>H</u>$_3)_2$. ^{13}C NMR ($CDCl_3$, 300 MHz): δ 155.6, ArC2 and ArC2'; 132.2, ArC6 and ArC6'; 130.0 ArC1 and ArC1'; 128.1, ArC4 and ArC4'; 120.4, ArC5 and ArC5'; 115.4, ArC3 and ArC3'; 71.2, 2 x O<u>C</u>H$(CH_3)_2$; 22.2, 2 x OC(<u>C</u>H$_3)_2$. MS (EI) *m/z* 270 (M^+, 25 %), 185 (100%).

5,5'-Dibromo-2,2'-diisopropoxy-1,1'-biphenyl (5)



To a solution of 2,2'-diisopropoxy-1,1'-biphenyl **4** (1.30 g, 4.81 mmol) in glacial acetic acid (50 mL) at 0 °C was added NaOAc (1.13 g, 13.78 mmol). Molecular bromine (0.550 mL in 25 mL glacial acetic acid, 10.68 mmol) was added dropwise over 2 h to the icy slurry. The reaction was allowed to come to room temperature and stirred for a further 2 h before being quenched with 10% sodium metabisulfite (80 mL) and partitioned with DCM (70 mL). The aqueous phase was further extracted with DCM (3 x 50 mL) and the combined organic layers were washed with water (3 x 100 mL), dried ($MgSO_4$), and concentrated to give an off white solid. The crude solid was purified by recrystallisation in hot absolute ethanol providing **5** as a white crystalline solid (1.94 g, 94%). mp: 60-61 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36, dd, *J* = 9.3 Hz, 2.7 Hz, 2H, ArH4 and ArH4'; 7.35, d, *J* = 2.1 Hz, 2H, ArH6 and ArH6'; 6.81, d, *J* = 9.3 Hz, 2H, ArH3 and ArH3'; 4.34, septet, *J* = 5.7 Hz, 2H, 2 x OC<u>H</u>$(CH_3)_2$; 1.19, d, *J* = 6 Hz, 12H, 2 x OCH(C<u>H</u>$_3)_2$. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.7, ArC2 and ArC2'; 134.4, ArC6 and ArC6'; 131.3, ArC4 and ArC4'; 130.3, ArC1 and ArC1'; 116.4, ArC3 and ArC3'; 112.4, ArC5 and ArC5'; 71.4, 2 x O<u>C</u>H$(CH_3)_2$; 22.1, 2 x OCH(<u>C</u>H$_3)_2$. IR: υ_{max} 2979m, 2366m, 1461s, 1373m, 1243s, 1137m, 1111s, 805s cm^{-1}. MS (EI) *m/z* 426 ($M^{79}Br^{79}Br$, 25%), 428 ($M^{81}Br^{79}Br$, 50%), 430 ($M^{81}Br^{81}Br$, 25%), 344 (100%). HRMS calculated for $C_{18}H_{20}O_2{}^{79}Br_2$: 425.9830, found 425.9839.

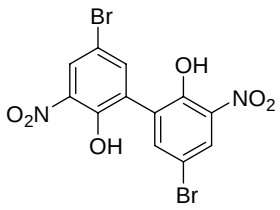
5,5'-Dibromo-2,2'-biphenol (6)



To a solution of 5,5'-dibromo-2,2'-dimethoxy-1,1'-biphenyl **5** (0.686 g, 1.85 mmol) in dry DCM (10 mL) at -10 °C under N_2 was added dropwise BBr_3 (1 M in DCM, 8.09 mL, 8.09 mmol). The reaction was allowed to come to room temperature while being stirred over 5 h. TLC analysis revealed the presence of only one spot, hence the reaction was poured onto crushed ice and partitioned with DCM (30 mL). The aqueous phase was extracted with EtOAc (3 x 40 mL) and the combined organic layers were washed with brine (3 x 75 mL), water (3 x 100 mL), dried ($MgSO_4$), and concentrated to give a grey solid. Recrystallisation of

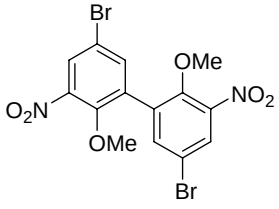
the crude solid from ether/hexane yielded biphenol **6** as a light brown crystalline solid (0.590 g, 94%), which was spectroscopically similar to that reported in the literature.[2,3] mp: 181-183 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.66, bs, 2 H, 2 x OH; 7.30, dd, J = 8.4 Hz, 2.7 Hz, 2H, ArH4 and ArH4'; 7.27, d, J = 2.7 Hz, 2H, ArH6 and ArH6'; 6.86, d, J = 8.4 Hz, 2H, ArH3 and ArH3'. ^{13}C NMR (DMSO-d_6, 75 MHz): 154.0, ArC2 and ArC2'; 133.4, ArC6 and ArC6'; 131.0, ArC4 and ArC4'; 126.5, ArC1 and ArC1'; 117.7, ArC3 and ArC3'; 109.5, ArC5 and ArC5'. IR: υ_{max} 3252 m, 1482m, 1394s, 1225s, 813s cm^{-1}. MS (EI) *m/z* 342 ($M^{79}Br^{79}Br$, 15%), 344 ($M^{81}Br^{79}Br$, 25%), 346 ($M^{81}Br^{81}Br$, 15%), 149 (100%). HRMS calculated for $C_{12}H_8O_2{}^{79}Br_2$: 341.8891, found 341.8898.

5,5'-Dibromo-3,3'-dinitro-2,2'-biphenol



To a suspension of 5,5'-dibromo-2,2'-biphenol **6** (0.496 g, 1.44 mmol) in glacial acetic acid (20 mL) at 0 °C was added dropwise 70% HNO_3 (0.270 mL, 4.26 mmol). The reaction was allowed to stir at room temperature for 45 min, after which time the reaction was quenched with water (50 mL) and extracted with DCM (3 x 50 mL). The combined extracts were washed with water (3 x 75 mL), dried ($MgSO_4$), and concentrated to give a yellow solid (0.576 g, 92%), with TLC analysis indicating only one product. The crude solid was recrystallised from hot ethanol to give 5,5'-dibromo-3,3'-dinitro-2,2'-biphenol as a pure, bright yellow crystalline solid (0.462 g, 74%), which was spectroscopically identical to that reported in the literature.[4] mp: 203-205 °C (Lit. 205 °C).[4] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.87, s, 2H, 2 x OH; 8.36, d, J = 2.7 Hz, 2H, ArH4 and ArH4'; 7.73, d, J = 2.4 Hz, 2H, ArH6 and ArH6'. ^{13}C NMR ($CDCl_3$, 75 MHz): 152.1, ArC2 and ArC2'; 141.6, ArC6 and ArC6'; 134.6, ArC3 and ArC3'; 128.1, ArC4 and ArC4'; 127.9, ArC1 and ArC1'; 111.4, ArC5 and ArC5'. IR: υ_{max} 3087w, 1528s, 1387m, 1332m, 1238s, 1163m, 880m, 704m cm^{-1}. MS (EI) *m/z* 432 ($M^{79}Br^{79}Br$, 20%), 434 ($M^{81}Br^{79}Br$, 30%), 436 ($M^{81}Br^{81}Br$, 20%), 59 (100%). HRMS calculated for $C_{12}H_6N_2O_6{}^{79}Br_2$: 431.8593, found 431.8510.

