A Convenient Synthetic Route to 7,8-Fused Heterocyclic Ring Derivatives of (*S*)-2,3-Dihydro-1,4-benzodioxin-2-methanol

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Abstract: A much improved synthesis of the dioxino[2,3-*e*]indolemethanol **9a** is described, which is shorter, higher-yielding and less hazardous than the previous synthesis of its racemic form. This novel procedure now allows preparation of multigram quantities of the enantiomerically pure compound. Application of this methodology to different 5-hydroxyheterocycles enables access to furo[3,2-*f*][1,4]benzodioxin, thieno[3,2-*f*][1,4]benzodioxin and 1,4-dioxino[2,3-*e*]indazole ring systems.

Key words: 5-hydroxyheterocycles, tricyclic-1,4-benzodioxin-2-methanols, formylation, Baeyer–Villiger oxidation, decarboxylation

During the course of our investigations to find a potent, novel antipyschotic agent, the dioxino[2,3-*e*]indolemethanol **9a** was required as a key intermediate in the synthesis of a lead compound. The racemic form of **9a** had previously been prepared by Ennis et al[1] but this process was long, low-yielding and used hazardous azide for construction of the indole nucleus. Consequently, an alternative preparation of the key intermediate **9a** was sought. We now wish to report a novel, shorter, higher-yielding and less hazardous preparation of the indole **9a** which is more suitable for scale-up (Schemes 1 and 2).

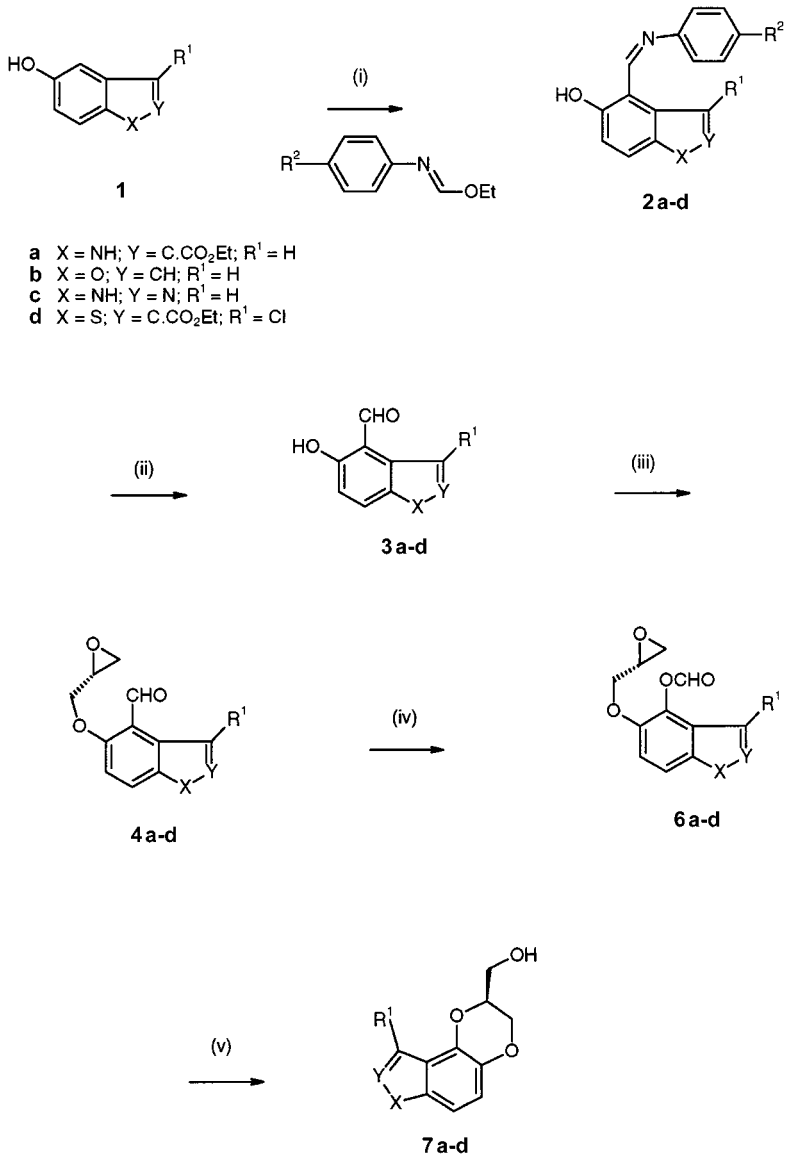
Julia and Lallemand [2] had previously reported that reaction of ethyl 5-hydroxyindole-2-carboxylate **(1a)** with 4-methoxyaniline and triethyl orthoformate at 165°C and then subsequent acid hydrolysis of the intermediate imine (**2a;** R^2 = MeO) gave the aldehyde **3a** in 48% yield. However, when we repeated this reaction a very low yield (9%) of the imine was isolated. A much more satisfactory preparation of the aldehyde **3a** was achieved by treating **1a** with commercially available ethyl *N*-phenylformimidate followed by hydrolysis of the intermediate imine (**2a;** R^2 = H) with 5 M hydrochloric acid. Not suprisingly, formylation of the much more reactive 5-hydroxyindole using these conditions produced very complex mixtures from which no pure product could be isolated. The aldehyde **3a** was elaborated to the dioxino[2,3-*e*]indole **7a** by the route outlined in Scheme 1. Alkylation of **3a** with (*R*)-glycidyl tosylate and K_2CO_3 in DMF at 60°C gave the epoxyether **4a**; small amounts of the bis-alkylated product **5** were also isolated from the reaction. Treatment of **4a** with 3-chloroperoxybenzoic acid (*m*CPBA) gave a moderate yield (47%) of the formate ester **6a**. However, it is well known that trifluoroacetic acid (TFA) can be used to accelerate Baeyer–Villiger oxidations,[3] and to that end addition of one equivalent of TFA to the oxidation reaction at 0°C gave a 75% yield of **6a** after only 30 minutes. Subsequent reaction of **6a** with aqueous K_2CO_3 in THF at room temperature furnished the dihydrodioxinoindole **7a**. The phenolic alkylation described above is of a type known to proceed with retention of configuration at the glycidyl asymmetric centre,[4] leading eventually to (*S*)-(2,3-dihyro-1,4-benzodioxin-2-yl)methanol derivatives. Hydrolysis of **7a** with lithium hydroxide monohydrate furnished **8a** which was then decarboxylated with copper in quinoline to afford the key intermediate **9a** (Scheme 2). It is worth noting that decarboxylation of **8a** at 257°C following the procedure of Ennis et al[1] produced consistently lower yields of **9a** than the method given above, and that yields were particularly poor on scale-up.

