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A concise and regioselective synthesis of 6-iodo-4-trifluoromethylisatin, an intermediate in the synthesis of the novel, non-peptidyl growth hormone secretagogue SM-130686

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Abstract—The synthesis of 6-iodo-4-trifluoromethylisatin, an intermediate in the synthesis of the growth hormone secretagogue SM-130686, is disclosed. The synthesis is achieved in seven steps, with an overall yield of 32%, and requires a single recrystallisation as the only purification step. 2-Methyl-3-nitrobenzotrifluoride was converted to (4-iodo-6-nitro-2-trifluoromethylphenyl)acetic acid via iodination, condensation with dimethyloxalate and oxidative decarboxylation. Subsequent esterification followed by reductive cyclisation gave 6-iodo-4-trifluoromethyloxindole. Oxindole 3,3-dibromination followed by hydrolysis gave 6-iodo-4-trifluoromethylisatin.

1. Introduction

Growth hormone (GH) is a hormone released from the somatotroph cells of the anterior pituitary gland under the action of the hypothalamic hormone growth hormone releasing hormone (GHRH) (also known as growth hormone releasing factor (GRF)).[1] Deficiency in GH, which can result in conditions such as pituitary dwarfism, can be treated by subcutaneous administration of recombinant human GH.[2] Recently it has been found that GH can also be released under a different mechanism, involving the activation of growth hormone secretagogue (GHS) receptors.[3] Researchers at Merck synthesised MK-677, which is an orally active, small peptidyl GHS receptor agonist and induces GH release in rats and humans.[4] We therefore initiated a program to find a novel, orally active GHS receptor agonist to be possibly used in the treatment of conditions resulting in GH deficiency, and this culminated in the discovery of the non-peptidyl oxindole derivative SM-130686.[5] Pharmacological evaluation of SM-130686 showed that it released GH from rat pituitary cells, with an EC_{50}=6.3 nM, and displaced [^{35}S] MK-677 binding to the GHS receptor, transiently expressed in Chinese Hamster Ovary cells, with an IC_{50}=1.2 nM.[6] Compared to other synthetic GHS agonists so far reported,[7] SM-130686 is structurally unique. For further toxicological and pharmacokinetic studies we required multi-ten gram quantities of SM-130686. We therefore set about to improve our initial synthesis of 6-iodo-4-trifluoromethylisatin (**2**), the key intermediate in the synthesis of SM-130686. Our previous synthesis of **2** was not amenable to scale up as it was unregioselective and required several chromatographic purification steps. An improved synthesis of **2** would also allow us to conduct a more detailed investigation into the structure–activity relationships (SARs) at C3 and C6 as substituents at these positions exert profound influence over the pharmacological activity (**3**, Scheme 1). In this paper we wish to disclose our improved synthesis of **2**.[8]

During preliminary investigations into the structure–activity relationships of the oxindole class of GHS, SM-130686 was synthesised from **1** by an optical resolution using preparative HPLC, with a chiral stationary phase, followed by palladium(0) catalysed nitrile formation and hydrolysis.[5] We synthesised **1** from **2** in two steps, by first *N*-alkylation and subsequent reaction of the *N*-alkylated isatin with (2-chlorophenyl)magnesium bromide. Our synthesis of **2** involved the reaction of 3-iodo-5-nitrobenzotrifluoride with ethyl (methylthio)acetate and sulphuryl chloride, followed by oxidation of the resulting regioisomeric 3-methylthiooxindoles.[9] This resulted in the formation of a 1:1 inseparable mixture of regioisomeric isatins that could only be separated by column chromatography after subsequent *N*-alkylation. Once we identified that the 6-carbamoyl and 4-trifluoromethyl substituents of the oxindole were optimal, we synthesized the isatin in a regioselective manner.[10] We wanted a route that would allow a degree of flexibility so as to allow further SAR studies, thus it was decided that a 6-iodo substituent would in fact be best. Standard chemistry could then be

Keywords: isatin; regioselective synthesis; growth hormone secretagogue; SM-130686.

