

Successful Development and Scale-up of a Palladium-Catalysed Amination Process in the Manufacture of ZM549865

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Abstract:

Key steps in the synthesis of ZM549865 (a 5-HT receptor antagonist) are the palladium-catalysed amination of ethyl 8-bromo-6-fluoro-4-oxo-4H-2-chromenecarboxylate and subsequent hydrolysis of the ester group. The development of a simple, robust process capable of making multikilogram amounts of the required intermediate is described. Performing the amination step at 125 °C instead of 80 °C and optimising the hydrolysis conditions led to an increase in overall yield from 44% to about 70% as well as reducing the reaction time from days to hours. The chromone ring was initially constructed by reaction of 2-bromo-4-fluorophenol with dimethyl acetylenedicarboxylate followed by cyclisation. A potentially cheaper route was developed that involved formation of a substituted acetophenone via the Fries rearrangement, followed by condensation with diethyl oxalate and cyclisation.

Introduction

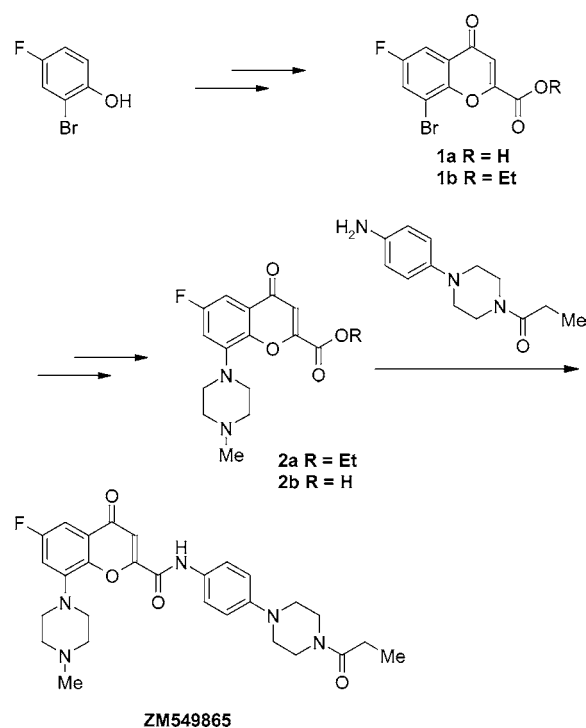
Serotonin (5-hydroxytryptamine, 5-HT) has been implicated in many psychiatric disorders including depression and anxiety. There are several subtypes of serotonin receptors, and compounds that interact with the 5-HT_{1B} family are known to have therapeutic potential in psychiatric disorders and diseases. ZM549865 is a potent, orally active 5-HT_{1B} receptor antagonist selected for development as a potential treatment for depression and anxiety.

The synthesis of ZM549865 requires introduction of the piperazine ring (Scheme 1) and our Medicinal Chemistry Group in Wilmington, DE, U.S.A., chose a synthetic strategy based on the palladium-catalysed amination process discovered by Buchwald and Hartwig.^{1,2} The required bromo substrate is readily obtained from 2-bromo-4-fluorophenol by reaction with dimethyl acetylenedicarboxylate (DMADC) followed by an acid-catalyzed cyclisation of the Z-alkene. A more efficient route to the bromochromone subsequently developed for scale-up employs a Fries rearrangement followed by a Claisen condensation of the product with diethyl oxalate and an acid-catalyzed cyclisation.

Results and Discussion

Campaign 1. The original amination process received from Wilmington employed toluene as solvent and Pd₂(dba)₃/

Scheme 1



BINAP as catalyst in the presence of cesium carbonate. The reaction was carried out at 80 °C and took 138 h to complete; additional portions of catalyst were added during the course of the reaction in an attempt to increase the conversion rate. Starting from 50 g of bromoester **1b**, the piperazine product **2a** was isolated in 73% yield after chromatography. Subsequent hydrolysis of the ester **2a** with lithium hydroxide afforded the piperazine acid **2b** in 95% yield. Thus, the overall yield was 69%. These processes were scaled up in the Large Scale Laboratory at Macclesfield to deliver 280 g of ZM549865 (Campaign 1). However, the conversion in the amination step was slower (69% after 138 h). Starting from 500 g of bromoester **1b**, the overall yield of piperazine acid **2b** was only 44%.

This procedure was clearly unsuitable for further scale-up.