The formylation procedure described above was then applied to 5-hydroxybenzofuran **(1b)**,[5] 5-hydroxyindazole **(1c)**[6] and ethyl 3-chloro-5-hydroxybenzo[*b*]thiophene-2-carboxylate **(1d)**.[7] This successfully furnished the corresponding 4-formyl derivatives **3b**,[8] **3c**, **3d** in varying yields (see experimental section). Elaboration of these aldehydes **3b**, **3c**, **3d** into the desired tricyclic systems was then achieved by the sequence outlined in Schemes 1 and 2.

In the furan series, final cyclisation of the formate ester **6b** with aqueous K_2CO_3 in THF furnished the required dihydrofuro[3,2-*f*][1,4]benzodioxinmethanol **7b** in 70% yield. Interestingly, small amounts of the formate **10** were also isolated from the reaction (no corresponding formates were observed to form in the other tricyclic systems).

Preparation of the indazole **7c** proved particularly problematical. In the Baeyer–Villiger oxidation of the aldehyde **4c** with *m*CPBA at 0°C a very complex reaction mixture resulted from which no formate ester **6c** could be isolated. However, careful chromatography of this crude reaction mixture enabled isolation of the desired dihydrodioxinoindazole **7c**, albeit in only 16% yield, suggesting that any intermediate formate ester **6c** may well be a very reactive or unstable species.

Baeyer–Villiger oxidation of the benzo[*b*]thiophene **4d** with *m*CPBA at room temperature proved to be a very slow reaction, producing the formate **6d** in only 7% yield after 24 hours reaction. In this case, preferential oxidation occurred at the benzo[*b*]thiophene sulfur. However, addition of one equivalent of TFA at 0°C accelerated the Baeyer–Villiger reaction such that a 50% yield of **6d** could be isolated after only 1 hour. Cyclisation with aqueous K_2CO_3 in THF produced the expected dihy-



Reagents and conditions: (i) Δ; (ii) 5 M aq HCl, Δ; (iii) (*R*)-glycidyl tosylate/K_2CO_3/DMF, 60°C; (iv) *m*CPBA/TFA; (v) aq K_2CO_3/THF

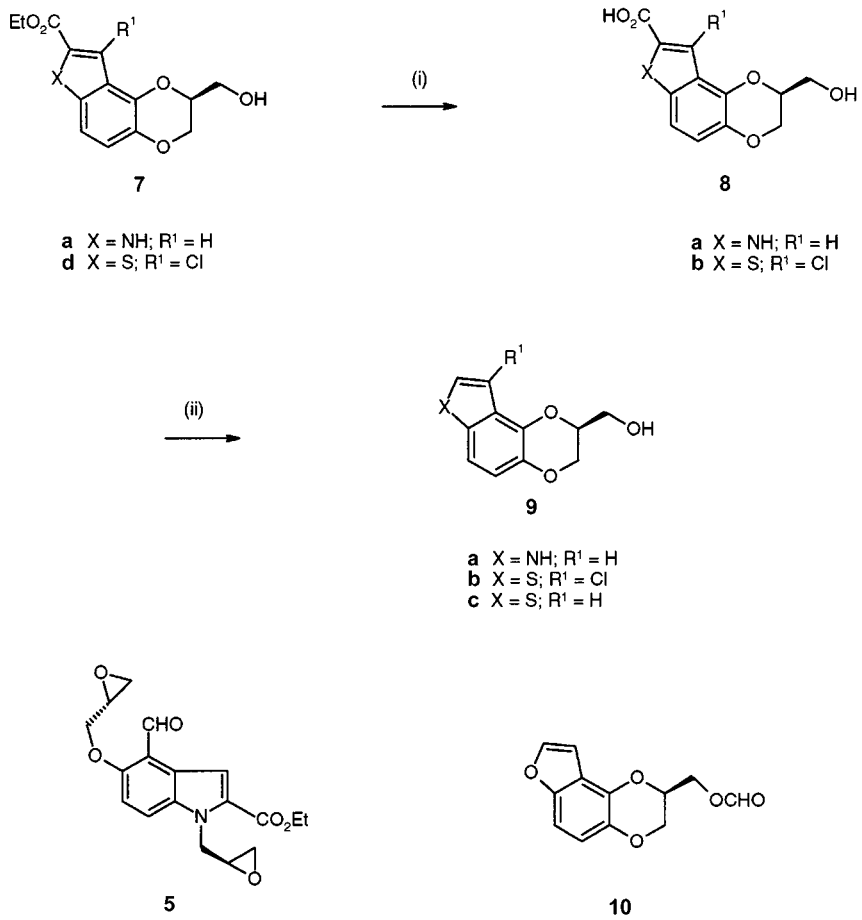
Scheme 1

drothienobenzodioxin **7d**, which was hydrolysed to the acid **8b** and then decarboxylated with copper in quinoline to afford the expected 9-chloro derivative **9b** in excellent yield (85%) together with a small amount (9%) of the dechlorinated product **9c**.

The stereochemistry at the 2-position in these tricyclic systems was assigned on the basis of the well-precedented S_N2 substitution of glycidyl arenesulfonates with phenoxides[4,9] and inversion of the stereochemistry upon intramolecular epoxide opening.[10] This was supported by a comparison of specific rotation and chiral HPLC data for (*S*)-2,3-dihydrofuro[3,2-*f*][1,4]benzodioxin-2-methanol **7b** and its (*R*)-enantiomer, which was prepared from (*S*)-glycidyl tosylate in an analogous manner.[11]

In summary, we have established a novel, shorter, higher-yielding and less hazardous synthesis of the enantiomerically pure dihydrodioxino[2,3-*e*]indole system **9a** which enables the preparation of multigram quantities. This route was then applied to transform appropriate hydroxy-heterocycles into the dihydrofuro[3,2-*f*][1,4]benzodioxin, dihydrothieno[3,2-*f*][1,4]benzodioxin and the dihydro-1,4-dioxino[2,3-*e*]indazole ring systems.

