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Robust Synthesis of Methyl 5-Chloro-4-fluoro-1*H*-indole-2-carboxylate: A Key Intermediate in the Preparation of an HIV NNRTI Candidate

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Abstract:

A synthetic preparation of methyl 5-chloro-4-fluoro-1*H*-indole-2-carboxylate, a key intermediate towards phosphoindole inhibitors of HIV non-nucleoside reverse transcriptase, is described. The five-step synthesis involved Boc protection of the commercially available 4-chloro-3-fluoroaniline and regioselective iodination at C-2. After facile Boc deprotection, cyclization of the resultant *o*-iodoaniline gave the corresponding 5-chloro-4-fluoro-indole-2-carboxylic acid which was subsequently esterified to provide the target indole ester in 56% overall yield. Identification of 6-chloro-7-iodo-2(3*H*)-benzoxazolone as a significant side product in the iodination step led to the development of conditions which eliminated its formation in subsequent batches. Advantages of this alternative approach relative to existing methodologies include (1) potentially hazardous diazonium and azido species were not required, (2) regioisomeric products were not generated, and (3) chromatographic isolations were avoided, as all intermediates were easily crystallized. As a result, the key indole ester was produced rapidly at 100-fold increased scale compared to previous reports with a 10-fold improvement in overall yield.

Introduction

This report describes a robust synthetic preparation of methyl 5-chloro-4-fluoro-1*H*-indole-2-carboxylate, **1** (Figure 1).[1] This key functionalized scaffold was required during a campaign to evaluate novel phosphoindoles as non-nucleoside reverse transcriptase inhibitor (NNRTI) candidates for the treatment of HIV infection.[2] The 2-carboxy-5-chloro-4-fluoroindole moiety has also been incorporated as an important feature of other NNRTIs, in particular indolyl aryl sulfones,[3] and of various heterocyclic anticoagulants.[4] The methyl ester **1** is not commercially available and until very recently, neither were its 2-carboxylic acid **2** and 2-ethyl ester **3** analogues. Supplies of these materials, however, are limited and expensive for large scale use. Accordingly, in order to rapidly fulfill the requirements of the HIV research program, investigations were conducted into the synthesis of **1** on multigram scale. Multiple methodologies exist for the synthesis of variously substituted indoles,[5] however, there are relatively few accounts of the efficient formation of 4,5-dihaloindole-2-carboxylates. The literature on 5-chloro-4-fluoro derivatives is limited to three distinct published examples, all of which bear certain synthetically unappealing aspects.

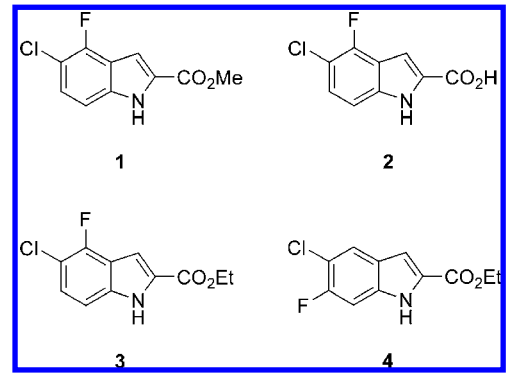

Figure 1

The initial route, by Silvestri et al. in 2002, to the ethyl ester **3** utilized the Fischer indole cyclization in three steps from 3-fluoroaniline ($420/kg).[6] The resultant 1:2 mixture of 5-chloro-4-fluoro **3** and 5-chloro-6-fluoro **4** regioisomers was separated by repeated chromatographic purification and provided 900 mg of the desired isomer **3** in a mere 5% overall yield.

The second published route to **1**, by Ohta et al., used the Hemetsberger indole procedure from 1-(bromomethyl)-3-chloro-2-fluorobenzene ($1660/kg) on 440 mg scale.[7] Although this three-step method did not generate regioisomers, it was hampered by a low overall yield (4.3%), multiple chromatographic purifications, and the use of the potentially hazardous methyl 2-azidoacetate.[8]

In the most recent (2008) literature preparation of ethyl ester **3**, Silvestri et al. utilized a Reissert indole synthesis starting

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(1) Part of this research is presented in the following patents: Storer, R.; Alexandre, F.-R.; Dousson, C.; Moussa, A. M.; Bridges, E. WO/2008/042240, 2008 (CAN 148:449766); Storer, R.; Alexandre, F.-R.; Dousson, C.; Moussa, A. M.; Bridges, E.; Stewart, A.; Wang, J.; Mayes, B. A. U.S. Pat. 2008/0213217, 2008.

(2) Patents WO/2008/042240, 2008, *vide supra*. U.S. 2008/0213217, 2008, *vide supra*.

(3) La Regina, G.; Coluccia, A.; Piscitelli, F.; Bergamini, A.; Sinistro, A.; Cavazza, A.; Maga, G.; Samuele, A.; Zanoli, S.; Novellino, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2007**, *50*, 5034–5038. Piscitelli, F.; Coluccia, A.; Brancale, A.; La Regina, G.; Sansone, A.; Giordano, C.; Balzarini, J.; Maga, G.; Zanoli, S.; Samuele, A.; Cirilli, R.; La Torre, F.; Lavecchia, A.; Novellino, E.; Silvestri, R. *J. Med. Chem.* **2009**, *52*, 1922–1934.

