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Process Development and Scale Up of a Selective JAK3 Covalent Inhibitor PF-06651600

Yong Tao,*[,†] J. Christopher McWilliams,[†] Kristin E. Wiglesworth,[†] Kevin P. Girard,[†] Teresa M. Makowski,[†] Neal W. Sach,[‖] Jason G. Mustakis,[†] Ruchi Mehta,[‡] John I. Trujillo,[§] Xiaofeng Chen,[⊥] Tangqing Li,[⊥] Feng Shi,[⊥] Chengfu Xie,[⊥] and Qing Zhang[⊥]

[†]Chemical Research and Development, [‡]Analytical Research and Development, and [§]Worldwide Medicinal Chemistry, Pfizer Worldwide R&D, Eastern Point Road, Groton, Connecticut 06340, United States

[‖]La Jolla Laboratories, Pfizer Worldwide Research and Development, 10770 Science Center Drive, San Diego, California 92121, United States

[⊥]STA Pharmaceutical Co. Ltd., 90 Delin Road, Waigaoqiao, China (Shanghai) Free Trade Zone, Shanghai 200131, China

ABSTRACT: A scalable process for PF-06651600 (**1**) has been developed through successful enabling of the first generation syntheis. The synthesis highlights include the following: (1) replacement of costly PtO_2 with a less expensive 5% Rh/C catalyst for a pyridine hydrogenation, (2) identification of a diasteroemeric salt crystallization to isolate the enantiomerically pure cis-isomer directly from a racemic mixture of cis/trans isomers, (3) a high yielding amidation via Schotten−Baumann conditions, and (4) critical development of a reproducible crystallization procedure for a stable crystalline salt (**1·TsOH**), which is suitable for long-term storage and tablet formulation. All chromatographic purifications, including two chiral SFC chromatographic separations, were eliminated. Combined with other improvements in each step of the synthesis, the overall yield was increased from 5% to 14%. Several multikilogram batches of the API have been delivered to support clinical studies.

KEYWORDS: *JAK3, chiral piperidine, unsaturated amide, acrylamide, metastable zone*

INTRODUCTION

Pfizer has established a leading kinase research capability with multiple unique kinase inhibitors in development as potential medicines. PF-06651600 (**1**, Figure 1)[1] is a highly selective and orally bioavailable Janus Kinase 3 (JAK3) inhibitor that represents a potential immunomodulatory therapy. With the favorable efficacy, safety profile, and ADME properties, this JAK3-specific covalent inhibitor has been under clinical investigation for the treatment of alopecia areata, rheumatoid arthritis, Crohn's disease, and ulcerative colitis. Supported by positive results from a Phase 2 study, **1** was granted Breakthrough Therapy designation by the FDA on Sept. 5, 2018 for treatment of alopecia areata.[2] As the program has progressed, the API demand has increased correspondingly, from initial kilograms to >100 kg. In this manuscript, we describe our process development efforts to provide a sufficient amount of the API with improved quality to support clinical trials.

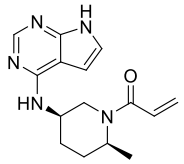

Figure 1. Structure of PF-06651600.

RESULTS AND DISCUSSION

Enabling Plan. The original synthesis of PF-06651600 (**1**) is shown in Scheme 1.[1] Beginning with the *N*-Boc protection of 6-methylpyridin-3-amine **2** to give protected pyridine **3**, the ring saturation was carried out through hydrogenation under 55 psi of H_2 at 50 °C in acetic acid with costly PtO_2, providing a 2:1 mixture of a cis/trans mixture of racemic piperidine **rac-4**. Protection of the piperidine nitrogen of mixture **4** as the Cbz carbamate gave the corresponding 2:1 mixture of cis **rac-5** and trans **rac-6**, respectively. At that stage, a chiral SFC method was capable of separating the cis and trans diastereomers, although not the enantiomers of **rac-5**, yielding purified cis-isomer **rac-5** free of the trans isomer **rac-6**. The obtained **rac-5** was treated with HCl in dichloromethane, removing the *N*-Boc group to afford the amine isolated as the crystalline HCl salt **rac-7**. An S_NAr reaction between **rac-7·HCl** and 2,4-dichloro-pyrrolopyrimidine **8** gave the intermediate **rac-9**. Subsequent hydrogenation with Pd/C catalysis removed both the *N*-Cbz group and the 2-chloro substituent to give **rac-10**. Treating **rac-10** with acryloyl chloride under Schotten−Baumann conditions,[3] followed by silica gel purification, generated a target compound as the racemate (**rac-1**), which was then subjected to another chiral SFC to separate the enantiomerically pure **1**. This route had delivered ∼60 g of **1** (∼95% achiral purity and >98% ee) in total, with the largest scale at 40 g, in an overall 5% yield to support biological assays, ADME evaluation, and early toxicology studies.

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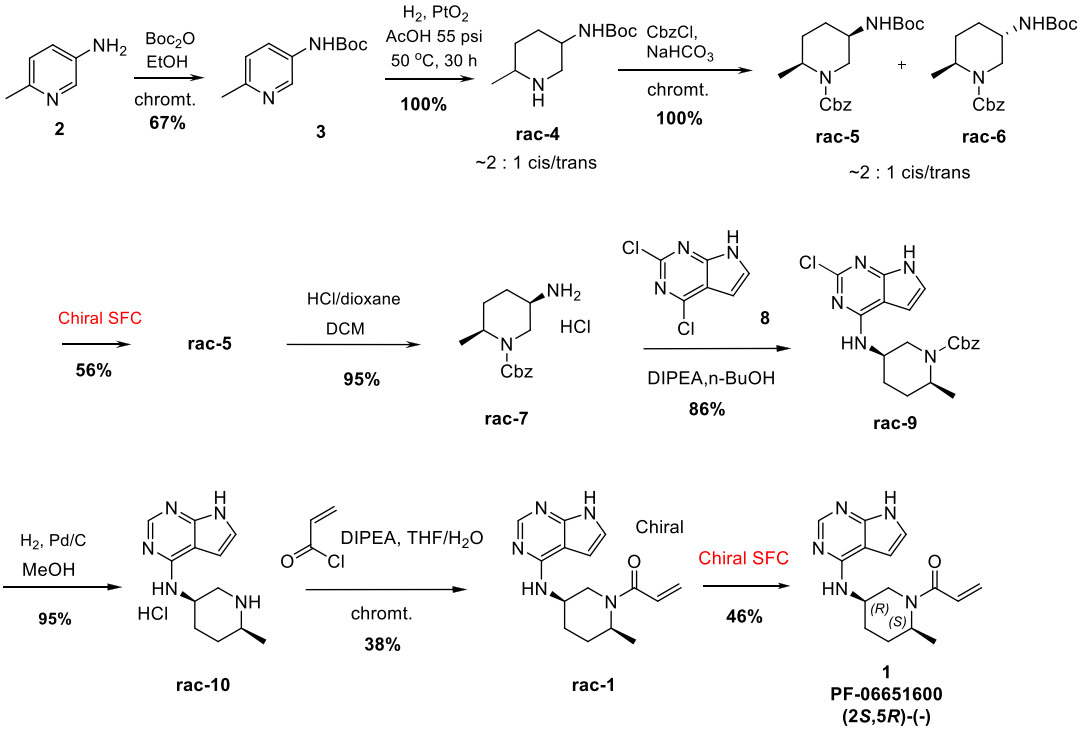
Scheme 1. First Generation Synthesis of 1