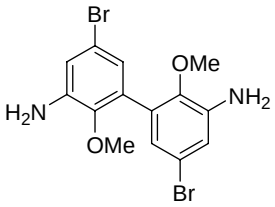
5,5'-Dibromo-2,2'-dimethoxy-3,3'-dinitro-1,1'-biphenyl (7)



To a solution of 5,5'-dibromo-3,3'-dinitro-2,2'-biphenol (0.545 g, 1.26 mmol) in acetone (30 mL) was added K_2CO_3 (1.96 g, 14.20 mmol) and methyl iodide (0.790 mL, 12.58 mmol). The reaction was heated at 30 °C under N_2 for 24 h, after which time further K_2CO_3 (0.697 g, 5.04 mmol) and methyl iodide (0.320 mL, 5.10 mmol) were added and stirred for another 24 h at 30 °C, forcing the conversion of mono-methylated compound to di-methylated compound. The solvent was evaporated, water (80 mL) was added to the crude residue and partitioned with diethyl ether (80 mL). The aqueous phase was extracted with further portions of diethyl ether (4 x 30 mL) and DCM

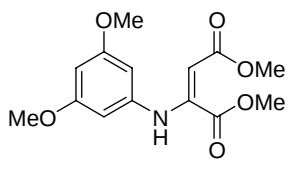
(1 x 15 mL) and the combined organic extracts were washed with 2M KOH (3 x 50 mL) and water (3 x 100 mL), dried ($MgSO_4$), and concentrated. The crude yellow solid was recrystallised from hot ethanol to give 5,5'-dibromo-2,2'-dimethoxy-3,3'-dinitro-1,1'-biphenyl **7** as light yellow needles (0.505 g, 87%), which were spectroscopically identical to that reported in the literature.[4] mp: 130-131 °C (Lit. 135-136 °C).[4] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.02, d, *J* = 2.4 Hz, 2H, ArH4 and ArH4'; 7.70, d, *J* = 2.7 Hz, 2H, ArH6 and ArH6'; 3.66, s, 6H, 2 x OCH_3. ^{13}C NMR ($CDCl_3$, 75 MHz): 150.5, ArC2 and ArC2'; 144.8, ArC3 and ArC3'; 138.2, ArC6 and ArC6'; 133.3, ArC1 and ArC1'; 128.7, ArC4 and ArC4'; 116.1, ArC5 and ArC5'; 62.7, 2 x OCH_3. IR: υ_{max} 1526s, 1341s, 1244s, 982s, 884s cm^{-1}. MS (EI) *m/z* 460 ($M^{79}Br^{79}Br$, 50%), 462 ($M^{81}Br^{79}Br$, 100%), 464 ($M^{81}Br^{81}Br$, 50%). HRMS (EI) calculated for $C_{14}H_{10}N_2O_6{}^{79}Br_2$: 459.8906, found 459.8902.

3,3'-Diamino-5,5'-dibromo-2,2'-dimethoxy-1,1'-biphenyl (8)



To a suspension of biaryl **7** (0.205 g, 0.445 mmol) in a mixture of glacial acetic acid (4 mL), ethanol (4 mL) and water (2 mL) was added reduced iron powder (0.285 g, 5.10 mmol). The reaction was sonicated at 30 °C for 1 h before it was filtered and washed with EtOAc/DCM. The filtrate was partitioned with 2M NaOH (50 mL) and extracted with further portions of EtOAc (3 x 30 mL), and the combined organic extracts were washed with water (3 x 50 mL), dried ($MgSO_4$) and concentrated to yield bianiline **8** as a brown/dark red crystalline solid (0.174 g, 98%), which was spectroscopically identical that reported in the literature.[4] mp: 172-175 °C (Lit. 185-186 °C).[4] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.89, d, *J* = 2.4 Hz, 2H, ArH4 and ArH4'; 6.80, d, *J* = 2.1 Hz, 2H, ArH6 and ArH6'; 3.96, bs, 4H, 2 x NH_2; 3.44, s, 6H, 2 x OCH_3. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.0, ArC2 and ArC2'; 141.5, ArC3 and ArC3'; 132.5, ArC1 and ArC1'; 122.8, ArC6 and ArC6'; 118.1, ArC4 and ArC4'; 116.8, ArC5 and ArC5', 60.1, 2 x OCH_3. IR: υ_{max} 3356m, 2973w, 2361m, 1618s, 1475s, 1221s, 987s, 836s cm^{-1}. MS (EI) *m/z* 400 ($M^{79}Br^{79}Br$, 50%), 402 ($M^{81}Br^{79}Br$, 100%), 404 ($M^{81}Br^{81}Br$, 50%). HRMS calculated for $C_{14}H_{14}N_2O_2{}^{79}Br_2$: 399.9422, found 399.9419.

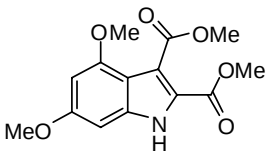
Dimethyl 2-(3,5-dimethoxyphenylamino)maleate (10)



To a solution of 3,5-dimethoxyaniline **9** (1.07 g, 7.01 mmol) in methanol (20 mL) was added dimethyl acetylenedicarboxylate (1.29 mL, 10.52 mmol) and the reaction stirred at 25 °C for 24 h. The solvent was removed *in vacuo* and the crude residue redissolved in EtOAc (50 mL). The organic layer was washed with water (3 x 50mL) and brine (1 x 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was subjected to flash silica gel column chromatography (10% EtOAc:hexane) to yield the desired Michael addition product **10** as a bright yellow viscous oil,

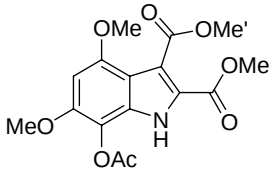
which after standing at room temperature for one week solidified to a yellow solid (1.96 g, 95%). mp: 57-59 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.57, bs, 1H, NH; 6.19, t, *J* = 2.0 Hz, 1H, ArC4; 6.04, d, *J* = 2.0 Hz, 2H, ArH2 and ArH6; 5.34, s, 1H, C=CH; 3.721, s, 6H, ArC3 and ArC5-OCH_3; 3.717, s, 3H, OCH_3; 3.714, s, 3H, OCH_3. ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.9, C=O; 165.1, C=O; 161.4, ArC3 and ArC5; 148.1, C=CH; 142.2, ArC1; 99.1, ArC2 and ArC6; 96.8, ArC4; 94.0, CH=C; 55.5, ArC3 and ArC5-OCH_3; 53.0, C(O)OCH_3; 51.4, C(O)OCH_3. MS (EI) *m/z* 295 (M^+, 100%). HRMS calculated for $C_{14}H_{17}NO_6$: 295.1056, found 295.1052.

