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Multi-Kilo Delivery of AMG 925 Featuring a Buchwald–Hartwig Amination and Processing with Insoluble Synthetic Intermediates

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Supporting Information

ABSTRACT: The development of a synthetic route to manufacture the drug candidate AMG 925 on kilogram scale is reported herein. The hydrochloride salt of AMG 925 was prepared in 23% overall yield over eight steps from commercially available raw materials, and more than 8 kg of the target molecule were delivered. The synthetic route features a Buchwald–Hartwig amination using BrettPhos as ligand and conducted to afford 12 kg of product in a single batch. In addition, this work highlights the challenges associated with the use of poorly soluble process intermediates in the manufacture of active pharmaceutical ingredients. Creative solutions had to be devised to conduct seemingly routine activities such as salt removal, pH adjustment, and heavy metal scavenging due to the low solubility of the process intermediates. Finally, a slurry-to-slurry amidation protocol was optimized to allow for successful scale-up.

INTRODUCTION

Clinical candidates and commercial drugs having planar, heteroaromatic polycyclic structures are ubiquitous in the pharmaceutical industry. One of the challenges involved in the development of robust processes to manufacture these materials is the low solubility of the synthetic intermediates in most common solvents. In these cases, creative solutions must be developed to address routine activities such as aqueous extractions, pH adjustments, and minimization of entrainment of starting material in the product. In the context of a recent oncology program targeting dual inhibition of FLT3[1] and CDK4,[2] we developed an eight-step manufacturing process to prepare a clinical candidate, AMG 925,[3] as its hydrochloric acid salt. The last three synthetic intermediates (Scheme 1) and the drug substance AMG 925 hydrochloride (AMG 925 HCl) have limited solubility in preferred process solvents. Examination of the manufacturing route reveals the specific challenges to be encountered considering the low solubility of the intermediates. For example, elimination of residual palladium from compound **3** following a Buchwald–Hartwig amination[4] and formation of the free-base of compound **4** necessitate methods to keep these molecules in solution in order to be successful. The amide formation step to prepare AMG 925 is a slurry-to-slurry transformation and effective process control is needed to avoid starting material entrainment in the product. More than 5 kg of AMG 925 hydrochloride were necessary to support GLP toxicology studies and initiate clinical activities. Consequently, the development of a robust process to deliver the first-in-human drug substance batch for this program was undertaken.

RESULTS

i. Manufacture of Aminopyrimidine 1. The preparation of eight kilograms of intermediate **1** was necessary to execute the planned manufacturing campaign as per the reaction sequence illustrated in Scheme 1. The route utilized to prepare **1** is shown in Scheme 2. None of the intermediates involved in the synthetic sequence to manufacture **1** had solubility liabilities that hampered processing. The procured raw material **5** contained 5 LCAP[5] of dimer impurity **6**. Fortunately, purification of **5** was made possible using two aqueous lactic acid washes, thus enabling the isolation of the starting material (**5**) with only 0.9 LCAP of residual **6**.

The manufacture of iodide **8** from **5** was carried out successfully to afford 39 kg of product. Regioselective deprotonation of 3-fluoropyridine (**9**) at the four position was achieved using lithium tri-*n*-butylmagnesiate[6] and the lithium tripyridylmagnesiate thus generated was treated with zinc bromide to afford the desired 4-pyridylzinc bromide reagent (**10**). This material was utilized in situ in a Pd-catalyzed Negishi cross-coupling with iodide **8**.[7] The formation of regioisomer **12** was observed and represented ∼10% of the mass balance. This side product was completely rejected during the purification by crystallization of the target fluoropyridine **11**. Overall, compound **11** was isolated in 54% corrected yield[8] from **8** (20 kg of **11**). Upon treatment with potassium *t*-butoxide, **11** underwent cyclization to afford aminopyrimidine **1**, and this material was isolated in high yield (85%) and purity (99 LCAP, 99 wt %) after an activated charcoal treatment followed by crystallization from dichloromethane and heptane.

ii. Solubility of Process Intermediates Used in the Manufacture of AMG 925 HCl. In order to allow for processing with high material throughput, it is generally preferable to utilize solvents in which the synthetic intermediates have a solubility of a 100 mg/mL or greater.[9] To highlight the challenges driven by the poor solubility of the intermediates shown in Scheme 1, solubility data in process solvents typically used for API manufacture are presented in

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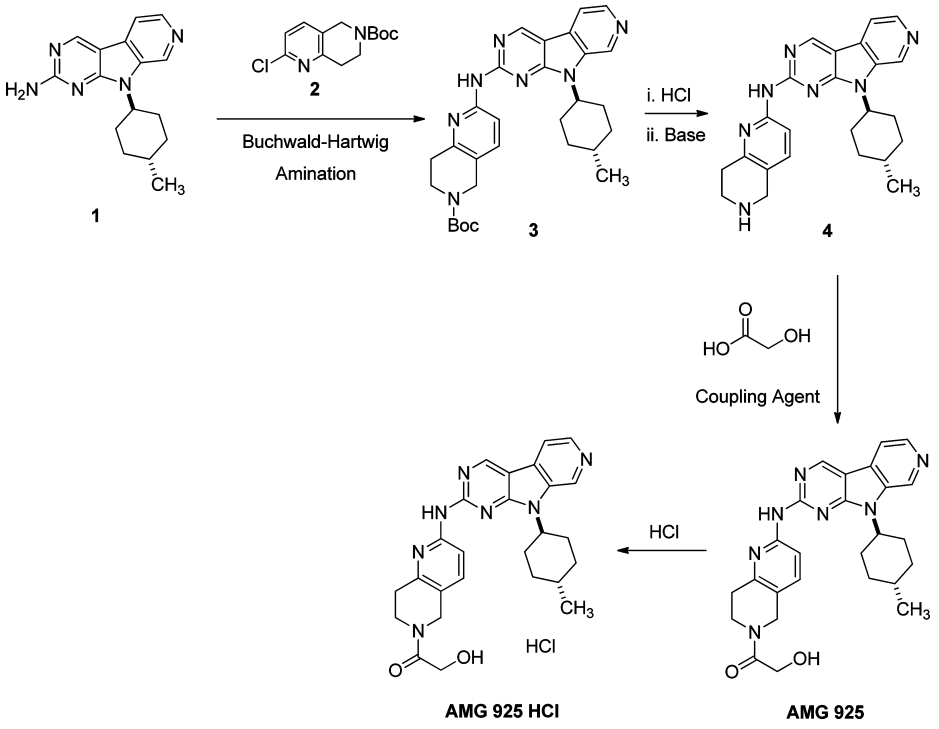
Scheme 1. Manufacturing route to AMG 925 hydrochloride



Scheme 2. Route to manufacture aminopyrimidine 1

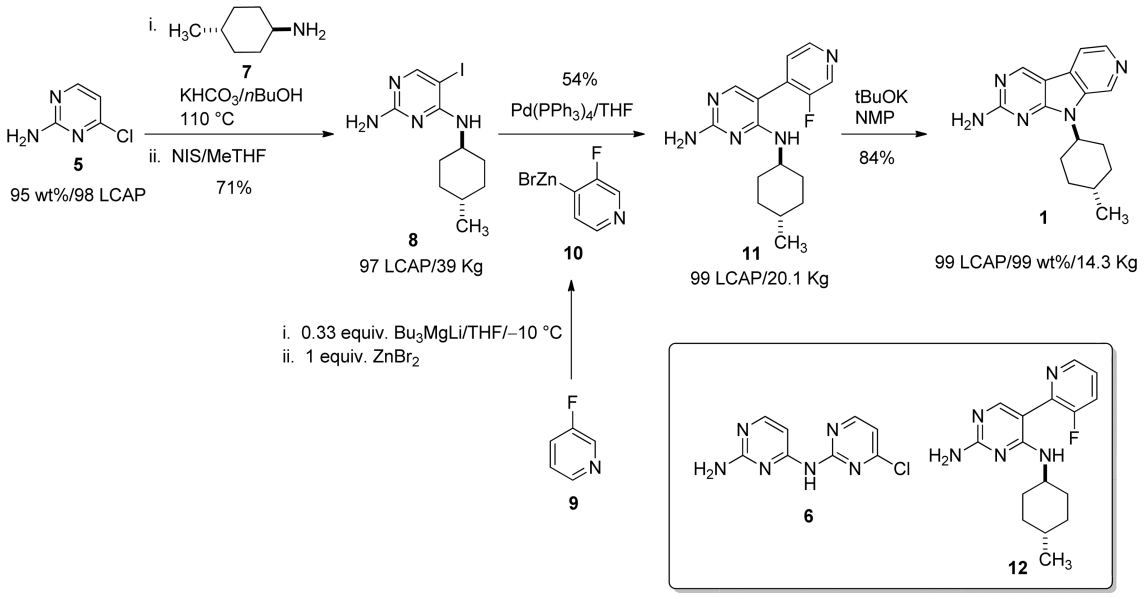


Table 1. The poor solubility of these materials in most preferred solvents (except acetic acid) is evident from examination of the table and necessitates processing of slurry-mixtures, use of large volumes of solvent (greater than 20 L/kilogram of intermediate), and/or use of elevated temperatures in order to complete the preparation of AMG 925 hydrochloride. As described below for the specific steps, this processing challenge required creative solutions to ensure robust drug substance manufacturing.