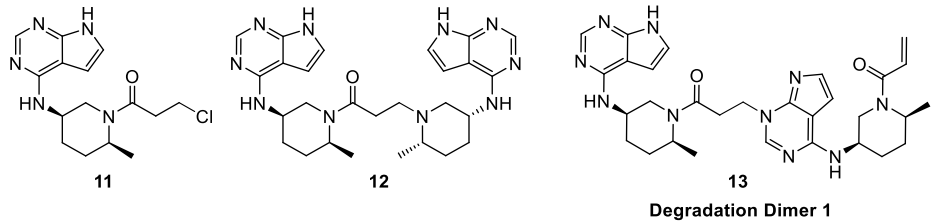
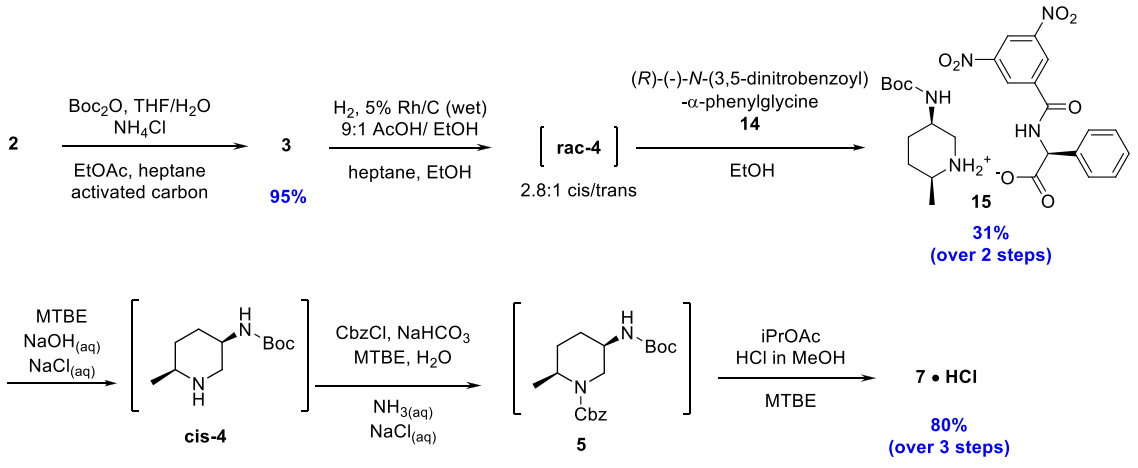


Figure 2. Major impurities identified in the API step.

Scheme 2. Enabled Synthesis to Intermediate 7



The challenges with developing an API such as **1**, with inherent Michael acceptor reactivity due to the presence of the acrylamide functionality, was made apparent early in development, wherein impurities arising from Michael addition were observed in the preparation, purification, storage, and formulation of **1**. This liability was exacerbated by the fact that **1** was isolated as an amorphous free base. Three major impurities arising from the additions were identified in the final step (Figure 2), two of which (**11** and **12**) were process related impurities that could be purged through by purification of **1**. However, impurity **13** was observed in all the stages and increased both in concentration and in the solid state over time, a particular liability for long-term development.

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Considering a balance of improving route efficiency and achieving speed to deliver bulk **1** supporting development, we focused on addressing the following issues early in development: (1) finding cost-effective hydrogenation conditions to reduce the pyridine intermediate, while ideally achieving improvement in cis/trans stereoselectivity; (2) identifying a scalable classical resolution approach to isolate enantioenriched piperidine early in the synthesis to obviate chiral chromatography; (3) establishing conditions to install the acrylamide moiety in higher yield; (4) eliminating all chromatography; and (5) key to long-term development, identifying a stable crystalline form for **1**, associated with a robust crystallization process to isolate it. The enabled route that successfully achieved all the targeted goals is shown in Schemes 2−4.

Toward Intermediate 7 through Classical Resolution (Scheme 2). The yield for the *N*-Boc protection of **2** was improved by increasing the loading of Boc anhydride from 1.3 to 1.5 equiv, elevating the reaction temperature from ambient to ∼55 °C and changing the reaction solvent from ethanol to a biphasic system of THF and a diluted aqueous ammonium chloride solution (containing 6 equiv of water and 0.03 equiv of NH_4Cl) to suppress the formation of the urea side product **16** (Figure 3). With the development of crystallization from heptane/ethyl acetate, the *N*-Boc protected **3** (>99.5% pure) was obtained in 95% isolated yield.

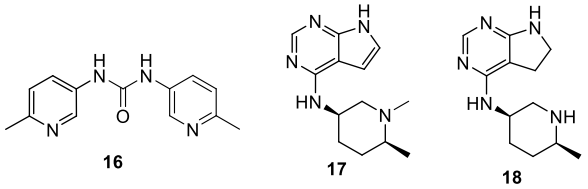

Figure 3. Impurities identified en route prior to the final step.

There are limited examples of the enantioselective reduction of pyridine to piperidine through asymmetric hydrogenation using a homogeneous Rh or Ir catalyst, and a 2,5-disubstituted pyridine poses a particularly difficult challenge for an asymmetric hydrogenation approach.[4] After an initial assessment of these conditions without a clear lead, the focus turned to replacing costly PtO_2 in the racemic hydrogenation conditions,[5] and ideally increasing the cis/trans diastereomeric ratio. A 20 wt % loading (relative to **3**) of 5% Rh/C in acetic acid at 50 °C under 50 psi hydrogen provided 100% conversion to **rac-4** as a 2:1 cis/trans mixture within 2 h. In contrast, a similar 20 wt % loading of 10% Pd/C gave <50% conversion over 24 h. Changing of the solvent from acetic acid to 9:1 ethanol/acetic acid using 5% Rh/C as the catalyst not only increased the cis/trans ratio to 2.8:1, but was also found to be more reproducible on scale. These conditions were successfully scaled up to >100 kg of **3**, with the hydrogenation completing within 10 h. After partial removal of acetic acid through azeotropic distillation with *n*-heptane, a solution of crude **rac-4** (as a 2.8:1 mixture of cis/trans diastereomers) in ∼20:1 ethanol and acetic acid was obtained as a near-colorless solution.