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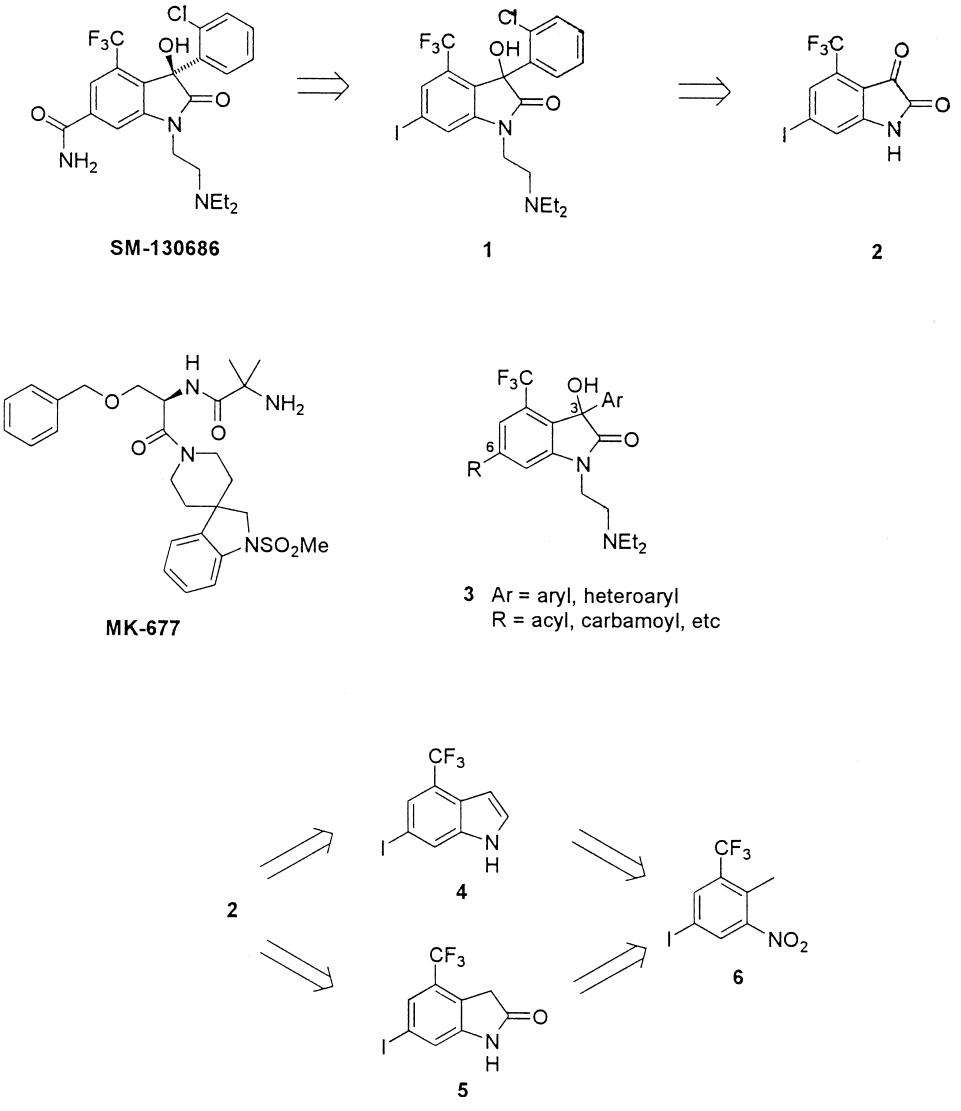
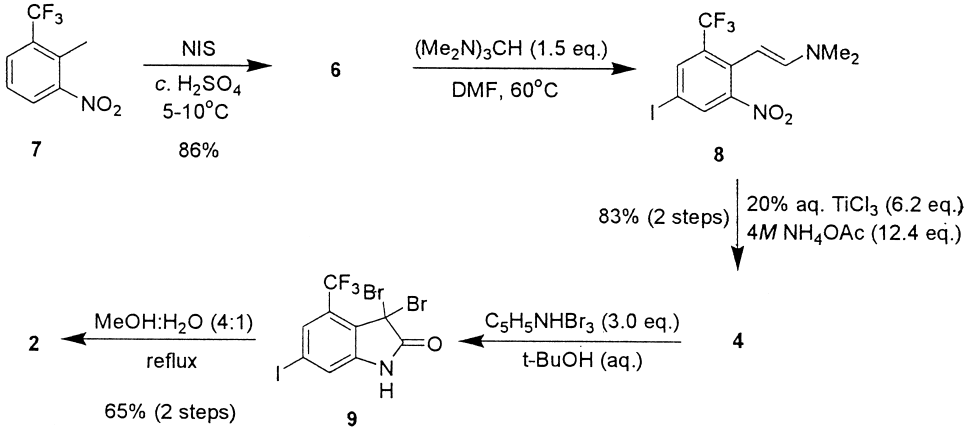
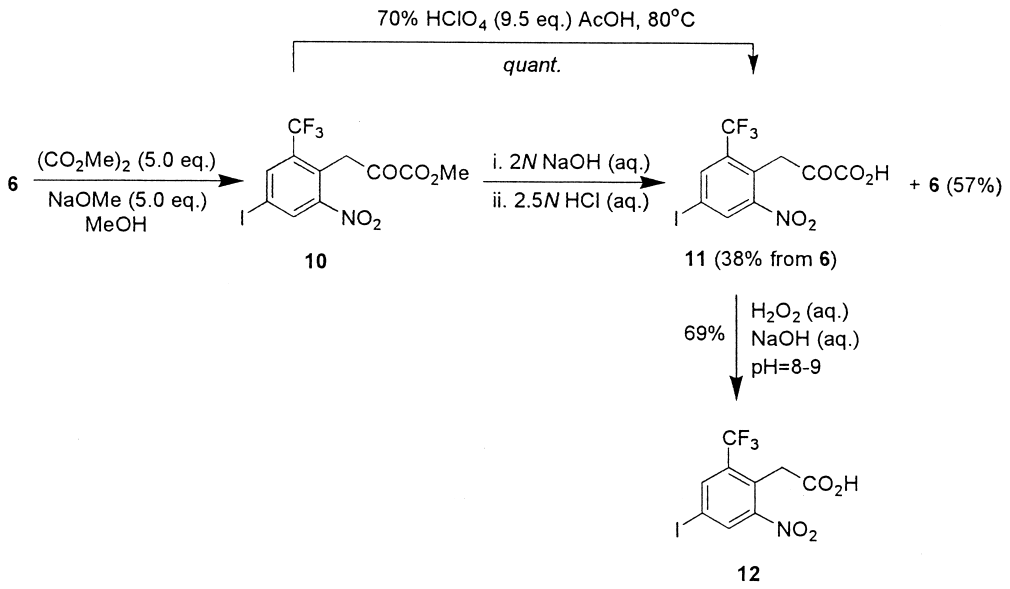