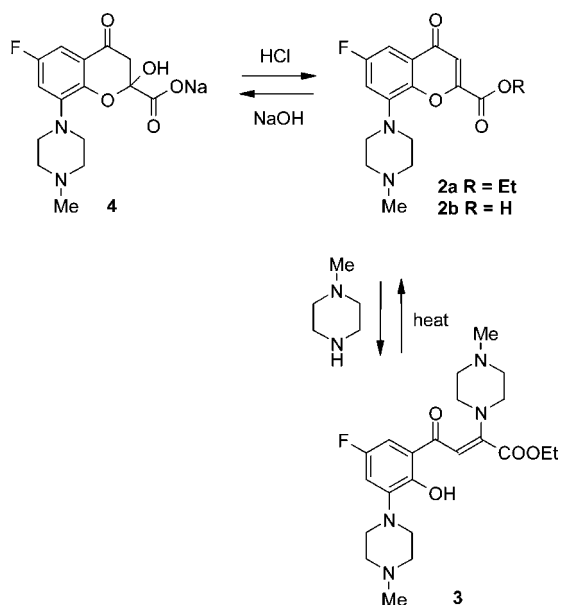
Development of a Process for Campaign 2. A mass balance investigation using HPLC analysis showed that ester hydrolysis occurred to a small extent in the amination process and this contributed to a small loss in yield upon isolation of the piperazine ester **2a**. This led to the conclusion that it would be better to avoid isolating the piperazine ester **2a** by

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(1) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350.

(2) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609–3612.

Scheme 2



telescoping the amination and ester hydrolysis steps. An additional benefit of this approach would be easier removal of organic-soluble waste products (dba and BINAP) arising from the palladium catalyst since piperazine acid **2b** could be extracted into aqueous alkali; in the Medicinal Chemistry process, these contaminants were removed by chromatography. If ester hydrolysis were to be performed in aqueous medium, it would be appropriate to switch from lithium hydroxide to aqueous sodium hydroxide.

The reactions were studied in detail using LC-MS to identify by-products and impurities. Two key findings emerged: (a) the chromone ring undergoes reversible ring opening in the presence of *N*-methylpiperazine to give **3**, and (b) the piperazine acid **2b** is converted to a hydrated form **4** in the presence of aqueous alkali (Scheme 2).

The observed reaction time of the amination process at 80 °C was unacceptably long for scale-up. Naturally, the option of using a higher temperature was investigated. Anisole was found to be a suitable solvent, and reactions carried out at 125 °C were complete in a reasonable time scale (<8 h). Surprisingly, the reaction profile (as judged by GC and HPLC analysis) looked much cleaner. In particular, product **3** resulting from ring opening with *N*-methylpiperazine was not observed; this suggested the equilibrium is in favour of the ring-closed form at the higher temperature.

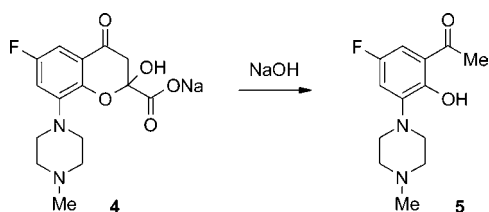
A simpler process was developed for Campaign 2. In outline, this consisted of adding a solution of *N*-methylpiperazine (1.1 mol equiv) and bromoester **1b** in anisole to a mixture of Pd₂(dba)₃ (2 mol %), racemic BINAP (4 mol %), and cesium carbonate (1.4 mol equiv) at 125 °C. Upon completion of the reaction (about 4 h after the start of the addition), the mixture was cooled and diluted with aqueous sodium hydroxide (2.2 mol equiv) to effect hydrolysis (1–2 h at room temperature). The aqueous phase was adjusted to pH 3 with hydrochloric acid and heated at 60 °C for about 1 h to dehydrate any of the hydrated species **4**. The mixture was then adjusted to pH 7 to precipitate the required piperazine acid **2b**.

The target quantity of ZM549865 (about 5 kg) required operation of the amination process in a 50-L glass reactor in our Large Scale Laboratory at Macclesfield. To our consternation, the first batch was a complete failure. Hardly any of the required piperazine ester **2a** was detected in the reaction mixture. The reaction profile was not improved by adding extra catalyst and BINAP; gradual degradation of the starting material occurred on prolonged heating, and the mixture was eventually discarded. An investigation of the problem revealed two possible causes: deactivation of the catalyst by oxygen and inadequate mixing during dissolution of the catalyst. An experiment in which the reaction mixture was exposed to air resulted in poor conversion to the required product and an abnormally high level of oxidised BINAP (this was also seen in the scale-up batch). In the unsuccessful batch, relatively small quantities of palladium catalyst and BINAP were charged to the reactor followed by cesium carbonate (a dense, hygroscopic solid) and solvent; agitation was finally started. It is likely that the sparingly soluble cesium carbonate physically prevented dissolution of the palladium by forming a protective coating. This effect too was simulated in an experiment. The operational procedure was modified for subsequent batches: (1) additional steps were introduced to ensure a strictly inert atmosphere for the reaction; (2) the Pd₂(dba)₃ and rac-BINAP were dissolved in anisole before being added to the main reactor (containing anisole and cesium carbonate). These changes were reasonably successful in the remaining batches, and the piperazine acid was obtained in 48–63% yield. However, there was still room for improvement since the scale-up yields were significantly below expectation (the target yield was 65–70% based on laboratory experiments), and the process was considered too complicated.