Dimethyl 4,6-dimethoxyindole-2,3-dicarboxylate (11)



A 50 mL round bottom flask was charged with the Michael product **10** (87 mg, 0.295 mmol), $Cu(OAc)_2.H_2O$ (5.9 mg, 10 mol%) and $Pd(OAc)_2$ (6.6 mg, 10 mol%), and *N*,*N*-dimethylacetamide (DMA) (2 mL). The reaction was stirred at 75 °C for 18 h, after which time TLC analysis showed complete conversion of the starting material to the desired indole (bright blue absorbance under UV light). The reaction was diluted with EtOAc (50 mL) and filtered through a short plug of gravity silica gel and washed with EtOAc (50 mL). The organic filtrate was then washed with 1M HCl (30 mL), which was back extracted with EtOAc (1 x 20 mL). The combined organic extracts were then washed with water (4 x 30 mL) and brine (1 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to provide the desired indole **11** as a light brown crystalline solid (69 mg, 80%), which upon ^{1}H NMR analysis showed >95% purity. The crude indole was subjected to flash silica gel column chromatography (20% acetone:hexane) to remove any slight impurities, giving the indole **11** as pale brown crystals (66 mg, 77%), which were spectroscopically identical to that reported in the literature.[5] mp: 178-180 °C (Lit. 195-196 °C).[5] ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 300 MHz): δ 11.90, bs, 1H, NH; 6.45, d, *J* = 1.8 Hz, 1H, ArH7; 6.17, d, *J* = 2.1 Hz, 1H, ArH5; 3.82, s, 3H, C=O(OCH_3); 3.81, s, 3H, C=O(OCH_3); 3.79, s, 3H, OCH_3; 3.78, s, 3H, OCH_3. ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 75 MHz) δ 166.1, C=O'; 160.3, C=O; 159.6, ArC6; 153.7, ArC4; 137.5, ArC7a; 121.3, ArC2; 113.8, ArC3; 110.4, ArC3a; 93.0, ArC5; 86.3, ArC7; 55.3, OCH_3; 55.1, OCH_3; 51.8, C=O(OCH_3); 51.6, C=O(OCH_3). IR: υ_{max} 3318m, 2912w, 1729m, 1685s, 1634m, 1584m, 1541m, 1459m, 1281s, 1215s, 1152s, 1130m, 1070m, 805m cm^{-1}. MS (EI) *m/z* 293 (M^+, 50%), 261 (100%). HRMS calculated for $C_{14}H_{15}NO_6$: 293.0899, found 293.0895.

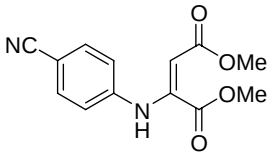
Dimethyl 7-acetoxy-4,6-dimethoxyindole-2,3-dicarboxylate



To a solution of the Michael product **10** (109 mg, 0.369 mmol) in DMA (3 mL) was added $Pd(OAc)_2$ (166 mg, 0.729 mmol). The reaction was stirred at

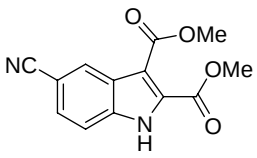
70 °C for 24 h with exposure to air, after which time EtOAc (50 mL) was added. The solution was filtered through celite with washes of EtOAc (50 mL), and the filtrate partitioned with water (50 mL). The aqueous layer was back extracted with EtOAc (2 x 15 mL), and the combined organic extracts were washed with water (4 x 50 mL), brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was subjected to flash silica gel column chromatography (40% EtOAc:hexane) yielding the title indole as an opaque semi-solid (70 mg, 54%). mp: 115-118 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.86, bs, 1H, NH; 6.31, s, 1H, ArH5; 3.96, s, 3H, C(O)OC$\underline{H}_3$'; 3.90, 3.892, 3.885, s, 2 x OCH_3 and C(O)OC$\underline{H}_3$; 2.39, s, 3H, C$\underline{H}_3$ (from OAc). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.0, $\underline{C}$(O)CH_3; 166.5, $\underline{C}$(O)OCH_3'; 161.0, $\underline{C}$(O)OCH_3; 152.3, 150.1, ArC4 and ArC6; 130.7, ArC7a; 123.1, ArC2; 118.6, ArC3a; 115.2, ArC3; 112.3, ArC7; 90.5, ArC5; 57.2, 56.1, 2 x OCH_3; 52.7, 52.5, 2 x C(O)O$\underline{C}H_3$; 20.6, CH_3. IR: υ_{max} 3432w, 2940w, 1737s, 1711s, 1649m, 1537m, 1460m, 1301s, 1250s, 1219s, 1127s, 789m cm^{-1}. MS (EI) *m/z* 351 (M^+, 75%), 277 (100%). HRMS calculated for $C_{16}H_{17}NO_8$: 351.0954, found 351.0953.

Dimethyl 2-(4-cyanophenylamino)maleate (12)



To a solution of 4-aminobenzonitrile (0.242 g, 2.05 mmol) in methanol (7 mL) was added dimethyl acetylenedicarboxylate (0.327 mL, 2.66 mmol) and the reaction stirred at 70 °C for 24 h. The solvent was removed *in vacuo* and the crude residue redissolved in EtOAc (25 mL) and absorbed onto gravity silica gel. The crude residue was subjected to gravity silica gel column chromatography (10% EtOAc:hexane) to yield the desired Michael addition product **12** as an off-white crystalline solid (0.459 g, 86%). mp: 108-109 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.69, bs, 1H, NH; 7.53, AA'XX' spin system, $J_{AA'XX'}$ = 8.5 Hz, 2H, ArH2 and ArH6; 6.85, AA'XX' spin system, $J_{AA'XX'}$ = 8.5 Hz, 2H, ArH3 and ArH5; 5.61, s, 1H, C=CH; 3.75, s, 3H, OCH_3; 3.74, s, 3H, OCH_3. ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.3, C=O; 164.1, C=O; 145.4, $\underline{C}$=CH; 144.4, ArC4; 133.3, ArC3 and ArC5; 119.8, ArC2 and ArC6; 118.9, CN; 106.4, ArC1; 98.6, C=$\underline{C}$H; 53.2, OCH_3; 51.7, OCH_3. IR: υ_{max} 3257w, 2950w, 2361w, 2223m, 1738m, 1682m, 1699s, 1515m, 1429m, 1279s, 1213s, 1192s, 1140s, 1025m, 806s cm^{-1}. MS (EI) *m/z* 260 (M^+, 75%), 169 (100%). HRMS calculated for $C_{13}H_{12}N_2O_4$: 260.0797, found 260.0807.