Scheme 1.

used to convert the 6-iodo into a carbamoyl substituent, or a variety of other substituents. The initial route that we chose comprised a regioselective synthesis of 6-iodo-4-trifluoromethylindole (**4**) followed by its oxidation to **2** (Scheme 1). Use of a substituted *ortho* nitrotoluene would allow the synthesis of a single indole regioisomer, hence single isatin regioisomer, by correct choice of synthetic method.



Scheme 2.



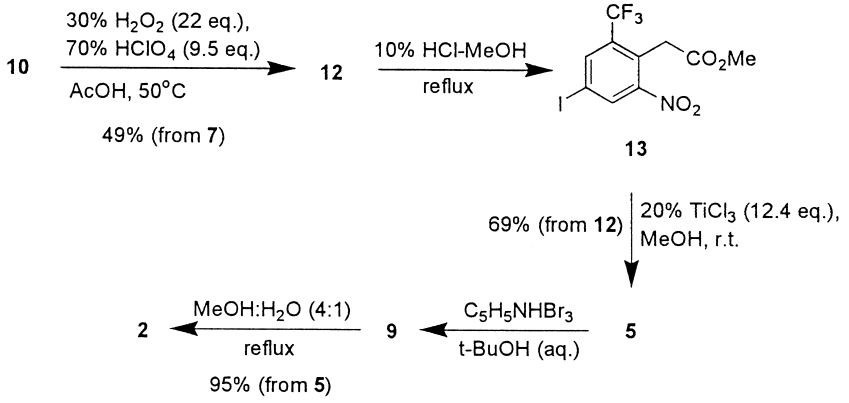
Scheme 3.