Palladium Contamination of the Product. Analytical measurements during Campaign 2 manufacture predicted that the drug substance would contain an unacceptably high level of palladium (≥ 100 ppm versus a limit of 20 ppm). This led to a hastily developed re-treatment process in which the palladium was removed by slurring the drug substance with hot dimethyl sulphoxide. A major objective during the design of a process for plant-scale operation was control of the palladium level during the preparation or isolation of piperazine acid **2b**. A number of options were evaluated, including the Smopex scavenging resins supplied by Johnson Matthey. Whilst these afforded a significant reduction in the level of palladium in piperazine acid **2b**, treatment with activated carbon was found to be even more effective and easily achieved the proposed limit of <50 ppm palladium in this key intermediate. Thus, a carbon treatment was incorporated into the process.

Source of Palladium Catalyst. Palladium catalyst from three different suppliers (Heraeus, OMG, and PMC) was evaluated. During initial experiments, the charge of catalyst was adjusted for palladium content according to the suppliers' descriptions of the product as Pd₂(dba)₃ or Pd(dba)₂. In fact, the measured palladium content was the same for all three samples (20.5–21.5%), whereas the formulae Pd₂(dba)₃ and

Scheme 3



Pd(dba)₂ require 23 and 18%, respectively. Discussion with the suppliers confirmed that the formulae are only intended to give an approximate representation of the product. For consistency with all the earlier experimental work, however, we decided to continue charging the palladium catalyst, assuming it had the nominal composition of Pd₂(dba)₃.

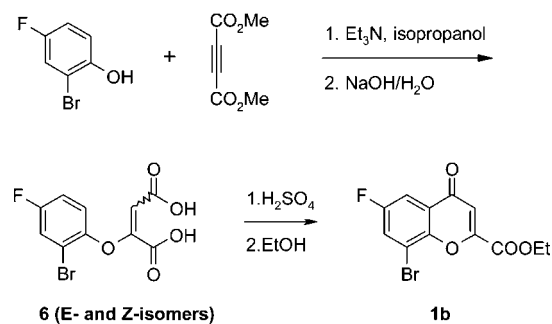
Development of a Process for Plant-Scale Operation.

Campaign 3 manufacture required operation of the amination process in our development-scale Pilot Plant at Macclesfield. In light of manufacturing experience in Campaign 2, we continued our investigation of the process for making piperazine acid **2b**. The main objectives were simplicity of operation and robustness. We had assumed the yield variability observed in Campaign 2 was due to sensitivity of the relatively complex amination step. To test this assumption, laboratory preparations were monitored by GC analysis which showed the yield of piperazine ester **2a** in the organic phase at the end of the amination step to be consistently 85%. Attention then turned to the apparently trivial ester hydrolysis. Perusal of the literature³ indicated that the hydrated species **4** formed under basic conditions could decompose by a number of pathways, including the retro-Dieckmann reaction to give acetophenone **5** (Scheme 3). The latter compound was indeed isolated from the reaction mother liquor.

To minimise the impact of this decomposition pathway, two options were considered: basic hydrolysis under milder conditions and acidic hydrolysis. Experimental work showed that a reduced charge of sodium hydroxide solution (1.3 instead of 2.2 mol equivalents) achieves complete hydrolysis in a reasonable time scale at 45 °C with little or no formation of hydrated compound **4**; hence, the pH 3 treatment at 60 °C was avoided. During the hydrolysis, activated carbon (5% w/w) was introduced to remove palladium. The piperazine acid **2b** was isolated in 70% yield by acidifying the aqueous phase. An alternative process involving hydrolysis of the ester with aqueous sulphuric acid at 96 °C was also developed. This process also afforded piperazine acid **2b** in 70% yield; in this case the palladium was removed effectively by separating and discarding the organic phase. However, the product tended to crystallise out of the aqueous phase on cooling with a consequent risk of transfer line blockage in the pilot plant. Therefore, the sodium hydroxide process was selected for scale-up.

