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Selection and Development of the Manufacturing Route for EP_1 Antagonist GSK269984B

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Abstract:

A potential manufacturing route for the EP_1 antagonist GSK269984B was developed. Four synthetic approaches were examined, and a successful realisation of each is presented. The rationale supporting selection of the preferred route is discussed. This route utilised a phenolic aldol reaction as the key step and relied on selective hydrogenolysis to reduce an intermediate diarylmethanol. Further optimisation of the selected route is presented, delivering GSK269984B in three stages and 46% overall yield from readily available starting materials.

Introduction

Recently GSK disclosed a series of EP_1 antagonists with potential therapeutic applications to inflammatory pain.[1] GSK269984B (**1**) is typical of this series, and the rationale behind its discovery has recently been reported.[2] We embarked upon an effort to identify the optimal route for long-term manufacture of GSK269984B, and the successful completion of this objective is the subject of this communication.

Results and Discussion

Our Medicinal Chemistry colleagues used two approaches to prepare GSK269984B (note that, initially, the sodium salt GSK269984A (**12**) was the target). For gram quantities the Negishi reaction of a benzylic zinc bromide and ethyl 5-bromopicolinate had been demonstrated (as Figure 2, Disconnection 2).[1a] To deliver increased quantities of up to 1 kg the Suzuki reaction of pinacolboronate **7** (or the corresponding boronic acid)[2] with chloromethylpicolinate **10** was utilised.[3] The detail of this last approach is illustrated in Scheme 1.

4-Chloro-2-iodoanisole (**2**) was demethylated and subsequently alkylated with 4-chloro-2-fluorobenzyl bromide (**4**). An aryl Grignard reagent was formed with isopropylmagnesium chloride and quenched with isopropoxy pinacolborolane **6**, yielding boronate **7**. Diethyl dipicolinate (**8**) was selectively monoreduced, and the resulting alcohol **9** was reacted with thionyl chloride to give ethyl 6-chloromethylpicolinate (**10**). Finally the key methylene linkage was formed by a Suzuki reaction. Some variability in reaction profile and isolated yield had been observed in this reaction. Additionally, chromatography was required to control residual palladium and impurity levels. Ethyl ester **11** could be hydrolysed with NaOH to yield the sodium salt, which was initially the preferred version. Extension of this route to target acid **1** by neutralisation of the sodium salt was anticipated to be trivial.

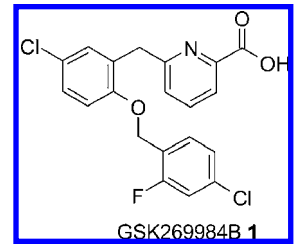

Figure 1. **Structure of target EP_1 antagonist GSK269984B.**

As we began to consider the long-term manufacturing route for **1**, it was clear that formation of the methylene linkage was the key synthetic challenge. Two broad disconnections were apparent (Figure 2). Disconnection 1 required the coupling of a chlorophenol derivative with a picolinic acid partner - as exemplified by the Suzuki reaction demonstrated above (Scheme 1) - and optimisation of this approach became Route A. It was felt that the parent chlorophenol could potentially be utilised directly, via either a Friedel−Crafts (Route B) or phenolic aldol reaction (Route C). Scission of the other diarylmethane bond gave Disconnection 2, as exemplified by the Negishi reaction utilised in Medicinal Chemistry. We explored the union of a chlorosalicylaldehyde derivative with 2,6-dibromopyridine, which became Route D. Other variations around the chemistry described here are clearly possible, but these four routes were prioritised and taken forward to practical evaluation.

Our first step in optimising Route A was to identify a source of 4-chloro-2-iodophenol (**3**), making this our starting material.[4] The alkylation and boronate formations were telescoped to remove the isolation of iodide **5** via exchanging the acetone solvent for toluene by distillation (Scheme 2). This decision was principally driven by the needlelike habit of the iodide which proved problematic to isolate. In scaling this sequence, we made some interesting observations about the equilibration of intermediates favoring the formation of the desired boronate **7**, and these have been reported elsewhere.[5] Optimisation of the preparation of chloromethylpicolinate **10** was not undertaken

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(1) (a) Hall, A.; Bit, R. A.; Brown, S. H.; Chowdhury, A.; Giblin, G. M. P.; Hurst, D. N.; Kilford, I. R.; Lewell, X.; Naylor, A.; Scoccitti, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1592. (b) Giblin, G. M. P.; Hall, A.; Hurst, D. N.; Scoccitti, T. PCT Int. Appl. WO 2007128752 (CAN 147: 541735), 2007. (c) For a review see: Hall, A.; Billinton, A.; Giblin, G. M. P. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 597.

(2) Hall, A.; Billington, A.; Brown, S. H.; Chowdhury, A.; Clayton, N. M.; Giblin, G. M. P.; Gibson, M.; Goldsmith, P. A.; Hurst, D. N.; Naylor, A.; Peet, C. F.; Scoccitti, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2599.

(3) Giblin, G. M. P.; Hall, A.; Hurst, D. N.; Rawlings, D. A.; Scoccitti, T. PCT Int. Appl. WO 2006066968(CAN 145:83231), 2006.

(4) Our thanks go to VUOS, http://www.vuosas.cz/.

(5) Hawkins, V. F.; Wilkinson, M. C.; Whiting, M. *Org. Process Res. Dev.* **2008**, *12*, 1265.

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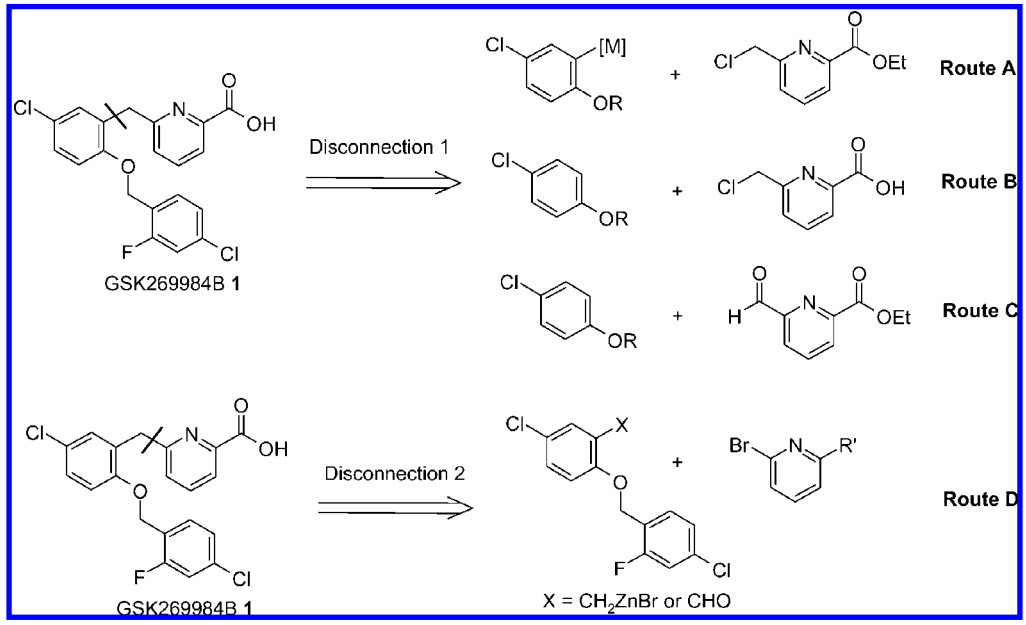
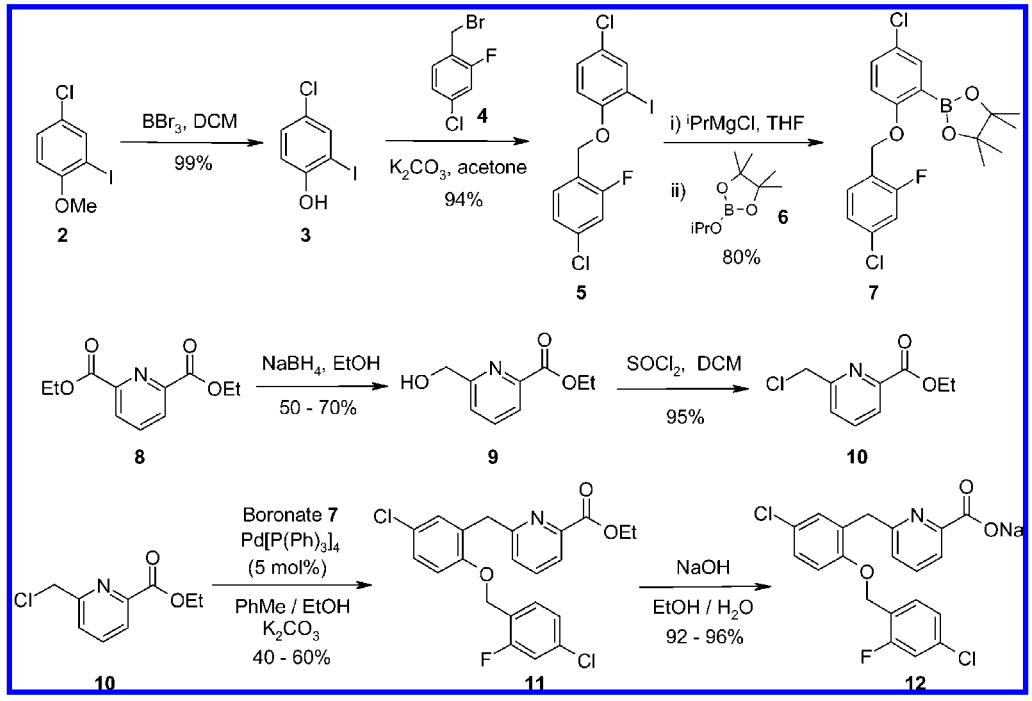


Figure 2. **Disconnections to GSK269984B.**

Scheme 1. **Medicinal Chemistry route (conversion of sodium salt 12 to target acid 1 not shown)**



at this time. We did, however, optimise the Suzuki reaction. A Pd/ligand screen was undertaken with Pd_2dba_3/DavePhos giving a rapid, clean reaction.[6] Decomposition of the boronate by homocoupling or deboronation limited the yield using Pd-$[P(Ph)_3]_4$, but was much reduced using this catalyst system. Catalyst loading could also be reduced from the initial 5 mol%, with reaction completion being achievable down to 1 mol% palladium (0.5 mol% Pd_2dba_3). However, in the lead up to a pilot-plant campaign, an unidentified impurity in chloromethylpicolinate **10** caused the reaction to stall.[7] This was overcome in this instance by recharging catalyst and ligand further.