2. Results and discussion

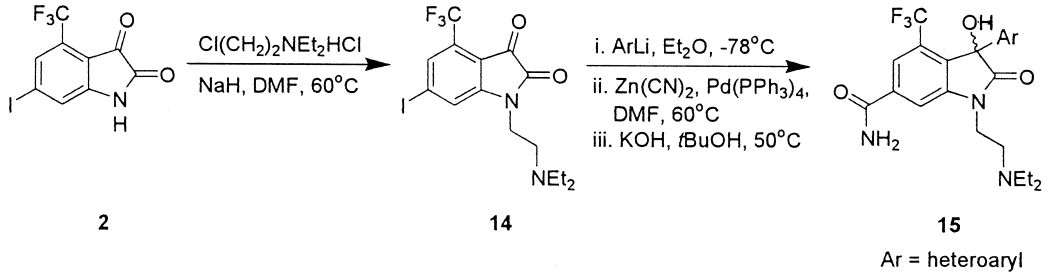
Iodination of commercially available 2-methyl-3-nitrobenzotrifluoride[11] (**7**) with *N*-iodosuccinimde, in 96% sulphuric acid,[12] gave 5-iodo-2-methyl-3-nitrobenzotrifluoride (**6**) which was reacted with tris(dimethylamino)methane,[13] in DMF at 60°C, to give enamine **8** (Scheme 2). Nitro group reduction using buffered aqueous titanium(III) chloride, with concomitant hydrolysis of the enamine,[14] gave **4**. Finally, indole bromination[15] gave 3,3-dibromooxindole **9**, which was hydrolysed[16] to give **2**. Unfortunately, this route suffered from two drawbacks that precluded its use in a larger scale synthesis. Firstly it required the use of the expensive tris(dimethylamino)methane[17] and secondly by-products arose from the indole bromination reaction[15] and these made the purification of the isatin difficult.

We then investigated a second route to **2**, via 6-iodo-4-trifluoromethyloxindole (**5**, Scheme 1). Use of a suitably substituted arene as in the previous route would permit the formation of a single oxindole regioisomer. Fortunately we were able to use the same intermediate **6** as that used in the previous synthesis. Thus, reaction of **6** with excess dimethyloxalate and sodium methoxide,[18] in methanol, gave methyl pyruvate **10** (Scheme 3). Oxidative decarboxylation of **10** to give acetic acid **12** required an initial ester hydrolysis[18] which unfortunately, under basic conditions, brought about a retro-condensation reaction and recovered **6** was obtained in 57% yield along with the desired pyruvic acid **11** (38%). The possibility of carrying out a one-pot reaction, without isolating **11** was investigated using various combinations of 30% hydrogen peroxide and bases, but retro-condensation still occurred. Examination of the hydrolysis under acidic conditions was then studied. Using 70% perchloric acid, **10** quantitively gave pyruvic acid **11**, no other product was observed in the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 3).

Owing to the lack of retro-condensation, a one-pot oxidative-decarboxylation was investigated.[19] At 50°C, using 9.5 equiv. of 70% perchloric acid and 11 equivalents of aqueous 30% hydrogen peroxide, in acetic acid, **12** was obtained, along with a small amount of **11**, but increasing the amount of hydrogen peroxide to 16 equiv. suppressed the formation of **11**. Increasing the amount of hydrogen peroxide still further, to 22 equiv., enhanced the conversion



Scheme 4.



Scheme 5.

of **10** to **12**, from 89 to 94%. It should be noted that these reactions were carried out on crude **10** and as such the sample contained unreacted dimethyloxalate from the previous step, thus probably accounting for the large amount of hydrogen peroxide required for this transformation (Scheme 4). Esterification of **12**, using 10% hydrogen chloride in methanol, gave methyl ester **13**. Aqueous 20% titanium(III) chloride reduction of the nitro group of **13** gave **5** as a crystalline solid, in 69% yield from **12**. Bromination of **5** gave 3,3-dibromide **9** which was subsequently hydrolysed to give isatin **2** in 95% yield from **5**.

This improved synthetic route to isatin **2** was then followed using 50.0 g of 2-methyl-3-nitrobenzotrifluoride (**7**). This gave 20.8 g of **2** in 32% overall yield and >99% purity, in seven steps. Purification of **5** was carried out by recrystallisation, which accounts for the only purification step that is required in the entire synthetic route.

As our synthesis of **2** was improved, this allowed us to further investigate the SARs, in particular the SAR at C3 (structure **3**, Scheme 1). Thus, alkylation of **2** with 2-(diethylamino)ethyl chloride hydrochloride gave **14** which was then reacted with various lithiated heteroaromatic compounds (e.g. 2-lithiopyridine, 2-lithiothiophene). Transformation of the iodo substituent into a carbamoyl was carried out by first palladium(0) catalysed nitrile formation followed by hydrolysis, which gave **15** (Scheme 5). Unfortunately compounds **15** exhibited much weaker biological activities than racemic SM-130686. Detailed results of the SAR at C3 will be published elsewhere.