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer and are reported in ppm on the δscale from internal TMS using $CDCl_3$ as solvent unless otherwise stated. IR spectra were obtained using a Mattson-Unicam 3000 FTIR spectrometer. Mass spectra were recorded on a Finnigan



(i) LiOH•H_2O/MeOH/H_2O; (ii) Cu/quinoline, Δ

Scheme 2

MAT 95S instrument under electron inpact (70 eV) or where indicated, by chemical ionisation (CI). Elemental analyses were determined by the Physical Chemistry Department (Knoll Pharmaceuticals, Nottingham). TLC was performed using Merck Silica gel 60F_{254} plates. Flash column chromatography was carried out on silica 60A. The term 'dried' refers to use of anhyd $MgSO_4$ or Na_2SO_4. Ethyl 5-hydroxyindole-2-carboxylate **(1a)** and ethyl *N*-phenylformimidate were purchased from Lancaster Synthesis. Ethyl 3-chloro-5-methoxybenzo[*b*]thiophene-2-carboxylate was purchased from Maybridge Chemicals and (*R*)-glycidyl tosylate from Aldrich. Petroleum ether used had bp 40–60°C unless otherwise noted.

Ethyl 5-Hydroxy-4-(*N*-phenyliminomethyl)indole-2-carboxylate (2a)

A flask containing a mixture of **1a**[12] (68.31 g, 0.33 mol) and ethyl *N*-phenylformimidate (97%; 54.5g, 0.35 mol) was submerged into a pre-heated oil bath at 160–180°C and the mixture stirred for 2 h, by which time all of the EtOH produced in the reaction had been removed. The cooled reaction mixture was dissolved in boiling MeOH (2000 mL) and the resulting yellow solid collected by filtration to give **2a** (R^2 = H) (44.42 g, 44%)

IR (KBr): ν = 3300, 1694 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.36 (t, 3 H, *J* = 7 Hz, CH_3CH$_2$), 4.36 (q, 2 H, *J* = 7 Hz, CH$_3$CH_2), 6.93 (d, 1 H, *J* = 9 Hz, ArH), 7.30 (m, 1 H, ArH), 7.49 (m, 5 H, ArH), 7.71 (d, 1 H, *J* = 1.5 Hz, 3-H), 9.45 (s, 1 H, CH = N), 12.01 (br s, 1 H, NH), 13.70 (br s, 1 H, OH).

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.15; H, 5.2; N, 9.1. Found: C, 70.2; H, 5.2; N, 9.05.

Ethyl 4-Formyl-5-hydroxyindole-2-carboxylate (3a)

A stirred suspension of **2a** (R^2 = H) (64.0 g, 0.176 mol) in 5 M HCl (1500 mL) was heated at 70°C for 2 h. The mixture was poured into H_2O (1500 mL) and extracted with EtOAc (4 × 800 mL). The combined extracts were washed with brine (800 mL), dried and evaporated in vacuo to give **3a** (40.5 g, 99%) as a pink solid; mp 218–219°C (Lit.[1] mp 220°C).

IR (KBr): ν = 3327, 1693, 1637 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.35 (t, 3 H, *J* = 7 Hz, CH_3CH$_2$), 4.34 (q, 2 H, *J* = 7 Hz, CH$_3$CH_2), 6.99 (d, 1 H, *J* = 9 Hz, ArH), 7.63 (s, 1 H, 3-H), 7.66 (d, 1 H, *J* = 9 Hz, ArH), 10.55 (s, 1 H), 10.64 (s, 1 H), 12.11 (br s, 1 H, OH or NH).

Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.8; H, 4.7; N, 6.0. Found: C, 61.7; H, 4.7; N, 6.1.

Ethyl (*R*)-5-(2,3-Epoxypropoxy)-4-formylindole-2-carboxylate (4a)

A stirred solution of **3a** (1.5 g, 6.44 mmol) in anhyd DMF (40 mL) under N_2 was treated with K_2CO_3 (0.89 g, 6.44 mmol). A solution of (*R*)-glycidyl tosylate (1.47 g, 6.44 mmol) in anhyd DMF (30 mL) was then added and the mixture stirred at r.t. for 10 min and then at 60°C for 3 h. The mixture was poured into H_2O (400 mL) and extracted with EtOAc (3 × 200 mL). The combined extracts were washed with brine (6 × 200 mL), dried and evaporated in vacuo to leave a brown oil (2.19 g). Purification by flash column chromatography on silica gel using a 1:1 mixture of EtOAc and petroleum ether as eluant gave unreacted starting aldehyde **3a** (0.31 g, 20%) as a yellow solid. Further elution of the column afforded **4a** (1.07 g, 58%) as an off-white solid; mp 152–154°C.

IR (KBr): ν = 1689, 1667 cm^{-1}.

^{1}H NMR: δ = 1.43 (t, 3 H, *J* = 7 Hz, C*H*$_3$CH$_2$), 2.81 (m, 1 H), 2.95 (t, 1 H, *J* = 4.5 Hz), 3.43 (m, 1 H), 4.12 (m, 1 H), 4.41 (m, 3 H), 7.07 (d, 1 H, *J* = 9 Hz, ArH), 7.63 (d, 1 H, *J* = 9 Hz, ArH), 7.97 (br s, 1 H, 3-H), 9.25 (br s, 1 H, NH), 10.75 (s, 1 H, CHO).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.3; H, 5.2; N, 4.85. Found: C, 62.2; H, 5.2; N, 4.7.

Further elution of the column gave ethyl 5-[(*R*)–(2,3-epoxypropoxy)]-1-[(*R*)-(2,3-epoxypropyl)]-4-formylindole-2-carboxylate **(5)** (0.20 g, 9%) as a fawn solid.

Compound **5**

Mp 145–147°C.

IR (KBr): ν = 1712, 1665 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.35 (t, 3 H, *J* = 7 Hz, C*H*$_3$CH$_2$), 2.41 (m, 1H), 2.63 (m, 1H), 2.68 (m, 1 H), 2.87 (t, 1 H, *J* = 5 Hz), 3.26 (m, 1 H), 3.43 (m, 1 H), 4.11 (m, 1 H), 4.36 (q, 2 H, *J* = 7 Hz, MeC*H*$_2$O), 4.61 (m, 2 H), 5.04 (m, 1 H), 7.34 (d, 1 H, *J* = 9 Hz, ArH), 7.80 (br s, 1 H, 3-H), 8.00 (d, 1 H, *J* = 9 Hz, ArH), 10.62 (s, 1 H, CHO).