(4) Ohta, T.; Komoriya, S.; Yoshino, T.; Uoto, K.; Nakamoto, Y.; Naito, H.; Mochizuki, A.; Nagata, T.; Kanno, H.; Haginoya, N.; Yoshikawa, N.; Nagamochi, M.; Kobayashi, S.; Ono, M. WO/2003/000680, 2003 (CAN 138:89801).

(5) Sundberg, R. J. *Indoles*; Academic Press: London, 1996.

(6) Silvestri, R.; De Martino, G.; Sbardella, G. *Org. Proced. Prep. Int.* **2002**, *34*, 517–520.

(7) Ohta, T.; Komoriya, S.; Yoshino, T.; Uoto, K.; Nakamoto, Y.; Naito, H.; Mochizuki, A.; Nagata, T.; Kanno, H.; Haginoya, N.; Yoshikawa, N.; Nagamochi, M.; Kobayashi, S.; Ono, M. U.S. 2005/0020645, 2005 (CAN 142:176829).

(8) Urben, P. G., Ed. *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Academic Press: Oxford, 2007; Vol. 2, see p51.

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Scheme 1. **Formation of indole ester 1**

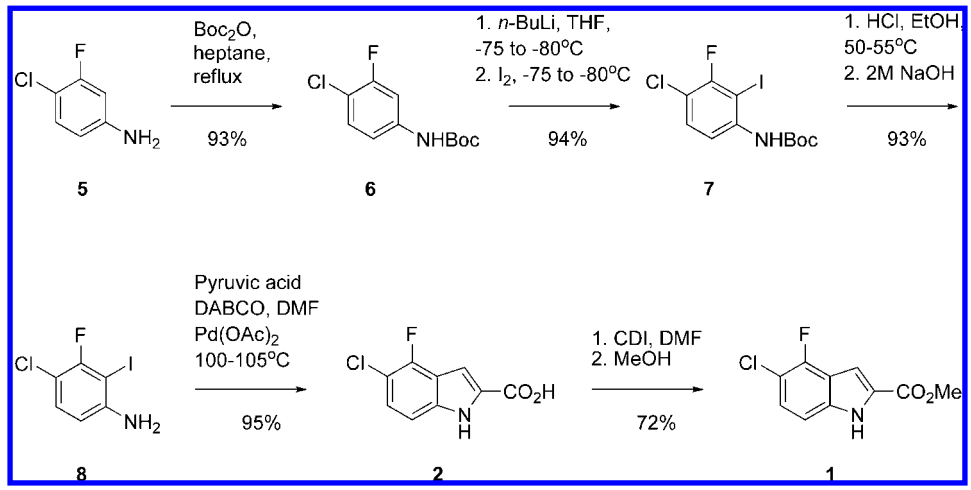


Table 1. **Effect of scale, reagent quantities, and internal temperature on the formation of benzoxazolone 9 and yield of 7**

entry	scale (g)	*n*-BuLi (equiv)	I_2 (equiv)	internal temperature (°C)	ratio[a] **7**:**6**	ratio[a] **7**:**9**	isolated yield of **7**
1	10	4.0	3.4	−70 to −75	11.6:1	2.54:1	10 g, 66%
2	80	4.0	3.4	−64 to −78	5.8:1	4.62:1	72 g, 60%
3	87	2.6	3.4	−68 to −73	45.2:1	4.22:1	90.3 g, 68%
4	141	2.6	3.4	−68 to −72	31.0:1	6.10:1	95.3 g, 44%[b]
5	5	2.5	3.3	−90 to −100	0.32:1	n.d.[c]	n.d.
6	5	3.6[d]	3.4	−80 to −95	14.6:1	75.8:1	6.1 g, 81%
7	3	3.0	3.4	−75 to −82	32.5:1	>200:1	3.95 g, 87%
8	80	3.1	3.5	−75 to −80	43.7:1	119:1	114 g, 94%

[a] In-process LCAP ratio at 272 nm. [b] Isolated 42.3 g of benzoxazolone **9** (25% yield). [c] Not determined. [d] 2.6 + 1.0 equiv.

from 3-fluoro-2-methylaniline ($1400/kg).[9] This six-step procedure gave **3** on a 330 mg scale, and although the overall yield (37%) was superior to the two previous methods, this route presented drawbacks in that three of the intermediates were oils requiring chromatographic isolation.

As a result of these limitations, an alternative approach to **1** was investigated to provide more rapid and convenient access to this valuable synthetic intermediate.

Results and Discussion

The target indole-2-carboxylate **1** was prepared in five steps from commercially available 4-chloro-3-fluoroaniline **5** ($450/kg) as shown in Scheme 1. After Boc protection of the aniline **5** and regioselective introduction of iodine at the 2-position, the free aniline **8** was liberated prior to indole cyclization. Final esterification of the indole acid **2** gave the desired indole ester **1** in 56% overall yield.