Campaign 3 Manufacture. Three batches of piperazine acid **2b** were produced from 116 kg of bromoester **1b** in an aggregate yield of 64% (the product was isolated in a

Scheme 4



pressure filter, and the heel was sacrificed). There were no significant technical or operational problems. The product contained <1.5% total related substances and <5 ppm palladium and was subsequently processed to ZM549865 of acceptable quality.

Alternative Conditions for the Amination Process.

During the development of a scaleable amination process we investigated a range of solvents, different bases (including alkali metal carbonates and alkoxides), and different catalysts and ligands. This investigation did not reveal any process conditions superior to those described above.

Bromoacid **1a** is a potentially attractive substrate for the amination process in view of the likely resistance of the carboxylic acid salt to side reactions which result from nucleophilic attack on the chromone ring. In the event, bromoacid **1a** was resistant to amination under the conditions optimised for bromoester **1b** (anisole, 125 °C); none of the required piperazine acid **2b** was produced, but a few percent of the product resulting from debromination was observed.

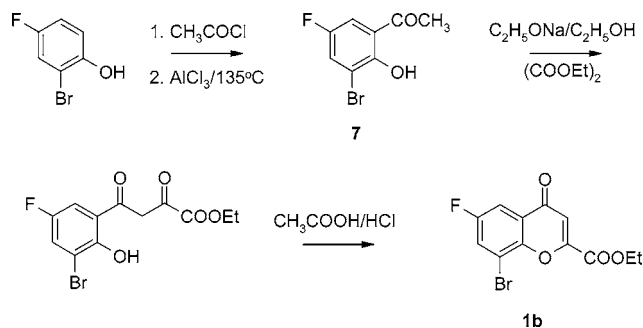
The possibility of coupling bromoacid **1a** to the substituted aniline prior to the amination step was also considered. However, our colleagues in Medicinal Chemistry found that the amide does not undergo the required amination.

Synthesis of Bromoester 1b. Bromoester **1b** was supplied by a contract manufacturer and prepared according to the route shown in Scheme 4. This route suffered from several drawbacks: (a) Dimethyl acetylenedicarboxylate is expensive and not widely available in bulk; (b) alkene **6** is produced as a mixture of Z- and E-isomers in approximately 2:1 ratio, but only the former cyclises; (c) both alkene **6** and bromoester **1b** are prone to long filtration times, and a considerable amount of resource was expended in developing crystallisation processes to give an improved physical form; (d) the cyclisation process involved portionwise addition of a solid substrate to hot sulphuric acid; and (e) ring sulphonation occurred to a variable, and sometimes considerable, extent in the cyclisation step.

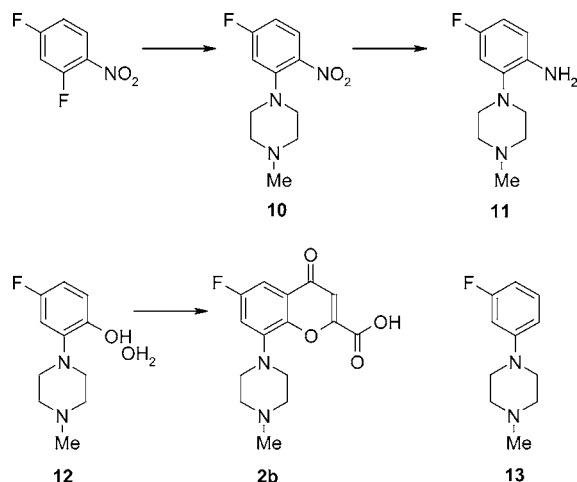
Although more than 100 kg of bromoester **1b** were manufactured by the initial route shown in Scheme 4, there were doubts about its viability on a commercial production scale, and this led to the exploration of alternative routes to the key chromone molecule. We investigated a potentially much cheaper route involving Fries rearrangement of the acetate ester of 2-bromo-4-fluorophenol, followed by Claisen condensation between the resulting acetophenone **7** and diethyl oxalate and finally acid-catalyzed cyclisation (Scheme

(3) *The Chemistry of Heterocyclic Compounds: Chromenes, Chromanones and Chromones*; Ellis, G. P., Ed.; Wiley and Sons: New York, 1977; pp 572 and 972.