iii. Manufacture of Aminopyrimidine 3. The conversion of **1** to aminopyrimidine **3** (Scheme 1) without the use of transition-metal catalysis was investigated[10] and very low yields (<10%) of desired product **3** were observed. Several sources of palladium were found to be competent in promoting this transformation (>90% yields) and palladium acetate was selected as a readily available precatalyst. Multiple ligands could be used to conduct this Buchwald–Hartwig amination; however, BrettPhos[11] offered a decisively shorter processing time (Table 2) and was selected for scale-up operations. Noteworthy is the fact that *tert*-amyl alcohol was initially utilized as solvent for ligand screening but was eventually replaced with isopropyl alcohol as this alternative solvent offered a slightly higher reaction rate at a lower temperature (60 °C vs 100 °C). This is not surprising considering that the necessary reduction of the precatalyst from Pd (II) to Pd (0) occurs in less than 30 min at 20 °C using a β-hydrogen donor

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Table 1. Solubility data for AMG 925 process intermediates (in mg/mL of solvent)[a]

	3	4	AMG 925		AMG 925 HCl	
solvent	20 °C	60 °C	20 °C	50 °C	20 °C	50 °C
MeOH	0.4	2.4	<1	<1	<1	<1
EtOH	0.3	2.5	<1	<1	<1	<1
IPA	0.5	<1	<1	<1	<1	<1
CH_3CN	<1	<1	<1	<1	<1	<1
H_2O	<1	<1	<1	<1	<1	<2
toluene	3.7	<1	<1	<1	<1	<1
THF	2.2	<1	<1	<1	<1	<1
IPAc	1	<1	<1	<1	<1	<1
acetone	<1	<1	<1	<1	<1	<1
MTBE	<1	<1	<1	<1	<1	<1
DMSO	1	2.4	2.5	3.0	<1	2.1
DMF	3	7	1.2	2.6	<1	1.2
NMP	18.4	25	2.2	7.3	<1	2.3
50% v/v toluene/MeOH	21	ND[b]	ND	ND	ND	ND
80% v/v toluene/MeOH	43	ND	ND	ND	ND	ND
80% v/v toluene/MeOH (at 40 °C)	120	ND	ND	ND	ND	ND
80% v/v toluene/MeOH (at 50 °C)	160	ND	ND	ND	ND	ND
50% v/v toluene/EtOH	23	ND	ND	ND	ND	ND
80% v/v toluene/EtOH	38	ND	ND	ND	ND	ND
NMP (at 80 °C)	ND	47	ND	ND	ND	ND
60% NMP/H_2O (at 80 °C)	ND	30	ND	ND	ND	ND
50% NMP/H_2O (at 80 °C)	ND	10	ND	ND	ND	ND
AcOH	49.5	ND	66	150	13	21
25% v/v AcOH/H_2O	ND	ND	ND	ND	ND	26
30% v/v AcOH/H_2O	ND	ND	ND	ND	ND	48
50% v/v AcOH/H_2O	ND	ND	ND	73	42	70
70% v/v AcOH/H_2O	ND	ND	ND	195	62	86

[a]Assayed by quantitative HPLC analysis of the filtrate obtained by agitation of a suspension of solute (in excess of soluble amount) in specified solvent for a minimum of 24 h at the listed temperature. [b]ND = not determined.

Table 2. Ligand screen for Buchwald–Hartwig amination[a]

entry	ligand	solvent	temp (°C)	time (h)	% AY[b] 3	% AY 1
1	BrettPhos	tAmOH	100	3.5	95.2	2.1
2	BrettPhos	tAmOH	100	21	97.6	0.4
3	XantPhos	tAmOH	100	3.5	66.4	29.1
4	XantPhos	tAmOH	100	19	95.5	0.2
5	XPhos	tAmOH	100	3.5	76.9	16.9
6	XPhos	tAmOH	100	19.5	93.1	4.0
7	BrettPhos	IPA	60	3.0	97.5	0.24

[a]The reported experiments were performed in the presence of 1 mol % Pd $(OAc)_2$, 1.5 mol % ligand, 1.5 equiv of NaOtBu, 15 volumes of solvent, and 1.1 equiv of **2**. [b]AY refers to assay yield.

solvent such as isopropyl alcohol as determined using ^{31}P NMR experiments. One additional benefit to using isopropyl alcohol as solvent for the amination is that this solvent is miscible with water at all compositions, as opposed to *tert*-amyl alcohol.

Upon its formation, product **3** crystallizes from the reaction mixture due to its low solubility in isopropyl alcohol (Table 1), allowing direct isolation of the product. In order to ensure solubilization of the byproduct sodium chloride to prevent blinding of the filter cloth during the filtration of **3**, water (5 volumes) must be added to the reaction mixture prior to filtration of the suspension. It is thus preferable to use a solvent miscible with water at all compositions and temperatures, such as isopropyl alcohol, to carry out this process and operate the filtration of **3** from a monophasic liquid phase.

The target levels of heavy metal in the drug substance AMG 925 hydrochloride were <100 ppm, per regulatory guidance,[12] much lower than the 700–800 ppm levels of palladium found in crude **3** cakes. Considering the poor solubility of downstream process intermediates and the limited knowledge of downstream metal rejection, the specification for heavy metal levels in intermediate **3** were set to <100 ppm. The removal of palladium using aqueous *N*-acetylcysteine washes[13] was not possible in this case since **3** has insufficient solubility in solvents that undergo phase separation with water. We consequently turned our attention to the use of solid-supported palladium scavengers and thus had to prepare a solution of **3** in reasonable volumes of solvent (<15 volumes). This would allow for palladium removal with the insoluble scavenger, filtration to afford a solution of **3**, and downstream crystallization of the desired compound.

As can be seen in Table 1, mixtures of toluene and alcoholic solvents uniquely offered high solubility for **3**. The solubility of **3** in 80% (v/v) toluene/MeOH is 160 mg/mL at 50 °C, allowing for both palladium scavenging using a solid scavenger and subsequent removal by filtration of the scavenger at 50 °C in only 10 volumes of solvent. After screening of potential scavengers, silicyle–thiourea[14] was selected since it adequately reduced palladium levels. Metal scavenging was performed using silicyle–thiourea (100 wt % relative to **3**) in 80% (v/v) toluene/MeOH and a total of 15 volumes of solvent (Scheme 3).[15] Crude **3** was treated for 3 h, and the metal scavenger was filtered. The resultant solution was seeded and cooled to 20 °C. The crystallization was completed by addition of heptane, and the slurry was filtered to afford product **3** containing <2 ppm of residual Pd.

iv. Manufacture of Amine 4. The *t*-butylcarbamate (BOC) cleavage process used to generate amine **4** presented challenges driven by the solubility of the desired product. The hydrolysis process to generate **4** required the use of multiple equivalents of acid in order to go to completion, even at elevated temperature (70–100 °C). Protonation of one or several of the basic nitrogen sites on **3** coupled with the poor solubility of the salts thus generated is the cause of this problem as demonstrated by chlorine content and HPLC analyses of reaction mixture solids isolated from this process. Additionally, the several equivalents of acid used in the deprotection process had to be subsequently quenched with an equimolar amount of base, thus generating large amounts of salt that needed to be separated from **4** prior to the next step.[16] Finally, product **4** did not have sufficient solubility (see Table 1) in solvents that are immiscible with water; thus, the salt byproducts could not be simply removed by aqueous extraction.