3. Conclusion

We have presented our syntheses of 6-iodo-4-trifluoromethylisatin (**2**). Our preliminary synthesis was unregioselective,[5] however the synthetic route was improved to a regioselective one, through initially intermediate **4** and subsequently intermediate **5**. This new synthesis required no chromatographic purification and was accomplished in seven steps from commercially available 2-methyl-3-nitrobenzotrifluoride (**7**).

4. Experimental

4.1. General

All reagents and solvents were obtained commercially and used without purification. Thin-layer chromatography and flash column chromatography were performed on silica gel glass backed plates (5719, Merck) and silica gel 60 (230–400 or 70–230 mesh, Merck), respectively. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer model 1640 FT-IR spectrometer using KBr discs. ^{1}H NMR spectra were recorded at 270 MHz on a Jeol GX-270 spectrometer and ^{13}C NMR spectra were recorded at 100 MHz on a Bruker AVANCE 400 spectrometer in choroform-*d* or dimethylsulfoxide-d_6 as solvents. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm) and coupling constants are measured in Hertz. The low-resolution mass spectroscopy, high resolution mass spectroscopy and elemental analyses were carried out by Sumitomo Analytical Centre, Inc.

4.1.1. 5-Iodo-2-methyl-3-nitrobenzotrifluoride (6). To H_2SO_4 (220 ml, 96%) stirring under a nitrogen atmosphere at 0–5°C was added *N*-iodosuccinimide (82.27 g, 365.6 mmol) portionwise. The resulting dark red coloured mixture was stirred at 0–5°C for 40 min, after which time 2-methyl-3-nitrobenzotrifluoride (**5**, 50.0 g, 243.8 mmol), in H_2SO_4 (150 ml, 96%), was added dropwise over ca. 1 h. The solution was stirred at 5–10°C for 5 h and warmed slowly to room temperature over 16 h. The resulting solution was poured carefully into ice (ca. 2 kg) and extracted with EtOAc (800 ml, 2×500 ml). The extracts were combined, washed with saturated aqueous sodium hydrogensulphite (2×500 ml) and H_2O (500 ml). The organic phase was then dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo to give crude **6** (83.68 g) as a light yellow oil which solidified on standing. The crude product was used for the preparation of **10** without purification, however for characterisation purposes a small amount was purified by flash column chromatography, hexane as eluent, to give an analytically pure sample as a white solid; mp 37–37.5°C; IR (KBr) 3112, 3073, 1534, 1367, 1306, 1171, 1126, 1093, 884, 699 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.19 (d, 1H, J=1.3 Hz), 8.14 (d, 1H, J=1.3 Hz), 2.49 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 138.3 (q, $^3J_{CF}$=5.9 Hz), 135.6, 132.9 (q, $^2J_{CF}$=30.8 Hz), 130.9, 122.2 (q, $^1J_{CF}$=275.1 Hz), 89.3, 14.6 (q, $^4J_{CF}$=2.8 Hz); MS (EI) *m/z* 331 (M^+, 34%), 314 (68), 286 (15), 158 (22), 18 (100); Analysis calculated for $C_8H_5F_3INO_2$: C, 29.03; H, 1.52; N, 4.23. Found: C, 29.03; H, 1.72; N, 4.05.

4.1.2. *trans*-2-(β-(Dimethylamino)vinyl)-5-iodo-3-nitrobenzotrifluoride (8). 5-Iodo-2-methyl-3-nitrobenzotrifluoride

(6, 29.06 g, 87.8 mmol) was dissolved in anhydrous DMF (170 ml) and tris(dimethylamino)methane (19.13 g, 131.7 mmol) was added. The resulting dark solution was heated at 60°C (bath temperature) for 5 h, under a nitrogen atmosphere. The solution was cooled and the solvent removed in vacuo to give crude **8** as a red oil, which solidified on standing. The crude product was used directly for the preparation of **4**, however for characterisation purposes a small amount was purified by crystallisation from hexane to give analytically pure **8** as an amorphous orange solid; mp 112–113°C (with decomposition); IR (KBr) 3468, 2906, 1634, 1588, 1525, 1461, 1385, 1301, 1268, 1178, 1131, 1101, 960, 880, 783 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.95 (d, 1H, J=2.0 Hz), 7.85 (d, 1H, J=2.0 Hz), 6.39 (d, 1H, J=13.0 Hz), 5.04 (d, 1H, J=13.0 Hz), 2.83 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 145.8, 137.7 (q, $^3J_{CF}$= 6.1 Hz), 135.3, 132.6, 130.0 (q, $^2J_{CF}$=29.8 Hz), 122.9 (q, $^1J_{CF}$=274.5 Hz), 85.2, 40.6; MS (EI) m/z 386 (M^+, 100%), 369 (55), 326 (18), 313 (51), 286 (61), 212 (21), 158 (26), 86 (97), 58 (22), 42 (45); Analysis calculated for $C_{11}H_{10}F_3IN_2O_3$: C, 34.22; H, 2.61; N, 7.26. Found: C, 34.26; H, 2.37; N, 7.01.