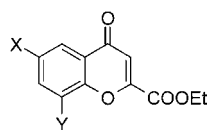
Scheme 5



Scheme 6



5).^{4,5} This route was developed and operated successfully in our pilot plant. A significant issue during development of this route was the discovery of impurities **8** and **9**, attributable to replacement of fluorine by chlorine and reductive removal of bromine during the Fries rearrangement. These impurities were potentially troublesome in the synthesis of ZM549865; fortunately, their formation was controlled by minimising the charge of aluminium chloride.



8 X=Cl, Y=Br
9 X=F, Y=H

Introduction of the Piperazine without Palladium Catalysis. Synthetic routes not involving palladium catalysis were considered. We reasoned that phenol **12**, readily accessible from 2,4-difluoronitrobenzene, should be capable of transformation into the required chromone (see Scheme 6) by methodology described above. *N*-Methylpiperazine reacted with 2,4-difluoronitrobenzene to give predominantly the required ortho isomer (4:1 ratio), isolated in 60% yield after column chromatography. Nitro compound **10** was reduced to aniline **11** in 93% yield with hydrogen and

palladium on carbon, but subsequent diazotisation afforded only a few percent yield of the required phenol **12**; instead, LC-MS showed the major product to be the reduced species **13**.

Conclusions

A two-step process involving palladium-catalysed amination and ester hydrolysis has been developed for the synthesis of a key intermediate in the manufacture of ZM549865. The process was scaled up successfully and reliably in our pilot plant. Complications arising from the susceptibility of the chromone ring to opening in the presence of nucleophiles and bases were avoided by careful selection of reaction conditions. In early manufacture the chromone ring was constructed by reaction between the corresponding phenol and dimethyl acetylenedicarboxylate. In view of the various disadvantages of this approach, an alternative route using Fries rearrangement of a phenyl ester followed by Claisen condensation was developed and successfully operated on the pilot-plant scale.

Experimental Section

Piperazine Acid **2b**. Procedure A (Basic Hydrolysis).

The reactors required for the amination stage were carefully dried by rinsing with acetone and heating to 110 °C under vacuum; they were then rinsed with anisole under partial reflux. An inert atmosphere was maintained during all charging operations by pressurising the reactors with nitrogen (two cycles) then evacuating and releasing the vacuum with nitrogen (two cycles). A mixture of tris(dibenzylideneacetone)dipalladium (2.25 kg, 0.02 mol equiv), rac-BINAP (3.06 kg, 0.04 mol equiv), and anisole (135 L) was adjusted to 25 °C and added to a stirred suspension of cesium carbonate (56.0 kg, 1.40 mol equiv) in anisole (230 L) at 25 °C followed by a line wash of anisole (19.5 L). The mixture was heated to 125 °C. A solution of bromoester **1b** (38.7 kg, 1.00 mol equiv) and *N*-methylpiperazine (13.5 kg, 1.10 mol equiv) in anisole (154 L) maintained at 45 °C was added in six portions over 90 min to the heated catalyst mixture; this was followed by a line wash of anisole (38.4 L). The resulting mixture was maintained at 125 °C for an additional 6.5 h then cooled to 45 °C and diluted with water (233 L). Sodium hydroxide solution (47% w/w, 13.6 kg, 1.30 mol equiv) was added, and the mixture was stirred at 45 °C for 6 h. Carbon Norit SX plus (1.9 kg) was added, and the mixture was stirred at 45 °C for an additional 2 h, cooled to 25 °C, and filtered through Harborlite 800 filter aid. The filter cake was washed with water (39 L) and anisole (50 L). After allowing the filtrate to settle, the aqueous layer was separated and diluted with tetrahydrofuran (77 L) and methanol (77 L). The solution was acidified with concentrated hydrochloric acid (38.7 kg, 3.20 mol equiv) at 20 °C. The precipitated solid was filtered off, washed with a mixture of tetrahydrofuran (58 L), methanol (58 L), and water (58 L) followed by methanol (50 L), and dried at 40 °C under a flow of nitrogen to give piperazine acid **2b**. The mean batch weight of product from three batches was 23.9 kg (corrected for strength) which represents a yield of 64%. Mp: decom-

(4) Bryan, J. D.; Goldberg, A. A.; Wragg, A. H. *J. Chem. Soc., Abstr.* **1960**, 1279.

