ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Full Paper

Process Development of the HCV NS5b-site D Inhibitor MK-8876

Michael James Williams, Qinghao Chen, Lorenzo Codan, Renee K. Dermenjian, Spencer D. Dreher, Andrew William Gibson, Xianliang He, Yan Jin, Stephen Philip Keen, Alfred Lee, David Lieberman, Wei Lin, Guiquan Liu, Mark McLaughlin, Mikhail Reibarkh, Jeremy P. Scott, Sophie Strickfuss, Lushi Tan, Richard J. Varsolona, and Feng Wen

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.5b00405 • Publication Date (Web): 25 Jan 2016

Just Accepted

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Process Development of the HCV NS5b-site D Inhibitor MK-8876

Michael J. Williams[*,†], Qinghao Chen[*,†], Lorenzo Codan,[ϕ] Renee K. Dermenjian,[†] Spencer Dreher,[†] Andrew W. Gibson,[‡] , Xianliang He,[§] Yan Jin,[†] Stephen P. Keen,[‡] Alfred Y. Lee,[†] David R. Lieberman,[‡] Wei Lin,[§] Guiquan Liu,[§] Mark McLaughlin,[†] Mikhail Reibarkh,[†] Jeremy P. Scott,[‡] Sophie Strickfuss,[‡] Lushi Tan,[†] Richard J. Varsolona,[†] and Feng Wen[§]

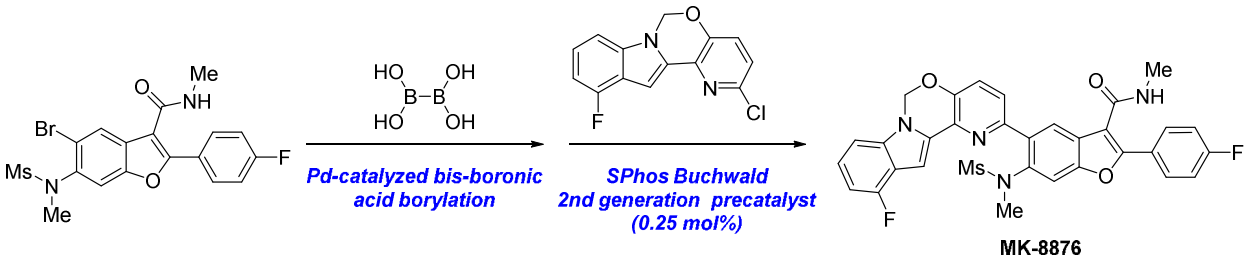
† Department of Process and Analytical Chemistry, Merck Research Laboratories, Rahway, New Jersey 07065, United States of America

‡ Department of Process Chemistry, Merck Sharp and Dohme Ltd., Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU, United Kingdom

ϕ Werthenstein BioPharma GmbH (MSD Switzerland), Industrie Nord 1, CH-6105 Schachen, Switzerland

§ WuXi AppTec Co., Ltd., No. 1 Building, #288 FuTe ZhongLu, WaiGaoQiao Free Trade Zone, Shanghai 200131, China

Table of contents Graphic:



MK-8876

Abstract:

We describe the route development and multi-kilogram scale synthesis of an HCV NS5b site D inhibitor, MK-8876. The key topics covered are: 1) process improvement of the two main fragments; 2) optimization of the initially troublesome penultimate step, a key bis-boronic acid (BBA) based borylation; 3) process development of the final Suzuki-Miyaura coupling; 4) control of the drug substance form. These efforts culminated in a 28 kg delivery of the desired API.

KEYWORDS: Pd-catalyzed borylation, bis-boronic acid, Suzuki-Miyaura coupling, Buchwald biaryl precatalyst, DoE design, High-throughput experimentation

Introduction:

Hepatitis C virus (HCV) is a leading cause of chronic liver disease, with an estimated 130-170 million people infected globally. This disease has a high degree of genetic heterogeneity and can be classified into six major genotypes that have distinct geographic distributions. A compelling medical need exists for new oral therapeutic agents with improved efficacy and tolerability that inhibit the virus across disease genotypes.[1] MK-8876 (**1**) is a small molecule non-nucleoside inhibitor developed to target the Site D binding pocket of NS5B polymerase that exhibited pan-genotypic activity in *in vitro* studies.[2] The discovery synthesis of compound **1** provided a convergent route to MK-8876 via two key intermediates: chloroindolopyridine **2** and boronate **3** (Scheme 1). Chloroindolopyridine **2** was synthesized in four steps from 4-fluoroindole (**4**), and boronate **3** was derived from 2-hydroxybenzeneacetic acid (**5**) (Scheme 2). Four key areas were defined as critical points of optimization to ensure multi-kilogram scalability and delivery of the drug substance:

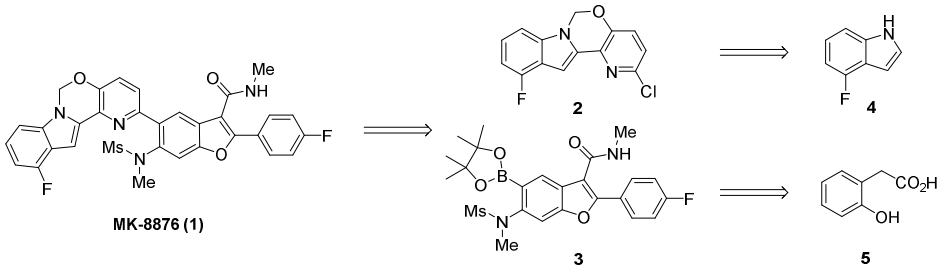
(1) The route to chloroindolopyridine **2** progressed through the unstable indoloboronic acid **7**; further process development would be necessary to support the handling times required on scale.

(2) Benzofuran **19** was synthesized via a long linear sequence with multiple chromatographic separations. The Claisen condensation and benzofuran formation, in particular, were targets for optimization.

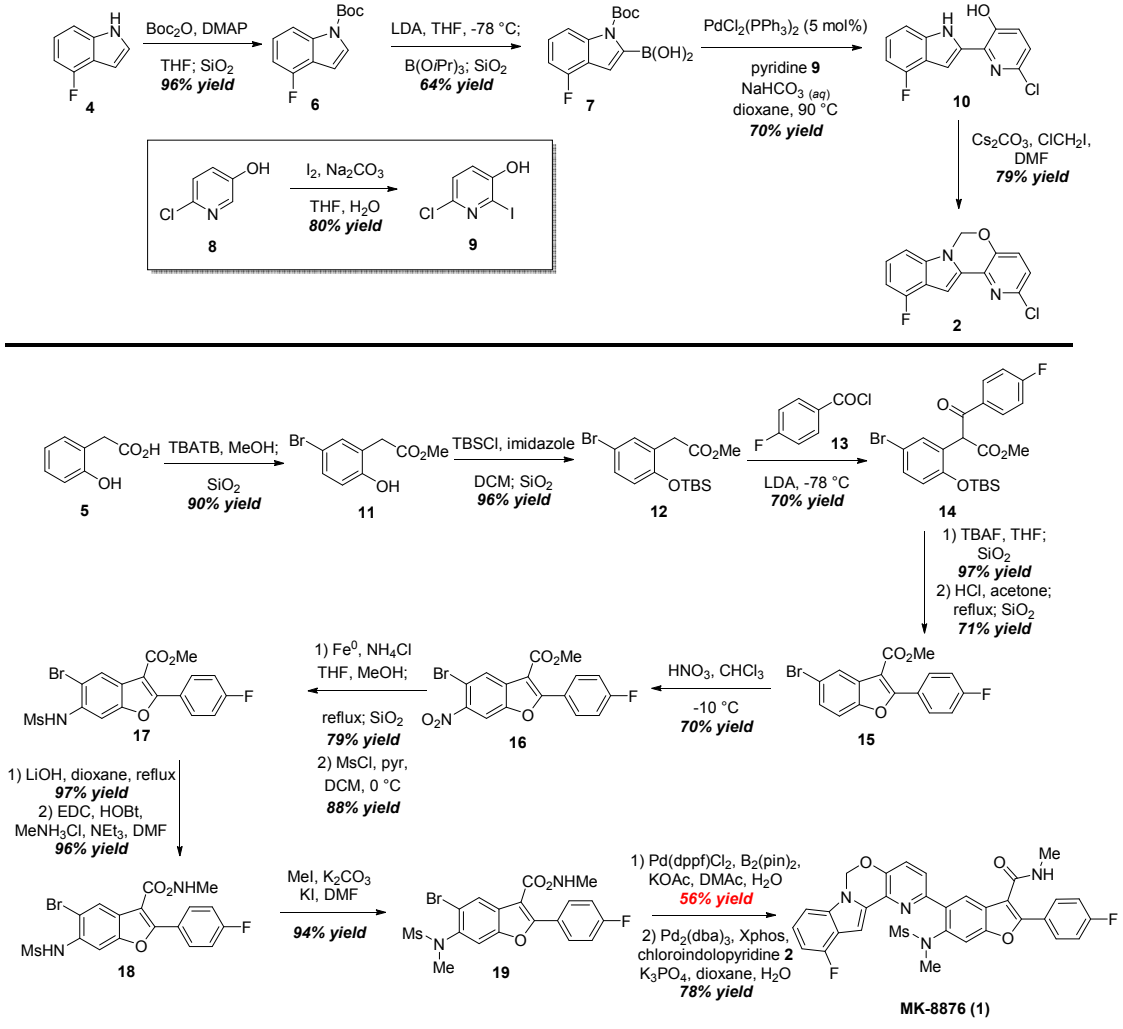
(3) The convergent endgame chemistry, specifically the borylation of bromobenzofuran **19,** suffered from a poor yield. Further, the final Suzuki-Miyaura coupling utilized dioxane as the reaction solvent, leading to both operational and safety concerns.

(4) A scalable procedure to access the desired drug substance crystal form of MK-8876 (**1**) was necessary.

Scheme 1: Retrosynthetic analysis of MK-8876 (1)



Scheme 2: Discovery Route to MK-8876 (1)

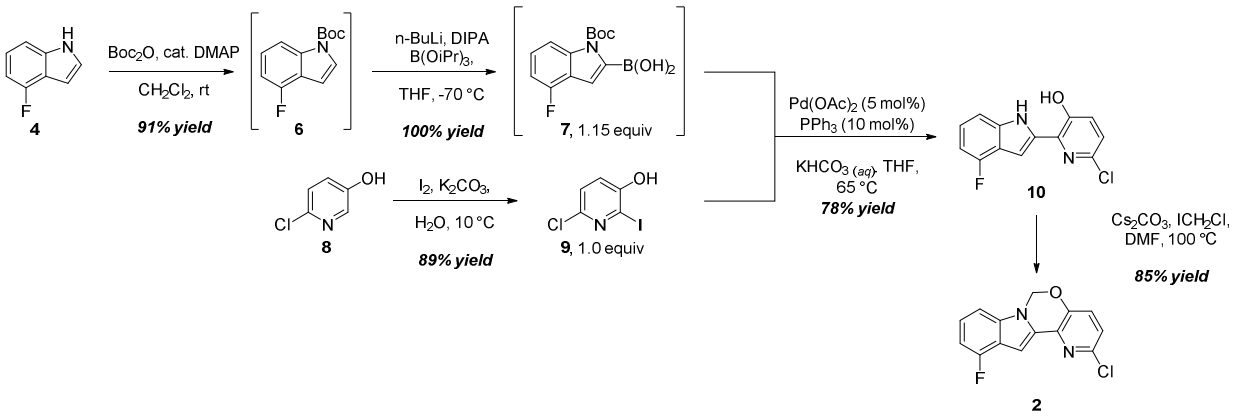


Results and Discussion:

Optimization of indole 2 synthesis

The original bond disconnections toward the preparation of indole **2** and benzofuran **19** were deemed suitable for further reaction development. We intended to eliminate all chromatographic purifications (7 out of 16 steps) and identify through-processing opportunities to increase yield without sacrificing purity. We focused our efforts initially on: 1) the one-step preparation of pyridine **9** and 2) its subsequent coupling with fluoroboronic acid **7** to afford indolopyridine **2** (Scheme 3). Altering the base from Na_2CO_3 to K_2CO_3 and running the iodination reaction in pure water as opposed to aqueous THF led to improved performance and isolation of pyridine **8**:[3] elimination of THF simplified the workup for this step and iodide **9** was isolated in 89% yield by crystallization from *n*-heptane. The coupling partner of iodide **9**, boronic acid **7,** was initially isolated in a modest 64% yield via deprotonation of indole **6** and quench with triisopropyl borate.[4] We surmised that the moderate yield of boronic acid **7** was a result of decomposition during processing, not a low yielding borylation reaction.[5] Indeed, the addition of triisopropyl borate to a mixture of LDA and indole **6,** followed by acidic workup, provided a solution of indoleboronic acid **7** in quantitative yield. Furthermore, the crude mixture obtained from Boc protection of indole **4** could be used in the borylation without impact on yield or purity.