Anal. Calcd for $C_{18}H_{19}NO_6$ 0.4H_2O: C, 61.35; H, 5.65; N, 3.95. Found: C, 61.7; H, 5.8; N, 3.75

Ethyl (*R*)-5-(2,3-Epoxypropoxy)-4-formyloxyindole-2-carboxylate (6a)

A stirred solution of **4a** (1.95 g, 6.75 mmol) in CH_2Cl_2 (40 mL) was cooled to 0°C. 3-Chloroperoxybenzoic acid (86%; 1.75 g, 8.43 mmol) was then added, followed by a solution of trifluoroacetic acid (0.77 g, 6.75 mmol) in CH_2Cl_2 (10 mL), added portionwise. The resulting mixture was stirred at r.t. for 30 min and then diluted with CH_2Cl_2 (200 mL), washed with 10% aq $NaHSO_3$ solution (100 mL), satd aq $NaHCO_3$ solution (3 × 150 mL), dried and evaporated in vacuo to leave a pale brown solid (1.98 g). Purification by flash column chromatography on silica using a 1:1 mixture of EtOAc and petroleum ether as eluant gave **6a** (1.55 g, 75%) as a pale-yellow crystalline solid; mp 123–125°C.

IR (KBr): ν = 3331, 1758, 1699 cm^{-1}.

^{1}H NMR: δ = 1.41 (t, 3 H, *J* = 7 Hz, C*H*$_3$CH$_2$), 2.72 (m, 1 H), 2.83 (t, 1 H, *J* = 4 Hz), 3.30 (m, 1 H), 4.01 (m, 1 H), 4.27 (m, 1 H), 4.40 (q, 2 H, *J* = 7 Hz, CH$_3$C*H*$_2$O), 7.15 (d, 1 H, *J* = 9 Hz, ArH), 7.19 (s, 1 H, 3-H), 7.28 (d, 1 H, *J* = 9 Hz, ArH), 8.42 (s, 1 H, OCHO), 8.90 (br s, 1 H, NH).

Anal. Calcd for $C_{15}H_{15}NO_6$: C, 59.0; H, 4.9; N, 4.6. Found: C, 58.9; H, 4.9; N, 4.4.

Ethyl (*S*)-2,3-Dihydro-2-(hydroxymethyl)-7*H*-1,4-dioxino[2,3-*e*]indole-8-carboxylate (7a)

A stirred solution of **6a** (22.0 g, 0.072 mol) in THF (250 mL) was treated with satd aq K_2CO_3 solution (200 mL) and the mixture stirred vigorously at r.t. for 72 h. The mixture was poured into H_2O (1000 mL) and extracted with EtOAc (4 × 400 mL). The combined extracts were dried and evaporated in vacuo to give **7a** (17.65 g, 89%) as a pale purple solid; mp 152–153°C.

IR (KBr): ν = 3506, 3293, 1697, 1672 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.33 (t, 3 H, *J* = 7 Hz, C*H*$_3$CH$_2$), 3.69 (m, 2 H), 4.01 (dd, 1 H, *J* = 11, 7 Hz), 4.26 (m, 2 H), 4.30 (q, 2 H, *J* = 7 Hz, CH$_3$C*H*$_2$O), 5.06 (t, 1 H, *J* = 6 Hz, CH$_2$O*H*), 6.84 (d, 1 H, *J* = 9 Hz, ArH), 6.89 (d, 1 H, *J* = 9 Hz, ArH), 7.00 (br s, 1 H, 3-H), 11.75 (br s, 1 H, NH).

CI-MS: *m*/*z* = 277 (M^+, 85%).

HRMS: *m*/*z* Calc. for $C_{14}H_{15}NO_5$:277.0950. Found:277.0950.

(*S*)-2,3-Dihydro-2-(hydroxymethyl)-7*H*-1,4-dioxino[2,3-*e*]indole-8-carboxylic Acid (8a)

A stirred solution of **7a** (15.0 g, 0.054 mol) in MeOH (150 mL) under N_2 was treated with a solution of LiOH•H_2O (4.74 g, 0.108 mol) in H_2O (80 mL) and the mixture heated at 60°C for 1 h. The solvent was evaporated in vacuo and the residue diluted with H_2O (200 mL). The aqueous solution was adjusted to pH 2 with dil HCl and the resulting precipitate collected by filtration, washed thoroughly with H_2O and then dried to leave **8a** (12.46 g, 93%) as a pink solid; mp 216–217°C.

^{1}H NMR (DMSO-d_6): δ = 3.69 (m, 2 H), 4.03 (m, 1 H), 4.28 (m, 2 H), 6.83 (d, 1 H, *J* = 9 Hz, ArH), 6.89 (d, 1 H, *J* = 9 Hz, ArH), 6.94 (d, 1 H, *J* = 2 Hz, 3-H), 11.64 (br s, 1 H, NH), 12.80 (br s, 1 H, CO_2H).

Anal. Calcd for $C_{12}H_{11}NO_5$.0.9H_2O: C, 54.3; H, 4.8; N, 5.3. Found: C,54.05; H, 4.5; N, 5.3.

(*S*)-2,3-Dihydro-7*H*-1,4-dioxino[2,3-*e*]indole-2-methanol (9a)

A flask containing a mixture of **8a** (4.60 g, 18.47 mmol), copper powder (1.20 g, 18.47 mmol) and quinoline (50 mL) under a N_2 atmosphere was submerged into a preheated oil bath at 230°C and heated at this temperature for 40 min. The mixture was cooled to r.t., poured into dil HCl (300 mL) and extracted with EtOAc (3 × 150 mL). The combined extracts were washed with dil HCl (100 mL), H_2O (100 mL), dried and evaporated in vacuo to leave a brown oil (3.88 g). Purification by flash column chromatography on silica gel using a 1:1 mixture of EtOAc and petroleum ether as eluant gave **9a** (2.32 g, 61%) as a fawn solid; mp 51–53°C.

^{1}H NMR (DMSO-d_6): δ = 3.68 (m, 2 H), 3.98 (dd, 1 H, *J* = 11, 7 Hz), 4.19 (m, 1 H), 4.26 (m, 1 H), 5.04 (t, 1 H, *J* = 5.7 Hz, exchangeable with D_2O, OH), 6.31 (br s, 1 H, indole H), 6.44 (d, 1 H, *J* = 9 Hz, ArH), 6.84 (d, 1 H, *J* = 9 Hz, ArH), 7.19 (br s, 1 H, indole H), 10.90 (br s, 1 H, NH).

CI-MS: *m*/*z* = 205 (M^+, 100%).

HRMS: *m*/*z* Calc. For $C_{11}H_{11}NO_3$:205.0740. Found:205.0740.