(5) *The Chemistry of Heterocyclic Compounds: Chromenes, Chromanones and Chromones*; Ellis, G. P., Ed.; Wiley and Sons: New York, 1977; p 944.

position at 285 °C; ¹H NMR (400 MHz, DMSO-*d*₆, CF₃-CO₂H) δ 2.94 (s, 3H), 3.20 (t, *J* = 12.0 Hz, 2H), 3.32 (t, *J* = 11.1 Hz, 2H), 3.62 (d, *J* = 12.0 Hz, 2H), 3.90 (d, *J* = 13.0 Hz, 2H), 6.93 (s, 1H), 7.31 (dd, *J* = 8.0, 3.0 Hz, 1H), 7.38 (dd, *J* = 10.4, 3.0 Hz, 1H); ¹³C NMR (100.6 MHz, DMSO-*d*₆) δ 42.6, 47.5, 52.9, 102.0 (*J*_{C-F} = 24.1 Hz), 111.7 (*J*_{C-F} = 27.9 Hz), 112.8, 125.9 (*J*_{C-F} = 9.0 Hz), 142.8 (*J*_{C-F} = 9.0 Hz), 145.5, 153.1, 159.8 (*J*_{C-F} = 244.9 Hz), 161.8, 177.7 (*J*_{C-F} = 2.3 Hz); FTIR (KBr, cm⁻¹) 3434, 1627, 1488, 1461, 1376, 1325, 1131, 982.

Procedure B (Acidic Hydrolysis). The vessels required for the amination stage were carefully dried, and processing was carried out under a nitrogen atmosphere. To a mixture of tris(dibenzylideneacetone)dipalladium (1.16 g, 0.02 mol equiv), rac-BINAP (1.58 g, 0.04 mol equiv), and anisole (200 mL) was added cesium carbonate (28.95 g, 1.40 mol equiv). The mixture was heated to 125 °C, and a solution of bromoester **1b** (20.0 g, 1.00 mol equiv) and *N*-methylpiperazine (6.99 g, 1.10 mol equiv) in anisole (90 mL) maintained at 45 °C was added in six portions over 90 min; this was followed by an anisole (10 mL) line wash. The resulting mixture was maintained at 125 °C for an additional 3 h, cooled to 75 °C, and diluted with water (200 mL). A solution of concentrated sulphuric acid (55.4 g, 8.8 mol equiv) in water (100 mL) was added at 75 °C, and the mixture was heated at 96 °C for 4 h. The mixture was cooled to 75 °C, and the layers were separated. Anisole (100 mL) and 47% w/w sodium hydroxide solution (37.75 g, 6.99 mol equiv) were added to the hot aqueous layer, and the mixture was cooled to 20 °C. The pH was adjusted to 7 by adding 47% w/w sodium hydroxide solution (39.26 g, 7.29 mol equiv), and the precipitated solid was filtered off, washed with a mixture of tetrahydrofuran (30 mL), methanol (30 mL) and water (30 mL), and then dried at 40 °C under vacuum. The yield of piperazine acid **2b** was 14.2 g (73%).

Preparation of Hydrated Species 4. The vessels required for the amination stage were carefully dried, and processing was carried out under a nitrogen atmosphere. To a mixture of tris(dibenzylideneacetone)dipalladium (1.16 g, 0.02 mol equiv), racemic-BINAP (1.58 g, 0.04 mol equiv), and anisole (200 mL) was added cesium carbonate (28.95 g, 1.40 mol equiv). The mixture was heated to 125 °C, and a solution of bromoester **1b** (20.0 g, 1.00 mol equiv) and *N*-methylpiperazine (6.99 g, 1.10 mol equiv) in anisole (90 mL) maintained at 45 °C was added in six portions over 90 min; this was followed by an anisole (10 mL) line wash. The resulting mixture was maintained at 125 °C for an additional 3 h, cooled to 20 °C, and diluted with water (120 mL); 47% w/w sodium hydroxide solution (17.83 g, 3.30 mol equiv) was added in four portions, and the mixture was stirred at 20 °C for 2 h. After allowing the filtrate to settle, the aqueous layer was separated and acidified to pH 3 with concentrated hydrochloric acid at 20 °C. The precipitated pale-yellow solid was filtered off, washed with a mixture of tetrahydrofuran (30 mL) and methanol (30 mL), and then dried at 60 °C under vacuum. The yield of compound **4** was 1.6 g (8%). Mp: decomposition at 285 °C; ¹H NMR (400 MHz, DMSO-*d*₆, CF₃CO₂H) δ 2.89 (s, 3H), 2.96 (m, 3H), 3.21 (m, 3H),

3.1(m, 3H), 3.53 (d, *J* = 13 Hz, 2H), 3.81 (d, *J* = 13 Hz, 2H), 7.08 (dd, *J* = 3, 8 Hz, 1H), 7.15 (dd, *J* = 3, 10 Hz, 1H).