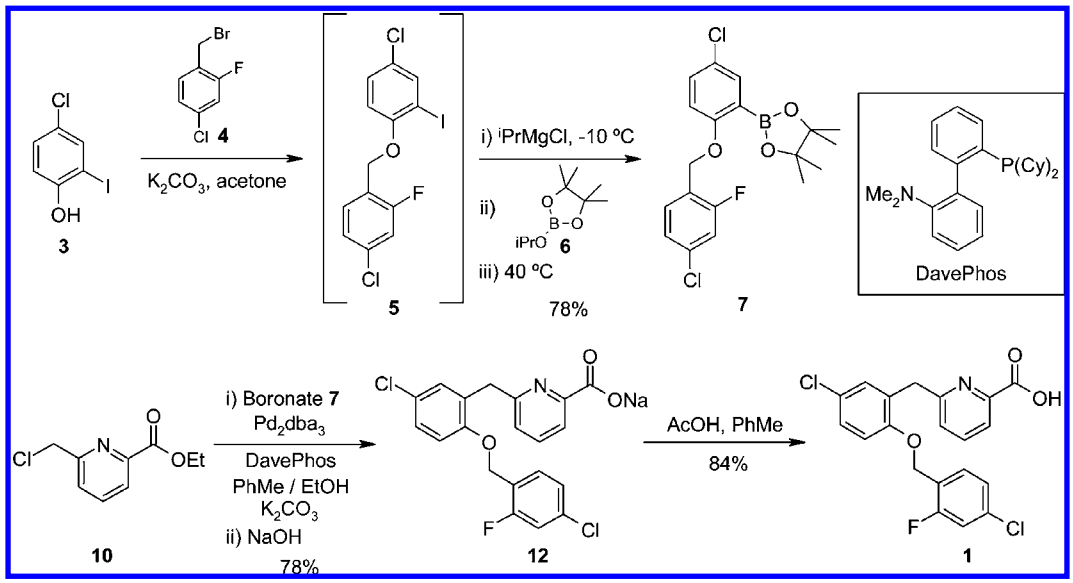
Options for removing palladium were screened, and treatment of the crude reaction mixture with trimercaptotriazine (TMT, 6 equiv wrt Pd) at reflux was found to be very effective,[8] reducing the palladium content to around 50 ppm. The sodium salt **12** was chosen as a useful isolation point, and a final toluene cake wash of **12** was introduced. It was anticipated this wash would displace water from the cake to aid drying, but it was also shown to be effective for decolourising the cake, removing

(6) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

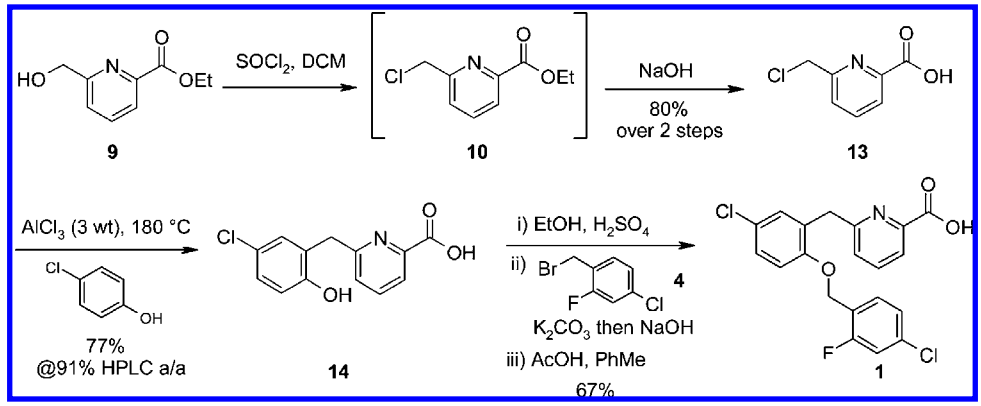
(7) Passing the chloromethylpicolinate **10** through a charcoal filter allowed the reaction to reach completion after the first [Pd]/ligand charge. We chose not to scale this option for our pilot-plant campaign.

(8) Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res. Dev.* **1997**, *1*, 311.

Scheme 2. **Route A - improved Medicinal Chemistry route**



Scheme 3. **Route B - Friedel−Crafts alkylation**



nonpolar impurities, and was associated with further reduction of the palladium content to <10 ppm. The sodium salt was crystallised as a hydrate with seemingly variable water content, but this was over dried to an amorphous anhydrate to give consistent input into the final stage. The sodium salt was neutralised with acetic acid, and the parent compound **1** was crystallised from toluene. With the application of the controls described above, the need for chromatography in this route was removed.

Upon analysing the raw material costs for Route A, it was clear that approximately half the total cost was involved in sourcing an ortho-functionalised phenol, preparing the boronate, and purchasing the catalyst and ligand to achieve their union. Any route that circumvented this had the potential to be significantly cheaper.

Thus, a Friedel−Crafts alkylation reaction appeared attractive (Scheme 3). The chloromethylpicolinate **10** prepared for Route A could potentially be used together with a simplified phenol partner (e.g., 4-chlorophenol, £10/kg bulk). However this reaction proved hard to realise, which we attributed to the electron-deficient nature of our electrophile 6-chloromethylpicolinic acid (**13**).[9] Acid **13** was easily prepared from the ethyl ester **10** which had been used in Route A. The use of the acid addressed the instability of the ethyl ester under the reaction conditions and was also much easier to isolate, as ester **10** had proved to be low melting and difficult to handle. Despite exploring a large range of Friedel−Crafts alkylations (including chloromethyl,[10] and hydroxymethyl[11] pyridine substrates), acylations,[12] and the corresponding Fries rearrangements[13] and screening various Lewis acid catalysts only the conditions illustrated in Scheme 3 gave good conversions. Reacting **13** with 4-chlorophenol promoted by 4 equiv (3 wt) of $AlCl_3$ at 180 °C as a melt gave material of 91% a/a HPLC purity in 77% yield. Selective alkylation of the phenol was achieved via in situ esterification of the competing carboxylic acid with ethanol. Post alkylation and ester hydrolysis, the target GSK269984B was crystallised in 67% overall yield for these three telescoped steps.

(9) It is believed that electronics are important rather than, for example, a chelating effect of the pyridine, due to comparisons with the reactivity of 2-picolinic acid derivatives, which reacted under significantly milder conditions.

(10) Jerchel, D.; Noetzel, S.; Thomas, K. *Chem. Ber.* **1960**, *93*, 2966.
(11) (a) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913. (b) Langer, R.; Buysch, H. J. Eur. Pat. Appl. EP 538704 (CAN 122:31111), 1993. (c) Zhang, J.; Schmidt, R. R. *Synlett* **2006**, 1729.
(12) (a) Zhang, S. J.; Li, Y. F.; Wang, X. L.; Yin, D. X.; Shao, Y.; Zhao, X. *Chin. Chem. Lett.* **2005**, *16*, 1165. (b) Sarvari, M. H.; Sharghi, H. *Helv. Chim. Acta* **2005**, *88*, 2282.
(13) Mereyala, H. B.; Sambaru, K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2005**, *44B* (3), 615.

Scheme 4. **Route C - phenolic aldol route**

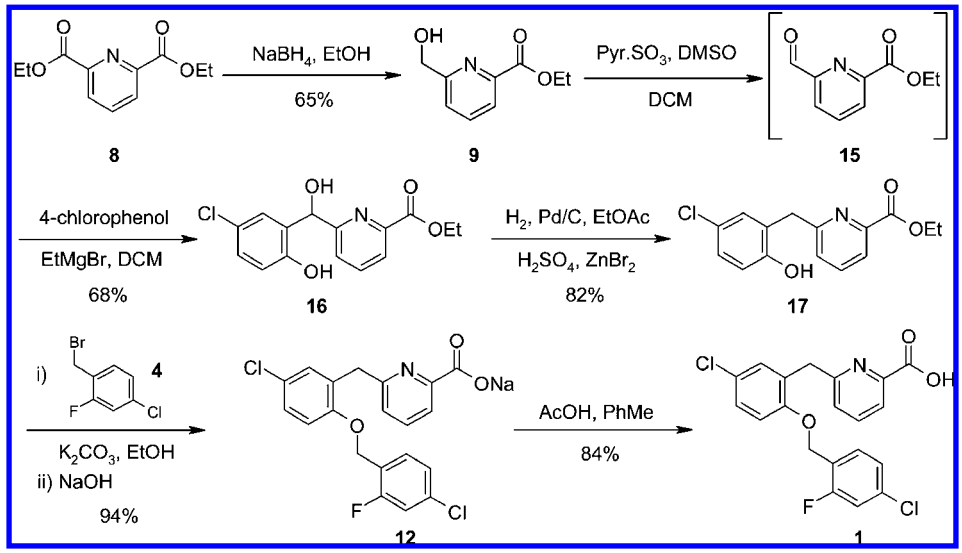
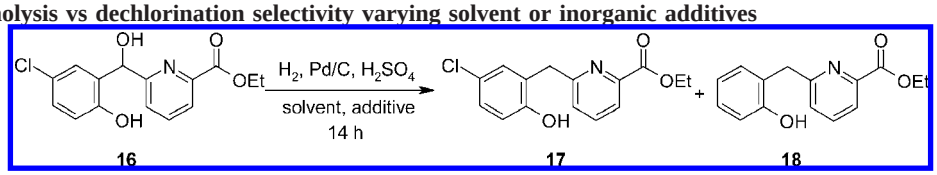