Scheme 3: Preparation of Indole 2



With efficient processes to boronic acid **7** and iodide **9** in hand, we turned our attention to the subsequent Suzuki-Miyaura coupling.[6] During the coupling, the unprotected indole **10** is formed under the reaction conditions rather than the expected *N*-Boc indole. While the Boc group of indole **7** is stable under basic conditions, we hypothesize that the presence of a neighboring phenol functionality in pyridine **10** allows the Boc group to migrate[7] from *N* to *O* followed by carbonate saponification. The original coupling process provided product **10** in 77% isolated yield utilizing 1,4-dioxane, an undesirable solvent for large scale synthesis.[8] THF was found to be an acceptable replacement, but due to the instability of boronic acid **7** during distillative solvent exchange, the reaction solvent was limited only to THF or THF mixtures. We, therefore, focused exclusively on THF with aqueous base rather than introducing an additional organic co-solvent to minimize the total reaction volume. Under the initial conditions (Table 1, entry 1), indole **6**, the result of protiodeborylation, was observed as the main byproduct.[9] We examined a series of common inorganic bases with a range of pK_a's (Table 1, entries 2, 5, and 6) using 5 mol% $Pd(OAc)_2$ and 10 mol% PPh_3. $KHCO_3$ was identified as the optimal base, providing the desired product in 85% assay yield; the formation of indole **6** was correspondingly reduced

by more than 50% from >10% LCAP[10] to 5% LCAP. Higher assay yield of product **10** was achieved by employing $Pd(OAc)_2$ instead of Pd_2dba_3 or $Cl_2Pd(PPh_3)_2$ (entries 5 vs. 1 and 9) for assay yield of product. In addition to PPh_3, 48 monodentate and bidentate phosphine ligands were surveyed in this chemistry. SPhos and the water soluble sulfonylated SPhos[11] ($NaSO_3$-SPhos) performed comparably as ligands in the Suzuki reaction.[12] However, the cost savings associated with reduction in Pd loading were offset by the higher ligand cost and long lead time. Therefore, the $Pd(OAc)_2/PPh_3$ system was utilized to prepare indole **10** in 85% assay yield and 78% isolated yield after crystallization from CH_2Cl_2 and MTBE. Finally, aminal formation from indole **10** using $ClCH_2I$ and Cs_2CO_3 in DMF provided chloroindolopyridine **2** in 95% assay yield and 85% isolated yield.[13]

Table 1: Screening results from the Suzuki-Miyaura coupling to generate indolopyridine 10

Entry[a]	Pd salt (mol%)	Ligand (mol%)	Base	10[b]	6[b]	Assay yield of 10
1	$Cl_2Pd(PPh_3)_2$ (5%)	None	$NaHCO_3$	54	24	N.D.
2	$Pd(OAc)_2$ (5%)	PPh_3 (10%)	$KHCO_3$	85	5	85%
3	$Pd(OAc)_2$ (2%)	PPh_3(4%)	$KHCO_3$	74	15	52%
4	$Pd(OAc)_2$ (3%)	PPh_3 (6%)	$KHCO_3$	81	10	71%
5	$Pd(OAc)_2$ (5%)	PPh_3 (10%)	$NaHCO_3$	69	19	N.D.
6	$Pd(OAc)_2$ (5%)	PPh_3 (10%)	KF	50	30	N.D.
7	Pd_2dba_3 (2.5%)	PPh_3 (10%)	K_2CO_3	64	18	N.D.
8	Pd_2dba_3 (2.5%)	PPh_3 (10%)	KHCO3	75	14	N.D.
9	Pd_2dba_3 (2.5%)	PPh_3 (10%)	$NaHCO_3$	57	20	N.D.

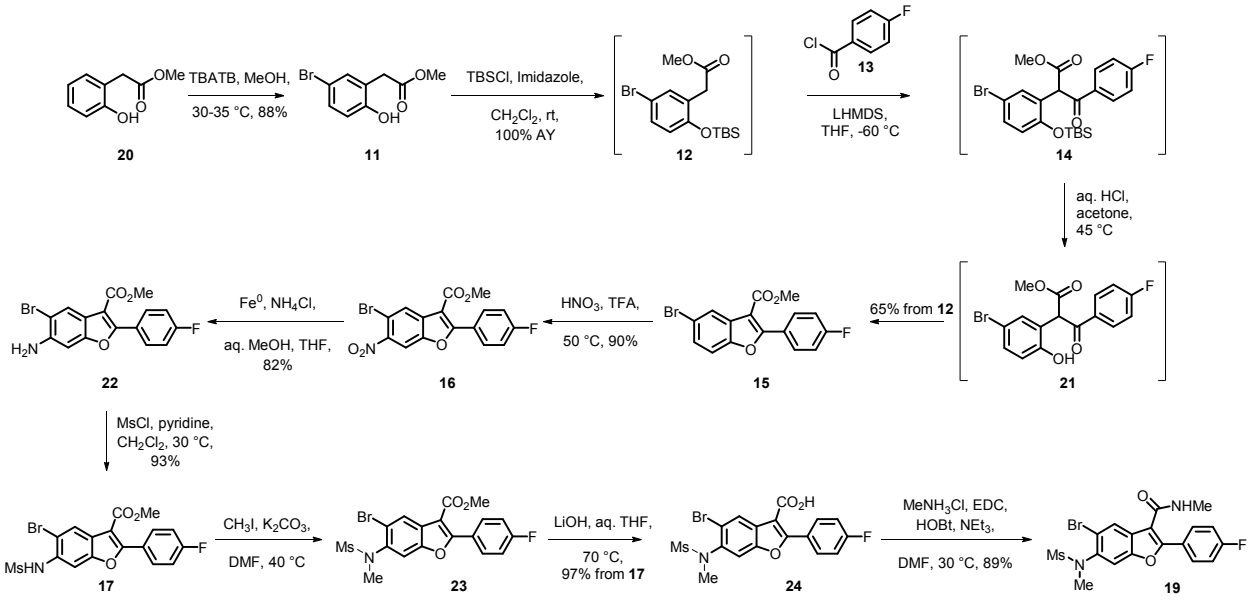
10	$Pd(OAc)_2$ (2%)	$NaSO_3$-SPhos (5%)	Cs_2CO_3	78	11	83%
11	$Pd(OAc)_2$ (2%)	SPhos (5%)	Na_2CO_3	78	13	85%

[a]: General coupling conditions: 1.0 equiv. **9**, 1.2 equiv. **7**, 3 equiv. base, THF (16 vols), water (2 vols), 70 °C, 12 h. Pd catalyst and ligand are as specified in Table 1.

[b]: LCAP of compound

Optimization of the synthesis of the benzofuran (19)

Scheme 4: Preparation of benzofuran 19



We next turned our attention to the synthesis of bromide **19**, the benzofuran core of MK-8876. Bromination of methyl ester **20** with tetra-*n*-butylammonium tribromide (TBATB)[14] in MeOH reproducibly achieved >90% solution assay yield and afforded **11** in 88% yield after crystallization from MTBE and *n*-heptane.[15] The next four steps from phenol **11** to benzofuran **15** were identified as a potential through-process sequence. TBS protection of phenol **11**

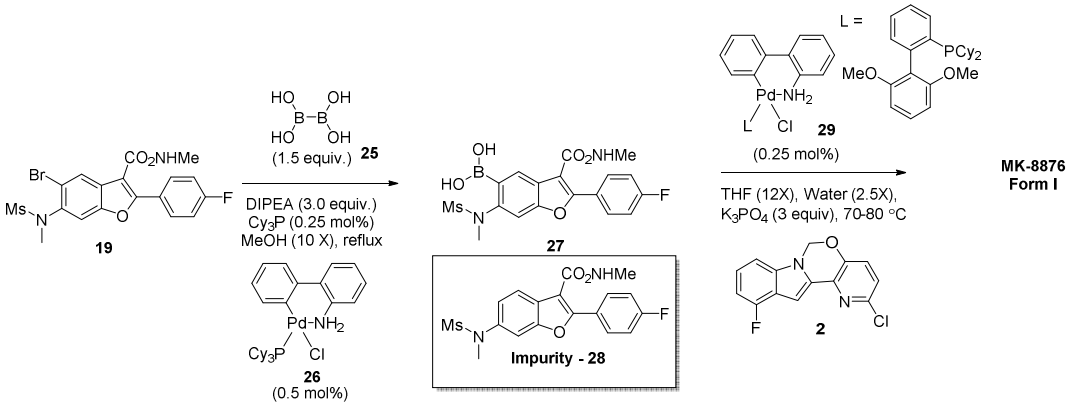
proceeded in quantitative yield under standard conditions, and the resultant crude THF solution of TBS ether **12** was enolized using LHMDS and acylated with *p*-fluorobenzoyl chloride (**13**) to afford β-ketoester **14** in 87 LCAP. Deprotection of the resultant TBS ether **14** under basic TBAF conditions generated up to 20% of an unidentified impurity, but this impurity could be avoided by deprotection under acidic conditions. Aqueous HCl was charged as part of the aqueous workup for ketoester **21** and up to 20% benzofuran **15** was observed during the distillative solvent exchange from MTBE/THF into acetone. Additional concentrated HCl was charged to complete the cyclization. Benzofuran **15** was purified by crystallization from CH_2Cl_2/MeOH in 65% yield from phenol **11** (average of 90% yield per step).

Nitration of benzofuran **15** in TFA at 50 °C provided nitroarene **16** in 90% yield, a 20% improvement over the original process.[16] This nitration process had no strongly exothermic events up to 360 °C by DSC measurement, well above the reaction temperature of 50 °C.[17] The nitroarene was reduced to the corresponding aniline **22** using iron powder and aqueous NH_4Cl in a mixture of THF and MeOH in 82% isolated yield.[18] Initially, we conducted this reaction by charging Fe powder in a single portion to the solution of nitroarene **16** at 20-25 °C, but a delayed exotherm was observed under these conditions. Reaction calorimetry measurements of this single charge process revealed an adiabatic temperature rise of 13 °C with a maximum batch temperature of 75 °C. Although this exotherm was expected to fall comfortably within the cooling capacity of our production equipment, we altered the process to add the iron powder portion-wise to the remainder of the reactants at 60-65 °C as an additional safety control.