Crude **rac-4** was used to screen resolving agents. Subjecting **rac-4** to 91 chiral acids (1.2 equiv each relative to the total moles of **rac-4**) in hot (70 °C) ethanol (50 volumes), followed by cooling to ambient temperature, generated two diastereomeric salts with >90% ee and >95% cis/trans ratios. With (*R*)-2-(3,5-dinitrobenzamido)-2-phenylacetic acid **14**, the desired enantiomer *N*-Boc-(3*R*,6*S*)-3-amino-6-methylpiperidine (**cis-4**) crystallized as the diastereomeric salt **15**, while (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate crystallized as a salt of the undesired enantiomer *N*-Boc-(3*S*,6*R*)-3-amino-6-methylpiperidine. Optimized conditions for the resolution with **14** used less equivalents of the resolving agent and lower volumes of ethanol compared to initial screening conditions. Applying high speed stirring and seeding with pure **15** were also found to improve the stereoisomeric purity of isolated **15**. The observation that the ee of **15** decreased from 98% to 91% when the stirring time of the slurry at 70 °C was increased from 3 to 16 h suggests that there was a kinetic component of the crystallization process that resulted in higher enantioselectivity than the thermodynamic equilibrium would provide. Therefore, the following process was developed to ensure reproducibility, which was then demonstrated several times on >50 kg scale. Charging a small amount of **15** seed, followed by slow addition of a solution of **rac-4**, to a heated (70 °C) solution of **14** (0.45 equiv) in ethanol with high speed stirring resulted in a white slurry of **15**. This slurry was stirred at 70 °C for no longer than 3.5 h and was then linearly cooled to 22 °C over 5 h. The solid that was collected in a centrifuge consisted of **15** in 97.1% ee. This material was subjected to a reslurry treatment in hot ethanol, yielding **15** in 99.1% ee as a white crystalline solid in 31% overall yield from **3**.

The subsequent three-step conversion of **15** to **7·HCl** was straightforward and was carried out as a telescoped process. Neutralizing **15** with aqueous NaOH in MTBE, followed by an aqueous NaCl wash, gave a **cis-4** free base solution in MTBE. After partial concentration, the solution was treated with benzyl chloroformate in the presence of $NaHCO_3$ to form **5**. Switching the solvent from MTBE to isopropyl acetate and exposing the solution to an excess of HCl in methanol removed the *N*-Boc group to give **7·HCl**, which was crystallized by addition of MTBE. In this way, **7·HCl** was obtained as a white powder in 80% yield with both an increased cis/trans ratio (100% cis) and chiral purity (99.8% ee). The stereocenters do not epimerize during the subsequent steps in the synthesis, so the enantiomeric excess of isolated **7·HCl** establishes the minimum diastereomeric and enantiomeric purity in **1**.

Preparing Penultimate 10. Biphasic S_NAr reaction conditions using K_2CO_3 (3.2 equiv) as the base in 5:1 (v/v) water and MIBK were developed to form **9** from **7** and **8** (Scheme 3).[6] A slight excess of **7** (1.03 equiv) was used to maximize conversion of **8**, as unreacted **7** was easier to purge in

Scheme 3. Enabled Conditions to 10

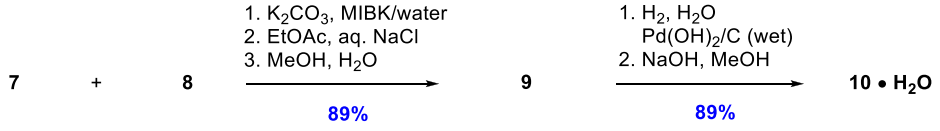

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Table 1. Two Optimal Conditions and Results To Convert 10 to 1

Conditions	Acylation Reagent (equiv)	Base (equiv), solvent (v), Temp	Intermediate (11)	Product (1)	Impurity (12)
A	Acryloyl chloride (1.10)	Hunig's base (2.5), THF/H_2O (10:5), 5 °C	1%	80%	10%
B	3-Chloropropionyl chloride (1.20)	K_3PO_4 (2.5), THF/H_2O (10:5), 5 °C	83%	9%	1%

the isolation. The reaction was completed within 22 h at 90 °C. The product **9** was extracted with EtOAc and then crystallized from the mixed solvents of methanol and water following azeotropic removal of the bulk of MIBK. Later in development, it was found that residual methanol could generate the *N*-methylated impurity **17** in the subsequent hydrogenolysis step. Control experiments suggested this impurity formed through a process of methanol dehydration to formaldehyde, followed by reductive amidation. The content of **17** increased under conditions wherein hydrogen was undersaturated, such as in the absence of purging the carbon dioxide byproduct and at high catalyst loading (supporting dehydration to formaldehyde), yet formation of **17** required hydrogen to be present in the system (supporting a mechanism involving reductive amination). To obviate the formation of **17**, a reslurry treatment of **9** in water, followed by drying, was applied to ensure the removal of any residual methanol in isolated **9**. This process consistently delivered **9** in ∼89% yield and >99.5% purity at scales ranging from 10 g to 100 kg.

The hydrogenolysis conditions from the first generation synthesis, using dry Pd/C catalyst in methanol/THF, often gave incomplete hydrogenolysis of the chloride and required resubjecting the filtered mixture to a second round of hydrogenolysis with fresh catalyst to achieve complete conversion.[1] A basic condition using wet 10% $Pd(OH)_2/C$ with the addition of NaOH in 1-butanol and water was found to provide much faster conversions, although over-reduction to form the partially saturated impurity **18** was sometimes observed. The reduction using 10% $Pd(OH)_2/C$ as the catalyst and water as the solvent at 80 °C under 50 psi of hydrogen pressure was then identified as the targeted conditions for scale up. While not as rapid as the hydrogenation with the addition of NaOH in a 1-butanol/water mixture, these conditions typically provided complete conversion within 8 h with no formation of **18**, and importantly, over-reduction to form **18** did not occur even though the reaction was extended to 24 h. However, it was found that this condition could generate impurity **17** over a prolonged reaction time if methanol was in the system, either carried over from **9** or introduced externally. Therefore, the level of residual methanol in **9** was controlled below 0.1 wt % and methanol-free conditions were applied to the hydrogenolysis. Once the reaction was complete, the aqueous solution containing product was filtered to remove the catalyst and then diluted with methanol. Neutralizing the HCl byproduct with NaOH resulted in crystallization of **10** as a monohydrate (**10·H_2O**). On 50 kg scale, **10·H_2O** was obtained in 89% yield and 99.7% purity.

End Game. The original amidation with acryloyl chloride in the presence of $NaHCO_3$ in THF/water produced **rac-1** from racemic **rac-10** in only 38% yield.[1] Our enabling efforts focused on identifying a better acylation reagent, base, and organic solvent, while retaining Schotten−Baumann conditions if possible. Readily available acryloyl chloride and 3-chloropropionyl chloride were chosen as the acylation reagents. Several rounds of reaction screening identified the optimal base, organic solvent, stoichiometry of base/acylation reagent, and temperature for either of the two acylation reagents (Table 1). From comparison of the two methods, it was deteremined that acylation of **10** with 3-chloroproprionyl chloride to form intermediate **11** minimized the concentration of **1** (by ∼90%) available to react with **10** to form impurity **12** (Conditions B). Consequently, only 1% of **12** was observed in the final reaction mixture due to partial conversion of **11** to **1**. In contrast, direct acylation with acryloyl chloride to form **1** (Conditions A) resulted in 10% of **12**, presumably because the higher concentration of **1** resulted in a more competitive rate of reaction with **10** leading to **12**. Analogously, the initial content of impurity **13**, which forms at a slower rate compared to **12**, was also reduced by ∼90% with Conditions B.