4.1.3. 6-Iodo-4-trifluoromethylindole (4). The above prepared crude **8** was dissolved in acetone (250 ml) and added slowly to a stirred solution of aqueous 20% titanium(III) chloride (420 g, 544 mmol) and aqueous 4 M ammonium acetate (840 g), while cooling in an ice-water bath. When the addition was completed, the cooling bath was removed and stirring continued at room temperature for 5 h. The resulting mixture was then extracted with EtOAc (12×250 ml). The organic extracts were combined and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo to give crude **4**. Purification was carried out by flash column chromatography, hexane/EtOAc 20:1 as eluent, to give **4** (22.71 g, 83% from **6**) as a light yellow oil; IR (KBr) 3790, 3441, 1608, 1442, 1399, 1356, 1331, 1302, 1248, 1189, 1121, 1078, 949, 897, 856, 777, 732, 643 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.38 (brs, 1H), 7.92 (s, 1H), 7.68 (s, 1H), 7.27 (m, 1H), 6.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 126.5, 126.3 (q, $^3J_{CF}$=4.8 Hz), 124.0 (q, $^1J_{CF}$=272.5 Hz), 123.9, 123.7, 123.6 (q, $^2J_{CF}$= 32.9 Hz), 102.2; HRMS calcd for $C_9H_5NIF_3$ (M^+) 310.9418. Found 310.9384.

4.1.4. 6-Iodo-4-trifluoromethylisatin (2) from 4.

*a. 3,3-Dibromo-6-iodo-4-trifluoromethyloxindole (**9**)*

6-Iodo-4-trifluoromethylindole (**4**, 22.71 g, 73.0 mmol) was dissolved in *tert*-butanol (810 ml) and water (5 ml) followed by pyridinium bromide perbromide (77.87 g, 219.1 mmol, 90%) were added. The mixture was stirred at room temperature for 4 h, under a nitrogen atmosphere, and then the solvent was removed in vacuo. The resulting brown solid was dissolved in EtOAc/H_2O (1:1, 2000 ml). The organic phase was separated and the aqueous phase extracted with EtOAc (4×250 ml). The organic phases were combined, washed with half saturated brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo to give crude 3,3-dibromo-6-iodo-4-trifluoromethyloxindole (**9**). The crude product was used in the following reaction without purification, however for characterisation purposes a small amount was purified by flash column chromatography, hexane/EtOAc 5:1 as eluent, to give an analytically pure sample as a grey solid; mp 160–162°C (with decomposition); IR (KBr) 3129, 1722, 1603, 1436, 1388, 1316, 1290, 1209, 1179, 1144, 1133, 956, 889, 861, 814, 702, 673, 653 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 11.73 (brs, 1H), 7.78 (s, 1H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 141.6, 129.5 (q, $^3J_{CF}$=5.0 Hz), 127.4 (q, $^2J_{CF}$= 33.8 Hz), 126.7, 124.2, 122.6 (q, $^1J_{CF}$=275.2 Hz), 99.6, 43.1; HRMS calcd for $C_9H_4Br_2F_3INO$ (MH^+) 483.7656. Found 483.7661.

*b. 6-Iodo-4-trifluoromethylisatin (**2**)*

The above prepared crude 3,3-dibromo-6-iodo-4-trifluoromethyloxindole (**9**, 20.94 g, 43.2 mmol) was dissolved in MeOH/H_2O (4:1, 1000 ml) and the mixture was then heated at reflux for 24 h. The solution was cooled and the MeOH removed in vacuo to give a brown solid. The solid was collected by filtration, washed with copious amounts of H_2O and dried in vacuo to give crude **2** as a brown solid. Purification was carried out by flash column chromatography, hexane/EtOAc 5:1 as eluent, to give **2** (16.26 g, 65% from **4**) as a brown solid; mp 223–224.5°C (with decomposition); IR (KBr) 3315, 3265, 1775, 1744, 1598, 1417, 1352, 1303, 1270, 1181, 1139, 1077, 926, 882, 871, 684 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 11.31 (brs, 1H), 7.68 (s, 1H), 7.55 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.0, 158.4, 152.9, 127.7 (q, $^3J_{CF}$=5.6 Hz), 126.1 (q, $^2J_{CF}$=35.2 Hz), 125.3, 121.7 (q, $^1J_{CF}$=274.6 Hz), 113.9, 107.0; MS (EI) m/z 341 (M^+, 74%), 313 (100), 286 (37), 158 (11), 131 (9); Analysis calculated for $C_9H_3F_3INO_2 \cdot H_2O$: C, 30.11; H, 1.40; N, 3.90. Found: C, 30.32; H, 1.30; N, 3.86.