Mono-mesylation of aniline **22** was found to be dependent on the identity and quantity of the amine base used in the reaction. Using 5 equivalents of trialkylamines, such as NEt_3 and DIPEA, gave only the bis-mesylated product, while the less basic pyridine gave predominantly the mesylated benzofuran **17**.[19] With compound **17** in hand, sulfonamide **23** was obtained after methylation. Subsequent saponification with LiOH afforded acid **24**. Amide coupling of acid **24** with methylamine hydrochloride salt under standard EDC/HOBt[20] conditions completed the synthesis of **19**.[21] The yield of the three step sequence from sulfonamide **17** to amide **19** was improved from 77% to 86%.

Endgame borylation development

Scheme 5: Borylation, Suzuki-Miyaura coupling, and form change



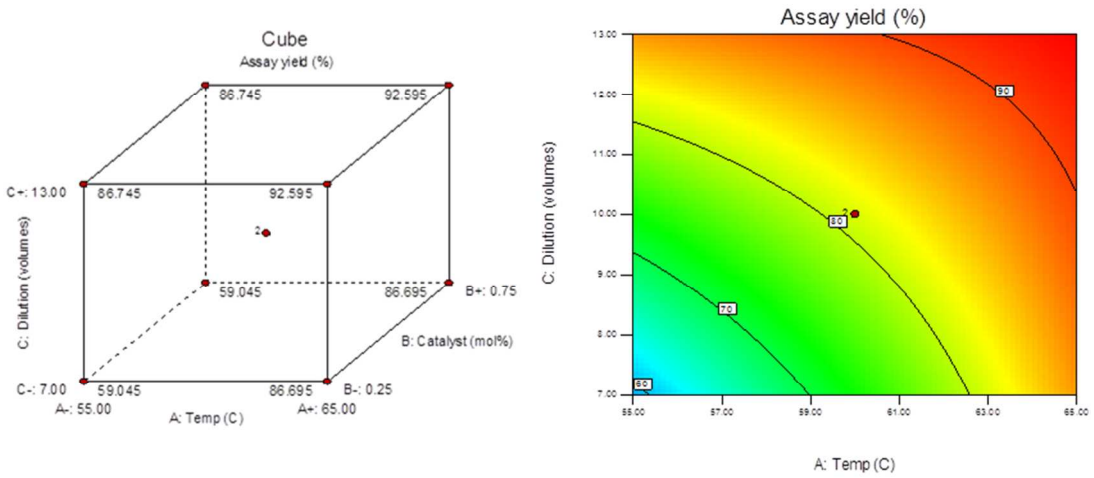
The borylation of benzofuran **19** proved low yielding using the discovery chemistry conditions (Scheme 2); as such, alternative conditions were sought to increase yield and, ultimately, throughput. Initial attempts to generate boronate ester **3** via halogen-metal exchange and quench with methoxyboronic acid pinacol ester proved unsuccessful because of failure to generate the requisite anion.[22] Concurrently, efforts were undertaken toward improving the palladium-catalyzed borylation with bispinacolatodiboron (B_2pin_2) via high

throughput experimentation (HTE). While yield improvements were observed under a variety of conditions, des-bromoarene **28** was still present as a large contaminant (~20-30%). We hypothesized that both approaches proved sub-optimal due to the steric hindrance about the aryl bromide conferred by the *ortho* sulfonamide group. Therefore, we evaluated the much smaller bisboronic acid (**25**) as an alternative borylation reagent. Gratifyingly, a significant increase in assay yield of arylboronic acid **27**, with concomitant decrease in the level of des-bromoarene **28**, was accomplished utilizing this reagent.[23] Early screening efforts identified conditions that utilized a 2nd generation Buchwald Cy_3P pre-catalyst (**26**) and a base at elevated temperature in methanol. Further studies revealed several key reaction parameters: 1) diisopropylethylamine (3.0 equiv.) as base provided the fastest reaction rate and highest yield[24]; 2) excess bisboronic acid (1.5 equiv.) was necessary to achieve complete conversion; and 3) exogenous sub-stoichiometric PCy_3 suppressed the formation of des-bromoarene **28** and prevented catalyst death, but also served to inhibit the reaction.[25]

To fully optimize the yield for the borylation step and minimize the Pd charge, a 3-factor design of experiment (DoE) study was constructed. The impact of the following three factors was evaluated: 1) pre-catalyst charge (0.25-0.75 mol %, with an equimolar charge of PCy_3), 2) temperature (55-65 °C for 6 h), and 3) concentration (7–13 volumes methanol).[26] The reaction temperature and concentration were identified as the significant factors from the study. The borylation yield was maximized at high temperature and high dilution (Figures 1). Surprisingly, catalyst loading was found not to be significant within the tested parameters, and no single factor appeared to have a significant effect on the formation of des-bromoarene **28**.

Figure 1: Borylation reaction DoE results for Aryl boronic acid **27**

(i) Cube plot and (ii) Response Surface Plot



Building on the results from above, the addition of precatalyst **26** to a refluxing mixture of aryl bromide **19**, bisboronic acid (**25**), and triethylamine afforded reproducible and consistently high yields with minimal formation of des-bromoarene **28**. To alleviate the heightened safety concerns with this elevated temperature charge of catalyst, calorimetry experiments were conducted to determine heat of reaction and adiabatic temperature rise.[27] The pre-catalyst was added to the complete reaction mixture at 60 °C and then aged at this temperature.[28] The heat of reaction was -248 kJ/mol, but with a large methanol heat sink, the adiabatic temperature rise was only 10.5 K over 3 h. Further safety testing revealed no significant concern to conducting this operation under the stated conditions.[29]

With the key borylation conditions developed, isolation of arylboronic acid **27** was accomplished directly from the reaction mixture with the addition of water, albeit without rejection of des-bromoarene **28**. While final isolation conditions were being developed, subsequent downstream development efforts revealed that experimental batches of API

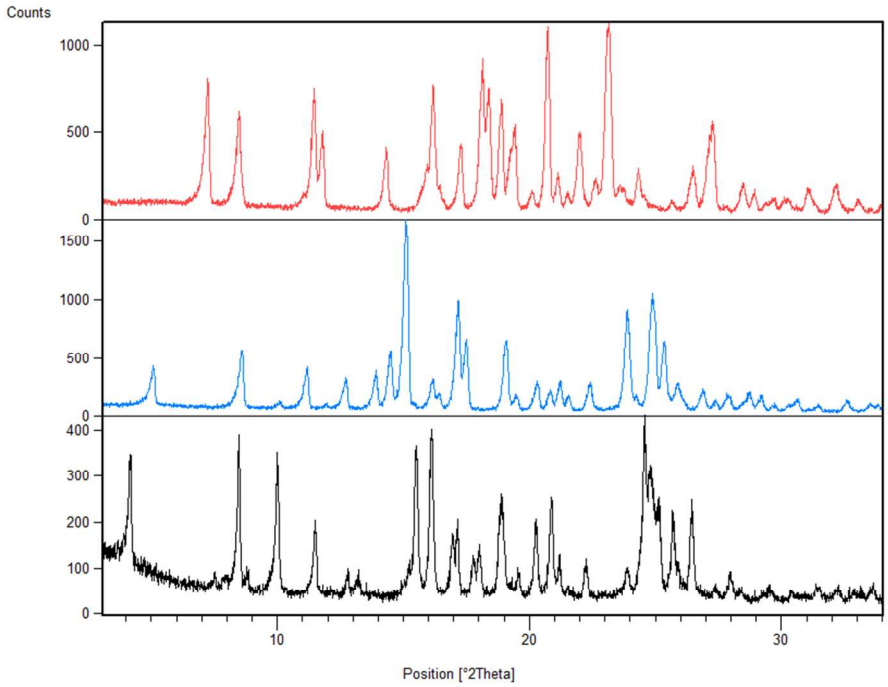
contained unacceptably high levels of palladium for use in clinical trials. MP-TMT resin[30] was identified from a multi-resin screen as the optimal treatment for the borylation stream, significantly reducing palladium with minimal product loss.[31] In the finalized process, methanol and DIPEA were added to a mixture of arylbromide **19** and bisboronic acid (**25**), and the resulting slurry was heated to 60 °C. The pre-catalyst (0.5 mol %)[32] was then charged as a solution in methanol, and the reaction mixture heated to reflux (63-65 °C). The reaction was complete after 1 h with 93.9% desired boronic acid **27**, 5.1% des-bromoarene **28**, and 0.5% starting bromide **19**. The batch was cooled to room temperature and treated with MP-TMT resin (50 wt%).[33] The resulting solution was concentrated and boronic acid **27** was crystallized with the addition of water. Boronic acid **27** was isolated in 88% yield (27.5 kg) with 6.3% of des-bromoarene **28** and 102 ppm palladium[34] and 93 ppm phosphorus.[35]

Suzuki-Miyaura coupling and final solid form development

The previous conditions for the final Suzuki-Miyaura coupling had employed arylboronate ester **3** as substrate and 1,4-dioxane as the solvent. Incorporation of boronic acid **27** as reaction partner required new Suzuki-Miyaura coupling conditions.[36] HTE efforts led to identification of SPhos Buchwald 2nd generation precatalyst **29** as the optimal catalyst.[37] The reaction was carried out in acetonitrile with aqueous K_3PO_4 (2.5 M), providing the desired product in excellent yield with minimal formation of protiodeborylation product **28**. Upon scaling these conditions, the desired product was observed to crystallize directly from the reaction mixture. Interestingly, the crystallized product preferentially migrated into the acetonitrile phase of the biphasic mixture on separation. This phenomenon simplified isolation/purification because the solids could be easily collected in excellent yield with

complete purge of des-bromoarene **28**.[38] However, while this process was conducted in glass reactors with 99% isolated yield, the isolation was not suitable for larger fixed equipment due to the expected poorer visible indication of phase separation.

Figure 2: Powder X-Ray Diffraction Patterns of MK-8876 Forms 1 (red), 2 (blue) and 3 (black).



MK-8876 was shown to exist as three non-solvated distinct polymorphic forms (Forms 1, 2 and 3[39] – See Figure 2) of which Form 1 is preferred at or below 85 °C.[40] Although the Suzuki-Miyaura coupling process in acetonitrile produced MK-8876 in high yield and purity, the high reaction temperature coupled with the reactive crystallization generated undesired Form 2 (Figure 2). To streamline isolation of the desired form, we sought to combine the Suzuki-Miyaura coupling and form change into a single step. THF and water mixtures conferred unique solubility properties on MK-8876[41] which were utilized to generate a high yielding, volume efficient crystallization process on multi-kilogram scale.[42] Replacement of acetonitrile with THF

(10 volumes) as the reaction solvent for the Suzuki-Miyaura coupling provided a successful solution: conversion to the desired product occurred in essentially quantitative yield, and importantly, no product crystallized from the reaction mixture after cooling to room temperature. The aqueous layer was removed, and the organic layer washed with 5 wt% aqueous sodium chloride solution to afford the desired product in 99% solution yield.[43] 2-Propanol was identified as the optimal anti-solvent for the crystallization of MK-8876 Form 1.[44] A new isolation process was developed by first concentrating the post work-up solution to 6 volumes while reducing the water content (11-19 wt%) via distillation, heating the concentrated mixture to 40-50 °C, seeding, and finally charging anti-solvent slowly (2-propanol – 7 volumes). The resulting mixture was aged for several hours (40-50 °C), ramp cooled (20 °C), and the solids isolated via filtration. Des-bromoarene **28** was completely purged during crystallization. Based upon these experimental findings, a single 25 kg Suzuki-Miyaura reaction was conducted in THF to afford the desired product in 98% solution assay yield containing 5% of des-bromoarene **28**[45] and 1.5% of chloropyridine **4**. Isolation as described above provided MK-8876 Form 1 in 86% yield (28.6 kg, 99.0 wt%) with just 18 ppm Pd. Interestingly, during development of the final crystallization process, a stable heterosolvate of MK-8876 (mixed mono-THF hemihydrate solvate) was encountered. A process phase map was generated to assess the relative stability of the solvated form in different water and solvent activities in order to identify a design space to manufacture Form 1 (Figure 4). Form 1 was observed to be the thermodynamically preferred phase at either elevated temperature or elevated 2-propanol composition. At room temperature and low 2-propanol composition, there is a minor regime in the phase map where the heterosolvate is favoured (Figure 4, highlighted in red). The

heterosolvate can be converted to Form1 by either raising the temperature or adding 2-propanol.