Surprisingly, treating the reaction mixture from condition B with 2 N aqueous NaOH (3.05 equiv) at 20 °C for ∼20 h cleanly converted all **11** to **1** with minimal increases in other impurities, including **13**. At the reaction end point, the purity profile of **11:12:1:13** was ∼0.2%:1.1%:93.5%:0.2%.[7] It was also confirmed that intermediate **11** is not a genotoxic impurity by AMES testing and could be treated as a normal process impurity. Thus, condition B was further developed for scale up, and its reproducibility was demonstrated on 50 kg scale. A unique workup procedure with partial purification was then developed, providing pure **1** free base. Upon completion of the elimination, KH_2PO_4 (5.3 equiv) was added to adjust the pH to ∼6.5, followed by phase separation and brine wash. Many of the impurities were purged to the aqueous phases and the purity increased to 96.2% in the organic phase. After switching solvent from THF to MEK, the mixture was further purified by stirring with silica gel (130 wt %), $MgSO_4$ (30 wt %), and Darco G-60 (15 wt %), followed by filtration. Concentrating the filtrates produced a 30 wt % solution of **1** in MEK with ∼98.5% purity in 81% yield. As **1** is not stable and its degradation to, predominantly, **13** was accelerated by heat, all distillation operations in the workup were performed at low temperature (<30 °C) and the solution of **1** in MEK was stored cold (2−10 °C) for a short period to minimize degradation.

From solutions of **1**, amorphous **1** was obtained for API solid form work. Numerous rounds of extensive screening were carried out to identify a crystalline solid form of the free base, a cocrystal or a salt. Fortunately, the monotosylate salt (**1·TsOH**) surfaced as a stable crystalline salt that not only met Pfizer's internal criteria for solid selection but also passed stability stress tests.[8] Therefore, the tosylate salt was chosen for development. Thus far, only one polymorph (Form 1) of **1·TsOH** has been found. However, it was recognized that the stability of the salt was strongly correlated to the process to prepare it, including factors such as temperature, solvent, and crystallization seeding. With the MEK solution of **1** in hand, we used this to develop a well-controlled and reproducible process, which was able to consistently provide highly crystalline **1·TsOH** with acceptable stability. The chemical stability measurements of the solutions of **1** (as the free base) and **1·TsOH** in 7.5 wt % aqueous MEK at 22, 40, and 60 °C (Figure 4) suggested that salt formation should be performed

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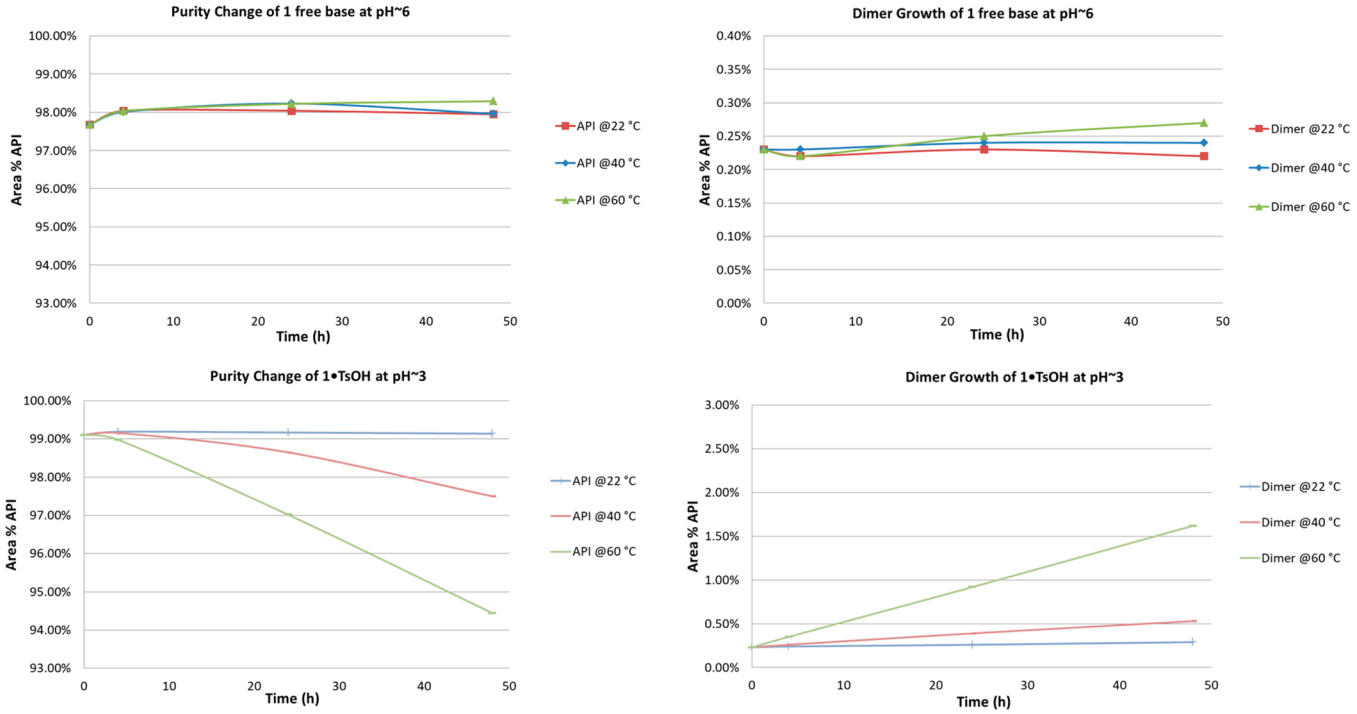

Figure 4. Chemical stability of **1** free base and **1·TsOH**.