As shown in Table 1, the solubility of this material in *N*-methylpyrrolidinone (NMP, 47 mg/mL at 80 °C) is higher than its solubility in alternative solvents. Moreover, the solubility of **4** in 60% (v/v) NMP/H_2O is 30 mg/mL, making possible the following procedure to perform this process:

(i) completion of the carbamate cleavage in NMP with the required equivalents of acid at elevated temperature,

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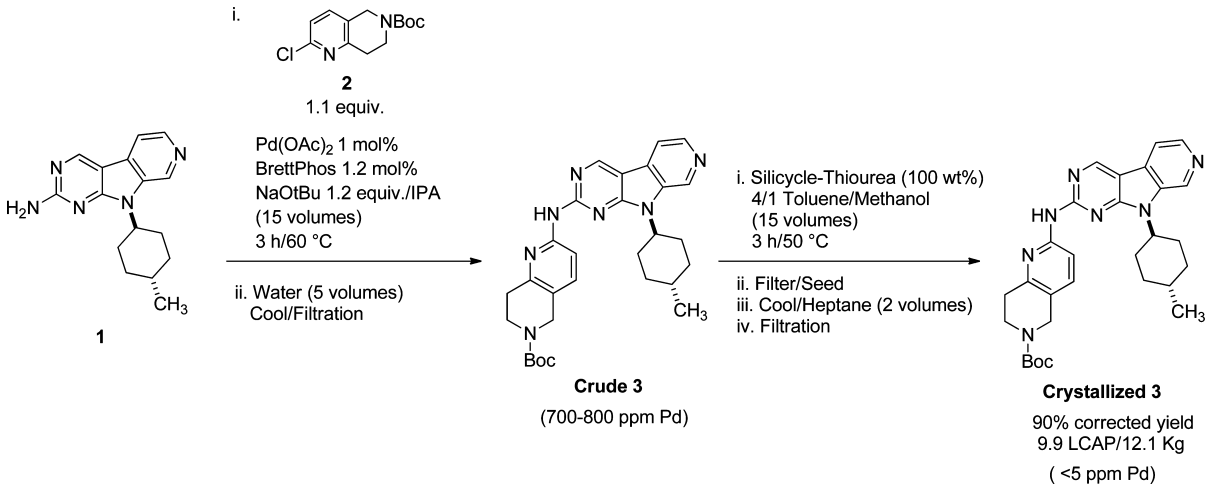
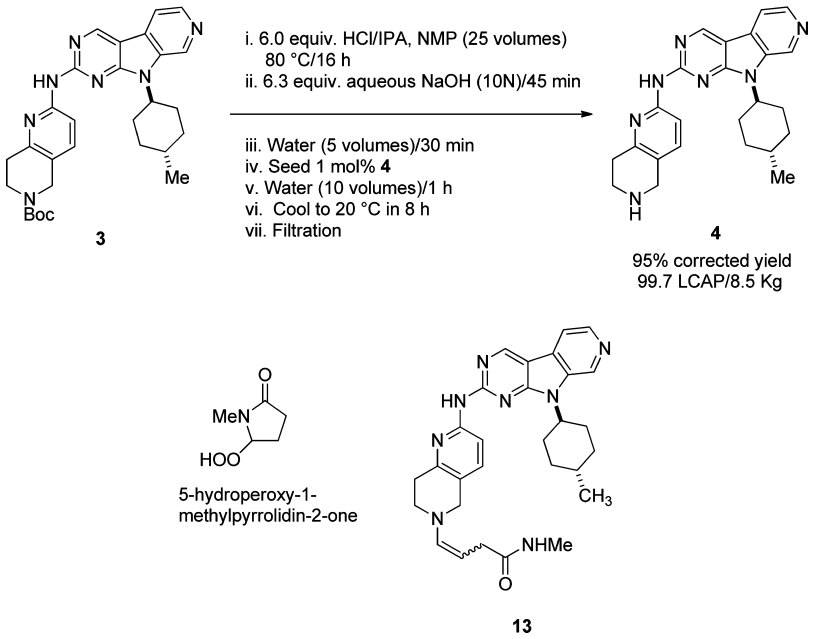
Scheme 3. Manufacture of aminopyrimidine 3



Scheme 4. Manufacture of amine 4



(ii) quenching of the acid with an equimolar amount of base added as an aqueous solution,
(iii) generation of a solution of **4** and the salts in NMP/H_2O at elevated temperature,
(iv) seeding of the crystallization with **4**,
(v) charging of additional water as antisolvent at elevated temperature,
(vi) cooling of the slurry of crystallized **4**,
(vii) filtration to isolate compound **4** free of salts.

Twenty-five volumes of NMP were utilized to perform the process, and it was possible to achieve complete cleavage of the *t*-butylcarbamate group at 80 °C using 6 equiv of HCl (charged as 5 N isopropyl alcohol solution) in 15 h.[17] After addition of 6.3 equiv of sodium hydroxide[18] as a 10 N aqueous solution, the pH was verified to be basic (pH 9−10). The solution was seeded with **4**, antisolvent water (10 volumes) was charged, and the cooled slurry was filtered to afford salt-free desired material **4** in high corrected yield (95%) and purity (99.7 LCAP, 99.2 wt %). To ensure process safety,[19] the batch protocol was evaluated by accelerating reaction calorimetry and was deemed safe to operate.[20] Gas evolution of isobutylene and carbon dioxide was experimentally measured to occur over the course of >4 h, and the venting area available on the reaction train employed was found to be sufficient to accommodate the needs of the process on this scale.

A subsurface nitrogen sparge was performed on the NMP solution of **3** prior to conducting the process in order to remove adventitious oxygen from the reaction mixture. The presence of oxygen in this case was found to cause the formation of impurity **13**[21] from reaction of **4** with NMP degradation product 5-hydroperoxy-1-methylpyrrolidin-2-one (Scheme 4), a derivative of *N*-methylpyrrolidinone formed in the presence of oxygen at high temperatures.[22]

v. Manufacture of AMG 925. As demonstrated in Table 1, the amidation process affording AMG 925 from **4** needed to be conducted as a slurry-to-slurry process in which the starting material and the product have limited solubility if practical solvent volumes were to be utilized for manufacture. The use of

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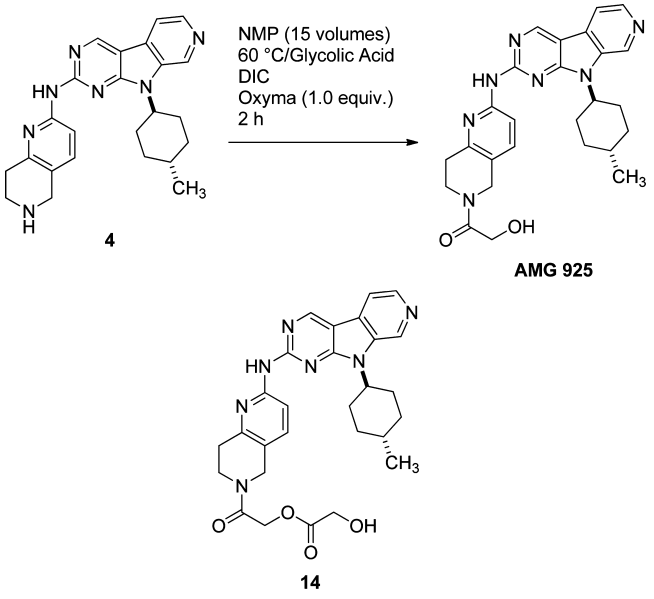
N-methylpyrrolidinone (NMP) as solvent for the process maximizes this limited solubility. Different coupling reagents were evaluated to prepare AMG 925 from **4** and glycolic acid. Whereas the use of carbonyl diimidazole (CDI) or propyl phosphonic anhydride (T3P) yielded the desired product in less than 25% assay yield, utilizing diisopropylcarbodiimide (DIC) in the presence of either hydroxybenzotriazole (HOBt) or 2-cyano-2-(hydroxyimino)acetate (Oxyma) as catalyst allowed formation of AMG 925 in greater than 95% assay yield.[23]

Diisopropylcarbodiimide was selected as the preferred reagent for this transformation due to its ease of handling (nonviscous liquid) as well as the fact that the coupling byproduct diisopropylurea has high solubility[24] in NMP and was thus completely rejected upon filtration of the product. Oxyma[25] was selected to promote this process since it has been shown to have lower explosion risks than HOBt[26] and that it does not carry shipping restrictions.[27] The main impurities observed in this transformation were ester **14**[28] (Scheme 5)

Scheme 5. Manufacture of AMG 925



and starting material **4**. Although these impurities are poorly rejected upon isolation of AMG 925, **4** shows better rejection (85% rejection starting with 1.5 LCAP) than **14** (20% rejection starting with 0.9 LCAP) during the crystallization of the drug substance AMG 925 hydrochloride. Consequently, the equivalents of DIC and glycolic acid utilized in the amidation process were screened with the primary objective of limiting the levels of **14** generated during the course of the reaction (see Table 3). The use of excess glycolic acid (two equivalents) led to the formation of prohibitively large (1.2 LCAP) amounts of ester **14**, and the amidation conditions presented in entry 3 (Table 3) were selected as a reasonable compromise to carry this transformation to completion and limit the amounts of **14** formed.