Figure 3: Solubility of MK-8876 Form 1 in THF-H_2O Mixtures at 25 °C and 50 °C.

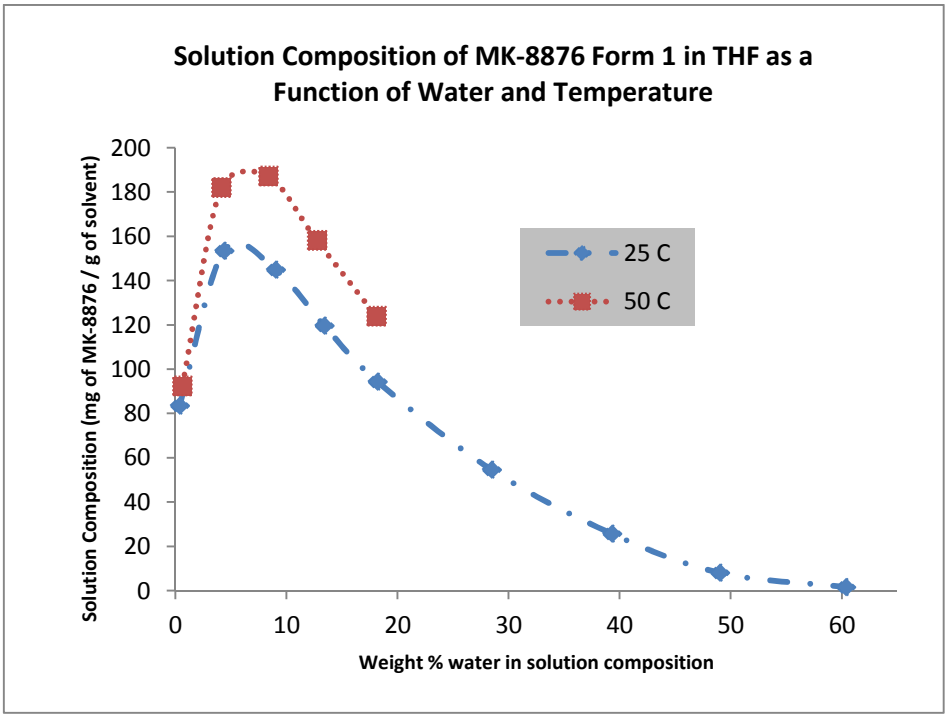
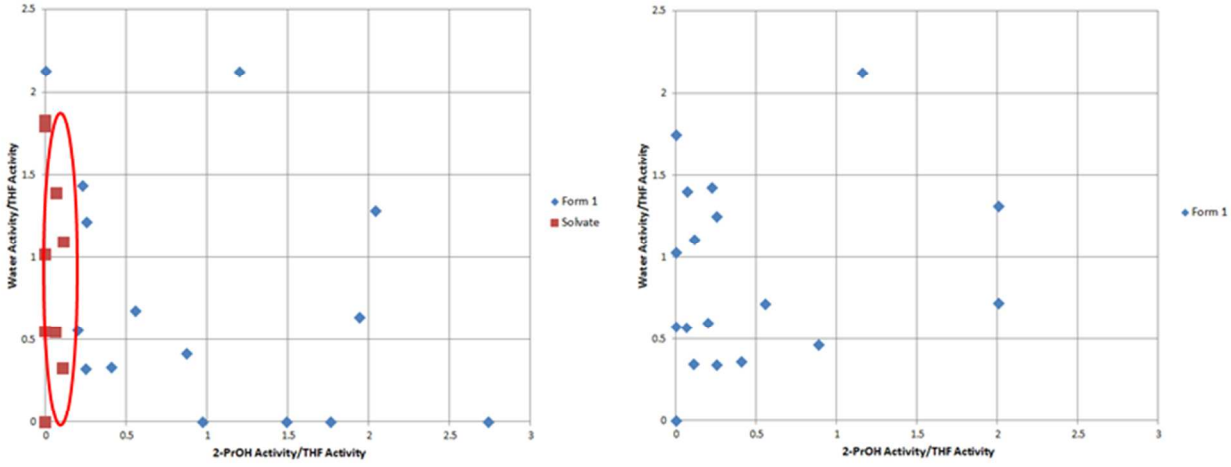


Figure 4: MK-8876 Phase Map in THF-H_2O-2-Propanol Mixtures at 20 °C (left) and 45 °C (right).



A recent related publication by these laboratories[46] focused specifically on the identification and control of potential mutagenic impurities (PMI's)/ mutagenic impurities (MI's) within the MK-8876 process. In our initial *in silico* PMI/MI screening, seven reagents/intermediates were flagged as necessary to understand and control: carbazole; arylboronic acid **27**; bis-boronic acid (**25**); EDC; MeI; $ClCH_2I$; and indoleboronic acid **7**. By conducting thorough analytical testing of stage gate intermediates along the process, full understanding and control of these impurities was obtained. Further, the experimental purge data facilitated the comparison with predicted impurity removal using the purge factor approach.[47]

Conclusion:

We have described the chemistry utilized in two GMP deliveries for the production of MK-8876 (**1**) on multi-kilogram scale. Indolopyridine **2** was prepared from 4-fluoroindole (**4**) in 5 steps and an overall yield of 57%. Development and implementation of a through-process for the formation of unstable boronic acid **7**, combined with an optimized Suzuki-Miyaura coupling, served to maximize the sequence yield. Benzofuran **19** was isolated in 33% yield via a 10-step linear procedure. Significant yield improvements were achieved by Claisen condensation base optimization and a through-process procedure yielding intermediate **15** in 65% isolated yield. HTE enabled the identification of bisboronic acid (**25**) as the optimal borylation reagent, providing a significant yield increase with concomitant reduction of undesired des-bromoarene **28**. An optimized final Suzuki-Miyaura coupling provided the desired product **1** in nearly quantitative yield. Finally, two API crystallization processes were developed to obtain the pure

desired phase while maximizing purity and yield. With these myriad improvements, the largest delivery yielded more than 28 kg of MK-8876.

Experimental:

All reactions were carried out under a nitrogen atmosphere unless otherwise stated. All solvents and reagents were purchased from commercial sources and were used without further purification. ^{1}H, ^{13}C, and ^{19}F NMR chemical shifts were reported relative to residual proton solvent peaks. All yields are corrected for purity and determined by reverse phase HPLC assay using purified standards.

Methyl 2-(5-bromo-2-hydroxyphenyl)acetate (11): Tetra-*n*-butylammonium bromide (33.7 kg, 104.6 mol, 0.35 equiv) was dissolved in MeCN (126.2 kg), and bromine (16.8 kg, 105.1 mol, 0.35 equiv) was added and aged at room temperature for 1 hour. Tetra-*n*-butylammonium tribromide (TBATB , 100.7 kg, 208.8 mol, 0.70 equiv) was added to the TBATB solution and aged at room temperature for 1 h. The resultant TBATB solution was diluted with MeOH (63.0 kg). The TBATB solution was slowly added to the solution of methyl ester **20** (49.5 kg, 298.1 mol, 1.0 equiv) in MeOH (42 kg) and MeCN (82.6 kg) at 30-35 °C. The mixture was aged at 30-35 °C for 5 h to achieve 99.8% conversion. The mixture was cooled to room temperature and 20 wt% aqueous $NaHSO_3$ (261.0 kg) was added. The product was extracted with MTBE (253 kg). The organic layer was concentrated to ~100 L and diluted with a mixture of MTBE (497.0 kg) and water (348.0 kg). The mixture was heated to 35 °C for 2 h and cooled to 20 °C. The layers were separated and the organic layer was washed successively with water (4x266 kg). The organic layer was concentrated to ~100 L and diluted with MTBE (30 kg). Bromide **11** was crystallized by

the addition of *n*-heptane (374 kg) over 2 h. The mixture was concentrated to ~425 L, aged at 30-35 °C for 9 h, then aged at 0-5 °C for 3 h. The product was isolated by filtration and dried under vacuum at 30-40 °C to give 65.8 kg (97.5 wt%, 98.0 LCAP, 261.8 mol, 87.8% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 7.31 (s, 1 H), 7.26-7.23 (m, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 3.57 (s, 3H), 3.34 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.7, 155.4, 133.9, 131.1, 124.5, 117.3, 110.1, 52.1, 35.1; *mp* 81.1 °C.

Methyl 2-(5-bromo-2-((*tert*-butyldimethylsilyl)oxy)phenyl)acetate (12): Bromide **11** (64.1 kg, 97.5 wt%, 255 mol, 1.0 equiv), imidazole (28.8 kg, 423 mol, 1.65 equiv) were dissolved in CH_2Cl_2 (389.6 kg) at room temperature. To this solution was added a solution of TBSCl (50.6 kg, 335.7 mol, 1.3 equiv) in CH_2Cl_2 (144.4 kg) over 3 hours while maintaining internal temperature of 20-25 °C. The mixture was stirred at room temperature for 5 h. The batch was cooled to 15-20 °C and water (326 kg) was added over 2 h while maintaining internal temperature of 15-25 °C. The mixture was stirred and the layers were separated. The organic layer was washed sucessively with water (328 kg, 322 kg, 334 kg). The CH_2Cl_2 was replaced with THF via distillation to give a THF solution of TBS ether **12** (384.4 kg, 24.4 wt%, 261 mol, 96.5 LCAP) in 100% assay yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22-7.21 (d, *J* = 2.4 Hz, 1H), 7.21-7.10 (dd, J = 8.8, 2.4 Hz, 1H), 6.61-6.59 (d, *J* = 8.8 Hz, 1H), 3.40 (s, 2H), 3.38 (s, 3H), 0.73(s, 9H), 0.1 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.6, 155.7, 136.7, 133.7, 130.7, 122.6, 114.9, 54.3, 37.8, 28.1, 20.5, -1.9; HRMS: *m/z* calcd for $C_{15}H_{23}BrO_3Si$: $[M+H]^+$ 359.0673; found 359.0656.