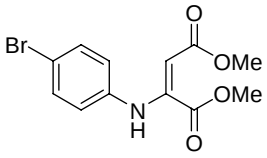
Dimethyl 5-cyanoindole-2,3-dicarboxylate (13)



A 50 mL round bottom flask was charged with the Michael product **12** (100 mg, 0.385 mmol), $Cu(OTf)_2$ (20.9 mg, 15 mol%) and $Pd(OAc)_2$ (8.64 mg, 10 mol%), and DMA (2 mL). The reaction was stirred at 70 °C for 24 h, after

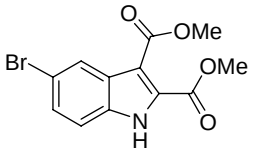
which time TLC analysis showed complete conversion of the starting material to the desired indole (bright blue absorbance under UV light). The reaction was diluted with EtOAc (50 mL) and filtered through a short plug of gravity silica gel and washed with EtOAc (50 mL). The organic filtrate was then washed with 1M HCl (30 mL), which was then back extracted with EtOAc (1 x 20 mL). The combined organic extracts were washed with water (4 x 30 mL) and brine (1 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was subjected to gravity silica gel column chromatography (30% EtOAc:hexane increased to 50% EtOAc:hexane), providing the desired indole **13** as a light yellow crystalline solid (35 mg, 35%). mp: 198-199 °C. ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 500 MHz): δ 12.93, bs, 1H, NH; 8.31, s, 1H, ArH4; 7.62, d, J = 8.5 Hz, 1H, ArH6; 7.52, d, J = 8.5Hz, 1H, ArH7; 3.92, s, 3H, OCH_3; 3.88, s, 3H, OCH_3. ^{13}C NMR (DMSO-d_6, 75 MHz) δ 163.1, C=O'; 160.8, C=O; 136.8, ArC7a; 132.0, ArC2; 127.3, ArC4; 127.1, ArC6; 125.2, ArC3; 119.4, ArC3a; 114.5, ArC7; 109.5, CN; 104.6, ArC5; 52.9, OCH_3; 51.8, OCH_3. IR: υ_{max} 3318s, 2955w, 2366w, 2217m, 1711m, 1679s, 1537s, 1435s, 1356s, 1315m, 1275s, 1231s, 1145m, 811m cm^{-1}. MS (EI) *m/z* 258 (M^+, 25%), 161 (100%). HRMS calculated for $C_{13}H_{10}N_2O_4$: 258.0641, found 258.0634.

Dimethyl 2-(4-bromophenylamino)maleate (14)



To a solution of 4-bromoaniline (0.375 g, 2.17 mmol) in methanol (7 mL) was added dimethyl acetylenedicarboxylate (0.346 mL, 2.82 mmol) and the reaction stirred at 70 °C for 24 h. The solvent was removed *in vacuo* and the crude residue redissolved in EtOAc (25 mL) and absorbed onto gravity silica gel. The crude residue was subjected to gravity silica gel column chromatography (5% EtOAc:hexane) to yield the desired Michael addition product **14** as a bright yellow oil (0.546 g, 79%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.59, bs, 1H, NH; 7.38, AA'XX spin system, $J_{AA'XX'}$ = 9.0 Hz, 2H, ArH3 and ArH5; 6.76, AA'XX' spin system, $J_{AA'XX'}$ = 9.0 Hz, 2H, ArH2 and ArH6; 5.45, s, 1H, C=CH; 3.74, s, 3H, OCH_3; 3.72, s, 3H, OCH_3. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.9, C=O; 164.6, C=O; 147.4, C=CH; 139.6, ArC1; 132.3, ArC2 and ArC6; 122.4, ArC3 and ArC5; 117.2, ArC4; 95.0, C=CH; 53.0, OCH_3; 51.5, OCH_3. MS (EI) *m/z* 313 (M^{79}Br, 60%), 315 (M^{81}Br, 60%), 224 (100%). HRMS calculated for $C_{12}H_{12}NO_4{}^{79}Br$: 312.9950, found 312.9950.

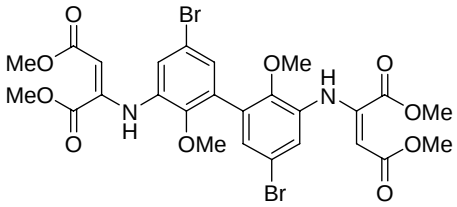
Dimethyl 5-bromoindole-2,3-dicarboxylate (15)



A 50 mL round bottom flask was charged with the Michael product **14** (88 mg, 0.280 mmol), $Cu(OAc)_2.H_2O$ (28.0 mg, 50 mol%) and $Pd(OAc)_2$ (6.30 mg, 10 mol%), and DMA (2 mL). The reaction was stirred at 70 °C for 24 h,

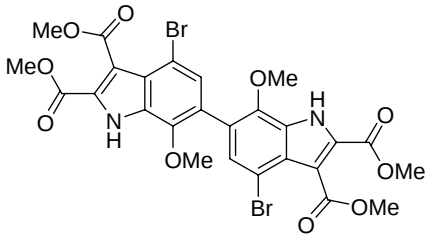
after which time TLC analysis showed complete conversion of the starting material to two major products. The reaction was diluted with EtOAc (50 mL) and partitioned with 1M HCl (30 mL), which was then back extracted with EtOAc (2 x 10 mL). The combined organic extracts were then washed with water (3 x 30 mL) and brine (1 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude indole was subjected to gravity silica gel column chromatography (50% EtOAc:petroleum spirit) providing the desired indole **15** as a yellow solid (19 mg, 22%), which was spectroscopically identical to that reported in the literature.[6] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.51, bs, 1H, NH; 8.22, d, *J* = 1.5 Hz, 1H, ArH4; 7.45, dd, *J* = 8.7 Hz, 1.8 Hz, 1H, ArH6; 7.32, d, *J* = 8.7 Hz, 1H, ArH7; 3.99, s, 3H and 3.98, s, 3H, 2 x C(O)OCH_3. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.1 and 161.2, 2 x $\underline{C}$(O)OCH_3; 133.4 and 133.2, ArC7a and ArC3a; 129.3, ArC2; 129.2, ArC4; 128.4, ArC3; 125.5, ArC6; 116.3, ArC5; 113.6, ArC7; 53.0 and 52.1, 2 x C(O)O$\underline{C}H_3$. IR: υ_{max} 1711m, 1245m, 780m cm^{-1}. MS (EI) *m/z* 331 (M^{79}Br, 50%), 333 (M^{81}Br, 50%), 279 (60%), 221 (100%). HRMS calculated for $C_{12}H_{10}NO_4{}^{79}Br$: 310.9793, found 310.9791.