A temperature screen for the amidation process was performed with the selected conditions, and the results are presented in Table 4. The transformation rate is sluggish at 25 °C (entry 1), and in general the use of temperatures below 60 °C leads to unacceptably high levels of residual starting material **4**. It is important to note that, within the temperature range

Table 3. Equivalents of DIC and glycolic acid used in the amidation process[a]

entry	glycolic acid equiv	DIC equiv	% AY[b] AMG 925	% AY **4**	% AY **14**
1	1.1	1.1	97.1	2.6	0.2
2	1.15	1.15	97.7	1.7	0.2
3	1.2	1.2	98.3	1.3	0.4
4	2.0	1.2	98.6	0.0	1.2

[a]DIC was added to a mixture of **4**, Oxyma (1.0 equiv), and glycolic acid in NMP (15 volumes) at 60 °C, and the mixtures were agitated for 2 h for these experiments. [b]AY refers to assay yield.

Table 4. Temperature screen for the amidation process[a]

entry	temperature (°C)	% AY[b] AMG 925	% AY **4**	% AY **14**
1	25	68.3	29.1	0.2
2	50	95.4	3.3	0.3
3	55	97.0	2.1	0.3
4	60	98.3	1.3	0.2

[a]DIC (1.2 equiv) was added to a mixture of 4, Oxyma (1.0 equiv), and glycolic acid (1.2 equiv) in NMP (15 volumes) at the designated temperature and the mixtures were agitated for 3 h for these experiments. [b]AY refers to assay yield.

studied (25−60 °C), a slurry-to-slurry reaction is observed and that after 3 h of proceeding at a given temperature, the reaction mixture levels of **4** cannot be decreased by elevating the temperature and/or providing additional equivalents of DIC and glycolic acid. To corroborate these results, samples of the reaction mixture at these different temperatures were analyzed, and residual **4** was found to be entrained in the solid cakes of product AMG 925. Consequently, we elected to conduct the process by charging DIC to a slurry of **4**, Oxyma, and glycolic acid in NMP at 60 °C in order to ensure that the transformation would occur within a narrow window (±3 °C) of the target temperature.[29]

Finally, the amount of time used to charge DIC to the amidation reaction mixture (**4**, glycolic acid, Oxyma, and NMP) at 60 °C was evaluated with the objective of limiting starting material entrainment. The results of this study are summarized in Table 5. Since only a minor exotherm accompanies the

Table 5. Time of addition of DIC at 60 °C for the amidation process[a]

entry	addition time at 60 °C	% AY[b] AMG 925	% AY **4**	% AY **14**
1	1 min	98.3	1.3	0.2
2	6 min	98.0	1.4	0.4
3	20 min	97.7	1.6	0.3
4	60 min	97.1	2.3	0.1

[a]DIC (1.2 equiv) was added to a mixture of 4, Oxyma (1.0 equiv), and glycolic acid (1.2 equiv) in NMP (15 volumes) at 60 °C for these experiments. [b]AY refers to assay yield.

addition of DIC over a period of 1 min (2 °C exotherm on measured on a scale of 40 g of **4**, 74 kJ/mol), the target addition time for DIC was set to <20 min, and the actual addition time in the pilot-plant was <2 min. The process was conducted using 8 kg of **4** with success, and AMG 925 was generated with less than 0.05 LCAP of either starting material **4** or amide **14**. After cooling of the suspension to 20 °C, methanol (5 volumes) was used as an antisolvent before filtration[30] of the batch.

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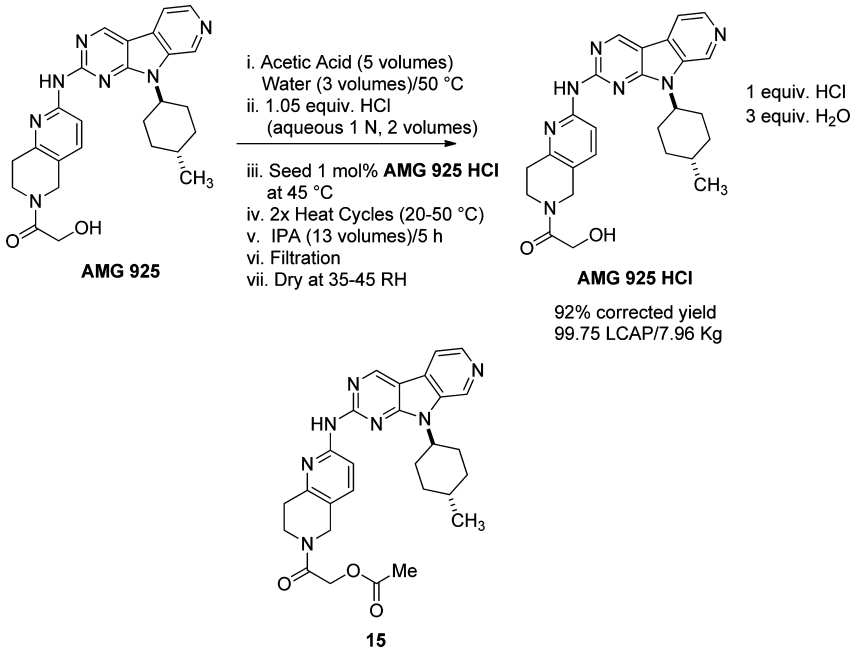
Scheme 6. Manufacture of AMG 925 HCl



vi. Manufacture of AMG 925 HCl. A hydrochloric acid salt of AMG 925 was prepared for drug product development, and this salt had very limited solubility in virtually all solvents (Table 1). A water/acetic acid solvent mixture was selected for the process since it offered a range of solubility values for the hydrochloric acid salt that would allow for design of a controlled crystallization. This selection was made despite the fact that the use of acetic acid as solvent to crystallize a molecule containing an alcohol group is clearly hampered by potential formation of the corresponding acetate by Fischer esterification. In this instance, 0.65 LCAP of ester **15** was generated during the manufacture of AMG 925 hydrochloride. This impurity was partially rejected and present in 0.25 LCAP in the product cake.

A crystalline trihydrate polymorph of the drug substance was determined to be the thermodynamically most stable form in aqueous mixtures of ≥15% water, and this polymorph was selected for the drug product formulation process. The salt was crystallized using a 1:1 mixture of acetic acid and water according to the protocol described in Scheme 6. Upon seeding of a solution of AMG 925 hydrochloride at 45 °C, roughly 30% of the material crystallized. After formation of this seed bed, two heat cycles between 50 and 20 °C were performed over the course of 12 h. These heat cycles successfully reduced the number of fine (<10 μm) particles and improved the filtration rate of the product on kilogram scale.[31] After crystallization of roughly 50% of the material at 20 °C, isopropyl alcohol was added as an antisolvent in preparation for filtration of the batch. The dynamic vapor sorption plot of AMG 925 hydrochloride showed a constant water level corresponding to three equivalents between 10% and 90% RH, and it was observed experimentally that the material retained this level of hydration upon drying with a humidified nitrogen stream having ≥10% RH. Accordingly, the relative humidity of the drying nitrogen stream utilized was maintained between 35% and 45% RH during manufacture.