Existing literature preparations of Boc aniline **6** report reactions on modest scale (2.5−10 g), extensive reaction times (3−4 days), and a high number of unit operations or moderate yields (71−79%).[10] In this instance, however, Boc protection of aniline **5** was achieved on a 250 g scale by refluxing the starting material in heptane with di-*tert*-butyl-dicarbonate. After 4 h, a simple isolation protocol was performed which entailed cooling the reaction to 45 °C and reducing the solvent volume by 75% *via* distillation to give a thick slurry. After further cooling, crystals of Boc aniline **6** were collected by filtration in 93% yield with 99% LCAP purity.[11]

Direct iodination of the Boc aniline **6** was anticipated to produce almost exclusively the undesired 4-chloro-5-fluoro-2-iodo regioisomer, with iodine installation para to fluorine, as reported for the analogous methyl carbamate using *N*-iodosuccinimide.[12] In a similar regioselective fashion, direct iodination of aniline **5** using $I_2/CaCO_3$ was found to give 85% yield of the undesired 4-chloro-5-fluoro-2-iodoaniline. Treatment of Boc aniline **6** with ICl/AcOH resulted in only the deprotected aniline **5**. Instead therefore, ortho-lithiation[13] was performed at low temperature using *n*-BuLi, followed by treatment with iodine in THF to give the desired 2-iodo Boc aniline **7**.[14] Initially, 4 equiv of *n*-BuLi were used with 3.4 equiv of iodine which resulted in modest yields (60−66%) on 10−80 g scale (Table 1, entries 1, 2). Due to the mechanistic requirement for only 2 equiv of *n*-BuLi, one to deprotonate the carbamate, the other to lithiate, an attempt was made to reduce this excess to 2.6 equiv which resulted in 68% yield on 87 g scale (Table 1, entry 3). A significant side product was consistently observed in these

(9) Piscitelli, F.; La Regina, G.; Silvestri, R. *Org. Proced. Prep. Int.* **2008**, *40*, 204–208.

(10) Bachmann, S.; Pflieger, P.; Rimmler, G.; Scalone, M., WO/2009/007259, 2009 (CAN 150:121489). Sugita, K.; Otsuka, M.; Oki, H.; Haginoya, N.; Ichikawa, M.; Ito, M., Jpn. Pat. 2008/291018, 2008 (CAN 149:576645). Terauchi, J.; Kuno, H.; Nara, H.; Oki, H.; Sato, K., WO/2005/105760, 2005 (CAN 143:460174).

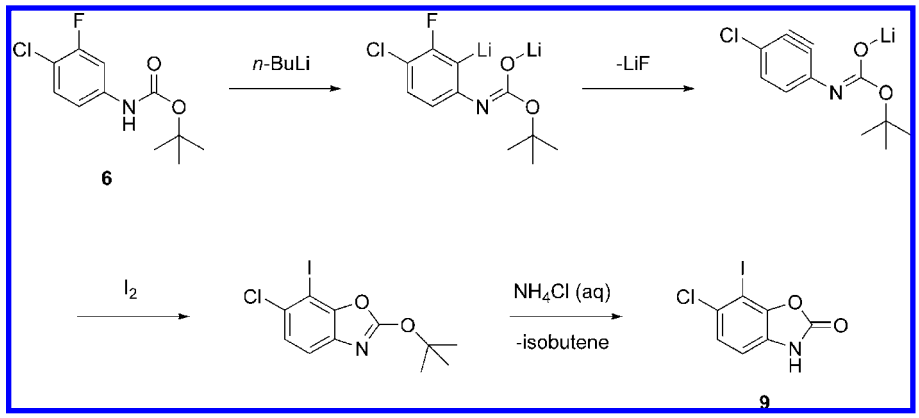
(11) Full characterization of Boc-aniline **6** is provided here for the first time.

(12) Conte, A.; Kuehne, H.; Luebbers, T.; Mattei, P.; Maugeais, C.; Mueller, W.; Pflieger, P. U.S. 2007/185182, 2007.

(13) March, J.; Smith, M. B., Eds. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 6th ed.; John Wiley and Sons, Inc.: NJ, 2007.

(14) Subsequent to the publication of Idenix patents WO/2008/042240 and U.S. 2008/0213217 *vide supra*, a similar procedure using the methyl carbamate analogue was reported to give the corresponding protected 2-iodoaniline, *vide supra* WO/2009/007259, 2009.

Scheme 2. **Formation of benzoxazolone 9 at internal temperature above −75 °C**



three batches, which were all performed at an approximate internal reaction temperature of −70 °C. On scaling further, this impurity made the isolation of **7** increasingly more problematic, and as a result, the yield on 141 g scale dropped to 44% (Table 1, entry 4). A substantial amount (25% yield) of this side product was isolated and positively identified as the benzoxazolone **9**. It was presumed that a slight elevation of the internal temperature led to the elimination of LiF with concomitant formation of the benzyne intermediate, which then underwent Boc side-chain cyclization, trapping with I_2 and subsequent release of isobutene on quenching to give **9** (Scheme 2). It is noteworthy that related reports with Boc aniline[15] and Boc 3-fluoroaniline[16] required the use of *t*-BuLi to effect similar ortho-lithiations, rather than *n*-BuLi. It was determined on small scale that the reaction temperature was the major factor controlling the extent of iodination and the impurity profile. With an internal temperature of −90 to −100 °C, the reaction mixture was observed to partially freeze, and a mere 25% conversion was obtained (Table 1, entry 5). On elevating the temperature to −80 to −95 °C and using 2.6 equiv of *n*-BuLi, in-process analysis indicated a significant amount of **6** remained unreacted, possibly due to partial precipitation of the starting material. A further 1 equiv of *n*-BuLi was added which resulted in a **7**:**6** ratio of 14.6:1. Importantly, a much improved ratio of **7** to benzoxazolone **9** (75.8:1) was obtained, raising the yield to 81% (Table 1, entry 6). An internal temperature range of −75 to −82 °C was next used along with 3 equiv of *n*-BuLi, to ensure good solubility and full conversion of Boc aniline **6** whilst attempting to maintain low levels of benzoxazolone **9**. The reaction mixture was observed to be completely solubilized in this temperature range, giving an improved conversion and an almost undetectable level of **9** (Table 1, entry 7). As a result, 2-iodo Boc aniline **7** was isolated in 87% yield. Encouraged by this data, the reaction was scaled to 80 g whilst raising the internal temperature slightly to −75 to −80 °C. The formation of **7** was smoothly effected, giving an improved **7**:**6** ratio of 43.7:1 whilst maintaining a highly beneficial ratio of **7**:**9** (119:1) (Table 1, entry 8).[17] After addition of the aqueous quenching solutions, the organic solvents were distilled off, efficiently precipitating the crude product **7**. Purification was then achieved by crystallizing the crude solid from hot aqueous ethanol to give **7** in 94% isolated yield and 99% LCAP purity.