4.1.5. Methyl (4-iodo-6-nitro-2-trifluoromethylphenyl)-pyruvate (10). Dimethyl oxalate (127.79 g, 1.08 mol) was added to sodium methylate (216.4 ml, 1.08 mol, 28%) and the mixture stirred at room temperature for 1.5 h. A solution of crude **6** (71.64 g) in MeOH (216 ml) was added and the dark red coloured mixture stirred at room temperature for 20 h. The solvent was removed in vacuo to give a red solid which was subsequently added to aqueous 2.5N HCl (800 ml) and extracted with EtOAc (500 ml, 2×300 ml). The extracts were combined and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo to give crude **10** (161.41 g) as a yellow solid. The crude product was used in the following reaction without purification, however for characterisation purposes a small amount was purified by flash column chromatography, hexane/EtOAc 15:1–10:1 as eluent, to give an analytically pure sample as a light yellow solid; mp 115–116°C; IR (KBr) 3086, 2963, 1734, 1543, 1356, 1307, 1278, 1170, 1151, 1125, 1109, 1093, 1065, 898, 696 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.54 (d, 1H, J=1.3 Hz), 8.29 (d, 1H, J=1.3 Hz), 4.63 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 160.1, 150.6, 139.8 (q, $^3J_{CF}$= 5.9 Hz), 137.3, 133.4 (q, $^2J_{CF}$=30.7 Hz), 127.4, 121.9 (q, $^1J_{CF}$=275.7 Hz), 92.3, 53.6, 39.4; MS (EI) m/z 358 (72%), 330 ($M^+ - C_3H_3O_3$, 100), 313 (65), 272 (20), 145 (53), 87 (16), 59 (49), 15 (22); Analysis calculated for $C_{11}H_7F_3INO_5$: C, 31.68; H, 1.69; N, 3.36. Found: C, 31.78; H, 1.85; N, 3.33.

4.1.6. (4-Iodo-6-nitro-2-trifluoromethylphenyl)acetic acid (12). To a suspension of crude **10** (157.9 g) in glacial AcOH (3 l) was added aqueous 30% H_2O_2 (1025 ml) and 70% $HClO_4$ (159 ml). The mixture was heated at 50°C (bath temperature) for 4 h and then cooled. To the solution was added portionwise sodium sulphite (400 g) (CAUTION: addition is very exothermic) and the solvent was removed in vacuo. The resulting solid was dissolved in H_2O (2 l) and extracted with EtOAc (3×1 l). The extracts were combined and subsequently extracted with aqueous 2N NaOH (9×500 ml). The aqueous extracts were combined, cooled in an ice-H_2O bath and acidified with aqueous 36% HCl. The precipitate was collected by filtration, washed with cold H_2O and dried in vacuo to give **12** (37.14 g, 49% from **7**) as a white solid; mp 194–195.5°C; IR (KBr) 3386, 3100, 2970, 2730, 2650, 2552, 1728, 1713, 1604, 1537, 1404, 1355, 1310, 1291, 1239, 1202, 1182, 1133, 1092, 929, 898, 853, 702, 688 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 12.92 (brs, 1H), 8.65 (d, 1H, J=1.6 Hz), 8.42 (d, 1H, J=1.6 Hz), 3.92 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 151.6, 139.1 (q, $^3J_{CF}$=5.6 Hz), 137.3, 131.3 (q, $^2J_{CF}$=30.4 Hz), 128.0, 122.7 (q, $^1J_{CF}$=275.3 Hz), 94.3, 34.2; MS (EI) *m/z* 375 (M^+, 19%), 331 (20), 329 (37), 314 (100), 286 (29), 202 (17), 159 (29), 145 (33); Analysis calculated for $C_9H_5F_3INO_4$: C, 28.82; H, 1.34; N, 3.73. Found: C, 28.76; H, 1.48; N, 3.78.