5-Hydroxy-4-(*N*-phenyliminomethyl)benzo[*b*]furan (2b, R^2 = H)

A flask containing a mixture of **1b**[5] (36.60 g, 0.27 mol) and ethyl *N*-phenylformimidate (42.50 g, 0.28 mol) was immersed in a preheated oil bath and stirred at 180–190°C for 2 h whilst EtOH produced in the reaction was removed by distillation. The cooled mixture was then purified by filtration through a flash silica gel pad using a 1:4 solution of EtOAc and petroleum ether as eluant to give **2b (**R^2 = H) (18.31 g, 29%) as an orange oil.

^{1}H NMR (DMSO-d_6): δ = 6.96 (m, 2 H), 7.3–7.6 (m, 6 H), 7.70 (d, 1 H, *J* = 2 Hz, ArH), 8.99 (s, 1 H, CH = N), 13.41 (br s, 1 H, OH).

Anal Calcd for $C_{15}H_{11}NO_2$: C, 75.95; H, 4.65; N, 5.90. Found: C, 75.8; H, 4.6; N, 6.15.

5-Hydroxybenzo[*b*]furan-4-carbaldehyde (3b)
A mixture of **2b (**R^2 = H) (0.19 g, 0.80 mmol) and 5 M HCl (20 mL) was heated with stirring at 50–60°C for 30 min. The mixture was then poured into H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 80 mL). The combined extracts were washed with H_2O (80 mL), dried and evaporated in vacuo to give **3b** (130 mg, ca 100%) as a yellow solid; mp 80–81°C (Lit.[8] mp 83°C).

IR (KBr): ν = 1639cm^{-1}.

^{1}H NMR: δ = 6.90 (d, 1 H, *J* = 9 Hz, ArH), 7.08 (d, 1 H, *J* = 2 Hz, ArH), 7.64 (d, 1 H, *J* = 9 Hz, ArH), 7.77 (d, 1 H, *J* = 2 Hz, ArH), 10.32 (s, 1 H, CHO), 11.40 (br s, 1 H, OH).

Anal Calcd for $C_9H_6O_3$: C, 66.65; H, 3.7. Found: C, 66.9; H, 3.8

(*R*)-5-(2,3-Epoxypropoxy)benzo[*b*]furan-4-carbaldehyde (4b)
A stirred solution of **3b** (3.04 g, 18.77 mmol) in anhyd DMF (30 mL) was treated with solid K_2CO_3 (2.85 g, 20.63 mmol) and then a solution of (*R*)-glycidyl tosylate (4.50 g, 19.70 mmol) in anhyd DMF (10 mL) added. The mixture was heated at 60°C for 2 h and then poured into ice (200 g) and diluted with H_2O (300 mL). The mixture was extracted with CH_2Cl_2 (3 × 300 mL) and the combined extracts washed with H_2O (8 × 200 mL), dried and evaporated in vacuo to leave a red oil (4.61 g). Purification by flash column chromatography on silica using a 3:7 mixture of EtOAc and petroleum ether as eluant gave **4b** (3.11 g, 76%) as a yellow oil which crystallised on standing; mp 64–65°C.

IR (KBr): ν = 1668 cm^{-1}.

^{1} H NMR: δ = 2.82 (m, 1 H), 2.95 (m, 1 H), 3.43 (m, 1 H), 4.11 (m, 1 H), 4.41 (m, 1 H), 6.96 (d, 1 H, *J* = 9 Hz, ArH), 7.55 (d, 1 H, *J* = 2 Hz, ArH), 7.65 (d, 1 H, *J* = 9 Hz, ArH), 7.75 (d, 1 H, *J* = 2 Hz, ArH), 10.69 (s, 1 H, CHO).

Anal Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.60. Found: C, 65.7; H, 4.65.

(*R*)-5-(2,3-Epoxypropoxy)benzo[*b*]furan-4-yl Formate (6b)
A stirred solution of **4b** (3.08 g, 14.1 mmol) in CH_2Cl_2 (40 mL) was treated with 3-chloroperoxybenzoic acid (86%; 3.88 g, 19.5 mmol) and then a solution of trifluoroacetic acid (1.61 g, 14.1 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was then stirred at r.t. for 30 min and poured into a 10% aq $NaHSO_3$ solution (200 mL). The mixture was extracted with CH_2Cl_2 (2 × 150 mL) and the combined extracts washed with satd aq $NaHCO_3$ solution (3 × 150 mL), dried and evaporated in vacuo to give **6b** (3.10 g, 94%) as a red oil.

^{1}H NMR: δ = 2.72 (m, 1 H), 2.88 (m, 1 H), 3.34 (m, 1 H), 4.01 (m, 1 H), 4.29 (m, 1 H), 6.71 (d, 1 H, *J* = 2 Hz, ArH), 7.06 (d, 1 H, *J* = 9 Hz, ArH), 7.36 (d, 1 H, *J* = 9 Hz, ArH), 7.62 (d, 1 H, *J* = 2 Hz, ArH), 8.40 (s, 1 H, OCHO).

(*S*)-2,3-Dihydrofuro[3,2-*f*][1,4]benzodioxin-2-methanol (7b)
A solution of **6b** (3.09 g, 13.2 mmol) in THF (30 mL) was treated with aq satd K_2CO_3 solution (15 mL) and the mixture stirred vigorously at r.t. for 72 h. The mixture was poured into H_2O (200 mL) and extracted with EtOAc (2 × 150 mL). The combined extracts were dried and evaporated in vacuo to leave an orange oil. Purification by flash column chromatography on silica using a 2:3 mixture of EtOAc and petroleum ether as eluant gave **10** (0.22 g, 7%) as a yellow oil which solidified on standing. Further elution of the column afforded **7b** (1.90g, 70%) as a yellow oil.

IR (film): ν = 3400 cm^{-1}.

^{1}H NMR: δ = 1.95 (t, 1 H, *J* = 6.4 Hz, CH_2OH), 3.92 (m, 2 H), 4.16 (m, 1 H), 4.34 (m, 2 H), 6.80 (d, 1 H, *J* = 2 Hz, ArH), 6.85 (d, 1 H, *J* = 8 Hz, ArH), 7.02 (d, 1 H, *J* = 8 Hz, ArH), 7.52 (d, 1 H, *J* = 2 Hz, ArH).

Anal. Calcd for $C_{11}H_{10}O_4$.0.15 EtOAc: C, 63.5; H, 5.1. Found: C, 63.1; H, 5.1.

Compound **10**

IR (KBr): ν = 1726 cm^{-1}.