Deprotection of the Boc group to provide the free aniline **8** was achieved in a facile manner using conc. HCl in ethanol at 50−55 °C. After a reaction time of 2 h, the mixture was neutralized with aqueous NaOH and the ethanol was distilled off, causing the free aniline to precipitate readily from the colorless aqueous solution. Recrystallization of the crude aniline with hot aqueous ethanol gave two crops of pure 2-iodoaniline **8**, both with 99% LCAP purity in a combined yield of 93%.

With the *ortho*-iodoaniline **8** in hand, the method of Chen et al. was used for indole cyclization, in which initial enamine formation with pyruvate is followed by an intramolecular Heck coupling to provide the indole 2-carboxylate.[18] In preliminary attempts to make the indole ester **1** directly from **8** using methyl pyruvate, only traces of the desired indole ester were observed along with multiple side products and unreacted **8**. This reaction was abandoned in favor of the two step procedure shown in Scheme 1, in which initial indole acid formation was followed by esterification. Thus, on a 75 g scale, iodoaniline **8** was dissolved in DMF at 7.7 v/w concentration with 3.1 equiv of DABCO base. After thoroughly degassing the solution with argon, an exothermic addition of 3 equiv of pyruvic acid was performed followed by 1 mol % palladium acetate. Three hours at 100−105 °C was sufficient to effect complete conversion of **8** to the indole acid **2** at which point a swift and simple workup protocol was employed: whilst keeping the internal temperature at 5−10 °C, dilute HCl was added gradually, until reaching pH 3.5, generating a slurry. The resulting precipitate was then collected by filtration and washed with water to provide indole acid **2** in 95% yield with 99% LCAP purity, as a tan solid. This crude material was determined to be of sufficiently high quality for use directly in the ultimate esterification step, thus bypassing the subsequent ethanol/water precipitation procedure which was carried out to provide an analytical sample of **2**. As a result, aqueous separations and chromatographic purifications were successfully avoided.

Esterification of indole acid **2** was performed using CDI as the carboxylic acid activating agent in DMF at ambient

(15) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798–4801.
(16) Clark, R. D.; Caroon, J. M. *J. Org. Chem.* **1982**, *47*, 2804–2806.
(17) It is also postulated that the improvement in conversion from **6** to **7** on scaling from 3 to 80 g may be in part due to more efficient stirring and decreased splashing of the reaction mixture on the walls of the vessel on larger scale.
(18) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676–2677.

temperature. After 3 h, in-process HPLC analysis indicated complete conversion to the acylimidazole. On addition of excess anhydrous methanol, the subsequent esterification occurred cleanly. The product ester was then precipitated from the reaction mixture with water and filtered to give **1** as a tan solid. Residual water and any insolubles remaining from the previous palladium coupling were removed by dissolving the crude ester in dichloromethane/ethyl acetate, drying over sodium sulfate and filtering through Celite. Partial distillation of the resulting filtrate yielded a slurry of crystals in ethyl acetate and these long white needles were collected by filtration to give the desired indole ester **1** in two crops (42 g) with 72% yield and >98% LCAP purity. Pending logical modifications, this process is expected to be viable on multikilogram scale, fulfilling the objective of an alternative scalable approach to **1**.

Conclusion

A robust five step preparation of functionalized indole **1** was demonstrated on multigram scale, starting from 4-chloro-3-fluoroaniline. This synthesis involved Boc protection of the starting aniline followed by iodination and facile Boc deprotection to give the *ortho*-iodoaniline **8**. Subsequent enamine formation and immediate palladium catalyzed cross-coupling gave the indole 2-carboxylic acid, which was then esterified to provide the indole ester **1**. Initial attempts to scale up the iodination step were hindered by the formation of a major side product. Isolation and identification of the side product as the 6-chloro-7-iodo-2(3*H*)-benzoxazolone **9** led to the discovery that elevated reaction temperature was the major culprit. Maintaining the internal temperature between −75 and −80 °C reproducibly eliminated its production in subsequent batches. This approach was shown to have several advantages enabling the rapid production of **1** relative to the three previously published syntheses: in particular, 1) the starting material was comparatively inexpensive; 2) the use of highly energetic and potentially hazardous diazonium and azido compounds was avoided; 3) there were no regioisomeric products generated to lower the overall yield and complicate isolations; 4) the need for multiple, time-consuming and low efficiency chromatographic purifications was made redundant, as all four intermediates, along with indole ester **1**, were well-defined, easily crystallized solids; and 5) the overall yield was 56%, representing a 51% increase over the Reissert synthesis and a greater than 10-fold improvement over the original Fischer and Hemetsberger methods.