Tetramethyl 2,2'-(5,5'-dibromo-2,2'-dimethoxy-1,1'-biphenyl-3,3'-diamino)dimaleate (16)



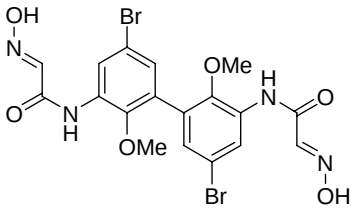
To a solution of bianiline **8** (40 mg, 0.010 mmol) in methanol (5 mL) was added dimethyl acetylenedicarboxylate (0.05 mL, 0.398 mmol) and the reaction was heated at reflux for 24 h. The solvent was removed *in vacuo*, and the crude residue was redissolved in EtOAc (30 mL), and washed with water (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was subjected to flash silica gel column chromatography (5% EtOAc:hexane) yielding the title compound **16** as a bright yellow viscous oil, which solidified to a yellow solid at room temperature after approximately 5 days (48 mg, 71%). mp: 121-122 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.65, s, 2H, 2 x NH; 7.11, d, *J* = 2 Hz, 2H, ArH4 and ArH4'; 7.03, d, *J* = 2 Hz, 2H, ArH6 and ArH6'; 5.54, s, 2H, 2 x C=CH; 3.78, s, 6H, 2 x C=CH-C(O)OC$\underline{H}_3$; 3.75, s, 6H, 2 x HC=C-C(O)OC$\underline{H}_3$; 3.40, s, 6H, 2 x OCH_3. ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.9, 2 x HC=C-$\underline{C}$(O)OCH_3; 164.1, 2 x C=CH-$\underline{C}$(O)OCH_3; 148.6, ArC2 and ArC2'; 147.1, 2 x $\underline{C}$=CH; 135.5, ArC1 and ArC1'; 132.5, ArC3 and ArC3'; 128.9, ArC6 and ArC6'; 124.1, ArC4 and ArC4'; 116.3, ArC5 and ArC5'; 94.8, 2 x C=$\underline{C}$H; 60.8, 2 x OCH_3; 53.0, C=CH-C(O)O$\underline{C}H_3$; 51.5, HC=C-C(O)O$\underline{C}H_3$. MS (EI) *m/z* 684 ($M^{79}Br^{79}$Br, 50%), 686 ($M^{81}Br^{79}$Br, 100%), 688 ($M^{81}Br^{81}$Br, 50%). HRMS calculated for $C_{26}H_{26}N_2O_{10}{}^{79}Br_2$: 683.9954, found 683.9973.

Tetramethyl-4,4'-dibromo-7,7'-dimethoxy-6,6'-biindole-2,2',3,3'-tetracarboxylate (1)



To a solution of the Michael product **16** (143 mg, 0.209 mmol) in DMA (3 mL) was added $Pd(OAc)_2$ (14 mg, 30 mol%) and $Cu(OAc)_2.H_2O$ (41.7 mg, 100 mol%). A $CaCl_2$ drying tube was placed on the flask and the reaction was heated at 80 °C while exposed to air for 18 h, until TLC analysis indicated that no starting material remained. The reaction was diluted with EtOAc (30 mL), filtered through a celite:gravity silica gel plug (1:1), washed with further portions of EtOAc (100 mL) and partitioned with 1M HCl (15 mL). The aqueous phase was back extracted with further portions of EtOAc (2 x 10 mL) and the combined organic extracts were washed with water (3 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was absorbed onto gravity silica gel and purified by flash silica gel column chromatography (40% EtOAc:petroleum spirit up to 50% EtOAc:petroleum spirit), providing the 6,6'-biindole **1** as an off-white solid (31 mg, 22%). mp: 282-284 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.36, bs, 2H, 2 x NH; 7.37, s, 2H, ArC5 and ArC5'; 4.03, s, 6H, and 3.98, s, 6H, 4 x C(O)OC<u>H</u>$_3$; 3.56, s, 6H, 2 x OCH_3. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.7 and 160.7, 4 x <u>C</u>(O)OCH_3; 143.6, ArC7 and ArC7'; 130.4, ArC7a and ArC7a'; 128.5, ArC5 and ArC5'; 125.9, ArC2 and ArC2'; 125.7, ArC6 and ArC6'; 125.6, ArC3 and ArC3'; 116.4, ArC3a and ArC3a'; 108.8, ArC4 and C4'; 61.3, 2 x OCH_3; 53.1 and 53.0, 4 x C(O)O<u>C</u>H_3. IR: υ_{max} 3339m, 3257m, 2955w, 1731m, 1706s, 1537m, 1455m, 1302s, 1234s, 1207m, 994m, 789m cm^{-1}. MS (EI) *m/z* 680 ($M^{79}Br^{79}Br$, 45%), 682 ($M^{81}Br^{79}Br$, 100%), 684 ($M^{81}Br^{81}Br$, 50%). HRMS calculated for HRMS calculated for $C_{26}H_{22}N_2O_{10}{}^{81}Br_2$: 683.9600, found 683.9602.