Methyl 5-bromo-2-(4-fluorophenyl)benzofuran-3-carboxylate (15): The THF solution of TBS ether **12** (384.4 kg, 24.4 wt%, 261 mol, 1.02 equiv) was charged to a vessel via a line filter. THF (720 kg) was added to this vessel and the solution was cooled to -60 °C. LHMDS (480.6 kg, 1 M

in THF, 574.4 mol, 2.2 equiv) was added over 3 h while maintaining internal temperature between -70 and -50 °C. The mixture was aged at -60 °C for 1 h and acid chloride **13** (46.2 kg, 291.3 mol, 1.14 equiv) was added while maintaining the internal temperature between -70 and -50 °C and the batch was aged at -60 °C for 1 h. The batch was warmed to -20 °C and quenched by the addition of 50 wt% HOAc in THF (161.2 kg solution) over 1 h. The batch was warmed to room temperature and aged for 1 h. Water (484 kg) was added and the layers were separated. The organic layer was concentrated to around 300 L and diluted with MTBE (1133 kg). This solution was washed successively with 0.5 M aqueous HCl (2x472 kg) and water (514 kg). The MTBE/THF was replaced by acetone via distillation to give an 890 L acetone solution. Concentrated HCl (263.1 kg) was added and the mixture was aged at room temperature for 20 h. The solution was concentrated to ~500 L and additional concentrated HCl (441.5 kg) was added. The mixture was aged at 45 °C for 2 h. The mixture was cooled to room temperature and diluted with MeOH (362 kg). The slurry was filtered and washed with MeOH (408 kg) to give crude benzofuran **15** (136.7 kg wet cake, 91.8 LCAP). The wet cake was dissolved in CH_2Cl_2 (1750 kg) and washed with water (4x500 kg). The organic layer was concentrated to ~200 L and cooled to 15-20 °C. MeOH (1600 kg) was charged and the mixture was aged at 15-20 °C for 4 h. The slurry was filtered, washed with MeOH (251 kg), and dried at 40-45 °C under vacuum to give benzofuran **15** (58.8 kg, 97.9 wt%, 165 mol, 99.5 LCAP) in 64.7% yield from TBS ether **12**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14-8.07 (m, 3H), 7.74 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.42 (ap. t, J = 8.8 Hz, 2H), 3.892 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.8 (d, $J_{C\text{-}F}$ = 247.9 Hz), 162.3, 159.7, 151.4, 131.5, 131.4, 127.8, 124.2, 123.8, 116.2, 114.8 (d, $J_{C\text{-}F}$ = 21.9 Hz), 113.0, 107.2, 51.3; ^{19}F NMR (376 MHz, DMSO-d_6): δ 108.7; *mp* 146.7 °C.

Methyl 5-bromo-2-(4-fluorophenyl)-6-nitrobenzofuran-3-carboxylate (16): Benzofuran **15** (58.7 kg, 97.9 wt%, 164.5 mol, 1.0 equiv) was dissolved in TFA (3160 kg) at 50 °C. While maintaining internal temperature between 40 and 55 °C, nitric acid (11.6 kg, 184.1 mol, 1.1 equiv) was added. The mixture was aged at 50 °C for 1 h, cooled to 5 °C, and diluted with water (648 kg) while maintaining internal temperature between 0 and 5 °C. The mixture was aged for 3 h and the batch was filtered. The wet cake was washed with water (460 kg, 465 kg, 280 kg) to give nitroarene **16** (110.3 kg, 52.8 wt%, 147.8 mol, 98.0 LCAP) in 89.8% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.38 (s, 1H), 8.15-8.11 (m, 2H), 7.49-7.44 (ap. t, J = 8.8 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3 (d, $J_{C\text{-}F}$ = 249.3 Hz), 164.1, 162.8, 151.2, 147.1, 132.8, 131.7, 127.5, 124.7, 116.2 (d, $J_{C\text{-}F}$ = 21.9 Hz), 110.5, 108.9, 108.4, 52.7; ^{19}F NMR (376 MHz, DMSO-d_6): δ 107.6; *mp* 200.9 °C.

Methyl 6-amino-5-bromo-2-(4-fluorophenyl)benzofuran-3-carboxylate (22): Nitroarene **16** (110.3 kg, 52.8 wt%, 147.8 mol, 1.0 equiv) and NH_4Cl (49.3 kg, 921.7 mol, 6.2 equiv)) were dissolved in a mixture of THF (608 kg), MeOH (371 kg), and water (172 kg) at 70 °C. Iron powder (28.4 kg, 578.4 mol, 3.9 equiv) was added portion-wise while maintaining batch internal temperature between 65 and 70 °C. The batch was aged for 2 h and cooled to 25-35 °C. Celite (154.1 kg) was added and the mixture was agitated for 1 h. The batch was filtered and washed with THF (708 kg). The filtrate was diluted with water (120 kg). The layers were separated and the organic layer was concentrated to ~600 L and cooled to 10-20 °C. Water (610 kg) was added and the batch was aged at 15 °C for 3 h. The batch was filtered, washed with water (193.2 kg), and dried at 50-60 °C under vacuum to give aniline **22** (44.5 kg, 99.0 wt%, 121.0 mol, 99.2 LCAP) in 81.9% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04-8.01 (m, 2H), 7.92 (s, 1H), 7.39-7.34 (m,

2H), 7.04 (s, 2H), 5.63 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.8, 163.4 (d, $J_{C\text{-}F}$ = 247.2 Hz), 157.4, 154.4, 145.0, 131.9 (d, $J_{C\text{-}F}$ = 8.7 Hz), 126.0 (d, $J_{C\text{-}F}$ = 2.9 Hz), 125.3, 117.7, 115.8 (d, $J_{C\text{-}F}$ = 21.9 Hz), 108.2, 106.3, 96.5, 52.2; ^{19}F NMR (376 MHz, DMSO-d_6): δ 109.9; HRMS: *m/z* calcd for $C_{16}H_{11}BrFNO_3$: $[M+H]^+$ 363.9979; found 363.9975; *mp* 183.7 °C.

Methyl 5-bromo-2-(4-fluorophenyl)-6-(methylsulfonamido)benzofuran-3-carboxylate (17): Aniline **22** (44.2 kg, 99.0 wt%, 120.1 mol, 1.0 equiv) was dissolved in CH_2Cl_2 (532 kg) and pyridine (48 kg, 607 mol, 5.1 equiv) at 30 °C. MsCl (24.0 kg, 210 mol, 1.7 equiv) was added over 2 h.The batch was aged at 30 °C for 20 h and diluted with water (333 kg). The mixture was aged at 30 °C for 3 h and then diluted with 1 N aqueuous HCl (200 kg). The batch was concentrated to ~560 L and adjusted to room temperature. The batch was filtered and washed with water (74 kg, 80 kg). The wet cake was dissolved in EtOAc (160 kg) at 45 °C and cooled to 5-10 °C. The batch was filtered, washed with EtOAc (110 kg), and dried at 50-60 °C under vacuum to give sulfonamide **17** (50.65 kg, 97.5 wt%, 111.7 mol, 98.8 LCAP) in 93.0% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1 H), 8.23 (s, 1 H), 8.12-8.08 (m, 2 H), 7.83 (s, 1 H), 7.45-7.40 (ap. t, *J* = 8.8 Hz, 2 H), 3.87 (s, 3 H), 3.11 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9 (d, $J_{C\text{-}F}$ = 247.9 Hz), 163.3, 161.1, 152.6, 133.2, 132.5 (d, $J_{C\text{-}F}$ = 9.5 Hz), 126.6, 125.9, 125.3, 116.9, 116.0 (d, $J_{C\text{-}F}$ = 21.9 Hz), 111.5, 108.1, 52.5, 40.6; ^{19}F NMR (376 MHz, DMSO-d_6): δ 108.6. HRMS: *m/z* calcd for $C_{17}H_{13}BrFNO_5S$: $[M+H]^+$ 441.9755; found 441.9750; *mp* 213.4 °C.

5-Bromo-2-(4-fluorophenyl)-6-(*N*-methylmethylsulfonamido)benzofuran-3-carboxylic acid (24): Sulfonamide **17** (50.55 kg, 97.5 wt%, 111.4 mol, 1.0 equiv) was dissolved in DMF (231 kg), and K_2CO_3 (31 kg, 224 mol, 2.0 equiv) was added. Methyl iodide (20.5 kg, 144.4 mol, 1.3 equiv)

was added in 1 h while maintaining internal temperature below 30 °C. The mixture was aged at 40 °C for 3 h and cooled to room temperature. The batch was diluted with water (402 kg) and quenched with HOAc (5.4 kg), The batch was filtered and washed with water (145 kg) to give crude **23** wet cake (63.2 kg). The wet cake and LiOH monohydrate (13.8 kg, 328.9 mol, 3.0 equiv) were dissolved in THF (776 kg) and water (98 kg).The mixture was heated to reflux and aged for 6 h. The batch was cooled to 30 °C, diluted with water (180 kg) and quenched with 6 N aqueous HCl (44 kg) while maintaining internal temperature bewteen 20 and 30 °C. The mixture was concentrated ~230 L and diluted with 2-MeTHF (480 kg). Additional 6 N HCl (36 kg) was added to adjust the pH to 3-4. The layers were separated and the organic layer was washed with 10% aqueous NaCl (194 kg). The layers were separated and the organic layer was concentrated to ~100 L. *n*-Heptane (298 kg) was added, and the slurry was aged at 30 °C for 2 h. The batch was filtered, washed with *n*-heptane (100 kg), and dried at 50-60 °C under vacuum for 20 h to give acid **24** (49.0 kg, 97.5 wt%, 108.0 mol, 99.9 LCAP) in 97.0% yield from **17**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.48 (br s, 1 H), 8.28-8.27 (d, J = 4.2 Hz, 1H), 8.12-8.11 (ap. d, J = 4.2 Hz, 3H), 7.45-7.41 (m, 2H), 3.33 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 163.9 (d, $J_{C\text{-}F}$ = 248.6 Hz), 161.3, 152.6, 137.6, 132.6 (d, $J_{C\text{-}F}$ = 8.8 Hz), 129.1, 126.1, 125.5, 120.8, 115.9 (d, $J_{C\text{-}F}$ = 21.9 Hz), 114.1, 109.2, 38.6, 33.2; ^{19}F NMR (376 MHz, DMSO-d_6): δ 108.8; HRMS: *m/z* calcd for $C_{16}H_{11}BrFNO_5S$: $[M+Na]^+$ 463.9574; found 465.9546; *mp* 133.4 °C.

Methyl 5-bromo-2-(4-fluorophenyl)-6-(*N*-methylmethylsulfonamido)benzofuran-3-carboxylate (**23)**:

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1 H), 8.20 (s, 1 H), 8.16-8.13 (m, 2H), 7.52-7.48 (t, J = 8.8 Hz, 2H), 3.96 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0 (d, $J_{C\text{-}F}$ = 248.6 Hz), 163.2, 161.8, 152.6, 137.8, 132.5 (d, $J_{C\text{-}F}$ = 8.8 Hz), 128.4, 126.0, 125.3, 121.1, 116 (d, $J_{C\text{-}F}$ = 21.9 Hz), 114.2, 108.2, 52.5, 39.3, methansulfonamide carbon overlapped with DMSO-d_6; ^{19}F NMR (376 MHz, DMSO-d_6) δ 108.4; *mp* 148.6 °C.