Experimental Section

General. Reagents and materials obtained from commercial suppliers were used without additional purification. All reactions were performed under an argon atmosphere. Reduced pressure distillations were performed between 250 and 50 mbar. HPLC spectra were obtained on an Agilent 1100 series instrument equipped with a UV detector at 272 nm and an Agilent Zorbax Eclipse XDB C_8 reverse phase column (4.6 mm × 75 mm × 3.5 μm) at 25 °C; flow rate 1.4 mL/min; mobile phase A: acetonitrile, B: 0.01 M ammonium acetate aqueous buffer; run time 10 min; gradient: 5% to 80% A over 5.5 min, hold at 80% A for 4.5 min.

***tert*-Butyl-4-chloro-3-fluorophenylcarbamate (6).** A mixture of 4-chloro-3-fluoroaniline (250.3 g, 1.719 mol) *n*-heptane (2.0 L) and di-*tert*-butyl-dicarbonate (450.3 g, 2.064 mol) was stirred under argon at room temperature for 15 min, allowing dissolution of the majority of the solids, prior to heating to reflux (90 °C) (caution: CO_2 gas evolution). After 4 h the reaction was cooled to 50−55 °C, and a total of 1.5 L of distillate was removed by concentration at 45 °C under reduced pressure to give a peach-colored solution with white crystals. The slurry was cooled to room temperature whilst stirring for 1.5 h and then stored at 4 °C for 15 h. The resulting crystals were filtered under vacuum and washed with 4 °C *n*-heptane (400 mL). After drying under vacuum at 35 °C for 7 h, very fine white crystals of *tert*-butyl-4-chloro-3-fluorophenylcarbamate **6** (393.1 g, 93% yield, >99% LCAP at 272 nm) were obtained. Mp: 103−104 °C. MS (ESI$^-$) *m*/*z*: 244.21 $[M - H]^-$, 170.24 $[M - C_4H_{11}O]^-$. IR (KBr disk, cm^{-1}) ν_{max}: 3314, 1691, 1600, 1525. ^{1}H NMR δ_H (400 MHz, $CDCl_3$): 1.51 (9H, s, $C(CH_3)_3$), 6.57 (1H, br-s, N-*H*), 6.94 (1H, ddd, $J_{6,5}$ 8.7 Hz, *J* 2.3 Hz, *J* 1.0 Hz, *H*-6), 7.25 (1H, t, *J* 8.4 Hz, *H*-5), 7.43 (1H, br-dd, $J_{2,F}$ 11.2 Hz, $J_{2,6}$ 1.7 Hz, *H*-2). ^{13}C NMR δ_C (100 MHz, $CDCl_3$): 28.26 ($C(CH_3)_3$), 81.31 ($C(CH_3)_3$), 106.99 ($^2J_{C,F}$ 26.1 Hz, *C*-2), 114.22 (*C*-1), 114.40 (*C*-6), 130.40 (*C*-5), 138.49 ($^2J_{C,F}$ 9.8 Hz, *C*-4), 152.26 (*C*═O), 158.19 ($^1J_{C,F}$ 245.2 Hz, *C*-3). ^{19}F NMR δ_F (376 MHz, $CDCl_3$, decoupled): −113.62 (1F, s). Anal. Calcd for $C_{11}H_{13}ClFNO_2$: C, 53.78; H, 5.33; N, 5.70. Found: C, 53.62; H, 5.13; N, 5.62. HPLC: t_R 6.22 min.

***tert*-Butyl-4-chloro-3-fluoro-2-iodophenylcarbamate (7).** A solution of *tert*-butyl-4-chloro-3-fluorophenylcarbamate **6** (80.2 g, 0.326 mol) and anhydrous tetrahydrofuran (640 mL) was cooled using a dry ice/acetone plus liquid nitrogen bath, ensuring an internal temperature of −80 °C < *T* < −75 °C at all times during the reaction. *n*-Butyllithium (2.5 M in hexane, 405 mL, 1.011 mol) was added over 2 h ensuring the drops were thoroughly dispersed but not splashed. After aging for 40 min, a solution of iodine (289.9 g, 1.142 mol) in anhydrous tetrahydrofuran (430 mL + 100 mL rinse) was added over 3 h, maintaining an internal temperature of −80 °C < *T* < −75 °C. The reaction mixture was warmed slowly to −30 °C over 14 h at which point nearly complete conversion of starting material (<1.6% LCAP) to product was observed. A solution of NH_4Cl (41.6 g in 160 mL water) was added, followed by a solution of $NaHSO_3$ (184.8 g in 560 mL water) ensuring internal *T* < −10 °C. The quenching mixture was warmed to 10 °C whilst stirring for 1.5 h, water (500 mL) was added and 1370 mL of THF distillate was removed under reduced pressure at 40 °C. The mixture was stirred vigorously at 4 °C for 15 h and filtered. After washing with water (400 mL) a beige solid was obtained with a colorless filtrate which contained no product by HPLC. The solid was digested with hot (65 °C) ethanol (700 mL) for 1 h and filtered whilst hot to remove insoluble material (3.5 g) which contained no product by HPLC. The clear, red filtrate obtained was concentrated at 45 °C under vacuum to a volume of 150 mL at which point solids began to precipitate. Water (32 mL) was added to the stirred mixture which was then cooled slowly to 4 °C over 1.5 h. After filtration under vacuum and washing with 4 °C ethanol/water, 2:1 (250 mL) the solid was dried under vacuum at 40 °C for 5 h to give *tert*-butyl-4-chloro-3-fluoro-2-iodophenylcarbamate **7** as a pale yellow solid (114.1 g, 94% yield, >99% LCAP at 272 nm). Mp: 66.0−67.0 °C.