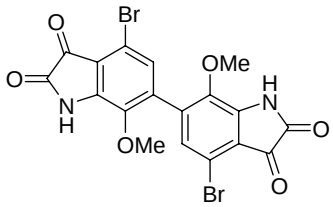
5,5'-Dibromo-3,3'-di(*N*-2-hydroxyiminoacetanilide)-2,2'-dimethoxy-1,1'-biphenyl (17)



To a suspension of bianiline **8** (40 mg, 0.100 mmol) in water (3 mL) heated at 50 °C was added a warmed solution (35 °C) of chloral hydrate (99 mg, 0.597 mmol) and solid Na_2SO_4 (0.509 g, 3.59 mmol) in water (3 mL), concentrated HCl (0.100 mL, 1.02 mmol), and finally a solution of hydroxylamine hydrochloride (125 mg, 1.79 mmol) in water (3 mL). The mixture was stirred and heated at 80 °C for 22 h before being diluted with water (40 mL). The reaction was allowed to cool to room temperature and filtered, leaving a white gum. Upon drying under high vacuum a white solid was obtained, and determined to be the title compound **17** (40 mg, 74%). mp: 231-234 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.48, bs, 2H, 2 x OH; 9.50, s, 2H, 2 x NH; 8.42, d, J = 2.4 Hz, 2H, ArH4 and ArH4'; 7.79, s, 2H, 2 x CH=N; 7.31, d, J = 2.4 Hz, 2H, ArH6 and ArH6'; 3.45, s, 6H, 2 x OCH_3. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 160.4, 2 x C=O; 146.6, ArC2 and ArC2'; 143.6, <u>C</u>H=N ; 132.6, ArC3 and ArC3'; 131.4, ArC1 and ArC1';

128.4, ArC6 and ArC6'; 123.5, ArC4 and ArC4'; 115.5, ArC5 and ArC5'; 60.9, 2 x OCH_3. IR: υ_{max} 3375m, 3185m, 2909m, 2361w, 1668s, 1615s, 1593s, 1519s, 1456s, 1418s, 1255s, 1228s, 1136m, 1020s, 868m, 754s cm^{-1}. MS (ES-) *m/z* 540.54 ($M^{79}Br^{79}Br$-1, 50%), 542.53 ($M^{81}Br^{79}Br$-1, 100%), 544.53 ($M^{81}Br^{81}Br$-1, 50%). HRMS calculated for $C_{18}H_{15}N_4O_6{}^{79}Br_2$: 540.9358, found 540.9359.

4,4'-Dibromo-7,7'-dimethoxy-6,6'-biisatin (2)



To concentrated H_2SO_4 (2.5 mL) at 50 °C was added **17** (26 mg, 0.048 mmol). The reaction was heated at 80 °C for 2 h, before being quenched by transferring onto crushed ice and diluted to 50 mL. The resultant solution was filtered and washed with water, then dried under high vacuum to yield 6,6'-biisatin **2** as a dark red solid (20 mg, 83%). mp: >280 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.49, bs, 2H, 2 x NH; 7.18, s, 2H, ArH5 and ArH5'; 3.53, s, 6H, 2 x OCH_3. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 181.3, ArC3 and ArC3'; 158.9, ArC2 and ArC2'; 145.5, ArC7a and ArC7a'; 141.9, ArC7 and ArC7'; 139.4, ArC3a and ArC3a'; 127.5, ArC5 and ArC5'; 117.8, ArC4 and ArC4'; 113.1, ArC6 and ArC6'; 61.2, 2 x OCH_3. IR: υ_{max} 3161w, 2986w, 2362m, 2328m, 1737s, 1615s, 1573m, 1473m, 1395m, 1300m, 1241s, 1192m, 973m, 887m cm^{-1}. MS (ES-) *m/z* 506.36 ($M^{79}Br^{79}Br$-1, 50%), 508.33 ($M^{81}Br^{79}Br$-1, 100%), 510.31 ($M^{81}Br^{81}Br$-1, 50%). HRMS calculated for $C_{18}H_9N_2O_6{}^{79}Br_2$: 506.8827, found 506.8868.

References:

1. A similar acetoxy-product was reported during an attempted aryl C–H intramolecular insertion on a naphthoquinone using an excess of $Pd(OAc)_2$ and no additional oxidant in acetonitrile, see Knölker, H-J.; O'Sullivan, N. *Tetrahedron* 1994, **50**, 10893-10908.
2. Facchetti, S.; Losi, D.; Iuliano, A. *Tetrahedron: Asymm.* **2006**, 17, 2993-3003.
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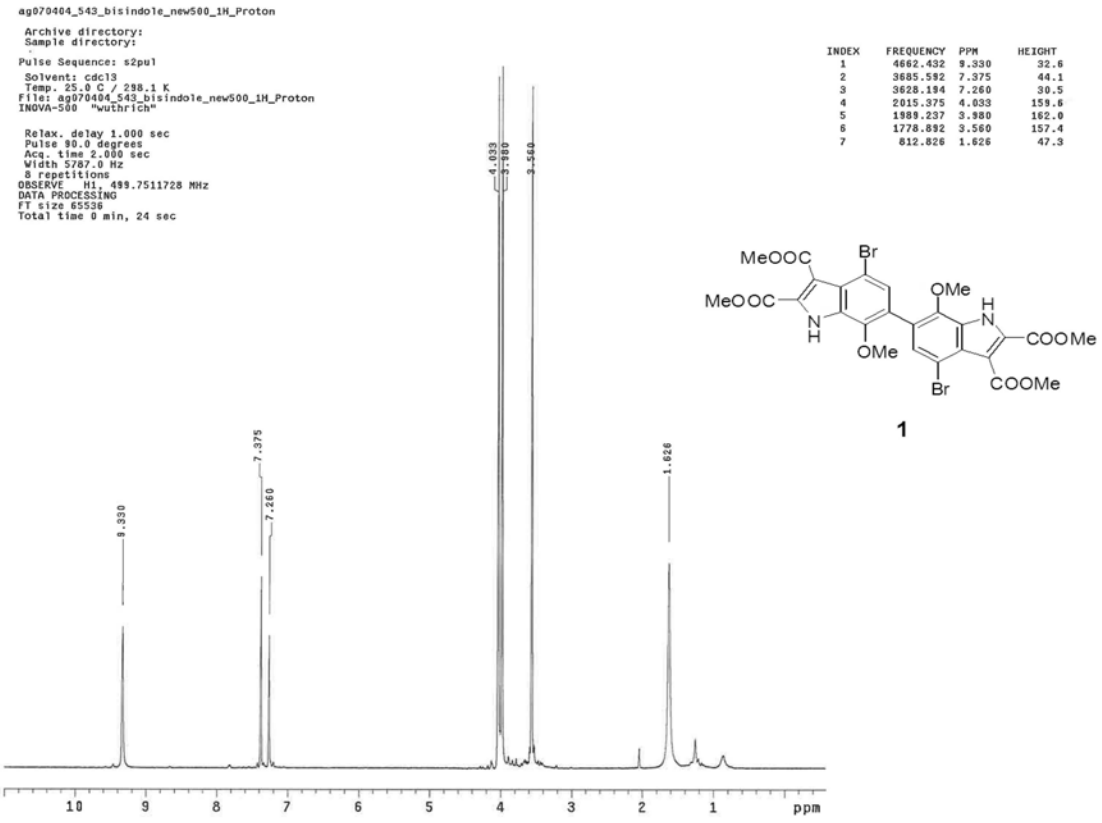
4. Viswanathan, N.; Patankar, S. J. *Ind. J. Chem.* **1985**, 24B, 1284-1285.
5. Black, D. St. C.; Kumar, N.; Wong, L. C. H. *Aust. J. Chem.* **1986**, 39, 15-20.
6. Miki, Y.; Umemoto, M.; Nakamura, M.; Hibino, H.; Ohkita, N.; Kato, A.; Aoki, Y. *Heterocycles* **2006**, 68, 1893-1899.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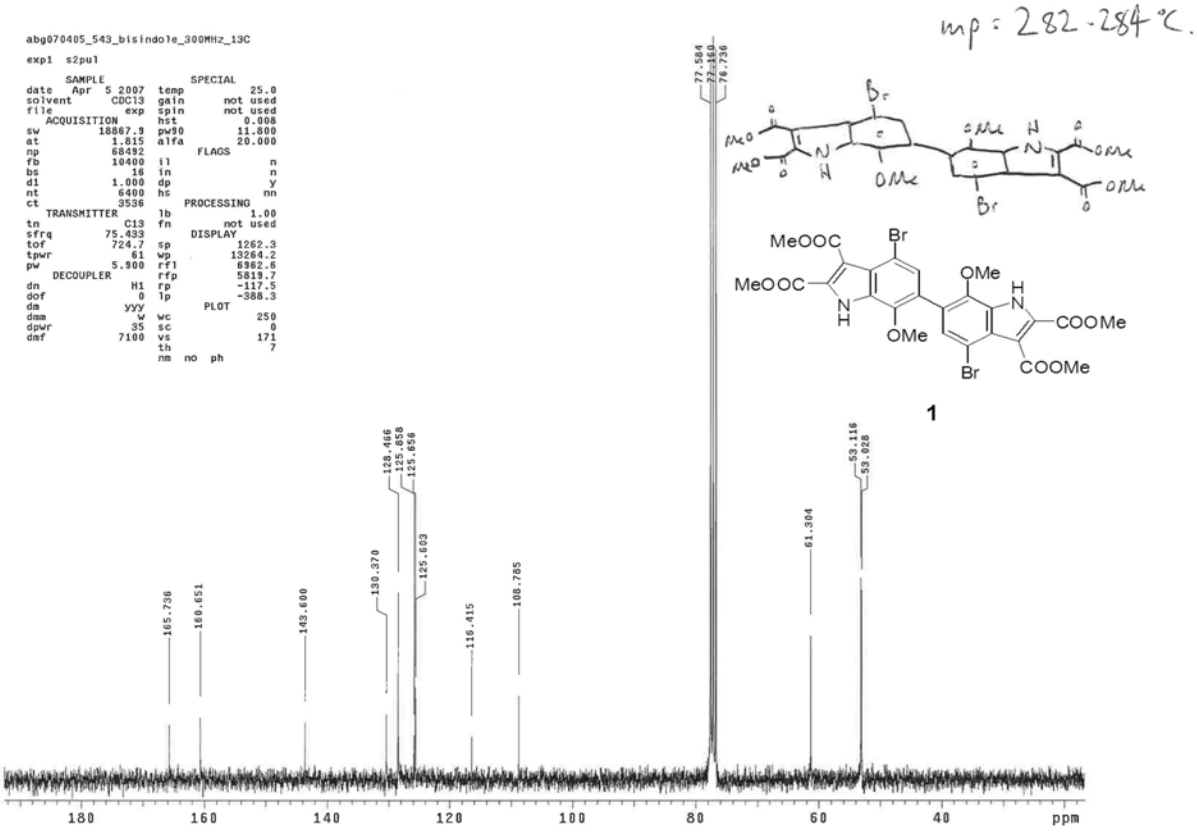
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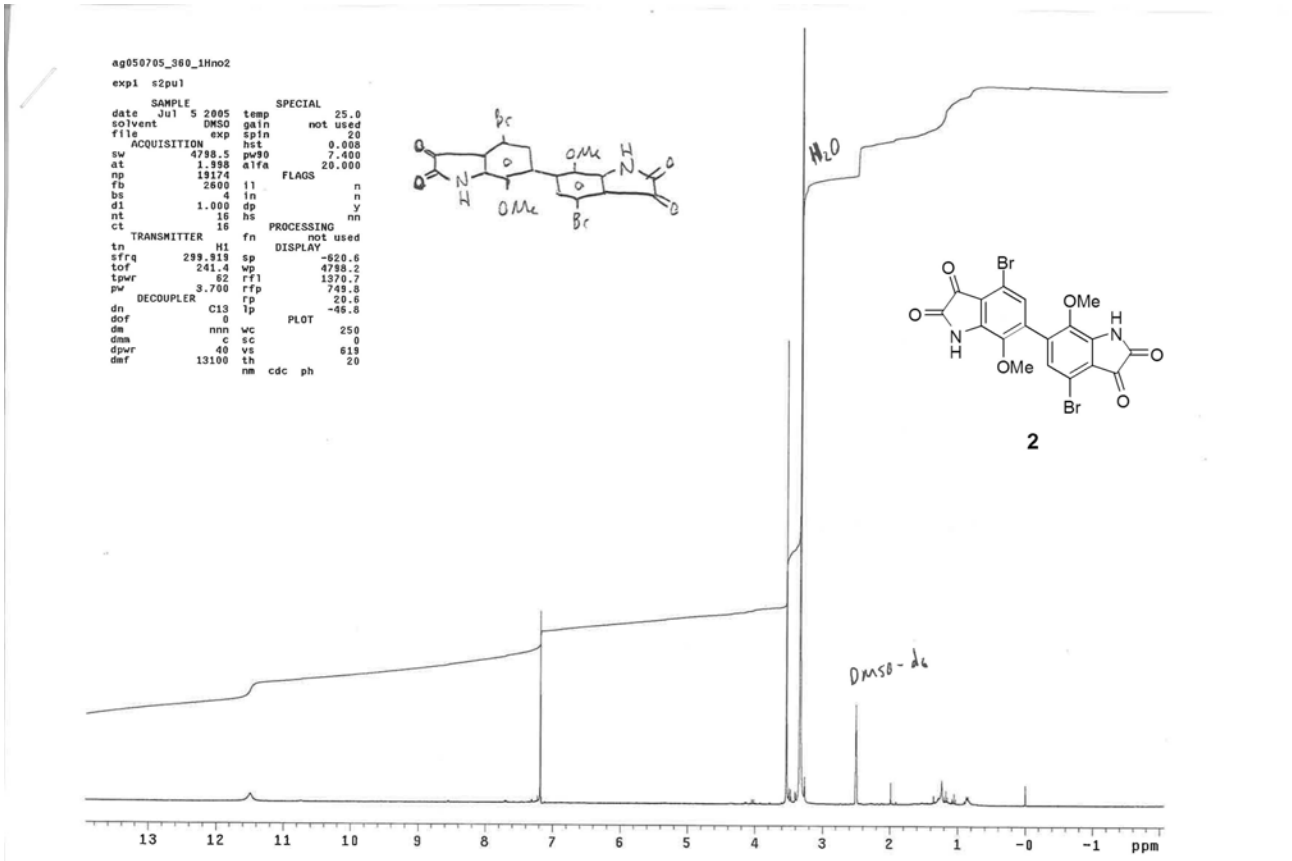
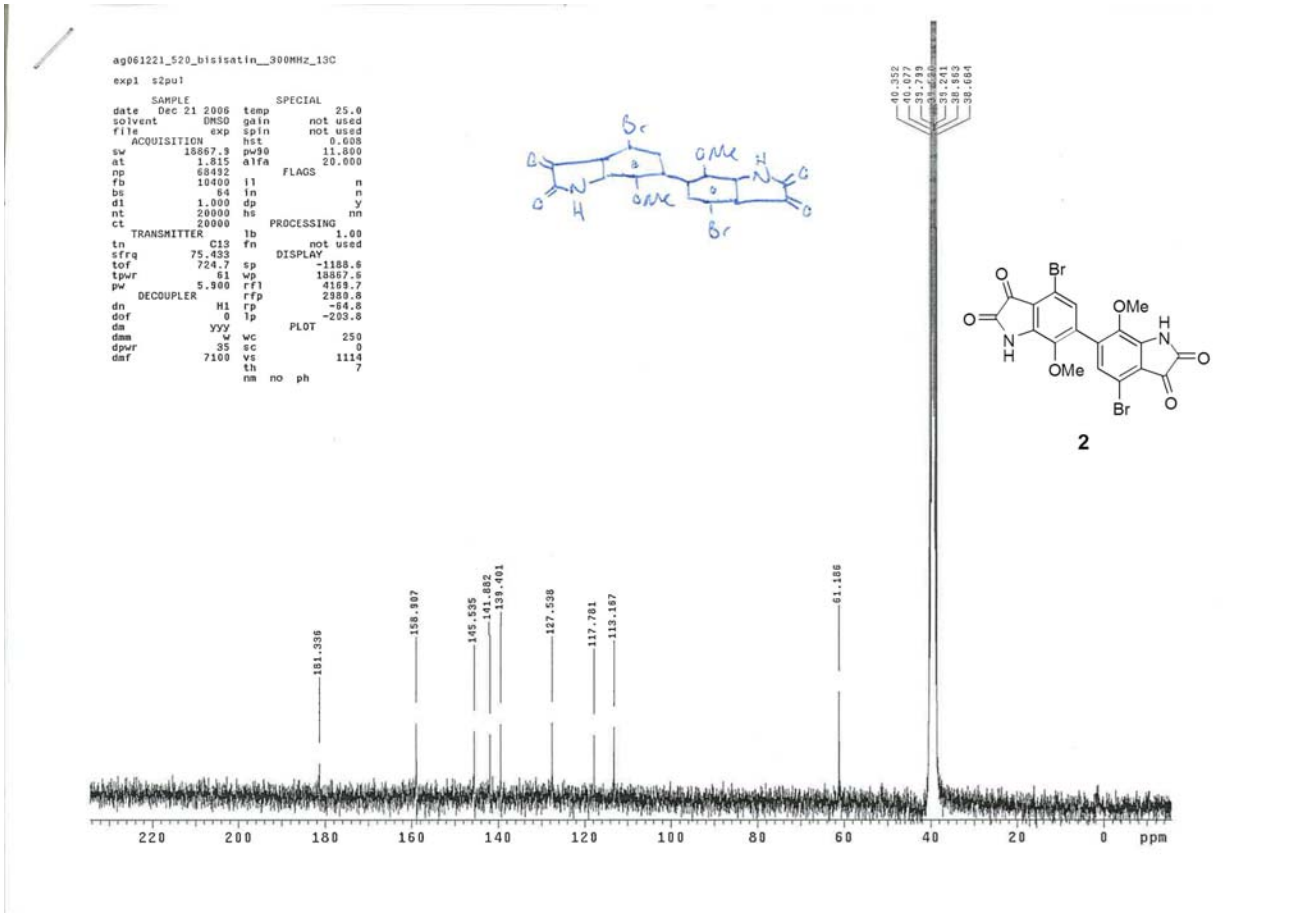
1