^{1}H NMR: δ = 4.14 (m, 2 H), 4.33 (m, 1 H), 4.51 (m, 2 H), 6.80 (d, 1 H, *J* = 2 Hz, ArH), 6.85 (d, 1 H, *J* = 9 Hz, ArH), 7.01 (d, 1 H, *J* = 9 Hz, ArH), 7.53 (d, 1 H, *J* = 2 Hz, ArH), 8.14 (s, 1 H, OCHO).

^{13}C NMR (62.9 MHz): δ = 160.4 (OCHO), 151.0 (qauternary), 144.8 (CH), 137.7 (quaternary), 135.1 (quaternary), 117.8 (quaternary), 114.2 (CH), 104.5 (CH), 103.6 (CH), 71.0 (OCH), 64.9 (OCH_2), 61.9 (OCH_2). Anal. Calcd for $C_{12}H_{10}O_5$: C, 61.55; H, 4.25. Found: C, 61.9; H, 4.3.

Ethyl 3- Chloro-5-hydroxybenzo[*b*]thiophene-2-carboxylate (1d)
A stirred solution of ethyl 3-chloro-5-methoxybenzo[*b*]thiophene-2-carboxylate (20.0 g, 0.084 mol) in CH_2Cl_2 (80 mL) was cooled to –20°C under a N_2 atmosphere. BBr_3 (1 M solution in CH_2Cl_2; 90 mL, 0.09 mol) was then added portionwise and the mixture allowed to warm to r.t. After stirring for 2 h at r.t. the mixture was poured into EtOH (400 mL), left to stand for 10 min and then evaporated in vacuo. The residue was dissolved in EtOAc (500 mL), washed with H_2O (300 mL), dried and evaporated in vacuo to give **1d** (18.68 g, 99%) as an off-white solid; mp 160–161 °C

^{1}H NMR: δ = 1.34 (t, 3 H, *J* = 7 Hz, CH_3CH_2), 4.35 (q, 2 H, *J* = 7 Hz, CH_3CH_2), 7.15 (dd, 1 H, *J* = 8 and 2 Hz, ArH), 7.24 (d, 1 H, *J* = 2 Hz, ArH), 7.91 (d, 1H, *J* = 8 Hz, ArH), 10.03 (s, 1 H, OH).

CI-MS: *m*/*z* = 256 (M^+, 100%).

HRMS: *m*/*z* Calc. For $C_{11}H_9S^{35}ClO_3$:255.9966. Required:255.9965.

Ethyl 3-Chloro-5-hydroxy-4-[*N*-(4-methoxyphenyliminomethyl]benzo[*b*]thiophene-2-carboxylate (2d; R^2 = OMe)
A flask containing a mixture of **1d** (6.04 g, 0.024 mol) and ethyl *N*-(4-methoxyphenyl)formimidate[13] (4.50 g, 0.024 mol) was immersed in a pre-heated oil bath at 160°C and the mixture stirred between 160 and 180°C for 4 h whilst the EtOH produced in the reaction was removed by distillation. More ethyl *N*-(4-methoxyphenyl)formimidate (0.80 g, 4.25 mmol) was then added and the heating continued at 180–190°C for 1 h. The mixture was cooled to r.t., heated in boiling MeOH (100 mL) and the resulting pale brown crystalline solid collected by filtration, washed with MeOH (10 mL) and dried to give **2d (**R^2 = OMe) (4.03 g, 43%); mp 162–163°C

^{1}H NMR: δ = 1.34 (t, 3 H, *J* = 7 Hz, CH_3CH_2), 3.81 (s, 3 H, OCH_3), 4.36 (q, 2 H, *J* = 7 Hz, $MeCH_2$), 7.07 (d, 2 H, *J* = 8 Hz, ArH), 7.20 (d, 1 H, *J* = 8 Hz, ArH), 7.46 (d, 2 H, *J* = 8 Hz, ArH), 8.08 (d, 1 H, *J* = 8 Hz, ArH), 10.26 (s, 1 H, CH = N), 15.85 (br s, 1 H, OH).

Anal. Calcd for $C_{19}H_{16}ClNO_4S$: C, 58.55; H, 4.1; N, 3.6; S, 8.2; Cl, 9.1. Found : C, 58.7; H, 4.0; N, 3.5; S, 8.0; Cl, 9.1.

Ethyl 3-Chloro-4-formyl-5-hydroxybenzo[*b*]thiophene-2-carboxylate (3d)
A stirred mixture of the imine **2d** (R^2 = OMe, 3.82 g, 9.86 mmol) in 5 M HCl (130 mL) was heated at 50–60°C for 4 h and then at 60–70°C for 3 h. The mixture was poured into H_2O (350 mL) and extracted with EtOAc (2 × 250 mL). The combined extracts were washed with H_2O (200 mL), dried and evaporated in vacuo to afford **3d** (2.80 g, 100%) as a pale green solid; mp 128–130°C

IR (KBr): ν = 1720, 1629 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.35 (t, 3 H, *J* = 7 Hz, CH_3CH_2), 4.37 (q, 2 H, *J* = 7 Hz, $MeCH_2$), 7.29 (d, 1 H, *J* = 8 Hz, ArH), 8.31 (d, 1 H, *J* = 8 Hz, ArH), 11.27 (s, 1 H, CHO), 12.74 (br s, 1 H, OH).

Ethyl (*R*)-3-Chloro-5-(2,3-epoxypropoxy)-4-formylbenzo[*b*] thiophene-2-carboxylate (4d)

A stirred solution of the aldehyde **3d** (4.90 g, 0.017 mol) in anhyd DMF (50 mL) was treated with solid K_2CO_3 (2.62 g, 0.018 mol) and then a solution of (*R*)-glycidyl tosylate (4.12 g, 0.018 mol) in anhyd DMF (50 mL) was added. The mixture was then heated at 60°C for 3 h and then poured into H_2O (1200 mL). The resulting pale green solid was collected by filtration, washed with H_2O (200 mL) and dried to give **4d** (5.15 g, 88%).

IR (KBr): ν = 1721, 1688 cm^{-1}.

1H NMR (DMSO-d_6): δ = 1.34 (t, 3 H, *J* = 7 Hz, CH_3CH$_2$), 2.74 (m, 1 H), 2.85 (m, 1 H), 3.34 (m, 1 H), 4.07 (dd, 1 H, *J* = 6 Hz), 4.36 (q, 2 H, *J* = 7 Hz, CH$_3$CH_2), 4.51 (m, 1 H), 7.58 (d, 1 H, *J* = 8 Hz, ArH), 8.25 (d, 1 H, *J* = 8 Hz, ArH), 10.87 (s, 1H, CHO).