Table 1. **Hydrogenolysis vs dechlorination selectivity varying solvent or inorganic additives**



entry	solvent	additive (mol%)	temp (°C)	conversion (%)	selectivity (**17**:**18**)
1	EtOH	none	50	80	3.3:1
2	EtOH	$ZnCl_2$ (100)	50	81	0.9:1
3	EtOH	$ZnBr_2$ (100)	50	22	40:1
4	EtOH	$MgBr_2$ (100)	50	40	90:1
5	EtOAc	none	50	85	32:1
6	EtOAc	$ZnCl_2$ (100)	50	85	24:1
7	EtOAc	$ZnBr_2$ (100)	50	80	>200:1
8	EtOAc	$MgBr_2$ (100)	50	50	2.5:1
9	EtOAc	$ZnBr_2$ (5)	50	83	>200:1
10	**EtOAc**	**$ZnBr_2$(1)**	**65**	**>99**	**>200:1**

A related strategy to ortho functionalise 4-chlorophenol would be to employ a phenolic aldol reaction.[14] There was one previous literature report of the aldol type reaction of a phenol with the parent 2-formyl pyridine.[15] For the preparation of GSK269984B the required aldehyde **15** could readily be produced by Parikh−Doering oxidation of the hydroxymethylpicolinate **9**, an intermediate in our current route. Upon addition of the magnesium phenoxide of 4-chlorophenol to aldehyde **15** we were delighted to achieve 50% conversion to **16** (Scheme 4). Use of 2.2 equiv of the magnesium phenoxide enabled the reaction to progress to completion, presumably as one equivalent was required to deprotonate the relatively acidic product. With the aldehyde proving to be a low-melting solid we telescoped the oxidation into the aldol reaction, returning a 68% overall yield of **16** post-crystallisation from ethanol/water.

Next we were required to reduce the intermediate diarylmethanol. Hydrogenolysis in acidic ethanol proved effective but was accompanied by dechlorination of the phenol ring. It has been shown that use of less polar solvents or halide additives can reduce the rate of reductive dehalogenation.[16] The use of EtOAc as solvent with a range of Mg or Zn halides was therefore investigated (Table 1).

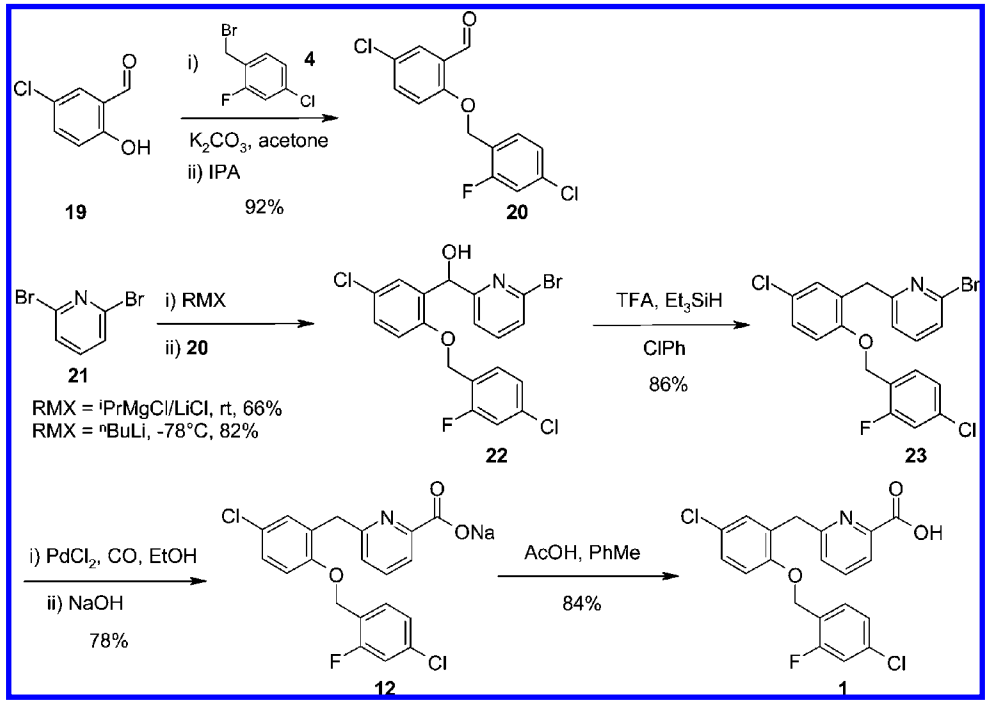
Addition of $ZnBr_2$ or $MgBr_2$ to the reaction in EtOH gave considerable increases in selectivity whilst also reducing the rate of reaction (Table 1, entries 3 and 4). Interestingly, the use of $ZnCl_2$ increased dehalogenation. Moving to EtOAc as solvent gave a 10-fold increase in selectivity over EtOH (entry 5). In this solvent, the addition of either $MgBr_2$ or $ZnCl_2$ increased the undesired formation of **18**. However, addition of $ZnBr_2$ gave a greatly improved selectivity of >200:1 with minimal impact on rate (entry 7). Reducing the amount of $ZnBr_2$ had no observable effect with loadings as low as 1 mol% still giving >200:1 selectivity. Finally 2 mol% $ZnBr_2$ was chosen as a robust additive loading. Other byproduct (hydrolysis to the acid and

(14) (a) Casiraghi, G.; Salerno, G.; Sartori, G. *Synthesis* **1975**, 186. (b) Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem.* **1988**, *53*, 4919. (c) Bigi, F.; Casnati, G.; Sartori, G.; Araldi, G.; Bocelli, G. *Tetrahedron Lett.* **1989**, *30*, 1121. (d) Cornia, M.; Casiraghi, G. *Tetrahedron* **1989**, *45*, 2869. (e) Saimoto, H.; Yoshida, K.; Tetsuya, M.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768. (f) Hewawasam, P.; Erway, M. *Tetrahedron Lett.* **1998**, *39*, 3981. (g) Rondot, C.; Retailleau, P.; Zhu, J. *Org. Lett.* **2007**, *9*, 247. (h) Chen, X.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3962.

(15) Sartori, G.; Maggi, R.; Bigi, F.; Arienti, A.; Porta, C.; Predieri, G. *Tetrahedron* **1994**, *50*, 10587.

(16) Wu, G.; Huang, M.; Richards, M.; Poirier, M.; Wen, X.; Draper, R. W. *Synthesis* **2003**, *11*, 1657.

Scheme 5. **Route D - route from 2,6-dibromopyridine**



benzylic ethyl ether formation) were minimised by using a Pd/C dry powder catalyst and conducting the reaction for 6 h at 65 °C.

Alkylation of the phenol **17** and saponification of the ester enabled isolation of the sodium salt, as before. Protonation of the sodium salt and crystallisation from toluene delivered the desired target.

The phenolic aldol route outlined above appeared very attractive. To implement Route C, we would desire to source significant quantities of formyl pyridine **15** or, less ideally, hydroxymethylpicolinate **9**. Whilst such sources could potentially be developed, at the time of making the final route assessment they did not exist, and the cost associated with this fragment was difficult to predict. To complete our route evaluation, and to mitigate any raw material sourcing risk, we considered whether a route existed from starting materials for which bulk supply was already in place. We became interested in a route bringing together 5-chlorosalicylaldehyde and 2,6-dibromopyridine, which had previously been demonstrated by colleagues in Medicinal Chemistry.[17] Post alkylation with 4-chloro-2-fluorobenzyl bromide, isolation of aldehyde **20** was achieved by crystallisation from IPA. Low-temperature generation of the mono-lithiated pyridine was performed in DCM,[18] and gave an excellent yield of 82% after reaction with aldehyde **20** and crystallisation (Scheme 5). However, with these cryogenic temperatures being unattractive for commercial manufacture, we sought milder conditions. Knochel has reported the high-yielding quench of 2,6-dibromopyridine with benzaldehyde (89%) using the LiCl/^{i}PrMgCl combination (termed "turbo" Grignard).[19] Whilst these conditions were successful with our substrate, we did not observe the same efficiency of metal−halogen exchange with the commercially available reagent and returned a 66% yield of **22** after crystallisation.[20] A TFA/Et_3SiH reduction of the undesired diarylmethanol in DCM had been demonstrated previously in Medicinal Chemistry.[17] The conditions used were quite efficient (2.5 vol TFA, 1.1 vol triethylsilane, 2 vol DCM), but we sought to optimise this reduction for potential use in manufacturing, especially to reduce the volumes of TFA required. Hydrogenation resulted in competitive dehalogenation or debenzylation, even in the presence of $ZnBr_2$ as used in the aldol Route C. A brief screen of acids indicated reasonable conversation (50%) with methanesulfonic acid, but TFA was clearly superior. Moving to chlorobenzene as solvent enabled the reaction to be run at elevated temperatures, allowing reduction of the TFA to 1 volume in combination with 1.5 volumes of Et_3SiH, which returned an 86% yield post-crystallisation. Numerous other literature conditions for diarylmethanol reductions were screened, with very limited success.[21]

