Organic Process Research & Development

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Development of a Multi-Kilogram-Scale Synthesis of AZD1283: A Selective and Reversible Antagonist of the $P2Y_{12}$ Receptor

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Supporting Information

ABSTRACT: Ethyl 6-chloro-5-cyano-2-methylnicotinate (**4**) was coupled with 4-piperidinecarboxylic acid (isonipecotic acid) in 81% yield to pyridine acid **10**. An amide coupling between **10** and benzylsulfonamide (**6**) afforded AZD1283 (**1**) in 79% yield using CDI as coupling reagent. The synthesis has been developed and scaled up to 20 kg batches of **1**, supporting preclinical and clinical studies. Development work towards 2-chloropyridine **4** and benzylsulfonamide (**6**) is included.

INTRODUCTION

Drug candidate AZD1283 (**1**) (Figure 1) has been identified as a potent reversible $P2Y_{12}$ antagonist.[1] Larger amounts were needed to support both preclinical and clinical studies and a synthetic route capable of delivering multikilo quantities as well as being a good choice on a commercial level was sought.

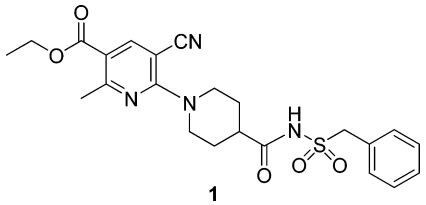


Figure 1. AZD1283.

The original in-house synthesis of **1** was performed by coupling the left-hand pyridine fragment to the central isonipecotic acid and then coupling the resulting pyridine acid to benzylsulfonamide (**6**) (Figure 2, Pyridine Acid Route).[1] The last step was low yielding and chromatography needed to isolate AZD1283 (**1**). In order to develop a scaleable route that would generate material for preclinical studies in a short time frame, it was critical to develop a crystallization method for the final product to avoid chromatography. In the original synthesis[1] it was observed that the S_NAr coupling between ethyl 6-chloro-5-cyano-2-methylnicotinate (**4**) and isonipecotic acid was high yielding and we envisaged using the S_NAr reaction between 2-chloropyridine **4** and acyl sulfonamide **8** as the final step to AZD1283 to increase the probability of crystallizing **1** from the reaction mixture (Scheme 1).

RESULTS AND DISCUSSION

GLP Campaign, Campaign 1. Small scale experiments confirmed the high yielding coupling between **4** and **8** (Scheme 1) and we were pleased to discover that the final compound **1** could be precipitated from the reaction mixture. Campaign 1 was performed using this approach and 0.5 kg of material for preclinical studies delivered.

The left-hand fragment ethyl 6-chloro-5-cyano-2-methylnicotinate (**4**), was prepared according to published procedures[2,3] after minor modifications: ethyl acetoacetate and DMF dimethyl acetal was condensed neat without the need for a catalytic amount of acid and instead of isolating sodium cyanoacetamide and reacting it with enaminone **2**; we formed sodium cyanoacetamide with NaOEt/EtOH and then added a solution of enaminone **2**. A small amount of methyl ketone byproduct was formed,[4] but could be removed with an aqueous bicarbonate wash. Pyridone **3** was converted into the corresponding 2-chloropyridine **4** in a good yield under Vilsmeier conditions using $SOCl_2$/DMF instead of oxalyl chloride/DMF[5] and the crude product was used directly in the downstream chemistry. It was necessary to add 1 equiv of DMF in the chlorination of **3**, since the reaction often stalled when substoichiometric amounts were employed. Although the pyridone **3** was a colorless solid, 2-chloropyridine **4** appeared as a bright orange solid. Despite attempts to identify the source of the color, we were unable to determine it in any way. In the limited time frame available we were unable to find suitable conditions for recrystallizing 2-chloropyridine **4** during Campaign 1. Starting from Boc-protected isonipecotic acid **5** and benzylsulfonamide (**6**), we assembled the right-hand fragment **7**. A screen of coupling conditions indicated that a TBTU coupling performed in THF was a high yielding procedure. Especially in the presence of LiCl as a Lewis acid, the yield was excellent. In order to avoid TBTU reacting with benzylsulfonamide (**6**) forming guanidine adducts, the protected isonipecotic acid **5** was allowed to react with TBTU for 1−2 h before the addition of **6**. During workup the solvent was swapped to EtOAc and the crude product washed with dilute aqueous acid (substantial loss under neutral or basic conditions) yielding acyl sulfonamide **7** in a good yield, after precipitation from 50% EtOH. Treatment of **7** with six