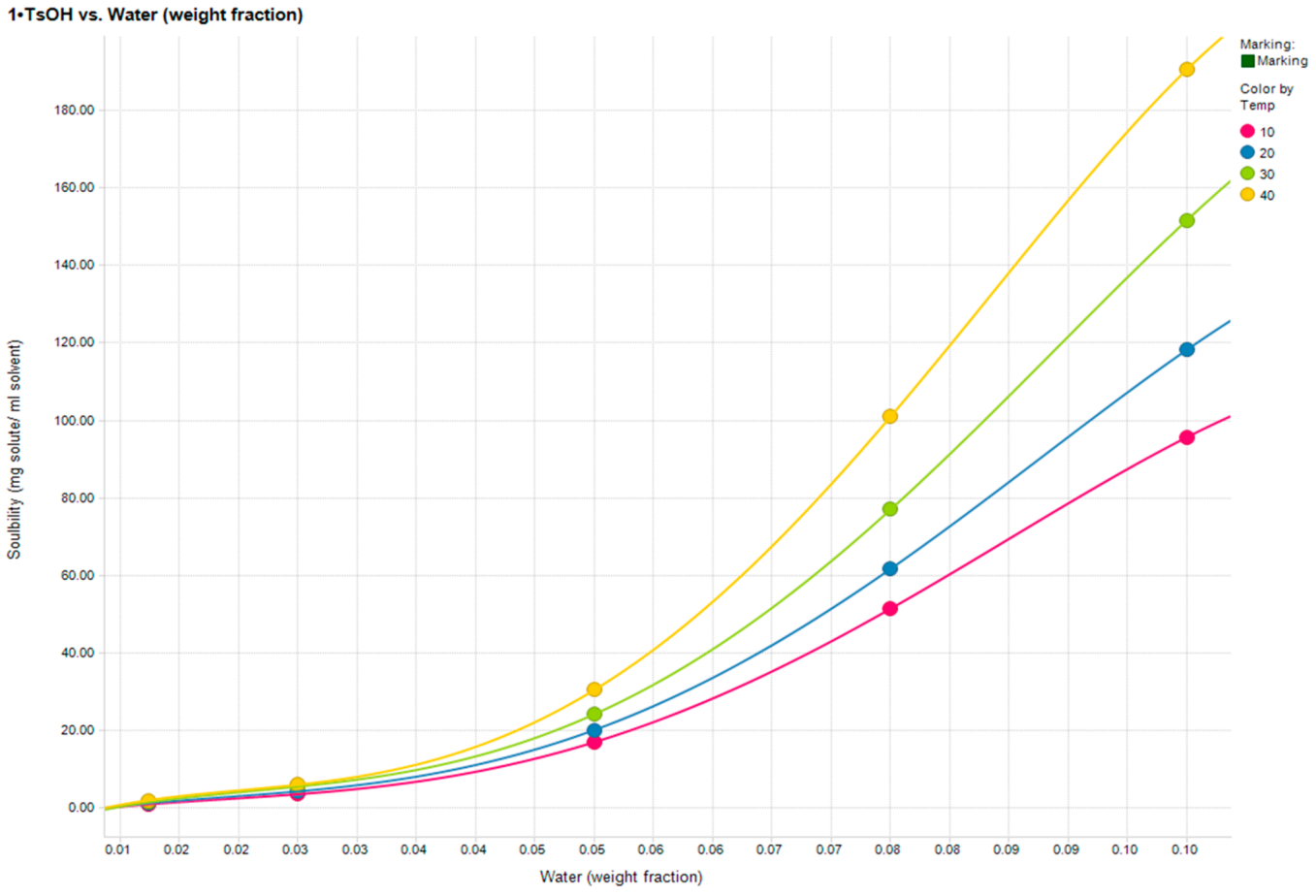

Figure 5. **1·TsOH** solubility in MEK/water vs temperature.

at ambient, while the solubility curve of **1·TsOH** in different MEK/water ratios at 10, 20, 30, and 40 °C (Figure 5) guided both starting and ending solvent compositions. Therefore, adding TsOH solution to a solution of **1** free base at 22 °C was

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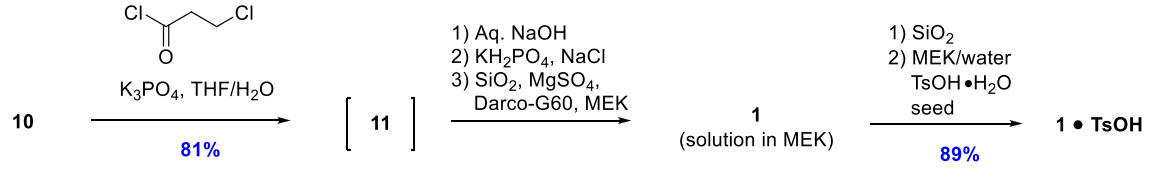
Scheme 4. Enabled End-Game



selected for the tosylate formation to minimize degradation during the course of the process. Delayed nucleation for the crystallization of **1·TsOH** was observed in all lab tests. Initial designs consisted of mixing **1** with TsOH (1.1 equiv) in 8 wt % aqueous MEK at a concentration just below the solubility limit and then slowly adding MEK to move the system into the metastable zone. It was found that the metastable zone of **1·TsOH** was very wide and nucleation onset was always delayed.[9] FBRM monitoring showed little change in crystal size or count until a supersaturation (c/c^*)[10] of 1.4−1.7 was approached without seed, where the counts increased sharply. Nucleation was expedited with large amounts of seed (2−5 wt %) added; however, crystallization was still kinetically slow and delayed at a supersaturation of 1.2−1.4. With the knowledge of this wide metastable zone width and slow kinetics of nucleation and growth, the final process was set to add the seed (4 wt %) at the supersaturation of 1.16, where the composition of water and MEK was 5.3%:94.7% (w/w).

An initial 3 kg scale up used a 30 wt % solution of **1** in MEK, which had been stored at 10 °C for 3 weeks, and the purity had decreased from 98.5% to 98.0% (the dimer **13** having increased from 0.2% to 0.5%). The salt formation started from pretreatment with SiO_2 (25 wt %) to partially purge **13** (from 0.5% to 0.2%) and other minor unidentified impurities. After adding MEK and water to this freshly pretreated solution of **1** in MEK, TsOH monohydrate (1.1 equiv) in MEK was added. At this point the solvent composition of water and MEK was 5.3%:94.7% (w/w). After adding seed (4 wt %), the mixture was stirred at high speed to form a well-dispersed, white slurry. Slow addition of MEK antisolvent brought the solvent composition to 2.3%:97.7% (w/w). Filtering the solids from this mixture produced **1·TsOH** in 89% yield and ∼99.6% purity. This enabled process of the final two steps (Scheme 4) was further demonstrated in several >50 kg batches to consistently produce highly crystalline PF-06651600 tosylate salt (**1·TsOH** Form 1) with acceptable stability for both API storage and tablet formulation.

CONCLUSION

Modifications to each step in the first generation synthetic route to prepare **1** enabled a lower cost, more efficient, robust, and scalable process. Changing the reaction solvent to a biphasic system (THF/aq. NH_4Cl) suppressed the formation of urea **16**, thereby improving the yield of **3** from **2**. Replacing costly PtO_2 catalyst with 5% Rh/C in the pyridine hydrogenation significantly reduced the cost and also improved the cis/trans stereoselectivity. Identification of classical resolution conditions to obtain enantiomerically enriched **cis-4** from a crystallization/reslurry sequence eliminated two expensive chiral SFC purifications. Telescoping the protecting group manipulations from **15** to **7·HCl** improved the process efficiency. The new conditions for the S_NAr reaction between **7·HCl** and **8** afforded higher purity **9**. The neutral hydrogenolysis conditions in water were able to obtain reproducible conversion of **9** to **10**. A new Schotten−Baumann process using 3-chloropropionyl chloride as the acylation agent, followed by basic elimination, afforded a much cleaner amidation to give **1**. A purified solution of **1** in MEK was obtained through aqueous wash and silica gel treatment. Finally, a stable crystalline **1·TsOH** salt was identified, and a corresponding robust crystallization process was developed to consistently produce **1·TsOH** on scale which was sufficiently stable for long-term storage and formulation. With these process improvements, the overall yield was increased from 5% to 14%, and several multikilogram batches of the API have been manufactured to support ongoing clinical studies.