Isolation of Acetophenone 5. The vessels required for the amination stage were carefully dried, and processing was carried out under a nitrogen atmosphere. To a mixture of tris(dibenzylideneacetone)dipalladium (1.16 g, 0.02 mol equiv), rac-BINAP (1.58 g, 0.04 mol equiv), and anisole (200 mL) was added cesium carbonate (28.95 g, 1.40 mol equiv). The mixture was heated to 125 °C, and a solution of bromoester **1b** (20.0 g, 1.00 mol equiv) and *N*-methylpiperazine (6.99 g, 1.10 mol equiv) in anisole (90 mL) maintained at 45 °C was added in six portions over 90 min; this was followed by an anisole (10 mL) line wash. The resulting mixture was maintained at 125 °C for an additional 3 h, cooled to 20 °C, and diluted with water (120 mL); 47% w/w sodium hydroxide solution (11.88 g, 2.20 mol equiv) was added, and the mixture was stirred at 20 °C for 0.75 h. After allowing the filtrate to settle, the aqueous layer was separated and filtered through Celite. Tetrahydrofuran (30 mL) and methanol (30 mL) were added to the filtrate, and the pH was adjusted to 7. The solid piperazine acid **2b** was filtered off, and the mother liquor was freeze-dried to give an orange-brown solid. This solid was subjected to chromatography on silica (acetonitrile/methanol, 10/00 to 9/1), yielding acetophenone **5** (0.72 g, 5%). Mp: 92–94 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.54 (s, 3H), 2.61 (s, 3H), 2.89 (br s, 4H), 3.30 (br s, 4H), 6.84 (dd, *J* = 3, 10 Hz, 1H), 7.07 (dd, *J* = 3, 8.5 Hz, 1H).

First Synthetic Route to Bromoester 1b. Alkene 6. Dimethyl acetylenedicarboxylate (91.3 kg, 1.12 mol equiv) was added to a stirred solution of 2-bromo-4-fluorophenol (110.0 kg, 1.00 mol equiv) and triethylamine (0.58 kg, 0.01 mol equiv) in 2-propanol (110 L) over 2 h whilst maintaining the batch temperature at 20–25 °C; this was followed by a line wash of 2-propanol (22 L). The mixture was adjusted to 40–45 °C, and a solution of sodium hydroxide (57.2 kg, 2.48 mol equiv) in water (440 L) was added over 1 h; ester hydrolysis was complete after an additional 4 h at 40–45 °C. The solution was concentrated (to 440 L) under reduced pressure at <40 °C, diluted with water (220 L), and again concentrated (to 440 L). The residual solution was cooled to 20–25 °C, diluted with *tert*-butyl methyl ether (440 L), and adjusted to pH 1 with 6 N hydrochloric acid (280 L) over 60 min. The temperature of the mixture was adjusted to 28–33 °C, and the layers were separated. The aqueous phase was extracted with more *tert*-butyl methyl ether (440 L) at 28–33 °C. The extracts were combined and washed with water (220 L) at 28–33 °C and then concentrated (to 660 L) at atmospheric pressure. More *tert*-butyl methyl ether (440 L) was added to the residue and the distillation repeated to ensure removal of water. The solution was further concentrated (to 440 L) under reduced pressure at <40 °C. Heptane (440 L) was added over 60 min and the resulting suspension concentrated (to 660 L) under reduced pressure at 20–25 °C. The resulting slurry was diluted with more heptane (660 L) over 1 h (the solvent contained <29 mol % *tert*-butyl methyl ether). The slurry was stirred for 1 h at

20–25 °C, and the product was collected by filtration, washed with heptane (2 × 330 L), and dried under vacuum at 35–40 °C. The yield of alkene **6** (2.3:1 mixture of Z- and E-isomers) was 166.7 kg (95%). HPLC (Genesis C₁₈ 4 μm, 3 mm × 250 mm at 40 °C with a flow rate of 1 mL/min, UV detection at 226 nm, and the following linear gradient: mobile phase A = water, mobile phase B = acetonitrile, and mobile phase C = 1% v/v trifluoroacetic acid in water, 0 min A/B/C 90:5:5, 20 min A/B/C 0:95:5) retention times 7.99 min (E-isomer) and 8.76 min (Z-isomer).