SUMMARY

A process to manufacture AMG 925 hydrochloride was developed and demonstrated to produce 8 kg. The overall yield over eight steps from commercially available aminopyrimidine **5** was 23%. The synthetic route features a Buchwald−Hartwig amination using BrettPhos as ligand and was conducted to afford 12 kg of product in a single batch. Due to the low solubility of the synthetic intermediates in most preferred solvents, processing had to be adjusted to facilitate seemingly routine activities such as salt removal, pH adjustment, and heavy metal scavenging. Finally, a slurry-to-slurry amidation was optimized to allow for successful scale-up.

EXPERIMENTAL SECTION

Manufacture of 5-Iodo-N^4-((1*R*,4*R*)-4-methylcyclohexyl)pyrimidine-2,4-diamine (Iodide 8). To a solution of 2-amino-4-chloropyrimidine (21.3 kg, 1 equiv, 156 mol) in *n*-butanol (170 L, 8 vol) were added finely ground potassium bicarbonate (65.4 kg, 3.06 equiv., 468 mol) followed by *trans*-4-methylcyclohexylamine (27.9 kg, 1.58 equiv., 246 mol). The mixture was heated to reflux (110−115 °C) and agitated for 10 h. The mixture was cooled to 20 °C. Water (85 L, 4 vol) and MTBE (105 L, 4.9 vol) were added, and the mixture was agitated at 20 °C for 45 min. The mixture was filtered through Celite (7 kg, 33 wt %), and the Celite cake was rinsed with MTBE (120 L, 5.7 vol). The phases were separated, and the organic phase was washed with saturated aqueous sodium chloride (42 L, 2 vol). The organic phase was distilled at atmospheric pressure to generate a distillate volume of 815 L while simultaneously adding heptane (730 L, 34 vol) to maintain the vessel fill level at 140−225 L. The mixture was cooled to 20 °C and agitated for 12 h. The mixture was filtered, and the filter cake was washed with water (3 × 70 L, 3 × 3.4 vol). The wet solid was dried at 50 °C for 72 h under nitrogen. The dried solid was dissolved in 2-methyltetrahydrofuran (160 L, 5.9 vol) and heated to 30 °C. *N*-iodosuccinimide (33.4 kg, 1.2 equiv) was added over a period of 2 h, and the mixture was agitated at 30 °C for 12 h. The mixture was cooled to 20 °C,

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and aqueous 5N sodium hydroxide (76 kg, 3.1 equiv) was added over 15 min at <25 °C. The biphasic mixture was agitated for 15 min, and the phases were separated. The aqueous layer was extracted with 2-methyltetrahydrofuran (26 L, 1 vol). The combined organic layers were washed with brine (3 × 50 L, 3 × 1.9 vol). The organic layer was distilled at reduced pressure (maximum temperature of 40 °C) to generate a distillate volume of 85 L. Heptane (240 L, 9.1 vol) was added, and the mixture was agitated at 20 °C for 1 h. The mixture was filtered, and the filter cake was washed with heptane (2 × 36 L, 2 × 1.4 vol). The wet solid was dried under vacuum at 40 °C for 22 h to afford 39.0 kg of iodide **8** in 72.2% yield (96.9 LCAP, 95.6 wt %). Mp 138−140 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 7.79 (s, 1H), 6.08 (s, 2H), 5.40 (d, 1H, J = 12 Hz), 3.69−3.83 (m, 1H), 1.52−1.79 (m, 4H), 1.15−1.37 (m, 3H), 0.72−0.96 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 162.5, 161.6, 159.4, 65.3, 49.9, 33.8, 33.0, 32.0, 22.2.

Manufacture of 5-(3-Fluoropyridin-4-yl)-N^4-((1*R*,4*R*)-4-methylcyclohexyl)pyrimidine-2,4-diamine (Fluoropyridine 11). To a cold (−10 °C) suspension of magnesium bromide (21.7 kg, 1.05 equiv) in tetrahydrofuran (230 L, 5.9 vol) was added *n*-butyllithium in hexane (99.6 kg, 23 wt %, 3.2 equiv) over 4 h at <−8 °C. 3-Fluoropyridine (32.9 kg, 3.0 equiv) was added to the reaction mixture over 5 h at <−8 °C. To the reaction mixture was added a solution of zinc bromide (76.5 kg, 3.0 equiv) in tetrahydrofuran (190 L, 4.9 vol) over 3 h at <−2 °C. The reaction mixture was warmed to 15 °C over 1 h. A use-test was conducted using a sample of the mixture, a sample of iodide **8**, as well as a sample of tetrakis-(triphenylphosphine) palladium, and the in-process control test at the intermediate time point (2 h) showed expected conversion. Consequently, iodide **8** (39.0 kg, 1.0 equiv) and tetrakis(triphenylphosphine) palladium (5 kg, 0.04 equiv) were added, and the mixture was heated to 65 °C. The mixture was agitated for 5 h and cooled to 20 °C. An aqueous solution of *N*-(2-hydroxyethyl)ethylendiamine-*N*,*N*′,*N*′-triacetic acid sodium salt dihydrate (490 L, 10 wt %) was added to the reaction mixture over 30 min. The biphasic mixture was agitated for 30 min. The layers were filtered and separated. An aqueous solution of *N*-(2-hydroxyethyl)ethylendiamine-*N*,*N*′,*N*′-triacetic acid sodium salt dihydrate (300 L, 5 wt %) was added to the reaction mixture over 30 min. The biphasic mixture was agitated for 30 min. The layers were separated. The organic phase was distilled at atmospheric pressure to generate a distillate volume of 500 L while simultaneously adding isopropanol (120 L, 3 vol). During this time, the product fluoropyridine **11** mostly precipitated out of solution. The suspension was agitated at 20 °C for 30 min. An aqueous solution of *N*-(2-hydroxyethyl)ethylendiamine-*N*,*N*′,*N*′-triacetic acid sodium salt dihydrate (250 L, 5 wt %) was added to the reaction mixture over 30 min. The mixture was agitated for 1 h and filtered. The filter cake was washed with deionized water (2 × 45 L) and dried at 50 °C for 48 h to afford 20.1 kg of fluoropyridine **11** in 52.3% yield (99.3 LCAP, 93.0 wt %). Mp 140−142 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 8.90−8.95 (m, 2H), 8.24 (d, 1H, J = 6 Hz), 7.82 (d, 1H, J = 6 Hz), 6.90 (s, 2H), 4.60−4.78 (m, 1H), 2.25−2.40 (m, 2H), 1.50−1.81 (m, 5H), 1.20−1.00 (m, 2H), 0.87 (d, 3H, J = 6 Hz).

Manufacture of 9-((1*R*,4*R*)-4-methylcyclohexyl)-9*H*-pyrido[4′,3′:4,5]pyrrolo[2,3-*d*]pyrimidin-2-amine (Aminopyrimidine 1). To a solution of fluoropyridine **11** (20.1 kg, 93 wt %, 1.0 equiv) in 1-methyl-2-pyrrolidinone (90 L, 4.5 vol) at 30 °C was added potassium *tert*-butoxide (20.0 kg, 3.0 equiv) in eight portions over 1 h, while maintaining the temperature of the mixture <40 °C. The mixture was heated to 70 °C and agitated for 3 h. An additional portion of *tert*-butoxide (6.6 kg, 1.0 equiv) was added, and the mixture was warmed to 75 °C and agitated for 3.5 h. The mixture was cooled to 20 °C. Deionized water (54 L, 2.7 vol) and 2-methyltetrahydrofuran (110 L, 5.5 vol) were added, and the biphasic mixture was agitated for 15 min. The phases were separated, and the aqueous layer was extracted with 2-methyltetrahydrofuran (2 × 75 L, 2 × 4 vol). The combined organic layers were filtered through a 0.25 μm cartridge and washed with brine (100 L, 5.3 vol). The aqueous brine layer was extracted with 2-methyltetrahydrofuran (75 L, 4 vol). The combined organic layers were washed with brine (2 × 100 L, 2 × 5.3 vol). The organic phase was filtered through a 0.25 μm cartridge. The organic phase was distilled at atmospheric pressure and 80 °C to generate a distillate volume of 270 L. Heptane (180 L, 9 vol) was added at 60 °C, and the suspension was cooled to 20 °C. The suspension was filtered. The filter cake was washed with heptane (2 × 40 L, 2 × 2 vol) and dried at 50 °C for 24 h. The material was dissolved in dichloromethane (170 L, 10 vol), and activated charcoal (0.85 kg, 5 wt %) was added. The mixture was agitated at 20 °C for 1 h and filtered through a 0.25 μm cartridge. The vessel and filter line were washed with dichloromethane (40 L, 2.2 vol). The combined dichloromethane phases were distilled at atmospheric pressure and 35 °C to generate a distillate volume of 195 L. Heptane (170 L, 10 vol) was added at 35 °C, and the suspension was cooled at 20 °C. The suspension was filtered. The filter cake was washed with heptane (2 × 40 L, 2 × 2 vol) and dried at 50 °C for 48 h to afford 14.3 kg of aminopyrimidine **1** in 84.9% yield (99.2 LCAP, 99.1 wt %). Mp 208−210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 8.43 (d, 1H, J = 3 Hz), 8.29−8.31 (m, 1H), 7.50 (s, 1H), 7.26−7.30 (m, 1H), 6.15 (s, 2H), 5.91 (d, 1H, J = 9 Hz), 3.82−3.96 (m, 1H), 1.51−1.71 (m, 4H), 1.08−1.28 (m, 3H), 0.75−0.95 (m, 5H).