CI-MS *m*/*z* = 340 (M^+, 100%).

HRMS: *m*/*z* Calc. for $C_{15}H_{13}{}^{35}ClO_5S$:340.0178. Found:340.0177.

Ethyl (*R*)-3-Chloro-5-(2,3-epoxypropoxy)-4-(formyloxy)benzo[*b*] thiophene-2-carboxylate (6d)

A stirred solution of **4d** (1.0 g, 2.94 mmol) in CH_2Cl_2 (20 mL) was treated with 3-chloroperoxybenzoic acid (70%; 0.75 g, 3.04 mmol) and the mixture cooled to 0°C. A solution of trifluoroacetic acid (0.35 g, 3.07 mmol) in CH_2Cl_2 (5 mL) was then added slowly and the mixture stirred at 0°C for 5 min and then allowed to warm to r.t. After 1 h, the mixture was poured into 10% aq $NaHSO_3$ solution (100 mL) and extracted with CH_2Cl_2 (2 × 200 mL). The combined extracts were washed with satd aq $NaHCO_3$ solution (2 × 150 mL), dried and evaporated in vacuo to leave a brown oil (1.06 g). Purification by flash column chromatography on silica gel using a 1:1 mixture of EtOAc and petroleum ether as eluant gave **6d** (0.52 g, 50%) as a pale yellow solid.

1H NMR: δ = 1.42 (t, 3 H, *J* = 7 Hz, CH_3CH$_2$), 2.73 (m, 1 H), 2.90 (m, 1 H), 3.34 (m, 1 H), 4.08 (m, 1 H), 4.36 (m, 1 H), 4.40 (q, 2 H, *J* = 7 Hz, CH$_3$CH_2), 7.33 (d, 1 H, *J* = 8 Hz, ArH), 7.65 (d, 1 H, *J* = 8 Hz, ArH), 8.40 (s, 1 H, OCHO).

Ethyl (*S*)-9-Chloro-2,3-dihydro-2-(hydroxymethyl)thieno[3,2-*f*][1,4]benzodioxin-8-carboxylate (7d)

A stirred solution of **6d** (1.85 g, 5.18 mmol) in THF (20 mL) was treated with satd aq K_2CO_3 solution (20 mL) and the mixture stirred vigorously at r.t. for 18 h. The mixture was poured into H_2O (200 mL) and extracted with EtOAc (2 × 200 mL). The combined extracts were dried and evaporated in vacuo to leave a yellow solid (1.60 g). Purification by flash column chromatography on silica gel using a 1:1 mixture of EtOAc and petroleum ether as eluant gave **7d** (1.44 g, 85%) as a pale yellow solid; mp 165–166°C.

IR (KBr): ν = 3520, 1713 cm^{-1}.

1 H NMR: δ = 1.41 (t, 3 H, *J* = 7 Hz, CH_3CH$_2$), 3.92 (m, 2 H), 4.16 (m, 1 H), 4.40 (q, 4 H, *J* = 7 Hz, MeCH_2 and 2 other H's), 7.09 (d, 1 H, *J* = 8 Hz, ArH), 7.23 (d, 1 H, *J* = 8 Hz, ArH).

Anal. Calcd for $C_{14}H_{13}ClO_5S$: C, 51.5; H, 3.95; S, 9.75; Cl, 10.80. Found: C, 51.45; H, 4.2; S, 9.9; Cl, 10.5.

Ethyl (*S*)-9-Chloro-2,3-dihydro-2-(hydroxymethyl)thieno[3,2-*f*][1,4]benzodioxin-8-carboxylic Acid (8b)

A stirred solution of the ester **7d** (1.30 g, 3.96 mmol) in MeOH (20 mL) was treated with a solution of LiOH•H_2O (0.17 g, 3.96 mmol) in H_2O (10 mL) and the mixture heated at 60°C for 1 h. The solvent was evaporated in vacuo and the residue dissolved in H_2O (50 mL). The aqueous solution was acidified with 2 M HCl and the resulting suspension collected by filtration, washed with H_2O and dried to give **8b** (1.15 g, 97%) as an off-white solid; mp 236–237°C.

IR (KBr): ν = 3389, 1717 cm^{-1}.

1H NMR (DMSO-d_6): δ = 3.69 (m, 2 H), 4.11 (m, 1 H), 4.31 (m, 1 H), 4.40 (m, 1 H), 5.11 (br s, 1 H, OH), 7.18 (d, 1 H, *J* = 8.5 Hz, ArH), 7.47 (d, 1 H, *J* = 8.5 Hz, ArH), 12.0-15.0(br s, 1 H, CO_2H).

Anal. Calcd for $C_{10}H_9ClO_5S.0.28H_2O$: C, 47.15; H, 3.15; S, 10.50; Cl, 11.65. Found: C, 47.3; H, 3.3; S,10.9; Cl, 11.9.

(*S*)-9-Chloro-2,3-dihydrothieno[3,2-*f*][1,4]benzodioxin-2-methanol (9b) and (*S*)-2,3-Dihydrothieno[3,2-*f*][1,4]benzodioxin-2-methanol (9c)

A flask containing a mixture of the carboxylic acid **8b** (0.80 g, 2.66 mmol), copper powder (0.17 g, 2.66 mmol) and quinoline (10 mL) was immersed in a pre-heated oil bath at 190°C and the mixture heated with stirring at this temperature for 30 min. The cooled mixture was poured into 2 M HCl (300 mL) and extracted with EtOAc (2 × 150 mL). The combined extracts were washed with 2 M HCl (150 mL), H_2O (150 mL), dried and evaporated in vacuo to leave a dark brown oil (0.78 g). Purification by flash column chromatography on silica using a 3:7 mixture of EtOAc in petroleum ether as eluant gave **9b** (0.58 g, 85%) as a fawn solid; mp 92–93 °C.

Compound **9b**

1H NMR: δ = 2.10 (t, 1 H, *J* = 6 Hz, exchangeable with D_2O, CH$_2$O*H*), 3.92 (m, 2 H), 4.14 (m, 1 H), 4.38 (m, 2 H), 6.98 (d, 1 H, *J* = 9 Hz, ArH), 7.17 (s, 1 H, ArH), 7.24 (d, 1 H, *J* = 9 Hz, ArH).

CI-MS: *m*/*z* = 256 (M^+, 100%).