ag050705_360_1Hno2
exp1 s2pul
SAMPLE
date Jul 5 2005
solvent DMSO
file exp
ACQUISITION
sw 4798.5
at 1.998
np 19174
fb 2600
bs 4
d1 1.000
nt 16
ct 16
TRANSMITTER
tn H1
sfrq 299.919
tof 241.4
tpwr 62
pw 3.700
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 40
dmf 13100
SPECIAL
temp 25.0
gain not used
spin 20
hst 0.008
pw90 7.400
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -620.6
wp 4798.2
rfl 1370.7
rfp 749.8
rp 20.6
lp -46.8
PLOT
wc 250
sc 0
vs 619
th 20
nm cdc ph
H2O
DMSO-d6
2
13 12 11 10 9 8 7 6 5 4 3 2 1 -0 -1 ppm


ag061221_520_bisisatin__300MHz_13C
exp1 s2pul
SAMPLE
date Dec 21 2006
solvent DMSO
file exp
ACQUISITION
sw 18867.9
at 1.815
np 68492
fb 10400
bs 64
d1 1.000
nt 20000
ct 20000
TRANSMITTER
tn C13
sfrq 75.433
tof 724.7
tpwr 61
pw 5.900
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 35
dmf 7100
SPECIAL
temp 25.0
gain not used
spin not used
hst 0.608
pw90 11.800
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -1188.6
wp 18867.6
rfl 4169.7
rfp 2389.8
rp -84.8
lp -203.8
PLOT
wc 250
sc 0
vs 1114
th 7
nm no ph
40.352
40.077
39.799
39.524
39.241
38.963
38.684
181.336
158.907
145.535
141.882
139.401
127.538
117.781
113.187
61.186
2
220 200 180 160 140 120 100 80 60 40 20 0 ppm