(17) Hall, A.; Rawlings, D. A. Unpublished results.
(18) Peterson, M. A.; Mitchell, J. R. *J. Org. Chem.* **1997**, *62*, 8237.
(19) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

(20) Other procedures for the monometalation of 2,6-dibromopyridine were not explored in this evaluation phase. For example see: (a) Mase, T.; Houpis, I. N.; Akao, A.; Dorziotis, I.; Emerson, K.; Hoang, T.; Iida, T.; Itoh, T.; Kamei, K.; Kato, S.; Kato, Y.; Kawasaki, M.; Lang, F.; Lee, J.; Lynch, J.; Maligres, P.; Molina, A.; Nemoto, T.; Okada, S.; Reamer, R.; Song, J. Z.; Tschaen, D.; Wada, T.; Zewge, D.; Volante, R. P.; Reider, P. J.; Tomimoto, K. *J. Org. Chem.* **2001**, *66*, 6775. (b) Iida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2001**, *42*, 4841.
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Table 2. **Comparison of the key attributes of Routes A−D**

route designation	A	B	C	D
key step	Suzuki	Friedel−Crafts	phenolic aldol	pyridine acylation
number of registered starting materials	3	3	3	3
number of stages	5	4	5	5
specialised equipment?	no	yes - high temperature	yes - hydrogenation	yes - carbonylation
current scale of operation	>10 kg	<10 g	>100 g	<10 g
current yield	40%th (from diethyl dipicolinate)	26%th (from diethyl dipicolinate)	28%th (from diethyl dipicolinate)	34%th (from 5-chlorosalicylaldehyde)
purity of API	excellent	good	excellent	adequate
potential genotoxins	chloromethylpicolinate **10**, benzyl bromide **4**	chloromethylpicolinate **10**, benzyl bromide **4**	benzyl bromide **4**	benzyl bromide **4**
raw material costs	1.0	0.51 Route A	0.49 Route A	0.54 Route A

Table 3. **Detailed comparison to differentiate Routes C and D**

Route designation	C	D
Key step	Phenolic aldol	Pyridine acylation
Raw material costs	0.49 Route A	0.54 Route A
Purity of API	Excellent	Adequate
Scope for further optimisation (current yield)	Improve diester reduction (65%) Improve oxidation (88%) Replace EtMgBr [expensive] with $MgCl_2$ [see text] (77%)	Improve Grignard reaction (66%) Improve carbonylation (78%)
Potential for telescoping	Excellent – choice of isolation points	Viewed as more challenging
Undesired solvents	DCM	TFA
Bulk sources of starting materials	To be developed	Currently available in bulk
Benzyl bromide **4** introduced	Final stage	First stage

To complete the synthesis, a copper-catalysed cyanation of the pyridyl bromide **23** was shown to be feasible.[22] However, palladium-catalysed carbonylation in ethanol was preferred,[23] followed by hydrolysis and isolation of the sodium salt **12**. Neutralisation and crystallisation of the target acid **1** could be achieved as previously.

Route Selection. Thus having demonstrated four viable routes, we next had to select the most suitable for long-term manufacture. Various factors describing the routes were tabulated (Table 2). From this analysis, it was clear that any of Routes B, C, or D would be considerably cheaper than the initial route—approximately halving the raw material costs. Within these, the Friedel−Crafts route (B) was deprioritised, due to its requirement for a high-temperature plant, and other processing concerns.[24] The aldol Route C and the dibromopyridine Route D were very close, and a more detailed analysis was performed (Table 3).

Whilst the cost difference between the routes was marginal, it was felt the aldol route had more scope for further improvement, including telescoping stages. Whilst DCM did raise questions as a solvent for Route C, the use and disposal of TFA in Route D posed more significant issues. For the aldol route, the raw material sourcing issue discussed previously remained to be addressed, and we would have to demonstrate the purge of the potentially genotoxic benzyl bromide introduced at the final stage. This analysis is represented in Table 3 as green - no issue; orange - less desirable; red - significant issues. Overall, the outcome of this evaluation was to further develop the phenolic aldol Route C for long-term manufacturing.

The first step in optimising the aldol Route C was to improve the reduction of diethyl dipicolinate (Scheme 6). This step had previously given modest and variable yields (50−70%). Stopping the reaction at the point of the consumption of starting material (avoiding over-reduction) and minimising processing temperatures on work up (avoiding ester hydrolysis or dimerisation) improved the yield to around 85%. However, the isolations examined at this point proved to be problematic, and we decided to extend the oxidation/aldol sequence to include the initial reduction as well (i.e., diester **8** telescoped to diarylmethanol **16** in three chemical steps).

(22) Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2005**, *11*, 2483.

(23) (a) Charbonnire, L. J.; Weibel, N.; Ziessel, R. J. *J. Org. Chem.* **2002**, *67*, 3933. (b) Friesen, R. W.; Ducharme, Y.; Ball, R. G.; Blouin, M.; Boulet, L.; Cote, B.; Frenette, R.; Girard, M.; Guay, D.; Huang, Z.; Jones, T. R.; Laliberte, F.; Lynch, J. J.; Mancini, J.; Martins, E.; Masson, P.; Muise, E.; Pon, D. J.; Siegl, P. K. S.; Styhler, A.; Tsou, N. N.; Turner, M. J.; Young, R. N.; Girard, Y. *J. Med. Chem.* **2003**, *46*, 2413.

Scheme 6. **Optimised phenolic aldol route**

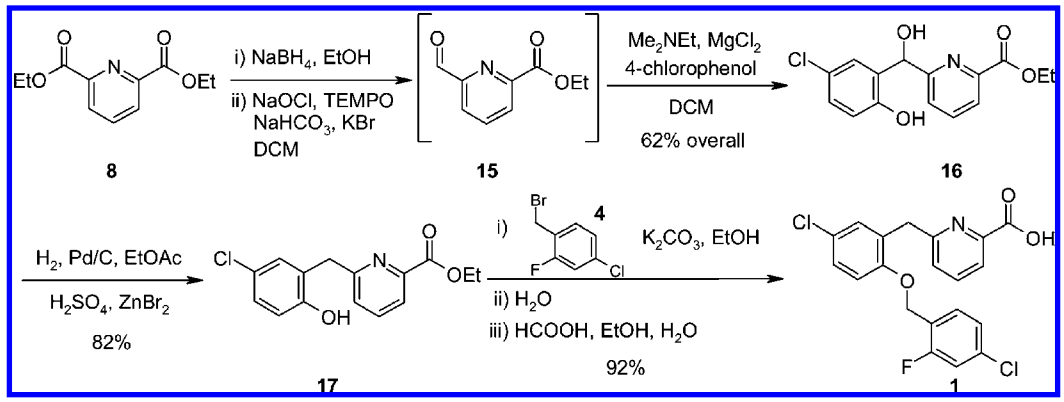

Table 4. **Final comparison of selected route**

route designation	A	B	B1
description	improved Medicinal Chemistry route	phenolic aldol at route decision point	optimised phenolic aldol route
number of stages	5	5	3
specialised equipment?	no	yes - hydrogenation	yes - hydrogenation
yield	40%th	28%th	46%th
potential genotoxins	chloromethylpicolinate **10**, benzyl bromide **4**	benzyl bromide **4**	benzyl bromide **4**
number of solvents	6	4	4
(process) mass intensity[27]	169 kg/kg API	172 kg/kg API	136 kg/kg API
raw material costs	1.0	0.49 Route A	0.36 Route A

The Parikh−Doering oxidation had served us well up to this point, but it was found that moving to NaOCl/TEMPO reduced impurities and hence returned a higher yield of ∼95%.

The main weakness of the aldol reaction was the cost and volume inefficiency associated with using 2.2 equiv of 1 M EtMgBr in TBME. We were aware of the use of $MgCl_2$/triethylamine to promote the related ortho formylation of phenols[25] and were delighted when these conditions gave 67% conversion with our substrate. After screening organic bases, we found Me_2NEt to be superior, giving 80% conversion. The stoichiometry was optimised, and slow addition of the aldehyde was introduced, increasing the single-stage conversion to 92% and the yield for the three-stage telescope to 62% (Scheme 6). This was slightly inferior to the 64% obtained with the Grignard reagent but much more preferable in terms of cost, throughput, and avoidance of ethane evolution. Our full experience around the phenolic aldol chemistry is reported elsewhere.[26]

The selective diarylmethanol reduction was not changed from the hydrogenation conditions discussed previously. To complete the route, we were required to install the 4-chloro-2-fluorobenzyl ether and hydrolyse the ethyl ester. Alkylation with **4** was carried out with ethanolic K_2CO_3, as before. However, it was found that the base could be reduced to 1.2 from 2 equiv without impact. Another valuable discovery was that hydrolysis of the ethyl ester could be achieved directly by the simple addition of 6 vol water at reflux. The resultant potassium salt was neutralised with formic acid, allowing direct isolation of **1** from a three-step telescoped process in a pleasing 92% overall yield from phenol **17** with excellent purity. Introduction of the potentially genotoxic 4-chloro-2-fluorobenzyl bromide (**4**) into the final stage was risky, but we were able to demonstrate that this telescoped progress gave low ppm levels in drug substance. Overall this optimisation had delivered significant improvements to our intended aldol route.

Conclusions

The significant cost and waste improvements of our route selection and optimisation work can be seen in Table 4. Raw material costs were around one-third those of the original route, and importantly, waste was reduced by 20%. One caveat is that the data for the improved Medicinal Chemistry Route A do not include the progress we ultimately made around the diester reduction for the aldol route, which would increase the efficiency of this route. There are also further options around the Suzuki partner that could be considered (for example returning to the boronic acid). It should also be stated that the optimised aldol Route B is presented in its current state of development. This is reflected in the Mass Intensity value of 136 kg of waste per kg of API. Whilst this was improved by our optimisation work, further effort would be required to meet a target of substantially less than 100 kg of waste. The objective of the work described in this paper was to identify the final *route*, with the ultimately most efficient *process* resulting from future work.