MS (ESI$^-$) *m/z*: 370.03 [M − H]$^-$. IR (KBr disk, cm^{-1}) ν_{max}: 3387, 2983, 1728, 1573. ^{1}H NMR δ_H (400 MHz, $CDCl_3$): 1.54 (9H, s, C(CH_3)$_3$), 6.90 (1H, br-s, N-*H*), 7.34 (1H, t, *J* 8.6 Hz, *H*-5), 7.89 (1H, dd, $J_{6,5}$ 9.0 Hz, $J_{6,F}$ 1.5 Hz, *H*-6). ^{13}C NMR δ_C (100 MHz, $CDCl_3$): 28.25 (C(CH_3)$_3$), 81.77 (*C*(CH_3)$_3$), 114.26 ($^2J_{C,F}$ 20.5 Hz, *C*-2), 115.17, 115.20 (*C*-1, *C*-6), 130.57 (*C*-5), 139.34 ($^2J_{C,F}$ 3.0 Hz, *C*-4), 152.26 (*C*═O), 156.92 ($^1J_{C,F}$ 241.9 Hz, *C*-3). ^{19}F NMR δ_F (376 MHz, $CDCl_3$, decoupled): −88.72 (1F, s). Anal. Calcd for $C_{11}H_{12}ClFINO_2$: C, 35.56; H, 3.26; N, 3.77. Found: C, 35.57; H, 3.01; N, 3.75. HPLC: t_R 6.80 min.

4-Chloro-3-fluoro-2-iodoaniline (8). A mixture of *tert*-butyl-4-chloro-3-fluoro-2-iodophenylcarbamate **7** (110.0 g, 0.296 mol) and ethanol (900 mL) was cooled to 5 °C. HCl (37%, 145.9 mL) was added dropwise over 10 min keeping the internal temperature below 15 °C. The mixture was warmed to 50−55 °C for 2 h (caution: gas evolution) by which point the solids had completely dissolved. The reaction was cooled to 5 °C and aqueous NaOH (80.0 g L^{-1}, 865 mL) was added gradually over 1 h keeping the internal temperature below 15 °C, monitoring the pH until neutral. The mixture was stored at 4 °C for 15 h. A total of 970 mL of distillate was removed by concentration under reduced pressure at 35 °C to give a colorless solution with precipitated solids. The slurry was cooled to 4 °C for 1 h after which time the solids were filtered under vacuum and washed with 4 °C ethanol/water, 1:4 (200 mL). After drying at 35 °C under vacuum for 72 h, crude aniline **8** (80 g, 99% yield, 95% LCAP at 272 nm) was obtained. The solids were dissolved in ethanol (450 mL) at 60 °C and filtered whilst hot to remove the fine insoluble material. The filtrate obtained was concentrated at 35 °C under vacuum to a volume of 175 mL. Water (70 mL) was added to the mixture over 3−4 h at 20 °C to induce formation of solids. The slurry was cooled to 4 °C and stirred for a further 0.5 h. Filtration under vacuum, washing with 4 °C ethanol/water, 3:2 (100 mL) and drying under vacuum at 35 °C gave 4-chloro-3-fluoro-2-iodoaniline **8** as orange needles (70.5 g, 88% yield, >99% LCAP at 272 nm). A second crop of material was obtained from the mother liquor by cooling to 3 °C, adding water (50 mL) and stirring for 1.5 h. Filtration, washing with 4 °C ethanol/water, 1:2 and drying under vacuum at 35 °C gave additional **8** as pale yellow needles (4.6 g, 5%, >99% LCAP at 272 nm). Combined yield of aniline **8** = 75.1 g, 93%. Mp: 80.5−81.0 °C. MS (ESI$^-$) *m/z*: 270.03 [M − H]$^-$. IR (KBr disk, cm^{-1}) ν_{max}: 3455, 3353, 1608, 1471. ^{1}H NMR δ_H (400 MHz, d_6-DMSO): 5.71 (2H, br-s, NH_2), 6.57 (1H, dd, $J_{6,5}$ 8.8 Hz, $J_{6,F}$ 1.5 Hz, *H*-6), 7.20 (1H, t, *J* 8.8 Hz, *H*-5). ^{13}C NMR δ_C (100 MHz, d_6-DMSO): 71.06 ($^2J_{C,F}$ 27.7 Hz, *C*-2), 104.12 ($^2J_{C,F}$ 21.0 Hz, *C*-4), 110.12 ($^4J_{C,F}$ 2.6 Hz, *C*-6), 129.87 ($^3J_{C,F}$ 1.1 Hz, *C*-5), 150.07 ($^3J_{C,F}$ 4.6 Hz, *C*-1), 156.60 ($^1J_{C,F}$ 236.3 Hz, *C*-3). ^{19}F NMR δ_F (376 MHz, d_6-DMSO, decoupled): −93.41 (1F, s). Anal. Calcd for C_6H_4ClFIN: C, 26.55; H, 1.49; N, 5.16. Found: C, 26.71; H, 1.27; N, 4.97. HPLC: t_R 5.48 min.