Bromoester 1b. Alkene **6** (113 kg, 1.00 mol equiv) was added in 10 equal portions to concentrated sulphuric acid (445.8 kg, 12.3 mol equiv) with stirring whilst maintaining a temperature of 70–75 °C. The mixture was held at 70–75 °C for an additional 4 h and then added to absolute ethanol (565 L) under reflux; this was followed by a line wash of ethanol (113 L). The mixture was maintained at 85 °C for 4 h, cooled to 75 °C, and diluted with toluene (565 L). The biphasic mixture was cooled to 50–55 °C, and the layers were separated. The lower phase was extracted with more toluene (565 L) at 50–55 °C. The organic extracts were combined and washed with 5% w/w aqueous sodium bicarbonate (3 × 339 L) at 15 °C and then with water (339 L) at 40–45 °C. The toluene solution was concentrated (to 339 L) under reduced pressure at <40 °C and then diluted with absolute ethanol (565 L). The resulting solution was again concentrated (to 565 L) under reduced pressure at <40 °C. More absolute ethanol (565 L) was added and the solution again concentrated (to 565 L) under reduced pressure at <40 °C to give a toluene content of <3.5 mol %. The residual mixture was heated under reflux for 1 h (a clear solution was obtained) and then cooled to 65 °C over 1 h. Seed crystals (0.015% w/w) were added, and the mixture was cooled to 50 °C over 6 h and held at that temperature for a further 6 h and then cooled to 25 °C over 10 h. The product was collected by filtration, washed with ethanol (2 × 226 L), and dried under vacuum at 30–35 °C. The yield of bromoester **1b** was 37.0 kg (32%). Mp: 130–131 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.37 (t, *J* = 7.1 Hz, 3H), 4.42 (q, *J* = 7.1 Hz, 2H), 6.99 (s, 1H), 7.76 (dd, *J* = 8.0, 3.0 Hz, 1H), 8.27 (dd, *J* = 7.9, 3.0 Hz, 1H); ¹³C NMR (100.6 MHz, DMSO-*d*₆) δ 13.8, 62.8, 109.5 (*J*_{C-F} = 23.7 Hz), 113.0, 113.2 (*J*_{C-F} = 9.4 Hz), 125.6 (*J*_{C-F} = 7.5 Hz), 126.6 (*J*_{C-F} = 27.9 Hz), 149.0 (*J*_{C-F} = 1.9 Hz), 152.4, 158.5 (*J*_{C-F} = 249.4 Hz), 159.5, 176.4 (*J*_{C-F} = 2.3 Hz); FTIR (KBr, cm⁻¹) 1741, 1658, 1460, 1356, 1265, 1185, 844.

Second Synthetic Route to Bromoester 1b. Acetophenone 7. A mixture of 2-bromo-4-fluorophenol (64.0 kg, 1.00

mol equiv) and acetyl chloride (62.5 kg, 2.39 mol equiv) was stirred and heated at 50–55 °C for 1 h. Excess acetyl chloride (10.8 kg) was removed by distillation, and the residue was cooled to 25–30 °C and then diluted with dichloromethane (120 L). The mixture was further cooled to 10–15 °C, and aluminium chloride (51.0 kg, 1.15 mol equiv) was added in two portions. The temperature of the mixture was raised to 130–135 °C over 1 h during which time dichloromethane (80 L) was removed by distillation. The mixture was maintained at 130–135 °C for 1 h, diluted with xylene (250 L), and cooled to 10–15 °C. The reaction mixture was added to a solution of 30% w/w hydrochloric acid (25 L) in water (500 L). The layers were separated, and the organic phase was extracted with 10% w/w sodium hydroxide solution (300 L). The aqueous extract was cooled to 10–15 °C and adjusted to pH 6.8–7.2 with 30% w/w hydrochloric acid (55.0 kg). The solid was filtered off, washed with water (60 L) and then with petroleum ether (100 L), and dried at 55–60 °C under vacuum. The yield of acetophenone **7** was 46.0 kg (60%).

Bromoester 1b. A mixture of acetophenone **7** (46.0 kg, 1.00 mol equiv) and diethyl oxalate (172.0 kg, 6.00 mol equiv) was added to a solution of sodium ethoxide (66.8 kg, 4.9 mol equiv) in absolute ethanol (250 L) at 60 °C. The mixture was stirred at 55–60 °C for 1 h, and ethanol (250 L) was removed by distillation. The residual mixture was diluted with water (300 L) and the precipitated solid isolated by filtration. This solid was heated with a mixture of acetic acid (210 L) and 30% w/w hydrochloric acid (55.5 L) at 70–80 °C for 2 h. After cooling to 25 °C, the mixture was diluted with water (400 L), and the precipitated solid was collected in a centrifuge. The solid was washed with water (150 and 100 L), with 12% w/w sodium bicarbonate solution (50 L), and finally methanol (100 L) before drying at 70 °C under vacuum. The yield of bromoester **1b** was 38.6 kg (63%).

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