4.1.7. Methyl (4-iodo-6-nitro-2-trifluoromethylphenyl)-acetate (13). A solution of **12** (34.7 g, 96.2 mmol) in 10% HCl–MeOH (300 ml) was heated at reflux for 4.5 h. The solution was cooled and the solvent removed in vacuo. The resulting oil was dissolved in EtOAc (400 ml), washed with saturated aqueous $NaHCO_3$ (2×100 ml) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo to give crude **13** (33.20 g) as a colourless oil. The crude product was used in the following reaction without purification, however for characterisation purposes a small amount was purified by flash column chromatography, hexane/EtOAc 10:1 as eluent, to give an analytically pure sample as a white solid; mp 81–82°C; IR (KBr) 3087, 3010, 2956, 1741, 1605, 1540, 1460, 1430, 1402, 1354, 1307, 1286, 1264, 1240, 1202, 1177, 1134, 1111, 1089, 1012, 949, 896, 889, 832, 704, 684 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.49 (d, 1H, J=1.3 Hz), 8.26 (d, 1H, J=1.3 Hz), 4.11 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 151.2, 139.4 (q, $^3J_{CF}$=5.9 Hz), 137.1, 133.0 (q, $^2J_{CF}$=30.9 Hz), 127.9, 122.1 (q, $^1J_{CF}$=275.5 Hz), 91.9, 52.7, 33.8; MS (EI) *m/z* 389 (M^+, 3%), 358 (9), 343 (100), 330 (15), 159 (16), 145 (46), 87 (21), 59 (70), 15 (30); Analysis calculated for $C_{10}H_7F_3INO_4$: C, 30.87; H, 1.81; N, 3.60. Found: C, 30.83; H, 1.88; N, 3.58.

4.1.8. 6-Iodo-4-trifluoromethyloxindole (5). To a solution of crude **13** (33.11 g) in MeOH (1 l) cooled to 0–5°C was added dropwise aqueous 20% $TiCl_3$ (815 g, 1.06 mol). The cooling bath was removed and the solution stirred at room temperature for 20 h after which time aqueous 6N HCl (900 ml) was added. The resulting mixture was extracted with EtOAc/toluene (1:1, 3×1 l; 2:1, 3×900 and 3×500 ml). The extracts were combined and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo to give a light brown solid which was purified by recrystallisation from EtOH (300 ml) to give **5** (21.59 g, 69% from **12**) as a light yellow solid; mp 263.5–265°C (with decomposition); IR (KBr) 3151, 3046, 1704, 1608, 1448, 1386, 1330, 1293, 1172, 1136, 974, 861, 696 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.93 (brs, 1H), 7.60 (s, 1H), 7.39 (s, 1H), 3.97 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.4, 146.8, 126.9 (q, $^2J_{CF}$=32.3 Hz), 125.7 (q, $^3J_{CF}$=4.2 Hz), 124.1 (q, $^3J_{CF}$=2.5 Hz), 123.2 (q, $^1J_{CF}$=273.6 Hz), 121.3, 93.4, 35.3; MS (EI) *m/z* 327 (M^+, 100%), 299 (12), 298 (11), 200 (7), 172 (10); Analysis calculated for $C_9H_5F_3INO$: C, 33.05; H, 1.54; N, 4.28. Found: C, 33.37; H, 1.70; N, 4.27.

4.1.9. 6-Iodo-4-trifluoromethylisatin (2) from 5.

a. 3,3-Dibromo-6-iodo-4-trifluoromethyloxindole (9)

To a suspension of **5** (21.00 g, 64.2 mmol) in *t*BuOH (610 ml) was added pyridinium bromide perbromide (91.32 g, 256.8 mmol, 90%) and the mixture stirred rapidly at room temperature for 4 h. Water (1.2 l) was added and the mixture stirred until a solution formed. The solution was extracted with EtOAc (4×250 ml), the extracts were combined and then dried over anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo to give crude **9** (35.2 g) as a light purple/grey solid.

b. 6-Iodo-4-trifluoromethylisatin (2)

To a solution of crude **9** (35.11 g) in MeOH (1.2 l) was added H_2O (300 ml) and aqueous 48% HBr (10 ml). The solution was heated at reflux for 27 h after which time the MeOH was removed in vacuo to give brown/yellow solid. The solid was collected by filtration, washed with copious amounts of H_2O and dried in vacuo to give **2** (20.82 g, 95% from **5**) as a light brown solid.

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