5-Chloro-4-fluoro-1*H*-indole-2-carboxylic Acid (2). 4-Chloro-3-fluoro-2-iodoaniline **8** (74.5 g, 0.275 mol) was dissolved in anhydrous DMF (575 mL) at 20−25 °C. 1,4-Diazabicyclo[2.2.2]octane (DABCO) (98%, 97.4 g, 0.851 mol) was added in one portion and the internal temperature dropped to 15 °C. The mixture was stirred for 20 min to effect dissolution, and the solution was then vigorously degassed with a stream of argon for 10 min. Pyruvic acid (98%, 58.50 mL, 0.824 mol) was added to the brown solution over 10 min, and the internal temperature rose to 36 °C. The solution was again degassed with argon for 10 min, and palladium acetate (98%, 0.691 g, 0.0030 mol) was added in one portion. The mixture was heated to 100−105 °C for 3 h and then cooled and stirred at 20−25 °C for 15 h. After cooling to 0−5 °C, aqueous HCl (1.15 N, 575 mL then 0.115 N, 280 mL) was added, keeping the temperature below 10 °C, monitoring until pH 3.5 was achieved. A tan solid precipitated from the solution, and the slurry was stirred for an additional 0.5 h at 5 °C. The solids were filtered under vacuum and washed with 10 °C water (3 × 200 mL). After drying at 40 °C under vacuum for 36 h, 5-chloro-4-fluoro-1*H*-indole-2-carboxylic acid **2** (55.9 g, 95% yield) was obtained as a tan solid (>99% LCAP at 272 nm). An analytical sample of **2** was obtained by dissolving a small portion of the tan solid in 10 vol of EtOH and then adding an equivalent volume of water. The precipitate was recovered by filtration and dried under vacuum at 50 °C to give **2** as an off-white solid (99.7% LCAP at 272 nm). Mp: 270−280 °C contracted and darkened; 280.5−281.8 °C melted. MS (ESI$^-$) *m/z*: 212.20 [M − H]$^-$, 168.22 [M − CO_2H]$^-$. IR (KBr disk, cm^{-1}) ν_{max}: 3463, 2925, 2625, 1676. ^{1}H NMR δ_H (400 MHz, d_6-DMSO): 7.13 (1H, dd, $J_{3,NH}$ 2.1 Hz, $J_{3,F}$ 0.5 Hz, *H*-3), 7.29 (1H, dd, $J_{7,6}$ 8.8 Hz, $J_{7,F}$ 0.5 Hz, *H*-7), 7.33 (1H, dd, $J_{6,7}$ 8.8 Hz, $J_{6,F}$ 6.5 Hz, *H*-6), 12.32 (1H, s, N*H*), 13.35 (1H, br-s, CO_2H). ^{13}C NMR δ_C (100 MHz, d_6-DMSO): 102.40 (*C*-3), 108.78 ($^2J_{C,F}$ 15.4 Hz, *C*-5), 110.15 ($^4J_{C,F}$ 3.9 Hz, *C*-7), 116.92 ($^2J_{C,F}$ 21.0 Hz, *C*-9), 125.40 (*C*-6), 130.25 (*C*-2), 137.89 ($^3J_{C,F}$ 9.9 Hz, *C*-8), 150.92 ($^1J_{C,F}$ 248.4 Hz, *C*-4), 162.04 (*C*O_2H). ^{19}F NMR δ_F (376 MHz, d_6-DMSO, decoupled): −123.16 (1F, s). Anal. Calcd for $C_9H_5ClFNO_2$: C, 50.61; H, 2.36; N, 6.56. Found: C, 50.44; H, 2.29; N, 6.48. HPLC: t_R 3.63 min.

Methyl 5-chloro-4-fluoro-1*H*-indole-2-carboxylate (1). 5-Chloro-4-fluoro-1*H*-indole-2-carboxylic acid **2** (55.9 g, 0.262 mol) was added to anhydrous DMF (695 mL) at 20−25 °C under argon and stirred for 20 min to obtain a brown solution. 1,1′-Carbonyldiimidazole (CDI) (51.0 g, 0.314 mol) was added in one portion, giving a brown suspension (caution: CO_2 gas evolution). The mixture was stirred for 1 h under argon at 20−25 °C at which point starting material was still observed (0.5% LCAP at 272 nm). Additional CDI (0.43 g, 0.0026 mol) and DMF (45 mL) were added, and the reaction was stirred for a further 2 h after which time analysis by HPLC indicated complete disappearance of acid **7**. Anhydrous methanol (297 mL, 7.34 mol) was added to the stirred reaction mixture under argon at 20−25 °C to give a cloudy brown suspension. After 3 h, the reaction mixture was cooled, keeping the internal temperature 15−20 °C, and water (2000 mL) was added over 0.5 h, precipitating a tan solid. The solid was filtered under vacuum and washed with 5 °C water (2 × 400 mL). After air drying, the solid was taken up in DCM (800 mL) and EtOAc (1600 mL) and dried using anhydrous sodium sulfate (400 g). Filtration through Celite and elution with DCM (1000 mL) yielded a clear, orange solution. The solution was concentrated under vacuum at 30 °C, leaving a slurry of crystals in EtOAc (160 mL). The stirred slurry was cooled to 0−5 °C for 15 min. Filtration under vacuum, washing with 4 °C EtOAc/*n*-heptane,