5-Bromo-2-(4-fluorophenyl)-*N*-methyl-6-(*N*-methylmethylsulfonamido)benzofuran-3-carboxamide (19): Acid **24** (49.0 kg, 97.5 wt%, 108.0 mol, 1.0 equiv), HOBt (22.6 kg, 167.2 mol, 1.5 equiv), and EDC-HCl (31 kg, 161.7 mol, 1.5 equiv) were dissolved in DMF (454 kg) at room temperature. Methylamine HCl salt (22.5 kg, 333.2 mol, 3.1 equiv) was added in portions. NEt_3 (51.6 kg, 510.0 mol, 4.7 equiv) was added at 30 °C over 2 h. The mixture was aged at 25-30 °C for 5 h. Water (497 kg) was added over 4 h while maintaining internal temperature of 25-30 °C. The mixture was acidified to pH 6-7 by the addition of 4 N aqueous HCl (58 kg). The slurry was filtered, and the wet cake was washed with water (4x379 kg). The wet cake was dried under vacuum at 50-60 °C for 24 h. The dry cake was redissolved in DMF (950 kg) at 25-30 °C. Water (95 kg) was added followed by the addition of seed (45 g). The mixture was aged for 4 h, and additional water (480 kg) was added over 4 h. The mixture was aged for 4 h. The batch was filtered, washed with water (360 kg), and dried under vacuum at 50-60 °C for 60 h to give benzofuran **19** (44.3 kg, 99.0 wt%, 96.3 mol, 99.8 LCAP) in 89.2% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 4.8 Hz, 1H), 8.08 (s, 1H), 8.01-7.96 (m, 3H), 7.42 (t, J = 8.8 Hz, 2H), 3.22 (s, 3H), 3.21 (s, 3H), 2.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.4 (d, $J_{C\text{-}F}$ = 247.2 Hz), 162.9, 154.9, 152.3, 137.4, 130.1 (d, $J_{C\text{-}F}$ = 8.7 Hz), 129.3, 125.7, 124.6, 120.2, 116.5 (d, $J_{C\text{-}F}$ = 21.9 Hz), 113.9, 113.4, 39.4, 26.7 methansulfonamide carbon overlapped with DMSO-d_6; ^{19}F NMR

(376 MHz, DMSO-d_6): δ 109.9. HRMS: *m/z* calcd for $C_{18}H_{16}BrFN_2O_4S$: $[M+H]^+$ 455.0071; found 455.0064; *mp* 247.7 °C.

6-Chloro-2-iodopyridin-3-ol (9): K_2CO_3 (28.3 kg, 205 mol, 2.1 equiv) was dissolved in water (116 kg) at 10 °C. Hydroxypyridine **8** (12.9 kg, 99.6 mol, 1.0 equiv) was added followed by the portion-wise addition of iodine (25.1 kg, 98.9 mol, 0.993 equiv) over 1 h. The mixture was aged at 10 °C for 2 h and quenched with 10 wt% aqueous $Na_2S_2O_3$ solution (20.8 kg). The mixture was aged at 10 °C for 1 h then warmed to 15 °C. The mixture medium was adjusted to pH 6 by the addition of 6 N aqueous HCl (57.9 kg) and then diluted with MTBE (100.5 kg). The layers were separated and the aqueous layer was washed with MTBE (100.5 kg). The combined organic layers were washed successively with water (70 kg) and 25 wt% aqueous NaCl solution (70 kg). The combined aqueous layers were extracted with MTBE (76.6 kg). The organic layers were combined and activated characoal 767 (2.2 kg) was added. The mixture was aged at 40 °C for 3 h. The slurry was filtered through celite (12 kg) and washed twice with MTBE (77 kg, 141 kg). The filtrate was azeotropically dried by MTBE distillation to achieve a water content of 0.8 wt% and an overall volume of ~70 L. The MTBE was replaced by *n*-heptane via distillation under vacuum. The slurry was aged at room temperature for 5 h. The batch was filtered, washed with *n*-heptane (19 kg), and dried under vacuum at 40-45 °C for 24 h to give iodopyridine **9** (22.8 kg, 99.4 wt%, 88.7 mol, 98.6 LCAP) in 89.1% yield. ^{1}H NMR (400 MHz DMSO-d_6) δ 11.15 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz DMSO-d_6) δ 107.9, 124.1, 1241.1, 138.3, 154.1. AHR-FAB-MS calcd for C_5H_3ClINO: $[M+H]^+$ 255.8948; found: 255.9019; *mp* 189.5 °C.

***Tert*-butyl 4-fluoro-1*H*-indole-1-carboxylate (6)**: Fluoroindole **4** (17.35 kg, 128.4 mol, 1.0 equiv), DMAP (0.559 kg, 4.58 mol, 3.6 mol%) were dissolved in CH_2Cl_2 (228 kg) at room temperature. A solution of Boc_2O (29.75 kg, 136.3 mol, 1.06 equiv) in CH_2Cl_2 (83 kg) was added over 90 minutes. The mixture was aged at room temperature for 3 h and diluted with water (38.3 kg). The layers were separated, and the organic layer was washed with water (36.4 kg, 40.2 kg). The CH_2Cl_2 in the organic layer was replaced by THF via distillation under vacuum to provide a THF solution of *N*-Boc indole **6** (80.1 kg, 34.3 wt%, 116.8 mol, 96.3 LCAP) in 91.0% yield. ^{1}H NMR (400 MHz DMSO-d_6) δ 7.90 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 3.6 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.07 (dd, J = 10.0, 8.0 Hz, 1H), 6.79 (d, J = 4.0 Hz, 1H), 1.64 (s, 9H); ^{13}C NMR (100 MHz DMSO-d_6) δ 155.5 (d, $J_{C\text{-}F}$ = 244.1 Hz), 149.3, 137.2 (d, $J_{C\text{-}F}$ = 9.5 Hz), 127.1, 125.7 (d, $J_{C\text{-}F}$ = 7.7 Hz), 119.0 (d, $J_{C\text{-}F}$ = 22.2 Hz), 111.7, 108.3 (d, $J_{C\text{-}F}$ = 18.2 Hz), 102.9, 84.3, 27.6; ^{19}F NMR (376 MHz DMSO-d_6) δ 122.0; *mp* 49.5 °C.

***Tert*-butyl 4-fluoro-2-(hydroperoxy-λ^2-boranyl)-1*H*-indole-1-carboxylate (7)**: Diisopropylamine (31.6 kg, 310.1 mol, 2.7 equiv) was dissolved in THF (173 kg) at -15 °C. To this solution was added *n*-BuLi solution (84.2 kg, 2.5 M, 312.3 mol, 2.7 equiv) over 3 h while maintaining internal temperature between -20 and -5 °C. The solution was aged at -15 °C for 2 h then cooled to -70 °C. The solution of *N*-Boc indole **6** (79.6 kg, 34.3 wt%, 116.1 mol, 1.0 equiv) was added over 3 h while maintaining the internal temperature between -75 and -65 °C. The transfer lines were rinsed with THF (10 kg) and the mixture was aged at -70 °C for 1 h. Triisopropyl borate (33.8 kg, 179.7 mol, 1.5 equiv) was added over 2 h while maintaining the internal temperature between -75 and -65 °C. The mixture was aged at -70 °C for 2 h. The mixture was quenched with a solution of acetic acid (51 kg) in THF (51 kg) while maintaining the internal temperature less

than -10 °C. The pH of the quenched mixture was 4. The temperature was adjusted to -15 °C and diluted with water (54 kg). The batch was then aged at 15 °C for 1 h. The layers were separated and the organic layer was washed twice with 10 wt% aqueous NaCl solution (119 kg, 157 kg) to give a solution of boronic acid **7** (386.6 kg, 8.4 wt%, 116.4 mol, 95.7 LCAP) in 100% assay yield. ^{1}H NMR (400 MHz DMSO-d_6) δ 8.30 (s, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.29 (m, 1H), 7.03 (dd, J = 9.6, 8.0 Hz, 1H), 6.68 (s, 1H), 1.61 (s, 9H); ^{13}C NMR (100 MHz DMSO-d_6) δ 154.8 (d, $J_{C\text{-}F}$ = 243.5 Hz), 149.6, 138.4 (d, $J_{C\text{-}F}$ = 10.2 Hz), 139.2 (br s), 124.9, 118.9 (d, $J_{C\text{-}F}$ = 21.9 Hz), 111.0, 107.6 (d, $J_{C\text{-}F}$ = 18.2 Hz), 106.6, 84.6, 27.5; ^{19}F NMR (376 MHz DMSO-d_6) δ 112.7; *mp* 79.0 °C.

6-Chloro-2-(4-fluoro-1*H*-indol-2-yl)pyridin-3-ol (10): The solution of boronic acid **7** (313.2 kg, 8.4 wt%, 94.3 mol, 1.15 equiv) was combined with iodide **9** (21 kg, 99.4 wt%, 81.7 mol, 1.0 equiv) and diluted with water (120 kg). The mixture was degassed by subsurface argon bubbling for 2 h. $KHCO_3$ (25 kg, 250 mol, 3.1 equiv), PPh_3 (2.2 kg, 8.39 mol, 10 mol%), and $Pd(OAc)_2$ (0.97 kg, 96 wt%, 4.15 mol, 5.1 mol%) were added. The mixture was degassed again by subsurface argon bubbling for 2 h. The mixture was aged at 65 °C for 24 h. The THF in the solution replaced by MTBE via vacuum distillation until residual THF was 3.3 wt%. The mixture was filtered through celite (12 kg) and the residue was washed with MTBE (2x78 kg). The layers in the combined filtrate were separated and the organic layer was washed with water (103 kg). The MTBE solution was dried by azeotropic distillation with additional MTBE to prepare a crude solution of indole **10** (~400 L). The water content of this solution was 0.8 wt%. Ecosorb C-941 (4.8 kg) was charged to this solution and the slurry was aged at 40 °C for 3 h. The slurry was filtered and washed four times with MTBE (101 kg, 80 kg, 120 kg, 120 kg). The MTBE in the

solution was replaced by CH_2Cl_2 via vacuum distillation to achieve a slurry of product in ~50 L of CH_2Cl_2 containing 1.4 wt% MTBE. The slurry was aged at room temperature for 5 h. The batch was filtered and washed with CH_2Cl_2 (41 kg), dried under vaccuum at room temperature for 24 h to give indole **10** (17.1 kg, 97.7 wt%, 63.6 mol, 99.2 LCAP) in 77.8% yield. ^{1}H NMR (400 MHz DMSO-d_6) δ 11.63 (s, 1H), 11.10 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.10 (m, 1H), 6.78 (m, 1H); ^{13}C NMR (100 MHz DMSO-d_6) δ 155.9 (d, $J_{C\text{-}F}$ = 243.4 Hz), 150.7, 139.0 (d, $J_{C\text{-}F}$ = 10.9 Hz), 138.8, 137.2, 133.8, 127.1, 123.1, 122.9 (d, $J_{C\text{-}F}$ = 7.3 Hz), 117.3 (d, $J_{C\text{-}F}$ = 21.8 Hz), 108.7 (d, $J_{C\text{-}F}$ = 3.6 Hz), 103.6 (d, $J_{C\text{-}F}$ = 18.2 Hz), 99.7; ^{19}F NMR (376 MHz DMSO-d_6) δ 122.5; AHR-FAB-MS *m/z* calcd for $C_{13}H_8ClFN_2O$: $[M+H]^+$ 263.0309; found 263.0385; *mp* 233.0°C.