In conclusion we have demonstrated four viable approaches to the EP_1 antagonist GSK269984B (**1**). The selected route relied upon a phenolic aldol coupling and selective hydro-

(24) As the completed reaction was cooled from the set point of ∼180 °C, it tended to set to a hard, glasslike material at ∼165 °C. Addition of a high boiling solvent (such as 1,2 dichlorobenzene) to mobilise the melt was demonstrated, but this overall workup was still judged to be risky (albeit after minimal development).

(25) (a) Hofslokken, N. U.; Skattebol, L. *Acta Chem. Scand.* **1999**, *53*, 258. (b) Hansen, T. V.; Skattebol, L. *Org. Synth.* **2005**, *82*, 64.

(26) Whiting, M.; Wilkinson, M. C.; Harwood, K. *Synlett* **2009**, 1609.

(27) Mass Intensity = non-aqueous mass of materials used to make 1 kg of API. Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521.

genolysis. The optimisation of this route to a highly efficient process suitable for long-term commercial manufacture has been presented, enabling the synthesis of **1** in three stages and 46% overall yield from readily available starting materials.

Experimental Section

Reagents and solvents were purchased from commercial sources and were used as received. ^{1}H NMR spectra were recorded at 400 MHz. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, *J* (Hz) and integration. ^{13}C NMR spectra were recorded at 100 MHz. Data for ^{13}C NMR were reported in terms of chemical shifts (ppm), and multiplicity (as above) followed by coupling constant (Hz) for fluorine-containing compounds. High-resolution mass spectra (HRMS) were recorded by the Chemical Development Analytical Sciences department at GSK, Stevenage. Elemental analysis was carried out at Butterworth Laboratories Ltd., Teddington.

6-[(5-Chloro-2-{[(4-chloro-2-fluorophenyl)methyl]oxy}phenyl)methyl]-2-pyridinecarboxylic Acid (1). *From Sodium Salt 12.* Sodium salt **12** (5.33 g, 1 wt, 12.45 mmol) was suspended in toluene (80 mL, 15 vol), water was added (16 mL, 3 vol) followed by glacial acetic acid (0.97 g, 0.182 wt, 0.174 vol, 1.3 equiv). The mixture was heated to 60 °C to form a biphasic solution and stirred for 10 min. The lower aqueous layer was removed. The residual toluene layer was washed with water (16 mL, 3 vol) and the aqueous layer removed. The toluene layer was heated to 70 °C and filtered, washing through with further toluene (16 mL, 3 vol), and the filtrate was distilled at atmospheric pressure to 32 mL (6 vol). The residual solution was allowed to cool to 65 °C, seeded (27 mg, 0.005 wt), and then further cooled to 2−5 °C and stirred at 2−5 °C for 1 h. The precipitated solid was filtered and then washed with cold toluene (12 mL, 2.3 vol). The product was dried at 50 °C in vacuo to give a crystalline white solid (4.25 g, 84%th). ^{1}H NMR (400 MHz, methanol-d_4): δ 4.18 (s, 2 H), 5.03 (s, 2 H), 7.04 (d, 1 H), 7.16 (m, 2 H), 7.28 (m, 3 H), 7.32 (d, 1 H), 7.81 (m, 1 H), 7.96 (d m 1 H); ^{13}C NMR (100 MHz, methanol-d_4): δ 39.2, 64.7, 114.5, 117.0, 123.8, 124, 125.8, 127.1, 127.7, 129.1, 130.7, 132.0, 132.2, 136.0, 139.7, 148.5, 156.4, 161.7, 161.8, 167.4; HRMS (EI) MH^+ 406.0413. $C_{20}H_{15}NO_3Cl_2F$ requires MH^+ 406.0408.

From Phenol Acid 14. Phenol acid **14** (2.5 g, 1 wt, 9.49 mmol) was dissolved in anhydrous ethanol (20 mL, 8 vol) and conc. H_2SO_4 added (0.61 mL, 1.2 equiv) and then heated to reflux. After 3 h, further conc. H_2SO_4 (0.1 mL, 0.2 equiv) was added, and reflux was continued. After 1.5 h, further conc. H_2SO_4 (0.1 mL, 0.2 equiv) was added, and reflux continued. After 3 h, further conc. H_2SO_4 (0.1 mL, 0.2 equiv) was added, and reflux continued. After 1.5 h, further conc. H_2SO_4 (0.2 mL, 0.4 equiv) was added, and reflux continued. After 20 h, 4-Cl-2-F-benzyl bromide **4** (2.65 g, 11.86 mmol, 1.25 equiv) was added followed by K_2CO_3 (3.4 g, 24.67 mmol, 2.6 equiv), and the mixture was refluxed for 2 h. Further K_2CO_3 (0.34 g, 2.47 mmol, 0.26 equiv) was added, and the mixture refluxed for 1 h. NaOH (12.2 mL of a 2 M aqueous solution, 24.2 mmol, 2.55 equiv) was added, and the mixture refluxed for 5 h. The pH was adjusted to 7 with AcOH, and the aqueous phase was extracted with toluene (3 × 50 mL, 3 × 20 vol). The combined toluene layers were concentrated to minimal volume, and further toluene (2.5 mL, 1 vol) was added. The slurry was heated to 80 °C, and the solution thus formed was cooled to 70 °C, seeded, cooled to ∼0 °C, and isolated by filtration, washing the cake with further chilled toluene (1 mL, 0.4 vol). The product was dried at 50 °C in vacuo to give a crystalline white solid (2.57 g, 67%th). The data were in accordance with those reported above.

From Hydrogenation Product 17. Phenol **17** (19 g, 1 wt, 65.2 mmol) was suspended in EtOH (266 mL, 14 vol) and treated with K_2CO_3 (10.33 g, 0.54 wt, 1.2 equiv) followed by 4-Cl-2-F-benzyl bromide **4** (15.52 g, 0.82 wt, 1.07 equiv). The reaction was heated to reflux for 90 min and cooled to 70 °C. Water (114 mL, 6 vol) was added and the reaction heated at reflux for a further 5 h. The reaction was cooled to 65 °C, and a solution of formic acid (11.21 g, 241 mmol, 3.7 equiv) in water (4.4 mL, 0.23 vol) was added. The temperature rose to 78 °C, and the solution was then cooled to 0 °C over 2 h. The temperature was maintained for 1 h, and the product was isolated by filtration. The product was washed with 30% aq ethanol (2 × 70 mL, 2 × 3.7 vol) and then water (2 × 70 mL, 2 × 3.7 vol) at 0 °C. The product was dried at 65 °C in vacuo to give a crystalline white solid (24.4 g, 92%th). The data were in accordance with those reported above.

2-(5-Chloro-2-{[4-chloro-2-fluorophenyl)methyl]oxy}phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborlane (7). To a solution of phenol **3** (21.5 kg, 1 wt) and 4-Cl-2-F-benzyl bromide **4** (18.88 kg, 0.878 wt) in acetone (215 L, 10 vol) at 19−23 °C was added potassium carbonate (23.44 kg, 1.09 wt). The stirred suspension was heated at reflux for 1 h. The solution was concentrated to ∼3.5 vol by atmospheric pressure distillation and toluene (150 L, 7 vol) added before the organic solution was washed with water (2 × 170 L, 2 × 8 vol). Further toluene (195 L, 9 vol) was added and the solution concentrated to ∼8 vol by atmospheric pressure distillation. The solution was cooled to −10 °C then slowly treated with isopropyl magnesium chloride (48.6 L, 2.26 vol of a 2 M solution in THF, 1.15 equiv), ensuring the temperature was maintained between −5 and −12 °C. The reaction was stirred at −10 °C for a further 10 min before 2-isopropoxy-4,4,5,5-tetramethyldioxaborolane **6** (21.5 L, 1 vol, 1.25 equiv) was added, maintaining the temp below 10 °C. The reaction mixture was allowed to warm to 22 °C and stirred for at 1 h before being quenched with 50% saturated ammonium chloride solution (170 L, 8 vol). The aqueous phase was separated, and the organics were filtered before being washed with water (2 × 170 L, 2 × 8 vol) and then concentrated by distillation at atmospheric pressure until either a volume of 3 vol was reached or until the internal temperature reached 116 °C, whichever occurred first. The temperature was lowered to 80 °C, IPA (365 L, 17 vol) was added and the solution was concentrated to 6 vol by atmospheric pressure distillation and then cooled to 71 °C before being seeded. The mixture was held at 71 °C for 1 h, then cooled to 0 °C, and held for 1 h before the product was collected by filtration, washing with further cold IPA (54 L, 2.5 vol) at 0−4 °C. After drying until constant product temperature was reached and maintained for

4 h, a white crystalline solid was recovered (26.3 kg, 78.4%th). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 12 H), 5.08 (s, 2 H), 6.88 (d, 1 H), 7.09 (dd, 1 H), 7.17 (dd 1 H), 7.36 (dd, 1 H), 7.68 (d, 1 H), 7.94 (t, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 24.9, 63.8, 83.8, 113.3, 115.6 (d, J = 24 Hz), 123.3 (d, J = 13 Hz), 124.3 (d, J = 3 Hz), 126.2, 130.0 (d, J = 5 Hz), 132.2, 133.9 (d, J = 10 Hz), 136.4, 159.4 (d, J = 247 Hz), 161.3. Anal. Calcd for $C_{19}H_{20}BCl_2FO_3$: C, 57.36; H, 5.07; B, 2.97; Cl, 17.26; F, 3.36. Found: C, 57.42; H, 4.98; B, 3.01; Cl, 17.49; F, 3.11.