1:1 (2 × 100 mL) then 1:3 (100 mL) and drying under vacuum at 35 °C gave methyl 5-chloro-4-fluoro-1*H*-indole-2-carboxylate **1** as long, white needles (37.3 g, 63% yield, >99% LCAP at 272 nm). A second crop of **1** was obtained from the mother liquor (after removing 360 mL of distillate) as off-white needles (5.3 g, 9% yield, >98% LCAP at 272 nm). Combined yield of indole ester **1** = 42.6 g, 72%. Mp: 216.5−218.0 °C. MS (ESI^-) *m*/*z*: 226.20 $[M - H]^-$. IR (KBr disk, cm^{-1}) ν_{max}: 3307, 1699. ^1H NMR δ_H (400 MHz, d_6-DMSO): 3.90 (3H, s, C*H*$_3$), 7.19 (1H, d, *J* 0.4 Hz, *H*-3), 7.30 (1H, dd, $J_{7,6}$ 8.8 Hz, $J_{7,F}$ 0.8 Hz, *H*-7), 7.36 (1H, dd, $J_{6,7}$ 8.8 Hz, $J_{6,F}$ 6.8 Hz, *H*-6), 12.49 (1H, s, N*H*). ^{13}C NMR δ_C (100 MHz, d_6-DMSO): 52.12 (CO_2CH_3), 102.88 (*C*-3), 109.00 ($^2J_{C,F}$ 15.3 Hz, *C*-5), 110.25 ($^4J_{C,F}$ 4.0 Hz, *C*-7), 116.83 ($^2J_{C,F}$ 21.0 Hz, *C*-9), 125.82 (*C*-6), 128.77 (*C*-2), 137.99 ($^3J_{C,F}$ 9.9 Hz, *C*-8), 150.97 ($^1J_{C,F}$ 248.8 Hz, *C*-4), 161.00 (CO_2CH_3). ^{19}F NMR δ_F (376 MHz, d_6-DMSO, decoupled): −122.92 (1F, s). Anal. Calcd for $C_{10}H_7ClFNO_2$: C, 52.77; H, 3.10; N, 6.15. Found: C, 52.41; H, 2.84; N, 6.14. HPLC: t_R 5.51 min.

6-Chloro-7-iodo-2(3*H*)-benzoxazolone (9). A solution of *tert*-butyl-4-chloro-3-fluorophenylcarbamate **6** (141.3 g, 0.575 mol) in anhydrous tetrahydrofuran (706 mL) was cooled using a dry ice bath, keeping the internal temperature −68 °C < *T* < −72 °C. *n*-Butyllithium (2.5 M in hexane, 593 mL, 1.483 mol) was added over 4 h. A solution of iodine (493.2 g, 1.943 mol) in anhydrous tetrahydrofuran (940 mL) was added, maintaining an internal temperature of −68 °C < *T* < −72 °C. The reaction mixture was warmed slowly to 20 °C over 14 h. The mixture was cooled to −5 °C < *T* < −15 °C, and a solution of NH_4Cl (74.4 g in 275 mL water) was added gradually over 40 min, followed by a solution of $NaHSO_3$ (325 g in 1.60 L water) over 30 min. The quenching mixture was warmed to 20 °C whilst stirring for 1.5 h. After adding water (650 mL), 2.26 L of THF distillate was removed under reduced pressure at 40 °C. The mixture was stirred vigorously at 20−25 °C for 1.5 h and filtered. After washing with water (450 mL) a beige solid was obtained. The crude solid (146 g) was digested with ethanol (287 mL) at 65 °C for 1 h, hot filtered under vacuum, washed with ethanol (115 mL) and dried under vacuum. 6-Chloro-7-iodo-2(3*H*)-benzoxazolone **9** (42.34 g, 25%, >99% LCAP at 272 nm) was obtained as an off-white solid. Mp: 314−316 °C. MS (ESI^-) *m*/*z*: 293.99 $[M - H]^-$, 588.88 $[2M - H]^-$. IR (KBr disk, cm^{-1}) ν_{max}: 3254, 3085, 1742, 1443. ^1H NMR δ_H (400 MHz, d_6-DMSO): 7.06 (1H, d, $J_{4,5}$ 8.3 Hz, *H*-4), 7.33 (1H, d, $J_{5,4}$ 8.3 Hz, *H*-5), 12.03 (1H, br-s, N*H*). ^{13}C NMR δ_C (100 MHz, d_6-DMSO): 79.37 (*C*-7), 110.36 (*C*-4), 124.09 (*C*-5), 128.35 (*C*-9), 129.94 (*C*-6), 146.24 (*C*-8), 153.20 (*C*-2). Anal. Calcd for $C_7H_3ClINO_2$: C, 28.46; H, 1.02; N, 4.74. Found: C, 28.58; H, 0.97; N, 4.69. HPLC: t_R 4.72 min. Concentration of the filtrate at 45 °C under vacuum, precipitation with water, and filtration and drying gave *tert*-butyl-4-chloro-3-fluoro-2-iodophenylcarbamate **7** (95.3 g, 44% yield) analysis of which corresponded to the previously stated data.

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