Manufacture of *tert*-Butyl-2-((9-((1*R*,4*R*)-4-methylcyclohexyl)-9*H*-pyrido[4′,3′:4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (Aminopyrimidine 3). NaOtBu (2.99 kg, 31.1 mol, 1.2 equiv), **2** (7.67 kg, 28.5 mol, 1.1 equiv), **1** (7.30 kg, 25.9 mol, 1.0 equiv), and IPA (100 L, 13.6 vol.) were charged via a sealed manhole to a 250 L vessel equipped with a reflux/return condenser. The contents of the 250 L vessel were agitated, and a subsurface N_2 sparge was performed for 20 min. $Pd(OAc)_2$ (0.058 kg, 0.26 mol, 0.01 equiv), BrettPhos (0.17 kg, 0.32 mol, 0.0125 equiv), and degassed[32] IPA (10 L, 1.4 vol.) were charged to a 10 L vessel under an atmosphere of N_2. The contents of the 10 L vessel were agitated for 0.5 h and charged to the 250 L vessel. The contents of the 250 L vessel were heated to 60 °C for 3 h. HPLC analysis of a process sample showed 97.5 LCAP **3** and 0.24 LCAP **1**. Degassed water (32.8 L, 4.5 vol.) was added to the contents of the 250 L reactor over 1 h. The contents of the 250 L vessel were agitated for 1 h at 60 °C, cooled to 20 °C over 2 h (linear ramp), and agitated for 12 h. The contents of the 250 L vessel were split in half and filtered through two 24 in. Aurora filter-driers equipped with 12 μm PTFE filter cloths and under a positive pressure of nitrogen (2−5 psig). The mother liquors were transferred to a 400 L vessel. The 250 L vessel was rinsed with a solution of IPA (25.6 L, 3.5 vol.) and water (11.0 L, 1.5 vol.), and the rinse solution was split in half to wash both process cakes. The wash solutions were transferred to a 400 L vessel. The combined mother

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liquors and wash solutions were assayed for **3** losses (2.1%). The filtration and wash process took approximately 2.5 h. The cakes were dried under positive nitrogen pressure (dry nitrogen, 0−5 psig) for 3 days. Cake samples showed weight losses by TGA (up to 180 °C) of 0.19% and 0.27%. Metals levels were measured in the cakes at 732−775 ppm Pd and 224−774 ppm of Na (ICP-MS analyses). Crude **3** (12.6 kg) was packaged and charged via a sealed manhole to a 250 L vessel equipped with a reflux/return condenser. Silicycle-Thiourea (7.3 kg, 100 wt %) and a degassed[22] solution of toluene (81.6 L, 11.2 vol.) and MeOH (20.4 L, 2.8 vol.) were charged. The contents of the 250 L vessel were heated to 50 °C and agitated under an atmosphere of N_2 for 3 h. The supernatant Pd levels in the 250L vessel were measured to be 0.7 ppm. The contents of the 250 L vessel were warmed to 60 °C and filtered through a 14 in. Aurora filter-drier (jacket temperature 60 °C) equipped with a 12 μm PTFE filter cloth under a positive pressure of nitrogen (2−5 psig). The filtrate was charged to a 400 L vessel with a jacket temperature set to 50 °C. The 250 L vessel was rinsed with a solution of toluene (11.7 L, 1.6 vol.) and MeOH (2.9 L, 0.4 vol.), the silicycle−thiourea cake was washed with this rinse solution, and the wash solution was transferred to the 400 L vessel. The agitated contents of the 400 L vessel were cooled to 35 °C under an atmosphere of N_2. A shaken slurry of **3** (0.133 kg, 0.25 mol, 0.018 equiv) in degassed heptane (1.8 L, 0.25 vol.) was charged to the contents of the 400 L vessel. After a period of 10 min, formation of a slurry in the 400 L vessel was visually observed. The contents of the 400 L were agitated at 35 °C for 1 h and cooled to 20 °C over 3 h (linear ramp). Degassed heptane (185 L, 25.4 vol.) was added to the contents of the 400 L vessel over 4 h (linear addition). The contents of the 400 L vessel were agitated for 12 h, and the supernatant concentration of **3** was measured by HPLC to be 1.3 mg/mL. The contents of the 400 L vessel were filtered through a 24 in. Aurora filter-drier equipped with a 12 μm PTFE filter cloth under a positive pressure of nitrogen (2−5 psig). The mother liquors were transferred to a 250 L vessel. The 400 L vessel was rinsed with a solution of toluene (11.0 L, 1.5 vol.), MeOH (2.9 L, 0.4 vol.), and heptane (22.6 L, 3.1 vol.), the cake was washed with this solution, and the wash solution was collected in a 250 L vessel. The combined mother liquors and wash solutions were assayed for **3** losses (2.4%). The filtration and wash process took approximately 1 h. The cake was dried under positive nitrogen pressure (dry nitrogen, 0−5 psig) for 2 days. A cake sample showed a weight loss by TGA (up to 180 °C) of 2.1%, and the material was packaged. Aminopyrimidine **3** was isolated in 90.6% yield (12.1 kg), 95.3% overall mass balance, 99 wt %, and 99.9 LCAP. The material contained 1 ppm of palladium. Mp 250−252 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 9.11 (s, 1H), 8.96 (s, 1H), 8.51 (d, 1H, J = 4 Hz), 8.39 (d, 1H, J = 8 Hz), 8.14−8.25 (br s, 1H), 7.84 (d, 1H, J = 4 Hz), 7.48 (d, 1H, J = 8 Hz), 4.68−4.78 (m, 1H), 4.59 (s, 2H), 3.77 (t, 2H, J = 6 Hz), 2.93 (t, 2H, J = 6 Hz), 2.53−2.66 (m, 2H), 1.93−2.03 (m, 4H), 1.51 (s, 9H), 1.20−1.36 (m, 2H), 1.06 (d, 3H, J = 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 158.0, 156.6, 154.8, 152.9, 152.0, 150.8, 141.0, 135.9, 134.8, 133.1, 129.9, 126.6, 114.0, 110.8, 106.6, 80.1, 54.6, 34.7, 32.1, 31.9, 30.2, 28.5, 22.3; exact mass $[C_{29}H_{35}N_7O_2 + H]^+$: calculated = 514.2930, measured = 514.2920.