Ethyl 6-(Hydroxymethyl)-2-pyrdinecarboxylate (9). To a stirred solution of diethyl dipicolinate **8** (50 g, 1 wt, 0.226 mol) in ethanol (10 vol, 500 mL) was added sodium borohydride (5 g, 0.1 wt, 0.132 mol) and the mixture stirred at ambient temperature for 6 h. Additional sodium borohydride (1.6 g, 0.032 wt, 0.043 mol) was added and stirring continued overnight. Water (50 mL, 1 vol) was added followed by glacial acetic acid (10 mL, 0.2 vol) and the mixture stirred for 30 min. The solvent was evaporated and the residue dissolved in dichloromethane (150 mL, 3 vol) and water (100 mL, 2 vol). The layers were separated and the aqueous phase further extracted with dichloromethane (2 × 100 mL, 2 × 2 vol). The combined dichloromethane solution was washed with sat. aq. sodium bicarbonate (250 mL, 5 vol) then water (100 mL, 2 vol,) and the solvent evaporated to leave the crude product as a white solid (29 g). The crude product was recrystallised from toluene (150 mL, 3 vol), filtered, and dried to constant weight, giving the product as a white crystalline solid (26.6 g, 65%th). ^{1}H NMR (400 MHz, D_2O): δ 1.43 (t, 3 H), 4.01 (t, 1 H), 4.46 (q, 2 H), 4.88 (d, 2 H), 7.55 (d, 1 H), 7.84 (t, 1 H), 8.03 (d, 1 H); MS (ES+): MH^+ = 182.

Ethyl 6-(Chloromethyl)-2-pyrdinecarboxylate (10). Thionyl chloride (13.8 mL, 0.48 vol, 0.188 mol) was added to a stirred solution of hydroxymethylpyridine **9** (28.5 g, 1 wt, 0.157 mol) in DCM (200 mL, 7 vol) at 10−15 °C and the mixture stirred at 20−25 °C for 1 h. The solvent was evaporated and the residue partitioned between toluene (100 mL, 3.5 vol) and saturated sodium hydrogen carbonate (100 mL, 3.5 vol). The layers were separated, and the organic phase was washed with water (150 mL, 5.25 vol). The solvent was removed to leave a pale oil which solidified on standing to a low melting beige solid (29.5 g, 95%th). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (t, 3 H), 4.49 (q, 2 H), 4.80 (s, 2 H), 7.72 (d, 1 H), 7.89 (t, 1 H), 8.07 (d, 1 H); MS (ES+): MH^+ = 200.

Sodium 6-[(5-Chloro-2-{[(4-chloro-2-fluorophenyl)methyl]-oxy}phenyl)methyl]-2-pyridinecarboxylate (12). *From Suzuki Coupling of Boronate 7 and Chloride 10.* Boronate **7** (23 kg, 1 wt), chloromethylpyridine **10** (11.55 kg, 0.502 wt, 1 equiv) and potassium carbonate (16.05 kg, 0.698 wt, 2 equiv) were charged to the reaction vessel. Toluene (205 L, 9 vol) and EtOH (23 L, 1 vol) were added, and the suspension was degassed by three cycles of evacuation followed by nitrogen purge. 2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (DavePhos) (0.228 kg, 0.0099 wt, 1 mol%) was added and the reaction vessel again evacuated and purged with nitrogen before tris(dibenzylideneacetone)−dipalladium(0) ($Pd_2(dba)_3$) (0.265 kg, 0.0115 wt, 0.5 mol%) was added and the vessel again evacuated and purged with nitrogen two times. The suspension was heated to reflux (86 °C); after 90 min further portions of DavePhos (0.046 kg, 0.0020 wt, 0.10 mol%) and $Pd_2(dba)_3$ (0.053 kg, 0.0023 wt, 0.10 mol%) were added, and the reaction was returned to reflux. After a further 90 min further portions of DavePhos (0.046 kg, 0.0020 wt, 0.10 mol%) and $Pd_2(dba)_3$ (0.053 kg, 0.0023 wt, 0.10 mol%) were added, and the reaction was returned to reflux. The reaction was cooled to 80 °C, trimercaptotriazine (TMT) (0.62 kg, 0.027 wt, 6 equiv wrt Pd) added, and the reaction was returned to reflux for a further 3 h, before being cooled to ambient temperature. The solids were removed by filtration, washing with toluene (58 L, 2.5 vol). The filtrate was washed with water (2 × 115 L, 2 × 5 vol). The toluene solution thus obtained was concentrated by atmospheric pressure distillation to ∼3 vol before being cooled to 75 °C, diluted with EtOH (250 L, 11 vol), and further concentrated by atmospheric pressure distillation to ∼7.5 vol. Further EtOH (250 L, 11 vol) was added and the reaction mixture again concentrated to 7.5 vol. The reaction mixture was heated to 70 °C and treated with aqueous sodium hydroxide (87 L, 2 M aqueous solution, 3.8 vol), followed by heating at reflux for a further 45 min. The reaction was cooled to 50 °C and held at this temp for 1 h before the hot solution was filtered, washing with 2:1 EtOH/H_2O (28 L, 1.2 vol) at 50 °C. The filtrate was heated to reflux (82 °C) before being slowly diluted with water (173 L, 7.5 vol) at a rate to maintain the internal temperature above 75 °C. After complete addition the transparent orange solution was cooled to 45 °C and seeded with the product **12** (0.11 kg, 0.005 wt). The seeded solution was cooled to room temperature over at least 1 h and stirred at this temp for at least 2 h. The product was collected by filtration, washing with 50% aqueous ethanol (70 L, 3 vol) followed by PhMe (70 L, 3 vol) and dried under vacuum at 70 °C until its water content was under 1% w/w (as determined by Karl Fischer analysis) to yield the product as an off-white solid (19.35 kg, 78%th). ^{1}H NMR (400 MHz, methanol-d_4): δ 4.18 (s, 2 H), 5.09 (s, 2 H), 7.02 (d, 2 H, J = 8 Hz), 7.20 (m, 3 H), 7.25 (d, 1 H, J = 2.5 Hz), 7.30 (t, 1 H, J = 8 Hz), 7.79 (t, 1 H, J = 7.5 Hz), 7.96 (d 1 H, J = 7.5 Hz); ^{13}C NMR (100 MHz, methanol-d_4): δ 39.2, 64.7, 114.5, 116.9, 122.4, 124.2, 124.8, 125.9, 127.2, 128.7, 131.6, 132.0, 132.1, 132.2, 135.7, 138.3, 156.2, 156.3, 160.7, 173.4.

Alkylation of Hydrogenation Product 17. Phenol **17** (100 g, 1 wt) was suspended in EtOH (900 mL, 9 vol) and treated with K_2CO_3 (0.95 wt, 2 equiv) followed by 4-Cl-2-F-benzyl bromide **4** (0.49 vol, 1.04 equiv). The reaction was heated to reflux for 2 h, filtered whilst hot, washing through with ethanol (100 mL, 1 vol). NaOH (510 mL, 5.1 vol of a 2 M aqueous solution, 3 equiv) was added and the reaction heated at reflux for a further 1 h. The hot reaction mixture was diluted with H_2O (1 L, 10 vol) before cooling to 56 °C and seeding. The slurry was cooled to 50 °C over 1 h then further cooled to 20 °C over 2 h. The slurry was stirred at 20 °C for 16 h before the product was collected by filtration, washing with 2:3 EtOH/H_2O (1 L, 10 vol) followed by PhMe (1 L, 10 vol). The cake was dried overnight at 40 °C under vacuum to furnish the desired product as a fluffy white solid (138.4 g, 94%th). The data were in accordance with those reported above.

Carbonylation of Bromopyridine 23. To 2-bromopyridine **23** (2 g, 1 wt, 4.54 mmol) was added palladium acetate (102 mg, 0.05 wt, 0.45 mmol, 10 mol%) and dppf (252 mg, 0.126 wt, 0.45 mmol, 10 mol%) followed by ethanol (30 mL, 15 vol) and triethylamine (1.26 mL, 0.63 vol, 9.08 mmol, 2 equiv). The suspension was purged with three vacuum/N_2 cycles, followed by three CO/N_2 cycles, and heated to reflux under a CO atmosphere for 20 h. NaOH (6.8 mL of a 2 M aqueous solution, 13.6 mmol, 3 equiv) was added, and reflux was maintained for 1 h. The solution was filtered whilst hot and washed through with ethanol/water (3:1, 4 mL, 2 vol). The solution was returned to reflux, and water (30 mL, 15 vol) was added slowly. The solution was cooled to 40 °C, seeded, and cooled to 21 °C. The slurry was stirred for 1 h at this temperature and then isolated by filtration, washing with ethanol/water (2:3, 20 mL, 10 vol) and then toluene (2 × 20 mL, 2 × 10 vol). The cake was dried to constant weight, giving the product as an off-white solid (1.57 g, 78%th). The data were in accordance with those reported above.