EXPERIMENTAL SECTION

General. All commercially available materials and solvents were used as received, unless otherwise stated. The resolving agent, (*R*)-2-(3,5-dinitrobenzamido)-2-phenylacetic acid **14**, was purchased from Shanghai Chiral Chemicals, Inc. with an HPLC purity of 99.4% and 99.3% e.e.[11] All reactions were executed under a nitrogen atmosphere. Reaction temperatures were measured internally, unless indicated otherwise. Achiral UPLC analyses were carried out on a Waters Acquity H-Class UPLC system using a Waters HSS T3 column (2.1 mm × 100 mm, 1.8 μm); column temperature 45 °C; flow rate 0.65 mL/min; detection UV 210 nm; mobile phase: 0.1% MsOH in water (Solvent A), acetonitrile (Solvent B); Gradient elution (12 min): 0−8.20 min increasing solvent B from 2% to 50%, 8.20−9.00 min increasing solvent B from 50% to 100%, 9.00−9.50 min holding solvent B at 100%, 9.50−9.51 min decreasing solvent B from 100% to 2%, 9.51−12.00 min holding solvent A at 2%. Chiral SFC analyses were carried out on a Waters ACQUITY UPC^2 system using Chiralcel OJ-H column (4.6 mm × 250 mm, 5 μm); column temperature 40 °C; flow rate 4.0 mL/min; detection UV 210 nm; back pressure 150 bar; mobile phase: CO_2 (Solvent A), 75:25 acetonitrile/MeOH + 0.1% TFA + 0.1% isopropylamine (Solvent B); Gradient elution (15 min.): 0−11.0 min increasing solvent B from 5% to 30%, 11.0−11.1 min holding solvent B at 30%, 11.1−11.2 min decreasing solvent B from 30% to 5%, 11.2−12.0 min holding solvent B at 5%.

***tert*-Butyl (6-Methylpyridin-3-yl)carbamate (3).** To a 3000 L reactor were charged **2** (72.00 kg, 665.8 mol) and THF (660 kg). A solution of NH_4Cl (1.07 kg, 20 mol) in water (72 kg, 4000 mol) was added. The mixture was heated to 57 °C, and di-*tert*-butyl dicarbonate (220.0 kg, 1003 mol) was added slowly with a rinse of THF (45 kg) while maintaining the temperature between 55 and 60 °C. The mixture was stirred at 55−60 °C for 10 h. Upon reaction completion, the slurry was cooled to 20 °C and ethyl acetate (654 kg) and water (367 kg) were added. The organic phase was separated, washed by water (2 × 360 kg), and stirred with active carbon (22 kg) for 5 h. The mixture was filtered through a layer of diatomaceous earth (22 kg) with a THF rinse, and the filtrates were concentrated under vacuum at <40 °C to a residual volume of ∼370 L. *n*-

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Heptane (500 kg) was added slowly over 1 h, and the resulting slurry was cooled to 20 °C and stirred for 2 h. The solid was collected by centrifuge with an *n*-heptane wash (420 kg) and then dried at 45 °C under vacuum for 20 h to give **3** (131.15 kg, 629.7 mol) as a white powder in 94.5% yield. HPLC purity: 99.9%. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.42 (brs, 1H), 8.48 (d, J = 1.9 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 2.38 (s, 3H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ ppm 153.34, 151.56, 139.75, 134.13, 126.10, 123.09, 79.87, 28.56, 23.70. HRMS (ESI) m/z: calculated for $C_{11}H_{17}N_2O_2$ $[M + H]^+$ 209.1290; observed 209.1285.

***tert*-Butyl (6-Methylpiperidin-3-yl)carbamate (rac-4).** To a 3000 L reactor were charged **3** (137.0 kg, 667.8 mol), ethanol (988 kg), and acetic acid (139 kg). The reactor was purged with nitrogen three times, and 5 wt % Rhodium on carbon (wet, 27.4 kg, 20 wt % loading relative to **3**) was added. The reactor was purged with nitrogen three times and then with hydrogen three times. The hydrogen pressure was adjusted to 0.34−0.38 MPa, and the reactor temperature was adjusted to 47 °C. The mixture was stirred at 45−60 °C under hydrogen pressure at 0.34−0.38 MPa for 10 h. Upon reaction completion, the reactor was cooled to 20 °C and flushed with nitrogen. The mixture was filtered through a layer of diatomaceous earth (20 kg) with an ethanol rinse (1320 kg), and the filtrates were concentrated under vacuum at <50 °C to a residual volume of ∼350 L. *n*-Heptane (571 kg) was added, and the mixture was concentrated under vacuum at <50 °C to a residual volume of ∼350 L. This operation was repeated twice until the residual acetic acid was <8.0%. Ethanol (672 kg) was added, and the mixture was concentrated under vacuum at <50 °C to a residual volume of ∼350 L. This operation was repeated twice until the residual *n*-heptane was <0.2% and water was <0.2%. Ethanol (889 kg) was added, and the solution (1254 kg) was transferred to drums for use in the subsequent classical resolution step. Achiral HPLC assay indicated that the solution contained 10.8 wt % of the total reduced product (**rac-4**) in 96% mass recovery, and chiral SFC showed that the solution contained 36.3% of the desired stereoisomer **cis-4**.

tert*-Butyl ((3*R*,6*S*)-6-Methylpiperidin-3-yl)carbamate (*R*)-2-(3,5-dinitrobenzamido)-2-phenylacetic Acid Salt (15).** To a 2000 L reactor (R1) was charged **rac-4** as a 10.8 wt % solution in ethanol (620.5 kg, ∼312.7 mol. of all 4 isomers). The solution was concentrated under vacuum at <45 °C to a residual volume of ∼210 L and then cooled to 20 °C. To a 3000 L reactor (R2) was charged (*R*)-2-(3,5-dinitrobenzamido)-2-phenylacetic acid **14** (Caution! Differential Scanning Calorimetry analysis of 14 indicated a very high thermal potential, with an exothermic energy release of up to ∼1900 J/g at onset temperatures ranging from ∼175 to 225 °C. The measured energy release and onset temperature were dependent upon the lot of 14 tested. BAM Fallhammer testing did not show signs of explosivity due to impact***)[12] (47.0 kg, 136.1 mol) and ethanol (1125 kg). With high speed agitation, reactor R2 was heated to 70 °C, stirred at 68−70 °C for ∼2 h to dissolve all solid **14**, and then seeded with crystalline **15** (11 g). The solution containing **4** in reactor R1 was slowly transferred to reactor R2 over 30 min with an ethanol rinse (160 kg). Reactor R2 was stirred at ∼74 °C for 3 h and then cooled to 22 °C with a linear cooling rate over a period of 5 h and stirred for 16 h. The solid was collected by centrifuge with an ethanol wash (2 × 200 kg). The wet cake (with 97.1% ee) was charged back to reactor R2. The slurry was heated to 74 °C, and the mixture was stirred for 17 h. The mixture was then cooled to 22 °C with a linear cooling rate over a period of 5 h and stirred for 4 h. The solid was collected by centrifuge with an ethanol wash (2 × 200 kg) and dried at 35 °C under vacuum for 25 h to give **15** (56.05 kg, 100.2 mol) as a white powder in 30.7% yield over two steps. Chiral HPLC purity: 99.1%. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 9.46 (d, J = 7.0 Hz, 1H), 9.07 (d, J = 2.2 Hz, 2H), 8.96 (t, J = 2.2 Hz, 1H), 7.49 (d, J = 7.3 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.23 (t, J = 7.3, 1H), 7.11 (m, 1H), 5.31 (d, J = 7.0 Hz, 1H), 3.66 (m, 1H), 2.98 (m, 3H), 1.63 (m, 2H), 1.45 (m, 2H), 1.40 (s, 9H), 1.11 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ ppm 172.71, 161.71, 155.42, 148.51, 141.27, 137.70, 128.29, 128.25, 128.02, 127.05, 121.12, 78.49, 59.74, 50.66, 46.29, 43.34, 28.66, 26.88, 26.11, 18.60.