2-Chloro-11-fluoro-6*H*-pyrido[2',3':5,6][1,3]oxazino[3,4-*a*]indole (2): Two batches of hydropyridine **10** (17.05 kg at 97.7 wt% and 1.1 kg at 99.5 wt%, 67.6 mol total, 1.0 equiv) and Cs_2CO_3 (45.0 kg, 138 mol, 2.0 equiv) were heated in *N*,*N*-dimethylacetamide (DMAc, 139 kg) at 110-115 °C. A solution of ICH_2Cl (14.8 kg, 83.9 mol, 1.2 equiv) in DMAc (34 kg) was added over 3 h. The transfer lines were rinsed with DMAc (9 kg). The mixture was aged at 110-115 °C for 15 h. The batch was cooled to room temperature, filtered through celite (10 kg), and washed twice with DMAc (2x33 kg). Water (143 kg) was added to the filtrate over 4 h while maintaining the internal temperature between 15 and 25 °C. The batch was aged at 20 °C for 1 h. The batch was filtered and washed successively with a mixture of DMAc and water (36 kg, 2:1 v/v) and water (36 kg) to give a wet cake of chloroindolopyridine **2** (24.5 kg, 67.3 wt%, 60.0 mol) in 88.8% yield.

Activated charcoal 767 (0.8 kg) and trimercaptotriazine trisodium salt (15.9 kg) were added to a solution of the wet cake dissolved in CH_2Cl_2 (1050 kg) at room temperature. The mixture was aged at 30 °C for 10 h. The batch was filtered through celite (6 kg) and washed twice with CH_2Cl_2 (80 kg, 81 kg). The filtrate was washed with water (173 kg). The CH_2Cl_2 in the organic layer was replaced by *n*-heptane via vacuum distillation. The slurry was aged at 0 °C for 3 h. The batch was filtered, washed with *n*-heptane (50 kg), and dried under vacuum at 50- 60 °C for 20 h to give chloroindolopyridine **2** (15.5 kg, 97.7 wt%, 55.1 mol, 99.0 LCAP) in 81.5% yield from **10**. ^{1}H NMR (400 MHz DMSO-d_6) δ 7.69 (d, J = 8.8 Hz, 1H), 7.48 (m, 2H), 7.28 (m, 1H), 7.11 (d, 1H), 6.95 (m, 1H), 6.23 (s, 2H); ^{13}C NMR (100 MHz DMSO-d_6) δ 155.8 (d, $J_{C\text{-}F}$ = 244.9 Hz), 147.5, 143.8, 137.1, 137.0, 131.0, 128.6, 124.6, 124.3 (d, $J_{C\text{-}F}$ = 7.3 Hz), 117.2 (d, $J_{C\text{-}F}$ = 22.5 Hz), 107.1, 105.5 (d, $J_{C\text{-}F}$ = 18.9 Hz), 95.2, 73.7; ^{19}F NMR (376 MHz DMSO-d_6) δ 122.1; *mp* 187.0 °C.

(2-(4-Fluorophenyl)-3-(methylcarbamoyl)-6-(*N*-methylmethylsulfonamido)benzofuran-5-yl)boronic acid (27): To a clean and dry 1000 L vessel were charged aryl bromide **19** (31.0 kg, 68.1 mol), hypodiboric acid (**25**) (9.44 kg, 102 mol, 1.5 equiv.), and tricyclohexylphosphine (95 g, 0.34 mol, 0.5 mol%). The reactor was inerted, and methanol (419.5 kg) was charged. To the resulting stirred mixture was added *N*,*N*-diisopropylethylamine (26.4 kg, 204 mol, 3.0 equiv.), followed by a methanol rinse (10 kg). The 1000 L vessel was inerted via 3 vacuum/nitrogen purge cycles, and the reaction mixture then sub-surface sparged with nitrogen for 30 min. To an adjacent clean and dry 160 L vessel was added chloro(tricyclohexylphosphine)-2-(2'-aminobiphenyl)palladium(II) catalyst **26** (201 g, 0.34 mol, 0.5 mol%), and the vessel was inerted. Methanol (61.7 kg) was then added. The 160 L vessel was inerted via 3 vacuum/nitrogen purge cycles, and the catalyst mixture then sub-surface sparged with nitrogen for 30 min. The slurry

in the 1000 L vessel was heated to 60 °C. The catalyst solution/thin slurry in the 160 L vessel was then transferred to the 1000 L vessel by nitrogen pressure. The combined reaction mixture was then heated to 63–65 °C, and the reaction mixture aged under gentle reflux for 1 h. The batch was sampled and shown to be complete (>99.5% conversion of **19**). The batch was then cooled to 20 °C, and the palladium content was determined (34.7 mg/L). A pressure filter was charged with MP-TMT resin (15.5 kg, 50 wt%) and connected to the vessel containing the batch. The solution was cycled through the resin in the pressure filter for a total of 3 h, and the solution analysed for residual palladium each hour. At the end of 3 h, the Pd level was 6.7 mg/mL. The batch was cycled back to the 1000 L reactor and then dropped to drums. The resin was then washed with fresh methanol (47.5 kg). The treated reaction solution, and wash were charged back to the reactor via a 1 μm in-line filter. The batch was then concentrated under partial vacuum, at <50 °C, to a final volume of 93 L. The batch was seeded with boronic acid **27** (50 g,0.16 wt%) and the temperature was adjusted to 50–55 °C. Water (85.0 kg) was then added over approximately 3 h. The batch was aged at 50–55 °C for 3 h, cooled to 20 °C over 6 h, and then aged for 3 h. The next day, the batch was a thick crystalline slurry. The batch was sampled, and mother liquor losses were determined to be 669 g. The batch was filtered, and the cake was washed twice with a mixture of methanol and water (7.9 kg MeOH and 20 kg water followed by 2.4 kg MeOH and 27 kg water). The resulting solid was dried *in vacuo* at 45 °C with a slight N_2 sweep. This afforded 27.54 kg of boronic acid **27** [88 % yield, 91.3 wt%; Pd = 102 ppm; P = 93 ppm]. ^{1}H NMR (400 MHz CD_3OD-d_4) δ 7.96-7.91 (m, 2H), 7.74 (s, 1H), 7.70 (s, 1H), 7.28-7.23 (m, 2H), 3.38 (s, 3H), 2.96 (s, 6H); ^{13}C NMR (100 MHz CD_3OD-d_4) δ 166.86, 165.12 (d, $J_{C\text{-}F}$ = 249.7 Hz), 155.73 (d, $J_{C\text{-}F}$ = 21.1 Hz), 143.57, 132.66 (broad s), 130.91 (d, $J_{C\text{-}F}$ = 8.6 Hz),

128.06, 127.04, 125.81, 117.01(d, $J_{C\text{-}F}$ = 22.3 Hz), 113.94, 110.12, 39.64, 36.01, 26.90; HR-ESI-MS *m/z* calc'd for $C_{18}H_{19}BFN_2O_6S^+$: $[M+H]^+$ 420.1072; found 420.1075.

2-(4-Fluorophenyl)-5-(11-fluoro-6Hpyrido[2',3':5,6][1,3]oxazino[3,4-a]indol-2-yl)-N-methyl-6-(N-methylmethanesulfonamido)-1-benzofuran-3-carboxamide (1): To a clean and dry 160 L vessel was charged water (62 kg), and then K_3PO_4 (34.2 kg, 161 mmol, 3.0 equiv.) was added portion-wise to the stirred contents of the vessel keeping the internal temperature of the vessels below 30 °C. The resulting stirred solution was cooled to 20 °C and then degassed (by running two vacuum/nitrogen cycles followed by sub-surface sparging with N_2). To a dry 400 L vessel was charged chloropyridine **2** (15.2 kg, 55.3 mol, 1.03 equiv.) and boronic acid **27** (24.7 kg, 91.3 wt%). THF (220 kg) was then added, using partial vacuum, and the resulting stirred slurry was degassed (by running a vacuum/nitrogen cycle followed by sub-surface sparging with N_2). To the resulting stirred slurry was added solid 2nd generation SPhos pre-catalyst (**29)** (97 g, 0.13 mol, 0.0025 equiv.), via the manway. Degassing of the reaction mixture was then continued by running a vacuum/nitrogen cycle followed by sub-surface sparging with N_2 for 15 min. The degassed K_3PO_4 solution, prepared in the 160 L vessel, was then added to the reaction mixture in the 400 L vessel, via a nitrogen-flushed hose using a positive pressure of N_2. The resulting reaction mixture was degassed by sub-surface sparging with N_2 for a further 15 min, and then heated to 60 °C. The batch was then aged at 60 °C for 3.5 h. The resulting reaction mixture was cooled to 20 °C. Water (12 kg) was added and the resulting biphasic mixture was allowed to settle. The lower aqueous layer was removed, and the remaining organic layer was washed with a 5% aqueous solution of sodium chloride (100 kg). The resulting organic layer was transferred to clean drums and then charged, via a 1 µm in-line cartridge filter, to a clean

and dry 1000 L vessel. THF (22 kg) was then charged to the vessel, via the in-line cartridge filter, as a rinse. The resulting stirred solution was then concentrated, by distillation under partial vacuum, to a volume of ~200 L (batch temperature was kept between 35 and 45 °C). 2-Propanol (10 kg) was then added to the batch, via the in-line cartridge filter, and the resulting solution was warmed to 45 °C (KF = 150 mg/mL). The resulting solution was seeded, by addition of MK-8876 Form 1 (120 g) in IPA (1.0 kg), and then aged at 45 °C for 6 h. The batch was then cooled to 20 °C over a period of 4 h (linear ramp) and held over for 57 h at 20 °C. The resulting slurry was heated back to 45 °C, and three portions of IPA (26 kg over 3 h, then 52 kg over 3 h, and finally 103 kg over 2.5 h) were then sequentially added in a controlled manner, via a 5 µm in-line cartridge filter while maintaining batch temperature at 45 °C. Once the additions were complete, the resulting slurry was aged at 45 °C for 1 h and then gradually cooled to 34 °C for 13 h. The resulting slurry was cooled to 28 °C and then filtered, washing the wet-cake initially with a mixture of IPA (59 kg) and THF (22 kg), and then with IPA (78 kg). The resulting filter-cake was dried under vacuum at 50 °C with a slight N_2 sweep (20 h). This afforded 28.64 kg of MK-8876 (**1**) as an off-white solid [86% yield, 99.0 wt%]. ^{1}H NMR (500 MHz DMSO-d_6) δ 8.56 (q, J = 4.7 Hz, 1H), 8.06-8.01 (m, 2H), 8.05 (s, 1H), 7.86 (s, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.46-7.40 (m, 2H), 7.29-7.22 (m, 1H), 7.11 (s, 1H), 6.94 (dd, J = 10.6, 7.9 Hz, 1H), 6.27 (s, 2H), 3.31 (s, 3H), 2.96 (s, 3H), 2.85 (d, J = 4.7 Hz, 3H); ^{13}C NMR (125.7 MHz DMSO-d_6) δ 162.86, 162.82 (d, $J_{C\text{-}F}$ = 248.5 Hz), 155.74 (d, $J_{C\text{-}F}$ = 246.1 Hz), 153.80, 152.43, 152.28, 147.20, 137.08, 137.00 (d, $J_{C\text{-}F}$ = 10.8 Hz), 136.36, 136.20, 132.37, 129.50 (d, $J_{C\text{-}F}$ = 8.6 Hz), 127.17, 125.45 (d, $J_{C\text{-}F}$ = 3.1 Hz), 125.08, 125.02, 123.70 (d, $J_{C\text{-}F}$ = 7.7 Hz), 122.28, 117.23 (d, $J_{C\text{-}F}$ = 22.4 Hz), 116.01 (d, $J_{C\text{-}F}$ = 21.9 Hz), 113.65, 111.76, 106.90 (d, $J_{C\text{-}F}$ = 3.5 Hz),

105.32 (d, $J_{C\text{-}F}$ = 18.5 Hz), 94.16, 73.57, 39.39, 37.24, 26.16; HR-ESI-MS *m/z* calc'd for $C_{32}H_{25}N_4O_5SF_2^+$: $[M+H]^+$ 615.1514; found 615.1500.