6-(Chloromethyl)-2-pyrdinecarboxylic Acid (13). Thionyl chloride (27.7 mL, 0.48 vol) was added to a stirred solution of hydroxymethylpyridine **9** (57.6 g, 1 wt) in DCM (400 mL, 7 vol) at 10−15 °C and the mixture stirred at 20−25 °C for 1 h. The solvent was evaporated and the residue partitioned between toluene (200 mL, 3.5 vol) and saturated sodium hydrogen carbonate (200 mL, 3.5 vol). The layers were separated, and the organic phase was washed with water (300 mL, 5.2 vol). The solvent was removed to leave a pale oil which solidified on standing to a low melting beige solid. The solid was dissolved in EtOH (300 mL, 5.2 vol), and aqueous NaOH was added (165 mL, 2 M aqueous solution, 2.9 vol). After 10 min the reaction was quenched with $KHSO_4$ (690 mL, 8% w/w aqueous solution, 12 vol) and extracted with ethyl acetate (2 × 300 mL, 1 × 150 mL, 2 × 5.2 vol, 1 × 2.6 vol). The combined organic phases were washed with water (120 mL, 2.1 vol), dried over $MgSO_4$, and concentrated under reduced pressure to give an off-white solid (43.4 g, 80%th). ^{1}H NMR (400 MHz, methanol-d_4): δ 4.79 (s, 2 H), 7.79 (d, 1 H, J = 7.5 Hz), 8.02 (t, 1 H, J = 7.5 Hz), 8.10 (d, 1 H, J = 7.5 Hz); MS (ES+): MH^+ = 172.

6-[(5-Chloro-2-hydroxyphenyl)methyl]-2-pyridinecarboxylic Acid (14). To $AlCl_3$ (15.5 g, 116 mmol, 4 equiv) was added 6-chloromethylpicolinic acid (**13**) (5 g, 1 wt, 29 mmol). The two dry powders were thoroughly mixed before *p*-chlorophenol (7.5 g, 58 mmol, 2 equiv) was added with vigorous stirring. The reaction was heated to 180 °C (internal) for 6 h. At this point the reaction was allowed to cool to room temperature, giving a glasslike solid. To the solid was added EtOAc (7 mL, 15 vol) and $KHSO_4$ (5% aq, 75 mL, 15 vol), and the mixture was heated to reflux with stirring to effect complete dissolution. The aqueous phase was separated [Aq 1] and further extracted with EtOAc (25 mL, 5 vol). The combined organics [Org 1] were extracted with K_2CO_3 (7% aq, 75 mL, 15 vol), and this aqueous phase was further washed with EtOAc (50 mL, 10 vol) [Org 2]. Next, this basic aqueous phase was acidified to pH 3 with $KHSO_4$ (5% aq, 100 mL, 20 vol) before being extracted with EtOAc (75 mL, 15 vol) [Org 3 and Aq 2]. The organic phase [Org 3] was washed with water (75 mL, 15 vol), giving [Org 4] and the combined aqueous phase (this water wash and [Aq 2]) were back extracted with EtOAc (50 mL, 10 vol) [Org 5]. HPLC analysis of the various washes indicated that Aq 1, Org 1, and Org 2 all contained ∼10% product. Aq 1 was therefore further extracted with EtOAc (2 × 25 mL, 2 × 5vol) [Org 6]. Org 1 and Org 2 were combined and extracted with K_2CO_3 (5% aq, 50 mL, 10 vol), followed by water (50 mL, 10 vol). These combined aqueous phases were acidified with 5% $KHSO_4$ and extracted with EtOAc (2 × 50 mL, 2 × 10 vol) [Org 7].

The combined organic phases [Org 4, 5, 6, 7] were filtered to remove traces of solid before being dried over $MgSO_4$ and concentrated to dryness under reduced pressure and then dried under vacuum at 40 °C to furnish the crude product (5.9 g, 77%, 91% HPLC a/a). ^{1}H NMR (400 MHz, DMSO): δ 4.09 (s, 2 H), 6.84 (d, 1 H, J = 8.5 Hz), 7.05 (dd, 1 H, J = 2.5, 8.5 Hz), 7.15 (d, 1 H, J = 2.5 Hz), 7.41 (m, 1 H), 7.89 (m, 2 H), 10.05 (br s, 1 H); MS (ES+): MH^+ = 264.

Ethyl 6-[(5-Chloro-2-hydroxyphenyl)hydroxymethyl]-2-pyridinecarboxylate (16). *From Hydroxymethylpyridine 9.* A solution of hydroxymethylpyridine **9** (120 g, 1 wt, 1 equiv) in DCM (1.2 L, 10 vol) was treated with DMSO (0.78 vol, 2 equiv) followed by Et_3N (3.08 vol, 4 equiv) and then cooled to 4 °C before being treated with pyridine SO_3 complex (1.76 wt, 2 equiv). After 5 min at 4 °C the reaction temperature was cautiously allowed to increase to rt (exotherm). After 4 h at room temperature, 2 M HCl (5.5 vol was added (exotherm)). The aqueous layer was removed and the organic phase washed with 7.5% w/w aq $KHSO_4$ (10 vol). The organic solution was concentrated by atmospheric pressure distillation to 2 vol, giving a maximum internal temperature of 40 °C. The concentrated solution was cooled to 23 °C.

A separate vessel was charged with DCM (5.2 vol) and *p*-chlorophenol (1.57 wt, 2.20 equiv) and the resultant solution cooled to 0 °C. A solution of 1 M EtMgBr in TBME (11.0 vol, 2 equiv) was slowly added, maintaining the internal temperature below 22 °C (exotherm, gas evolution). The resulting suspension was equilibrated to 23 °C, and the DCM solution of the aldehyde prepared above was added. The reaction was stirred at room temperature for at 2 h. The reaction was cautiously quenched by addition of HCl (4.75 vol of a 2 M aqueous solution), keeping the internal temperature below 35 °C (exotherm) followed by $KHSO_4$ (3.5 vol of a 7.5% w/w aqueous solution). The aqueous layer was removed, and the organic phase was further washed with a mixture of water (4.3 vol) and brine (3 vol). The organic phase was concentrated to 5 vol by atmospheric pressure distillation before EtOH (13 vol) was added and the solution further concentrated to 8.6 vol. Water (8.6 vol) was slowly added at reflux, and the solution was held for 10 min before being cooled to 68 °C, seeded, and then slowly cooled to 0 °C over a period of 3 h. The resultant slurry was held at 0 °C for at 1 h before the product was collected by filtration, washing with 1:1 EtOH/H_2O (2 × 3 vol) at 0 °C and dried overnight under vacuum at 45 °C to furnish an off-white crystalline solid (140 g, 68%th). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (t, 2 H), 3.49 (d, 1 H), 4.46 (q, 3 H), 6.09 (d, 1 H), 6.93 (d, 1 H), 7.12 (dd, 1 H), 7.39 (d, 1 H), 7.74 (d, 1 H), 7.93 (t, 1 H), 8.05 (d, 1 H); MS (ES+): MH^+ = 308.

From Diethyl Dipicolinate 8. A solution of diethyl dipicolinate **8** (25 g, 1 wt, 1 equiv) in EtOH (250 mL, 10 vol) at 23 °C was treated with $NaBH_4$ (2.5 g, 0.1 wt, 0.6 equiv). After stirring for 3 h further $NaBH_4$ was added (0.83 g, 0.033 wt, 0.2 equiv), and the reaction was stirred for a 5 h. The reaction was cooled to 15 °C before being quenched by the cautious addition of AcOH (5 mL, 0.2 vol) (gas evolution) followed by H_2O (12.5 mL, 0.5 vol) (exotherm). The reaction mixture was then concentrated to 2 vol by vacuum distillation, ensuring the internal temperature did not rise above 45 °C. The concentrated solution was returned to room temperature before being diluted with 50% saturated aqueous $NaHCO_3$ (100 mL, 4 vol) followed by DCM (100 mL, 4 vol). The lower organic phase was separated and the aqueous further extracted with DCM (2 × 50 mL, 2 × 2 vol). The combined organics were washed with H_2O (50 mL, 2 vol), back extracting the aqueous phase with more DCM (2 × 50 mL, 2 × 2 vol). The combined organics were concentrated to 4 vol by atmospheric pressure distillation, diluted with DCM (250 mL, 10 vol), and further concentrated to 4.5 vol. TEMPO (15 mg, 0.0060 wt, 0.85 mol%), KBr (113 mg, 0.0045 wt, 0.85 mol%), $NaHCO_3$ (4.8 g, 0.192 wt, 0.51 equiv), and H_2O (150 mL, 6 vol) were added at room temperature, and the resulting biphasic solution was cooled to 0 °C. NaOCl solution (53 mL, 15% active chlorine titrated prior to use, 2.12 vol, 1.0 equiv) was added at a rate which maintained the internal temperature below 5 °C. Ten minutes after complete addition the reaction was allowed to warm to room temperature, the lower organic phase was removed, and the aqueous phase was back extracted with DCM (50 mL, 2 vol). The combined organics were washed with water (100 mL, 4 vol), and the aqueous phase was back extracted with DCM (50 mL, 2 vol). The combined organics were concentrated by atmospheric pressure distillation to 2.8 vol, giving a maximum internal temperature of 40 °C. The concentrated solution was cooled to 23 °C.

A separate vessel was charged with *p*-chlorophenol (29 g, 1.16 wt, 2.0 equiv) and $MgCl_2$ (34.3 g, 1.37 wt, 3.2 equiv). DCM (150 mL, 6 vol) was added and the resultant suspension equilibrated to 23 °C. Me_2EtN (21.3 mL, 0.85 vol, 0.58 wt, 1.76 equiv) was added, keeping the internal temperature below 30 °C (exotherm). The reaction mixture was equilibrated to 23 °C, and the DCM solution of the aldehyde prepared above was added over 4 h. The reaction was stirred at room temperature for 15 h before being cooled to 0 °C and cautiously quenched by addition of HCl (94 mL of a 2 M aqueous solution, 3.76 vol, 1.67 equiv), keeping the internal temperature below 25 °C (exotherm) followed by $KHSO_4$ (55 mL of a 7.5% w/w aqueous solution, 2.2 vol, 0.27 equiv). The temperature was adjusted to 21 °C before the lower organic layer was separated. The aqueous phase was extracted with DCM (25 mL, 1 vol, the combined organics were washed with water (100 mL, 4 vol), and the aqueous phase was again back extracted with DCM (25 mL, 1 vol). The combined organics were concentrated to 3 vol by atmospheric pressure distillation before EtOH (250 mL, 10 vol) was added and the solution further concentrated to 7 vol. Water (175 mL, 7 vol) was slowly added at reflux. The solution was maintained at reflux for 5 min before being cooled to 73 °C, seeded, held for 1 h, and then slowly cooled to 0 °C over 2 h. The resultant slurry was held at 0 °C for at least 1 h before the product was collected by filtration, washing with 1:1 EtOH/H_2O (2 × 62.5 mL, 2 × 2.5 vol) at 0 °C. The fluffy, off-white solid was dried overnight under vacuum at 40 °C to furnish the desired product (86%w/w, 62.5%th). The data were in accordance with those reported above.