Manufacture of 9-((1*R*,4*R*)-4-Methylcyclohexyl)-*N*-(5,6,7,8-tetrahydro-1,6-naphthyridin-2-yl)-9*H*-pyrido-[4′,3′:4,5]pyrrolo[2,3-*d*]pyrimidin-2-amine (Amine 4). **3** (11.0 kg, 99.0 wt %, 21.4 mol, 1.0 equiv) and degassed[22] NMP (275 L, 25 vol.) were charged via a sealed manhole to a 400 L vessel equipped with a reflux/return condenser and a NaOH scrubber. The contents of the 400 L vessel were agitated (100 rpm) and degassed using a subsurface N_2 sparge (20 min). HCl in IPA (21.1 kg, 5.56 M, 128.5 mol, 6.0 equiv) was charged. The contents of the 400 L vessel were heated to 80 °C over 1.5 h and agitated for 16 h. HPLC analysis of a process sample showed 99.7 LCAP **4** and 0.1 LCAP **3**. A degassed aqueous NaOH solution (17.8 kg, 10.0 N, 135.0 mol, 6.3 equiv) was added over 45 min to the contents of the 400 L vessel. Degassed water was added over 30 min (50 L, 4.5 vol.) to the contents of the 400L vessel. The pH of the contents of the 400 L reactor was measured to be above 10. A shaken slurry of **4** (81 g, 0.21 mol, 0.01 equiv) in a degassed[22] mixture of NMP (0.55 L, 0.05 vol.) and water (0.22 L, 0.02 vol.) was charged to the contents of the 400 L vessel. After a period of 10 min, formation of a slurry in the 400 L vessel was visually observed, and the contents of the 400 L were agitated at 80 °C for 30 min. Degassed water was added over 1 h (105 L, 9.5 vol.) to the contents of the 400L vessel. The contents of the 400 L were cooled to 20 °C over 8 h (linear ramp), agitated for 4 h, and the supernatant concentration of **4** in the slurry was measured by HPLC to be 0.4 mg/mL. The contents of the 400 L vessel were filtered through a 24 in. Aurora filter-drier equipped with a 12 μm PTFE filter cloth under a positive pressure of nitrogen (2−5 psig). The mother liquors were transferred to a 250 L vessel. The 400 L vessel was rinsed with a solution of NMP (20.7 L, 1.9 vol.) and water (12.3 L, 1.1 vol.), the cake was washed with this solution, and the wash solution was collected in a 250 L vessel. The 400 L vessel was rinsed with water (33.0 L, 3.0 vol.), the cake was washed with this water, and the wash solution was collected in a 250 L vessel. The last unit operation (water rinse) was repeated twice. The cake was washed with heptane (22.0 L, 2.0 vol.), and the wash solution was collected in a 250 L vessel. The filtration and wash process took approximately 16 h. The cake was dried under positive nitrogen pressure (dry nitrogen, 0−5 psig) for 6 days. A cake sample showed a weight loss by TGA (up to 180 °C) of 0.4%, and the material was packaged. Amine **4** was isolated in 95.2% yield (8.53 kg), 97.6% overall mass balance, 99.2 wt %, and 99.7 LCAP. Mp 276−278 °C; ^{1}H NMR (400 MHz, AcOH-d_4) 9.48 (d, 2H, J = 3 Hz), 8.72 (d, 1H, J = 6 Hz), 8.49−8.53 (m, 2H), 7.82 (d, 1H, J = 9 Hz), 4.85−4.96 (m, 1H), 4.55 (s, 2H), 3.74 (t, 2H, J = 6 Hz,), 3.26 (t, 2H, J = 7 Hz), 2.60−2.80 (m, 2H), 1.74 (br s, 1H), 1.28−1.40 (m, 2H), 1.07 (d, 3H, J = 7 Hz); ^{13}C NMR (100 MHz, AcOH-d_4) 159.5, 159.3, 155.8, 152.4, 150.7, 139.3, 135.9, 134.5, 133.3, 127.8, 120.5, 117.5, 114.0, 107.3, 57.1, 44.7, 42.5, 35.2, 32.8, 30.8, 27.8, 22.6; exact mass $[C_{24}H_{27}N_7 + H]^+$: calculated = 414.2406, measured = 414.2390.

Manufacture of 2-Hydroxy-1-(2-((9-((1*R*,4*R*)-4-methylcyclohexyl)-9*H*-pyrido[4′,3′:4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-ethanone (AMG 925). Glycolic acid (1.76 kg, 23.1 mol, 1.2 equiv), Oxyma (2.73 kg, 19.3 mol, 1.0 equiv), **4** (7.96 kg, 19.3 mol, 1.0 equiv), and NMP (119 L, 15 vol.) were charged via a sealed manhole to a 250L vessel equipped with a reflux/return condenser. The contents of the 250 L vessel were agitated (130 rpm) under an atmosphere of N_2 and heated to 60 °C. DIC (2.91 L, 23.1 mol, 1.2 equiv) was added to the contents of the 250 L vessel over 1 min (5 °C exotherm was recorded), and the addition line was rinsed with NMP (0.3 L, 0.04 vol., the rinse

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solution was added to the contents of the 250 L vessel). The contents of the 250 L vessel were agitated for 1.3 h. HPLC analysis of a process sample showed 91.0 LCAP AMG 925 and 0.05 LCAP **4** (Oxyma accounts for 7.9 LCAP). The contents of the 250 L were cooled to 20 °C over 2.5 h (linear ramp, 100 rpm agitation). MeOH (39.8 L, 5 vol.) was added to the contents of the 250L vessel over 40 min (linear addition), and the contents of 250 L vessel were agitated (60 rpm) for 12 h at 20 °C. The supernatant concentration of AMG 925 in the slurry was measured by HPLC to be 2.2 mg/mL. The contents of the 250 L vessel were filtered through a 24 in. Aurora filter-drier equipped with a 12 μm PTFE filter cloth under a positive pressure of nitrogen (2−5 psig). The mother liquors were transferred to a 400 L vessel. The 250 L vessel was rinsed with MeOH (59.7 L, 7.5 vol.), the cake was washed with this MeOH, and the wash solution was collected in a 400 L vessel. The last unit operation (MeOH rinse) was repeated. The filtration and wash process took approximately 8 h. The cake was dried under positive nitrogen pressure (dry nitrogen, 0−5 psig) for 36 h. A cake sample showed a weight loss by TGA (up to 180 °C) of 1.0%, and the material was packaged. AMG 925 was isolated in 91.5% yield (8.31 kg), 95.5% overall mass balance, 99.9 wt %, and 99.7 LCAP. Mp 213−215 °C; ^{1}H NMR (400 MHz, acetic acid-d_4, mixture of two rotamers at 20 °C) 9.47−9.59 (m, 2H), 8.76 (d, 1H, J = 6 Hz), 8.55 (d, 1H, J = 6 Hz), 8.48 (d, 1H, J = 9 Hz), 7.79−7.92 (m, 1H), 4.95 (t, 1H, J = 12 Hz), 4.87 and 4.68 (2 singlets, 2H), 4.47−4.59 (m, 2H), 4.04 and 3.80 (2 triplets, 2H, J = 6 Hz), 3.03−3.17 (m, 2H), 2.65−2.82 (m, 2H), 1.96−2.15 (m, 4H), 1.77 (br s, 1H), 1.39 (q, 2H, J = 12 Hz), 1.09 (d, 3H, J = 7 Hz); ^{13}C NMR (100 MHz, acetic acid-d_4, mixture of two rotamers at 20 °C) 171.9, 171.8, 158.4, 157.8, 154.7, 149.0, 148.9, 141.6, 135.2, 132.9, 126.3, 124.1, 123.6, 117.7, 113.7, 113.6, 107.5, 107.4, 60.1, 59.9, 56.3, 43.7, 42.6, 40.5, 38.7, 34.0, 31.5, 29.8, 28.8, 28.1, 21.5.