HRMS: *m*/*z* Calc. for $C_{11}H_9{}^{35}ClO_3S$:255.9948. Found:255.9948.

Further elution of the column gave **9c** (50 mg, 9%) as a pale-brown oil.

Compound **9c**

1H NMR (DMSO-d_6): δ = 3.70 (m, 2 H), 4.06 (m, 1 H), 4.33 (m, 2 H), 5.11 (t, 1 H, *J* = 5.8 Hz, CH$_2$O*H*), 6.95 (d, 1 H, *J* = 9 Hz, ArH), 7.35 (d, 1 H, *J* = 6 Hz, 2-or 3-H), 7.41 (d, 1 H, *J* = 9 Hz, ArH), 7.67 (d, 1 H, *J* = 6 Hz, 2-or 3-H).

CI-MS: *m*/*z* = 222 (M+, 100%).

HRMS: m/z Calc. For $C_{11}H_{10}O_3S$:222.0345. Required:222.0346.

5-Hydroxyindazole-4-carbaldehyde (3c)

A flask containing a mixture of 5-hydroxyindazole[6] (14.0 g, 0.10 mol) and ethyl *N*-phenylformimidate (17.0 g, 0.10 mol) was immersed in a pre-heated oil bath at 175°C and the EtOH produced in the reaction was removed by distillation. After 2 h, the mixture was cooled to r.t. and then triturated with boiling MeOH (100 mL). The resulting orange solid was collected by filtration and dried to leave **2c (**R^2 = H) (15.24 g). The filtrate was evaporated in vacuo and the residue eluted through a silica gel pad using a 2:1 mixture of petroleum ether (bp 60–80°C) and EtOAc to give 2.88 g of product (total yield:18.12 g, 76%). The intermediate imine (**2c;** R^2 = H) (18.12 g, 76.4 mmol) was treated with 5 M HCl (300 mL) and heated at 50–60°C with stirring for 2 h. The cooled mixture was diluted with H_2O (400 mL) and extracted with EtOAc (6 × 250 mL). The combined extracts were washed with H_2O (300 mL), dried and evaporated in vacuo to give **3c** (11.37 g, 94%) as a yellow solid; 98–99°C.

IR (KBr): ν = 1639 cm^{-1}.

1H NMR (DMSO-d_6): δ = 7.09 (d, 1 H, *J* = 9 Hz, ArH), 7.79 (d, 1 H, *J* = 9 Hz, ArH), 8.38 (br s, 1 H, 3-H), 10.54 (s, 1 H, CHO), 10.71 (br s, 1 H, NH or OH), 13.24 (br s, 1 H, NH or OH).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.25; H, 3.70; N, 17.30. Found: C, 59.6; H, 3.9; N, 17.3.

(*R*)-5-(2,3-Epoxypropoxy)indazole-4-carbaldehyde (4c)

A mixture of **3c** (3.30 g, 0.02 mol) and (*R*)-glycidyl tosylate (5.0 g, 0.02 mol) in anhyd DMF (75 mL) was heated to 50 °C under a N_2 atmosphere. Solid K_2CO_3 (2.80 g, 0.02 mol) was then added in por-

tions over 2 h. The resulting cooled mixture was extracted with EtOAc (3 × 250 mL) and the combined extracts washed with H_2O (200 mL), dried and evaporated in vacuo. The residue was purified by flash column chromatography on silica using a 1:1 mixture of EtOAc and petroleum ether (bp 60–80 °C) as eluant to give **4c** (1.65 g, 39%) as a colourless oil.

IR (KBr): ν = 1664, 1645 cm^{-1}.

^{1}H NMR: δ = 2.82 (m, 1 H), 2.97 (m, 1 H), 3.44 (m, 1 H), 4.12 (m, 1 H), 4.49 (m, 1 H), 7.19 (d, 1 H, *J* = 9 Hz, ArH), 7.73 (d, 1 H, *J* = 9 Hz, ArH), 8.74 (s, 1 H, 3-H), 10.72 (s, 1 H, CHO), 10.80 (br s, 1 H, NH).

CI-MS: *m*/*z* = 218 (M^+, 39%)

HRMS: *m*/*z* Calc. For $C_{11}H_{10}N_2O_3$:218.0698. Found:218.0699

(*S*)1,4-Dioxino[2,3-*e*]indazole-5-methanol (7c)

A stirred solution of the aldehyde **4c** (1.65 g, 8.0 mmol) in CH_2Cl_2 (200 mL) at 0 °C was treated with 3-chloroperoxybenzoic acid (50%; 10.0 g, 0.029 mol) and the mixture stirred at 0 °C for 2 h. The solvent was evaporated in vacuo and the residue dissolved in 2.5 M aq NaOH solution (200 mL). The resulting blue solution was heated on a steam bath for 1 h, cooled, diluted with H_2O (200 mL) and extracted with EtOAc (3 × 250 mL). The combined extracts were washed with brine (250 mL), dried and evaporated in vacuo to give **7c** (0.27 g, 16%) as a pale green solid; mp 63–66°C.

^{1}H NMR (DMSO-d_6): δ = 3.70 (m, 2 H), 4.02 (m, 1 H), 4.31 (m, 2 H), 5.11 (t, 1 H, *J* = 5.7 Hz, CH_2OH), 6.95 (m, 2 H, ArH), 7.91 (br s, 1 H, 3-H), 12.93 (br s, 1 H, NH).

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(11) ***(S)*-2,3-Dihydro[3,2-*f*][1,4]benzodixin-2-methanol (7b):** $[\alpha]_D$ –25.7(*c* = 0.191g/100mL MeOH); HPLC: Chiralpak As, (λ = 218 nm, 35°C 300psi/2mL/min, mobile phase :90% CO_2/ 10% (IPA + 0.2% Et_2NH): Retention Time(min):5.8 (96% ee) ***(R)*-2,3-Dihydro[3,2-*f*][1,4]benzodioxin-2-methanol:** $[\alpha]_D$ +26.5 (*c* = 0.755g/ 100mL MeOH); HPLC(conditions as above): Retention time(min): 7.02 (90.3% ee).

(12) If necessary, ethyl 5-hydroxyindole-2-carboxylate (1a) could be prepared in good yield by BBr_3 demethylation of its commercially available (Aldrich) 5-methyl ether.

(13) Ethyl *N*-(4-methoxyphenyl)formimidate was prepared in good yield and excellent purity by reaction of 4-methoxyaniline, a catalytic amount of concentrated hydrochloric acid and triethyl orthoformate.

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