HPLC Method

Column:	Ascentis Express C_{18} 2.7 µm (fused core), 100 mm x 4.6 mm.
Detector:	U.V. @ 210 nm.
Column Temperature:	40 °C.
Flow Rate:	1.8 mL/min.
Injection Volume:	5.0 µL
Gradient:	Gradient from 90% A to 5% A over 11 min. Hold at 5% A for 2 min. Gradient back to 90% A over the next 0.1 min, and then hold at 90% A for 2.9 min.
Run Time:	16 min.
Data Collection:	Acquisition for first 13 minutes.
Mobile Phase:	Solvent A: Water with 0.1% H_3PO_4. Solvent B: Acetonitrile.

Identity	Retention Time
Boronic acid **27**:	4.24 min
Des-bromoarene **28**:	5.33 min
MK-8876 (**1**):	7.89 min
Chloropyridine starting material **2**:	8.03 min
BHT:	10.22 min

Author Information

Corresponding Authors

michael.williams22@merck.com and qinghao.chen@merck.com

Acknowledgments:

The authors wish to thank Tiebang Wang, Robert Reamer, and Thomas Novak for analytical support, Jonathan P. McMullen and Sofia Golbert for engineering input, Sarah Dolman and Cameron Cowden for helpful discussions and Rebecca Ruck for helpful editing and suggestions during the preparation of this manuscript.

References:

[1] (a) Hajarizadeh, B.; Grebely, J.; and Dore, G. J. *Nature Reviews: Gastroenterology & Hepatology* **2013**, *10*, 553-562; (b) Fellay, J.; Thompson, A. J.; Ge, D.; Gumbs, C. E.; Urban, T. J.; Shianna, K. V.; Little, L. D.; Qiu, P.; Bertelsen, A. H.; Watson, M. Nature **2010**, *464*, 405; (c) Lavanchy, D. *Liver Int.* **2009**, *29*, 74.

[2] (a) He, S.; Li, P.; Dai, X.; McComas C. C.; Huang, H.; Zhan, C.; Chang, L.; Liu, Y.; Chen, S.; Lai, Z.; Liu, H.; Yin, J.; Dan, Q.; Xiao, D.; Zorn, N.; Peng, X.; Nargund, R. P.; Palani, A. *Tet. Lett*. **2013**, *54*, 3755-3758; (b) McComas, C. C.; Liverton, N. J.; Habermann, J.; Koch, U.; Narjes, F.; Li, P.; Peng, X.; Soll, R.; Wu, H.; Palani, A.; He, S.; Dai, X.; Liu, H.; Lai, Z.; London, C.; Xiao, D.; Zorn, N.; Nargund, R. Preparation of pyridooxazinoindole derivatives and analogs for use as antiviral

agents. WO 2013033971 A1 20130314, 2013; (c) McComas, C. C.; Liverton, N. J.; Habermann, J.; Koch, U.; Narjes, F.; Li, P.; Peng, X.; Soll, R.; Wu, H. Preparation of tetracyclic heterocycle compounds for the treatment of HCV infection. WO 2013033900 A1 20130314, 2013.

[3] Changing from sodium to potassium carbonate led to an increase in solubility of the base in the reaction medium. Mathes B. M.; Filla S. A. *Tet. Lett.* **2003**, *44*, 725-728.

[4] Vazquez, E.; Davies, I. W.; Payack J. F. *J. Org. Chem.* **2002**, *67* ,7551–7552.

[5] Kuivila, H. G.; Reuwer Jr. J. F.; Mangravite, J. A. *Can. J. Chem.* **1963**, *41*, 3081–3090.

[6] For representative examples see: (a) Yang, J.; Liu, S.; Zheng, J.-F.; Zhou, J. (S.) *Eur. J. Org. Chem*. **2012**, 6248-6259. (b) Zou, Y.; Yue, G.; Xu, J.; Zhou, J. (S.) *Eur. J. Org. Chem.* **2014**, 5901-5905. (c) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412-443.

[7] Bunch, L.; Norrby, P.-O.; Frydenvang, K.; Krogsgaard-Larsen, P.; Madsen, U. *Org. Lett.*, **2001**, 433-435.

[8] Dioxane is an ICH Q3C class 2 solvent with PDE of 3.8 mg/day.

[9] While we could overcome this decomposition by charging additional boronic acid, the higher cost of indole **4** relative to pyridine **8** dictated that we should minimize the molar equivalent of boronic acid **7** in the coupling.

[10] LCAP: Area percent by HPLC analysis.

[11] Anderson K. W.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 6173-6177.

[12] At lower Pd loadings, these ligands, in conjunction with $Pd(OAc)_2$, provided higher yields of indole **10** than the analogous reactions using $Pd(OAc)_2/PPh_3$ (Table 1, entries 3 vs. 10 and 11).

[13] A single unknown impurity level increased from 0.2 to 0.6 LCAP when the water in the Cs_2CO_3 was increased from 1.1 wt% to 3.3 wt%.

[14] These conditions provided the best bromination results. Additionally, crude TBATB, prepared from tetra-*n*-butylammonium bromide (TBAB) and bromine in situ, also provided the desired product in comparable yield and purity. For examples of TBATB synthesis, see: Popov, A. I.; Buckles R. E.; Schumb, W. C.; George, J. W. Typical Polyhalogen Complex Salts In Inorganic Syntheses; Moeller. T. Ed.; John Wiley & Sons, Inc., 1957; Vol. 5, pp 176-178.

[15] The commercial availability of methyl ester **20** alleviated the methyl ester formation reproducibility issues encountered in the bromination of phenol acid **5** using TBATB in MeOH.

[16] The nitration reaction was originally conducted in chloroform at -10 °C.

[17] For processes where nitration exhibited strong exotherms, see: Gustin, J. L. *Org. Process Res. Dev.* **1998**, *2*, 27−33.

[18] (a) Whritenour, D. C.; Brenek, S. J.; Tom, N. J. *Org. Process Res. Dev.* **2001**, *5*, 539–541. (b) Grimm, J.; Liu, F.; Stefanick, S.; Sorgi, K. L.; Maryanoff, C. A. *Org. Process Res. Dev.* **2003**, *7*, 1067–1070.

[19] Increasing the molar equivalents of pyridine from 5 to 20 increased the level of bis-mesylated product from 0.9% to 10.1%.

[20] Due to the initial success and simplicity of the EDC/HOBt conditions, no other amide coupling systems were examined.

[21] By comparison, batches of acid with <1 wt% water only generated 0.25% of this impurity under otherwise identical coupling conditions.

[22] Halogen-metal exchange was attempted with *i*-PrMgCl, *i*-PrMgCl·LiCl, and *n*-Bu_3MgLi. In all cases, incomplete conversion to the desired anion was observed.

[23] Molander, G. A.; Trice, S. L. J.; Kennedy, S. M.; Dreher, S. D.; Tudge, M. T. *J. Am. Chem. Soc.* **2012**, *134*, 11667-11673 and references therein.

[24] Published conditions with KOAc led to significantly slower rates, See reference 20.

[25] 0.25 mol % was found to be optimal at a precatalyst loading of 0.5 mol % while higher levels (3 mol %) slowed reaction rates but still afforded complete conversion. Utilization of the tricyclohexylphosphine HBF_4 salt was never attempted due to timeline constraints. Tricyclohexylphosphine was readily available from commercial sources.

[26] Alternative solvents were examined (*i.e.* ethanol, *tert*-butanol, 1:1 tetrahydrofuran:dimethylacetamide, and 20% dimethylacetamide in methanol.

[27] These experiments were conducted in a Mettler-Toledo RC1 reactor.

[28] To alleviate the impact of refluxing solvent on the measurement, this experiment was conducted at 60 °C. Complete conversion was observed after 3 h.

[29] Differential Scanning Calorimetry (DSC) and Advanced Reactive System Screening Tool (ARSST) results were also carried out with no significant concerns identified.

[30] (a) Lijun Wang, L.; Green, L.; Li, Z.; Dunn, J. M.; Bu, X.; Welch, C. J.; Li, C.; Wang, T.; Tu, Q.; Bekos, E.; Richardson, D.; Eckert, J.; Cui, J. *Org. Process Res. Dev.* **2011**, *15*, 1371-1376; (b) Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev.* **2005**, *9*, 198-205; (c) See the

following website for commercial availability: http://www.biotage.com/product-page/metal-scavengers.

[31] During the bulk production, palladium content was measured on the crude reaction stream before and after treatment. The palladium content was lowered from 34.7 mg/L to 6.7 mg/L (81% reduction) after the treatment with MP-TMT resin.

[32] 0.5 mol % was charged because of robustness reasons, but the content of Pd in the residual boronic acid could be purged to acceptable levels.

[33] The batch was circulated through an oyster-style pressure filter for approximately 3 hours (palladium lowered from 34.7 mg/L to 6.7 mg/L – 81% purge)

[34] Assuming no Pd rejection through isolation, a charge of 0.5 mol % pre-catalyst affords a theoretical Pd level of 1269 ppm.

[35] The solution yield of boronic acid **27** was 91.5%.

[36] Previously, boronate ester **3** was utilized as the coupling partner with XPhos as the ligand; however, with the change in coupling partner from boronate ester **3** to boronic acid **27**, new reaction conditions were required.

[37] Several early attempts were tried to combine the borylation and Suzuki-Miyaura reactions into a one-pot reaction. However, we were not able to achieve full conversion in the Suzuki-Miyaura reaction using crude borylation reaction mixtures.

[38] A biphasic solvent mixture resulted from the acetonitrile and the 2.5 M potassium phosphate tribasic.

[39] Form 3 is metastable and readily converts to Form 1 or Form 2, and is obtained from a co-crystallization attempt with succinic acid that went awry.

[40] The thermodynamic stability of the two forms was determined through competitive slurry experiments carried out in *n*-BuOAc indicating that Form 1 is preferred at or below 85 °C. The temperatures explored were 70, 85, 90, 104 and 120 °C, and Form 2 is preferred at or greater than 120 °C The region of 85 – 120 °C was not explored since it was reasoned that the process would not go above 85 °C.

[41] Additionally, it was observed that the API had excellent solubility (> 250 mg/mL) in NMP, DMAc, and DMSO. While crystallization of Form 1 from these systems might be successful, residual solvent levels of these high boiling class II solvent could be problematic if elevated in the isolated solids.

[42] Pure MK-8876 Form 2, isolated from acetonitrile, was transformed into Form 1 in moderate yield.

[43] Treatment of the Suzuki stream with a resin was explored, and MP-TMT (20 wt% loading) provided acceptable results in aqueous THF; however, treatment was deemed unnecessary given the subsequent crystallization development.

[44] Crystallization of the desired MK-8876 Form 1 was explored first utilizing water as the anti-solvent; however, significant gumming was observed with impure reaction streams.

[45] Des-bromoarene **28** was carried as a 5.1% impurity from the previous borylation reaction.

[46] McLaughlin, M.; Dermenjian, R. K.; Jin, Y.; Klapars, A.; Reddy, M. V.; Williams, M. J. *Org. Process Res. Dev.* **2015**, *19*, 1531-1535.

[47] Teasdale, A.; Fenner, S.; Ray, A.; Ford, A.; Phillips A. *Org. Process Res. Dev.* **2010**, *14*, 943-945.