Manufacture of 2-Hydroxy-1-(2-((9-((1*R*,4*R*)-4-methylcyclohexyl)-9*H*-pyrido[4′,3′:4,5]pyrrolo[2,3-*d*]pyrimidin-2-yl)amino)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)-ethanone Hydrochloride (AMG 925 HCl). AMG 925 (7.01 kg, 14.88 mol, 1.0 equiv) was charged via a sealed manhole (due to the cytotoxic potential of the material) to a 250 L vessel equipped with a reflux/return condenser. Acetic acid (35.0 L, 5 vol) and water (17.5 L, 2.5 vol) were charged to the 250 L vessel. The contents of the 250 L vessel were heated to 55 °C under an atmosphere of nitrogen and held for 8 h. Mechanical agitation was initiated in the vessel (100 rpm), and the solution was stirred for 1 h. The contents of the 250 L vessel were passed through a 5 μm cartridge filter and transferred in a preheated (50 °C) 400L reactor, equipped with a reflux/return condenser. The 250 L vessel was rinsed with a solution of acetic acid (7.0 L, 1.0 vol) and water (3.5 L, 0.5 vol), and the rinse solution was transferred, through the cartridge filter, in the 400 L vessel. To the mechanically agitated (100 rpm) content of the 400 L vessel at 50 °C and under an atmosphere of nitrogen were added an aqueous 1 N HCl solution (15.6 L, 15.6 mol, 1.05 equiv) over 10 min and water (4.6 L, 0.65 vol) over 5 min. The contents of the 400L reactor were cooled to 45 °C and the agitation rate was reduced (25 rpm). A shaken slurry of AMG 925 HCl (240 g, 0.42 mol, 0.028 equiv., unmilled, D_{10} = 3.9 μm, D_{50} = 15.5 μm, D_{90} = 35.3 μm, V_M= 18.1 μm) in IPA (0.88 L, 0.125 vol) and water (0.88 L, 0.125 vol) was charged and after a period of 10 min, formation of a slurry in the 400 L vessel was visually observed. The contents of the 400 L vessel were agitated at 45 °C for 1 h, cooled to 25 °C over a period of 1 h (linear cooling ramp), and heated again to 50 °C. The contents of the 400 L vessel were agitated at 50 °C for 4 h, cooled to 20 °C over a period of 1 h (linear cooling ramp), and agitated at 20 °C for 4 h. The concentration of AMG 925 HCl in solution was measured by HPLC to be 53.4 mg/mL. The contents of the 400 L vessel were heated to 50 °C, agitated for 4 h, cooled to 20 °C over a period of 1 h (linear cooling ramp), and agitated at 20 °C for 1 h. The concentration of AMG 925 HCl in solution was measured by HPLC to be 60.5 mg/mL. IPA (35.0 L, 5.0 vol) was added to the contents of the 400 L vessel over 2.5 h (linear addition ramp). The agitation rate was increased (35 rpm), and IPA (77.0 L, 11.0 vol) was added to the contents of the 400 L vessel over a period of 2.5 h (linear addition ramp). The contents of the 400 L vessel were agitated for 12 h (25 rpm), and the supernatant concentration of AMG 925 HCl was measured by HPLC to be 2.4 mg/mL. The contents of the 400 L vessel were filtered through a 24 in. Aurora filter-drier equipped with a 12 μm PTFE filter cloth under a positive pressure of nitrogen (2−5 psig). The mother liquors were transferred to a 250 L vessel. The 400 L vessel was rinsed with a solution of IPA (56.0 L, 8.0 vol) and water (14.0 L, 2.0 vol), the cake was washed with this solution, and the wash solution was collected in a 250 L vessel. The 400L vessel was rinsed with water (21.0 L, 3.0 vol), the cake was washed with this water, and the wash solution was collected in a 250 L vessel. The combined mother liquors and wash solutions were assayed for AMG 925 HCl losses. The filtration and wash process took approximately 8 h. The cake was dried under positive nitrogen pressure (dry nitrogen, 0−5 psig) for 3 days. The water content (KF) of the solids was measured to be 14.5%. The cake was dried using wet nitrogen (measured at 30−45% relative humidity with a hygrometer) for 14 h. The water content (KF) was 9.6%, which met in process testing specifications. The levels of IPA (actual 611 ppm, IPT ≤ 4000 ppm) and acetic acid (actual 3800 ppm, IPT ≤ 4000 ppm) of the solids also met in process testing specifications, and the material was packaged. AMG 925 HCl was isolated in 92.5% yield (7.96 kg), 99.1% overall mass balance, 83.8 wt % AMG 925, 99.75 LCAP AMG 925, 6.2 wt % Cl, 9.6 wt % water, 3800 ppm AcOH, d_{10} 4.0 μm, d_{50} 15.2 μm, d_{90} 38.8 μ, V_m 18.7 μm, BET surface area 1.5 m^2/g. ^{1}H NMR (400 MHz, acetic acid-d_4, mixture of two rotamers at 20 °C) 9.63 (s, 1H), 9.56 (s, 1H), 8.71−8.76 (m, 1H), 8.60−8.66 (m, 1H), 8.20−8.29 (m, 1H), 7.90−7.98 (m, 1H), 4.90−5.01 (m, 1H), 4.86 and 4.70 (2 singlets, 2H), 4.53 and 4.51 (2 singlets, 2H), 4.05 and 3.82 (2 triplets, 2H, J = 6 Hz), 3.11−3.26 (m, 2H), 2.68 (q, 2H, J = 12 Hz), 1.95−2.13 (m, 4H), 1.74 (br s, 1H), 1.36 (q, 2H, J = 12 Hz), 1.06 (d, 3H, J = 8 Hz); ^{13}C NMR (100 MHz, acetic acid-d_4, mixture of two rotamers at 20 °C) 174.9, 174.8, 161.3, 161.2, 160.5, 157.5, 151.6, 151.5, 149.3, 148.9, 145.5, 138.1, 136.0, 129.3, 129.2, 127.1, 126.6, 120.9, 116.7, 116.6, 110.8, 110.7, 63.0, 62.9, 59.3, 46.4, 45.3, 43.2, 41.3, 36.9, 34.3, 32.6, 31.3, 30.6, 24.4; exact mass $[C_{26}H_{29}N_7O_2 + H]^+$: calculated = 472.2461, measured = 472.2451.

Structural data for ester **15**: ^{1}H NMR (400 MHz, acetic acid-d_4, mixture of two rotamers at 20 °C) δ 9.51 (s, 1H), 9.49 (s, 1H), 8.69−8.77 (m, 1H), 8.49−8.55 (m, 1H), 8.41−8.47 (m, 1H), 7.78−7.86 (m, 1H), 4.87−5.02 (m, 3H), 4.83 and 4.74 (2 singlets, 2H), 4.00 and 3.86 (2 triplets, 2H, J = 6 Hz), 3.00−3.18 (m, 2H), 2.70 (q, 2H, J = 12 Hz), 2.17 (s, 3H), 1.95−2.11 (m, 4H), 1.74 (br s, 1H), 1.36 (q, 2H, J = 12 Hz), 1.07 (d, 3H, J = 8 Hz); exact mass $[C_{28}H_{31}N_7O_3]^+$: calculated = 514.2567, measured = 514.2564.

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■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, XRPD, DVS plot, and PSD graph. HPLC method description and retention times of process intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) Yield corrected for isolated product wt %.
(9) In such a case, no more than 10 L of solvent per kilogram of intermediate have to be used in order to maintain a solution during processing.
(10) Starting materials **1** and **2** were treated with various bases (KHMDS, NaHMDS, LiHMDS, KOtBu, NaOtBu, LiOtBu) in NMP (10 volumes) at 100 °C.
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(14) Commercialized as SiliaMetS Thiourea by Silicycle.
(15) The use of 15 volumes of solvent ensured that compound **3** stayed in solution during filtration of the silicyle−thiourea as the temperature of the mixture upon filtration decreased to >30 °C.
(16) The amidation step success was shown to be dependent on the elimination of these salts from starting material **4**.
(17) Methanesulfonic acid was also evaluated to operate the carbamate cleavage but offered a lower assay yield (<80%).
(18) Lithium hydroxide and ammonium hydroxide solutions were also tested; however, their use led to the isolation **4** with high levels of salts.
(19) All processes discussed in this manuscript have undergone a thorough process safety review prior to being run on kilogram scale.
(20) No exotherm was observed upon heating up to 150 °C.
(21) As much as 8 LCAP of **13** were observed in nondegassed small scale experiments.
(22) Patton, D. E.; Drago, R. S. *J. Chem. Soc., Perkin Trans, 1* **1993**, 1611 As discussed in this report, 5-hydroperoxy-1-methylpyrrolidin-2-one is generated by oxidation of NMP at elevated temperatures in the presence of oxygen but absent from purchased lots of NMP.
(23) Of note is the fact that CDI only provide AMG 925 in less than 5% assay yield in the absence of catalyst HOBt or Oxyma.
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(27) Oxyma also has high solubility in NMP (>200 mg/mL) and consequently is fully rejected upon filtration of the product. One equivalent of this reagent was used for convenience to continue the development of this process for this first-in-human program.
(28) The structure of this impurity was assigned by mass spectroscopy (MW 529 g/mol).
(29) Performing the amidation at 60 °C provided a 65 °C buffer relative to the reaction mixture exothermic onset (125 °C, 45 J/g energy released).
(30) The AMG 925 supernatant concentration upon filtration was ∼2 mg/mL.
(31) FBRM data was gathered and corroborated the minimization of fine particles using heat-cycles.
(32) Subsurface N_2 sparge.

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