Ethyl 6-[(5-Chloro-2-hydroxyphenyl)methyl}-2-pyridinecarboxylate (17). Diarylmethanol **16** (70 g, 1 wt) and Pd/C (5.25 g, 7.5 wt% of 10 wt% Pd on activated carbon dry powder, JM type 487, 2.17 mol% Pd) were charged to the hydrogenation vessel. EtOAc (525 mL, 7.5 vol) was added, and further EtOAc (525 mL, 7.5 vol) was used to wash in the $ZnBr_2$ (1.4 g, 2 wt%, 2.7 mol%). H_2SO_4 (70 mL, 1 vol, conc.) was cautiously added with vigorous stirring. The flask was flushed with N_2 followed by H_2 at 1 atm (above atmospheric pressure) before the reaction was heated to 65 °C for 6 h. The reaction was cooled to rt, flushed with N_2, and filtered through a short plug of Celite, washing with further EtOAc (3 × 70 mL, 3 × 1 vol). The combined filtrates were washed with H_2O (700 mL, 10 vol). The aqueous phase was diluted with further water (14 vol) before being back extracted with EtOAc (350 mL, 5 vol). The combined organics were washed with Na_2SO_4 (2 × 420 mL, 2 × 6 vol of a 10% w/w solution) followed by water (420 mL, 6 vol). The organic phase was concentrated to 350 mL (5 vol) by atmospheric pressure distillation, then diluted with IPA (1400 mL, 20 vol) and further concentrated to 490 mL (7 vol). The resultant solution was cooled to 55 °C, seeded, then further cooled to 0 °C over 2 h and held at 0 °C for 1 h before the product was collected by filtration, washing with cold IPA (140 mL, 2 vol). The cake was dried overnight under vacuum at 40 °C, furnishing the desired product as a white crystalline solid (54.44 g, 82%th). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (t, 3 H), 4.12 (s, 2 H), 4.46 (q, 2 H), 6.95 (d, 1 H), 7.10 (m, 2 H), 7.49 (d, 1 H), 7.87 (dd, 1 H), 8.02 (d, 1 H, 11.17 (s, 1 H); MS (ES+): $MH^+ = 292$.

5-Chloro-2-{[(4-chloro-2-fluorophenyl)methyl]oxy}benzaldehyde (20). To a solution of 5-chlorosalicyaldehyde **19** (15 g, 1 wt, 0.096 mol) in acetone (180 mL, 12 vol) was added 4-chloro-2-fluorobenzyl bromide **4** (21.84 g, 1.454 wt, 0.098 mol, 1.02 equiv), followed by K_2CO_3 (26.5 g, 1.77 wt, 0.192 mol, 2 equiv). The suspension was stirred at 21 °C for 90 min, then heated to 35 °C for 90 min. The slurry was cooled to 21 °C, and solids were removed by filtration, with the cake washed with further acetone (5 × 4 vol) then toluene (5 × 4 vol). The filtrate and washes were combined and concentrated to minimum volume. The residue was dissolved in refluxing propan-2-ol (255 mL, 17 vol), cooled to 80 °C, and seeded. The slurry was cooled to 21 °C over 90 min, then further cooled to 2 °C, and held for 1 h. The product was isolated by filtration and washed with propan-2-ol (2 vol then 3 vol). After drying to constant weight the product was recovered as a white crystalline solid (26.4 g, 92%th). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (s, 2 H), 7.02 (d, 1 H, $J = 9$ Hz), 7.18 (m, 2 H), 7.42 (t, 1 H, $J = 8$ Hz), 7.49 (dd, 1 H, $J = 3, 9$ Hz), 7.81 (d, 1 H, $J = 3$ Hz), 10.42 (s, 1 H); MS (ES+): $MH^+ = 299$.

6-[(5-Chloro-2-{[(4-chloro-2-fluorophenyl)methyl]oxy}-phenyl)hydroxymethyl]-2-bromopyridine (22). *BuLi Medi-*

ated. A solution of 2,6 dibromopyridine **21** (14.22 g, 60 mmol, 1.11 equiv) in DCM (280 mL, 19.7 vol) was cooled to −74 °C (internal temperature), and a solution of *n*-butyllithium (24 mL of a 2.5 M solution in hexane, 60 mmol) was added over 5 min. The solution was stirred at this temperature for 30 min; then a solution of aldehyde **20** (16.15 g, 1 wt, 0.54 mmol) in DCM (150 mL, 10.5 vol) was added over 5 min. An exotherm to −65 °C was observed. The reaction mixture was allowed to warm further to room temperature over 2 h. The DCM phase was washed with an 7.5% w/w aqueous solution of $KHSO_4$ (80 mL, 5.6 vol) and then further washed with water (120 mL, 8.4 vol). The DCM layer was concentrated to minimum volume and dissolved in propan-2-ol (74 mL, 5.2 vol) at reflux. The solution was cooled to 82 °C, seeded, and cooled to room temperature over 2 h. Stirring was continued for 17 h, and then the slurry cooled to 0 °C and held for 30 min. The product was isolated by filtration, washed with chilled propan-2-ol (14 mL then 28 mL, 1 vol then 2 vol), and dried to constant weight to give a white crystalline solid (20.37 g, 82.5%th). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.06 (d, 1 H, J = 12.5 Hz), 5.12 (d, 1 H, J = 12.5 Hz), 5.88 (d, 1 H, J = 5 Hz), 6.25 (d, 1 H, J = 5 Hz), 7.11 (d, 1 H, J = 9 Hz), 7.32 (m, 3 H), 7.47 (m, 4 H), 7.67 (m, 1 H); MS (ES+): MH^+ = 458.

Grignard Mediated. To a solution of ^{i}PrMgCl/LiCl (9.4 mL, 2.8 vol, 1.4 M in THF, Chemetall) was added 2,6 dibromopyridine **21** (2.84 g, 12 mmol, 1.06 equiv) as a solid. The temperature was maintained below 25 °C and then held at 20−25 °C for 3 h. At this time, further ^{i}PrMgCl/LiCl (0.88 mL, 0.26 vol, 1.4 M in THF) was added, the solution stirred for 2 h and then warmed to 30 °C for 2 h. After the mixture was cooled to room temperature, a solution of the aldehyde **20** (3.36 g, 1 wt, 0.0112 mol) in THF (20 mL, 7 vol) was added over 5 min. The solution was stirred for 16 h. To the resultant slurry was added ethyl acetate (20 mL, 7 vol) followed by $KHSO_4$ (7.5% w/w aqueous solution, 6 vol). The aqueous layer was removed and back extracted with ethyl acetate (2 vol). The combined organic layers were washed with water (6 vol) and concentrated to dryness. The residue was dissolved in propan-2-ol (15 mL, 4.5 vol) at reflux, cooled to 73 °C, seeded, and further cooled to 3 °C over 3 h. The product was isolated by filtration, washed with chilled propan-2-ol (2 × 1.5 vol), dried to constant weight, and recovered as a white crystalline solid (3.42 g, 66%th). The data were in accordance with those reported above.

6-[(5-Chloro-2-{[(4-chloro-2-fluorophenyl)methyl]oxy}phenyl)methyl]-2-bromopyridine (23). To a slurry of diarylmethanol **22** (3 g, 1 wt, 6.56 mmol) in chlorobenzene (7.5 mL, 2.5 vol) was added trifluoroactic acid (3 mL, 1 vol) followed by triethylsilane (4.5 mL, 1.5 vol). The mixture was heated to reflux for 2 h. The solution was cooled to room temperature and further chlorobenzene (18 mL, 6 vol) added followed by a saturated aqueous solution of carbonated sodium hydrogen (33 mL, 11 vol). Water (20 mL, 6.7 vol) was added and the lower chlorobenzene layer removed. The upper aqueous phase was further extracted with chlorobenzene (2 × 18 mL, 2 × 6 vol). The combined chlorobenzene layers were concentrated to minimum volume. Propan-2-ol (24 mL, 8 vol) was added, and the concentration to minimum volume was repeated. The purple solid thus produced was dissolved in propan-2-ol (6 mL, 2 vol) at reflux, cooled to 72 °C, seeded, and held for 10 min. The thick slurry was heated to 75 °C and then allowed to cool slowly to room temperature before being further cooled to 0−3 °C and held for 30 min. The product was isolated by filtration and washed with 1 vol chilled propan-2-ol. After drying to constant weight the product was recovered a white crystalline solid (2.50 g, 86.5%th). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (s, 2 H), 5.03 (s, 2 H), 6.86 (m, 1 H), 6.94 (d, 1 H, J = 7.5 Hz). 7.09 (dd, 1 H, J = 2, 10 Hz), 7.15 (dd, 1 H, J = 1.5, 8.5 Hz), 7.20 (m, 2 H), 7.30 (d, 1 H, J = 8 Hz), 7.38 (t, 1 H, J = 8 Hz); MS (ES+): MH^+ = 440.

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