Benzyl (2*S*,5*R*)-5-Amino-2-methylpiperidine-1-carboxylate Hydrochloride (7·HCl) - Telescoped Process. To a 2000 L reactor was charged **15** (70.0 kg, 125 mol) and MTBE (500 kg). The mixture was cooled to 12 °C, and 6.9 wt % aqueous NaOH solution (378 kg, 652 mol) was added slowly while maintaining the temperature between 10−25 °C. The mixture was stirred at 18 °C for 1 h. The organic phase was separated and washed with 3.8 wt % aqueous NaOH solution (2 × 221 kg) and then 25 wt % aqueous NaCl solution (2 × 220 kg). The organic layer (containing the free base **cis-4**) was concentrated under vacuum at <40 °C to a residual volume of ∼300 L and then cooled to 20 °C. $NaHCO_3$ (53 kg, 632 mol) and water (200 kg) were added, and the mixture was cooled to 7 °C. Benzyl chloroformate (32.30 kg, 189.3 mol) was added slowly while maintaining the temperature between 5 and 20 °C. The mixture was stirred at 17 °C for 20 h. Upon reaction completion, the mixture was cooled to 12 °C, 25 wt % aqueous ammonium hydroxide solution (79 kg, 1160 mol) was added slowly while maintaining the temperature between 10−20 °C, and the mixture was stirred at 15 °C for 1 h. The organic phase was separated and washed with 25 wt % aqueous NaCl solution (3 × 90 kg). The organic layer (containing **5**) was concentrated under vacuum at <45 °C to a residual volume of ∼150 L. Isopropyl acetate (310 kg) was added, and the mixture was concentrated under vacuum at <45 °C to a residual volume of ∼150 L. This operation was repeated twice to meet the criteria of water <0.1% (by KF). Isopropyl acetate (130 kg) was then added, and the mixture was cooled to −3 °C. 4−5 N HCl in methanol (181 kg, ∼ 730 mol) was added slowly while maintaining the temperature between −5 to 5 °C, and the mixture was stirred at 3 °C for 12 h. Upon reaction completion, the mixture was cooled to −3 °C, and MTBE (940 kg) was added slowly while maintaining the temperature between −5 and 5 °C. The resulting slurry was stirred at 3 °C for 3 h. The solid was collected by centrifuge with MTBE washes (4 × 70 kg) and then dried at 45 °C under vacuum for 20 h to give **7·HCl** (28.60 kg, 100.4 mol) as a white powder in 80.3% yield. Achiral HPLC purity: 100%. Chiral SFC purity: 99.8% ee. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 8.36 (brs, 3H), 7.37 (m, 5H), 5.09 (s, 2H), 4.31 (m, 1H), 4.16 (d, J = 8.2 Hz, 1H), 3.00 (m, 2H), 1.82 (m, 2H), 1.59 (m, 2H), 1.11 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ ppm 154.71, 137.24, 128.92, 128.34, 128.00, 66.89, 47.20, 45.66, 40.68, 28.16, 23.02, 15.67. HRMS (ESI) m/z: calculated for $C_{14}H_{20}N_2O_2$ $[M + H]^+$ 249.1603; observed 249.1598.

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Benzyl (2*S*,5*R*)-5-((2-Chloro-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-yl)amino)-2-methylpiperidine-1-carboxylate (9). To a 2000 L reactor were charged **7·HCl** (88.6 kg, 311.12 mol), **8** (56.0 kg, 298 mol), K_2CO_3 (133.0 kg, 962.3 mol), water (570 kg), and MIBK (101 kg). The mixture was heated to 90 °C and stirred at this temperature for 22 h. Upon reaction completion, the mixture was cooled to 56 °C, and ethyl acetate (531 kg) was added. After cooling the mixture to 22 °C, the organic phase was separated, washed with water (570 kg), and concentrated under vacuum at <40 °C to a residual volume of ∼220 L. Methanol (360 kg) was added slowly over a period of 1 h, and the mixture concentrated under vacuum at <50 °C to a residual volume of ∼220 L. This operation was repeated three times until residual MIBK reached <5 wt %. Methanol (270 kg) was added, followed by seeding with **9** (120 g). The mixture was stirred at 22 °C for >4 h, and water (286 kg) was added slowly over 4 h. The slurry was stirred for 10 h, and the solid was then collected by centrifuge. The wet cake (165.6 kg) was charged back to a clean reactor, and water (896 kg) was added. The slurry was heated to 55 °C and stirred at this temperature for 7 h, and then cooled to 22 °C and stirred at this temperature for 2 h. The solid was collected by centrifuge with water wash (3 × 170 kg) and dried at 55 °C under vacuum for 20 h to give **9** (106.62 kg, 266.6 mol) as a white powder in 89.5% yield. Achiral HPLC purity: 99.7%. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 11.71 (brs, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.38 (m, 5H), 7.10 (s, 1H), 6.57 (d, J = 2.7 Hz, 1H), 5.11 (m, 2H), 4.39 (m, 1H), 4.17 (m, 1H), 4.01 (m, 1H), 3.36 (s, 2H), 2.77 (m, 1H), 1.73−1.81 (m, 4H), 1.16 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ ppm 156.65, 154.74, 153.04, 151.31, 137.43, 128.89, 128.27, 127.96, 122.13, 101.65, 99.51, 66.75, 49.10, 47.32, 45.64, 42.98, 29.05, 25.08. HRMS (ESI) m/z: calculated for $C_{20}H_{22}ClN_5O_2$ $[M + H]^+$ 400.1540; observed 400.1535.

***N*-((3*R*,6*S*)-6-Methylpiperidin-3-yl)-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-amine Monohydrate (10·H_2O).** To a 1600 L reactor was charged water (570 kg). The reactor was purged with nitrogen three times. 10% $Pd(OH)_2/C$ (wet, 3.2 kg) and **9** (53.34 kg, 133.2 mol) were added with water rinses (2 × 55 kg). The reactor was purged with nitrogen three times and then with hydrogen three times. The hydrogen pressure was adjusted to 0.34−0.38 MPa, and the reactor temperature was adjusted to 77 °C. The mixture was stirred at 75−80 °C under a hydrogen pressure of 0.34−0.38 MPa for 10 h. Upon reaction completion, the reactor was cooled to 20 °C and purged with nitrogen. The mixture was filtered through a layer of diatomaceous earth (8 kg) with a water rinse (460 kg), and the filtrates were transferred to a 3000 L reactor. Methanol (260 kg) was added, followed by slow addition of 50 wt % aqueous sodium hydroxide (12.0 kg, 150 mol) while maintaining the temperature between 15 and 25 °C. The slurry was heated to 55 °C and stirred for 2 h, then cooled to 22 °C, and stirred for 10 h. The solid was collected by centrifuge with a 10:1 water/methanol wash (3 × 110 kg) and then dried at 55 °C under vacuum for 20 h to give **10·H_2O** (30.90 kg, 266.6 mol) as a white powder in 89.1% yield. Achiral HPLC purity: 99.7%. Chiral SFC purity: 99.8% ee. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 11.48 (brs, 1H), 8.08 (s, 1H), 7.07 (s, 1H), 6.85 (d, J = 7.3 Hz, 1H), 6.64 (s, 1H), 4.16 (m, 1H), 3.35 (brs, 2H), 2.96 (d, J = 12.7 Hz, 1H), 2.82 (d, J = 12.7 Hz, 1H), 2.67 (m, 1H), 2.04 (brs, 1H), 1.92 (m, 1H), 1.63 (m, 1H), 1.44 (m, 1H), 1.33 (m, 1H), 1.03 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ ppm 155.95, 151.87, 150.74, 121.20, 102.97, 99.20, 51.27, 49.94, 44.78, 29.97, 28.69, 22.35. HRMS (ESI) m/z: calculated for $C_{12}H_{17}N_5$ $[M + H]^+$ 232.1562; observed 232.1558.

1-((2*S*,5*R*)-5-((7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)-amino)-2-methylpiperidin-1-yl)prop-2-en-1-one (1). To a 100 L reactor were charged water (18.0 L), **10·H_2O** (3.60 kg, 14.4 mol), and THF (36.0 L). The mixture was heated to 53 °C and stirred for 15 min to dissolve all the solids. The solution was then cooled to 18 °C, and K_3PO_4 (6.38 kg, 30.1 mol) was added. The mixture was stirred at 18 °C for 10 min to dissolve all the solids and then cooled to 10 °C. 3-Chloropropionyl chloride (2.20 kg, 17.3 mol) was added while maintaining the temperature <20 °C. The mixture was then stirred at 20 °C for 2 h. Upon reaction completion, 2 N aqueous NaOH solution (23.50 kg, 43.76 mol) was added while maintaining the temperature <25 °C. The mixture was stirred at 22 °C for >12 h until the elimination reaction was complete (**11** < 0.2%). KH_2PO_4 (10.32 kg, 75.8 mol) was added, and the mixture was stirred at 20 °C for 10 min. The organic phase was separated and then washed with 23.5 wt % aqueous NaCl solution (2 × 8.5 kg). The isolated organic phase was concentrated under vacuum at <30 °C to a residual volume of ∼10 L, whereupon MEK (39.6 L) was added. This operation was repeated once or twice until residual THF was <1% and water was <2%. $MgSO_4$ (0.96 kg), Silica gel (4.90 kg), and Darco G-60 (0.48 kg) were added to the MEK solution, and the mixture was stirred at 20 °C for 1 h and then filtered through a layer of Diatomaceous Earth with a MEK rinse (76 L). The combined filtrates were concentrated under vacuum at <30 °C to a residual volume of ∼8 L. The concentration of the residual solution was measured by qNMR, and the solution was transferred to a container with a rinse using the calculated amount of MEK to adjust the final concentration to 30 wt %. Thus, a 30 wt % solution of **1** in MEK (11.09 kg, 11.66 mol of **1**) with 98.7% purity was obtained in 81% yield, which was stored in a cold room (2−8 °C) for the next step.

1-((2*S*,5*R*)-5-((7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)-amino)-2-methylpiperidin-1-yl)prop-2-en-1-one *p*-Toluenesulfonate (1·TsOH). To a 20 L reactor were charged a 30 wt % solution of **1** in MEK (9.80 kg, 10.30 mol of **1**) and silica gel (0.74 kg). The mixture was stirred at 22 °C for 15 min and filtered through a 0.45 μm Teflon cartridge filter with a MEK rinse (7.89 kg, 9.8 L), collecting in a 100 L reactor. Water (1.27 L) was added, followed by a solution of *p*-toluenesulfonic acid monohydrate (2.18 kg, 11.3 mol) in MEK (4.75 kg, 5.9 L) with a MEK rinse (3.14 kg, 3.9 L), followed by the addition of **1·TsOH** seed (188 g, 0.41 mol). The mixture was stirred at 22 °C for 4 h to form a slurry, and MEK (31.56 kg, 39.2 L) was added slowly over a period of 3 h. The slurry was stirred at 22 °C for an additional 2 h and then filtered. The cake was washed with MEK (4.02 kg, 5 L) and then dried at 50 °C under vacuum for 10 h to give **1·TsOH** (4.41 kg, 9.64 mol) as a white powder in 89.6% yield (accounting for the amount of seed charged). Achiral HPLC purity: 99.6% with 0.22% of dimer **15**. Chiral SFC purity: >99.7%. Mp 199 °C. Rotomers observed for NMR spectroscopies. ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 12.68 (brs, 1H), 9.22 (brs, 1H), 8.40 (s, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.45 (m, 1H), 7.12 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 1.2 Hz, 1H), 6.84 (m, 1H), 6.13 (m, 1H), 5.70 (m, 1H), 4.81 (m, 0.5H), 4.54 (m, 0.5H), 4.41 (m, 0.5H), 4.12 (m, 0.5H), 3.99 (m, 1H), 3.15 (m, 0.5H), 2.82 (m,

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0.5H), 2.29 (s, 3H), 1.91−1.72 (m, 4H), 1.24−1.17 (m, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ ppm 165.52, 165.13, 150.50, 145.64, 143.06, 138.48, 129.51, 129.24, 128.67, 127.99, 127.73, 125.97, 125.02, 102.30, 49.53, 48.92, 47.27, 43.83, 42.96, 29.37, 28.41, 25.22, 21.28, 16.97, 15.51. HRMS (ESI) *m*/*z*: calculated for $C_{15}H_{20}N_5O$ $[M + H]^+$ 286.1668; observed 286.1692.

AUTHOR INFORMATION

Corresponding Author

*E-mail: y_tao@yahoo.com.

ORCID

Yong Tao: 0000-0001-9773-7807

J. Christopher McWilliams: 0000-0002-4764-735X

Notes

The authors declare no competing financial interest.

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(10) Supersaturations listed are relative supersaturations: $S = c/c^*$, where c = the solution concentration and c^* is the measured solubility at the solvent composition and temperature of the process.

(11) A SciFinder search of (*R*)-2-(3,5-dinitrobenzamido)-2-phenylacetic acid (**14**) lists >70 vendors providing quantities ranging in scale of up to 100 kg, with costs as low as $7.6/g. Accessed July 5, 2019.

(12) While internal testing indicating no signs of explosivity based upon dropping 40 L of powder using a 10 kg weight from 60 cm (60 Joules), end-users of **14** are strongly advised to conduct their own safety testing and analysis, including DSC and explosivity testing.

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