Received: October 14, 2013
Published: November 13, 2013

   dx.doi.org/10.1021/op400288v | *Org. Process Res. Dev.* 2013, 17, 1543−1551

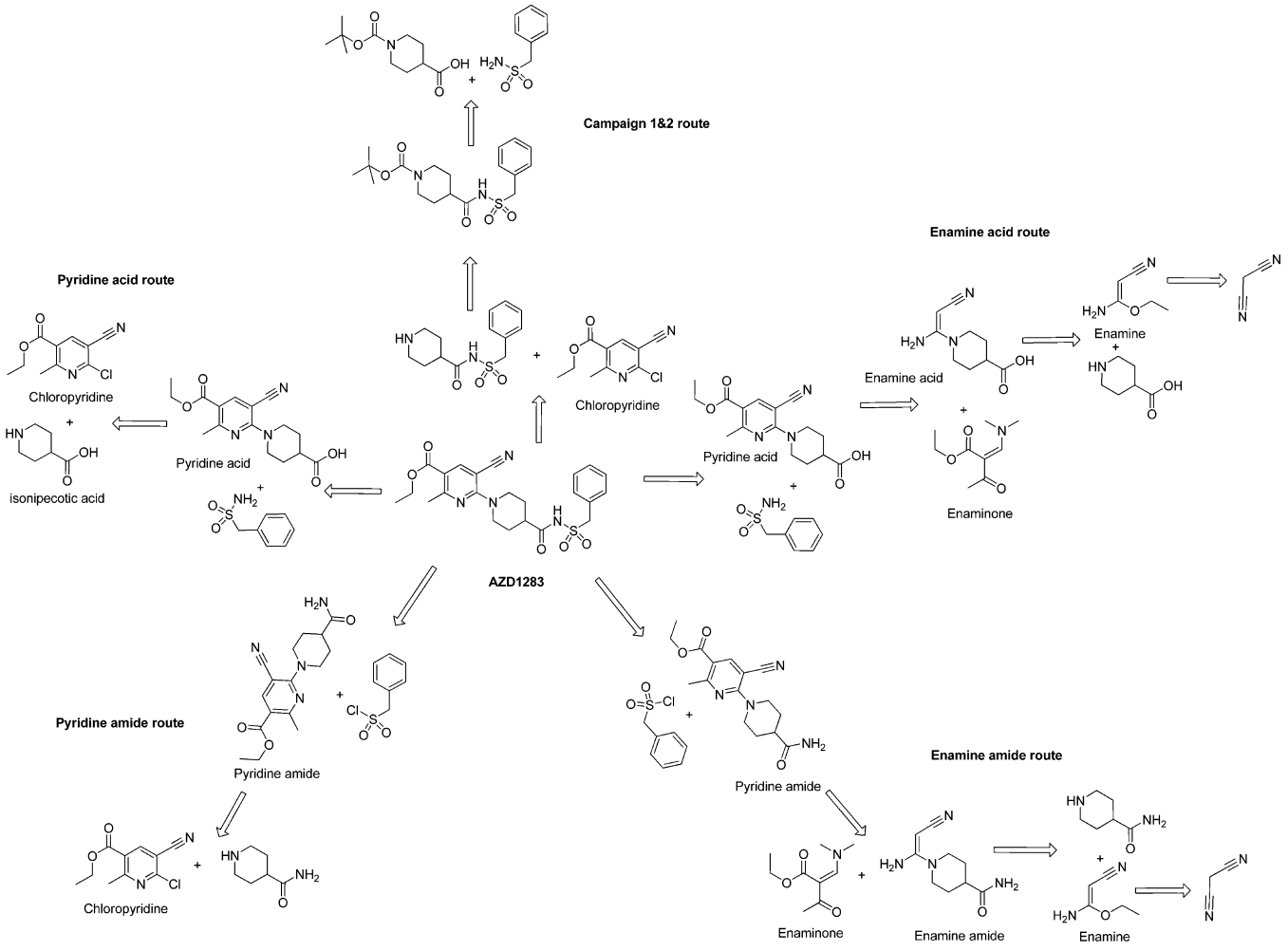
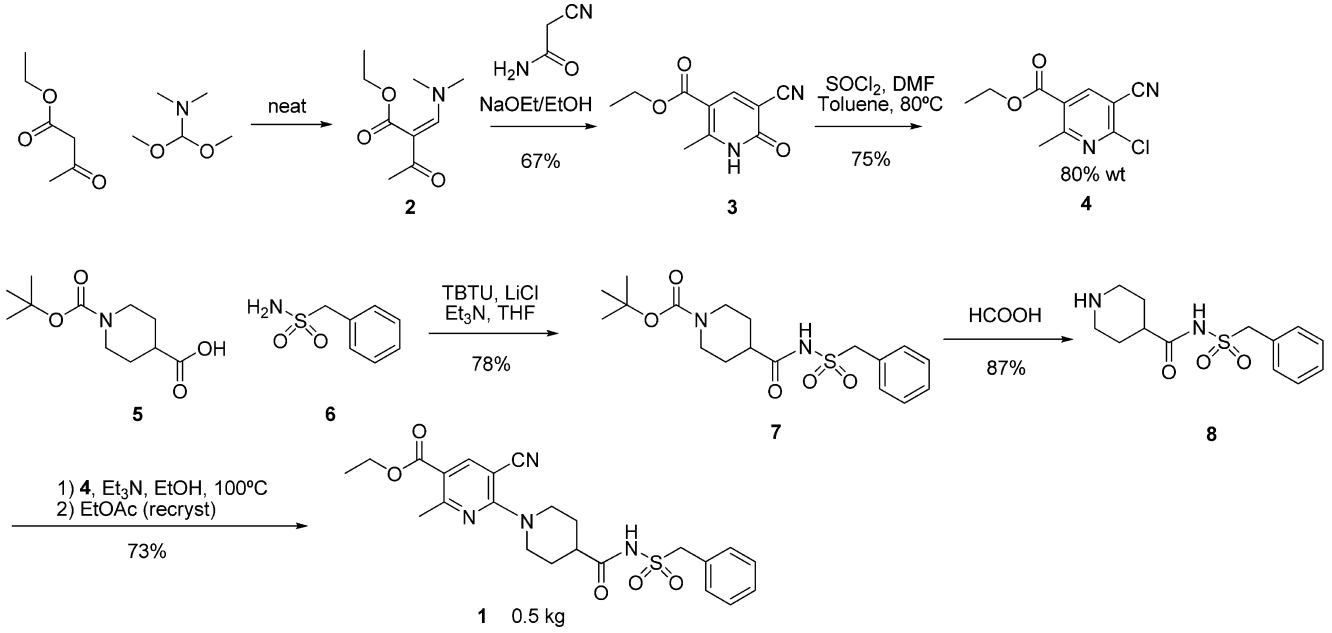


Figure 2. Tested routes to AZD1283.

Scheme 1. Campaign 1



volumes of formic acid afforded isonipecotic amide **8**, which was precipitated as a zwitterion at pH 6 from an aqueous solution in high purity and yield. Significant foaming was observed during deprotection of **7** and it was barely manageable

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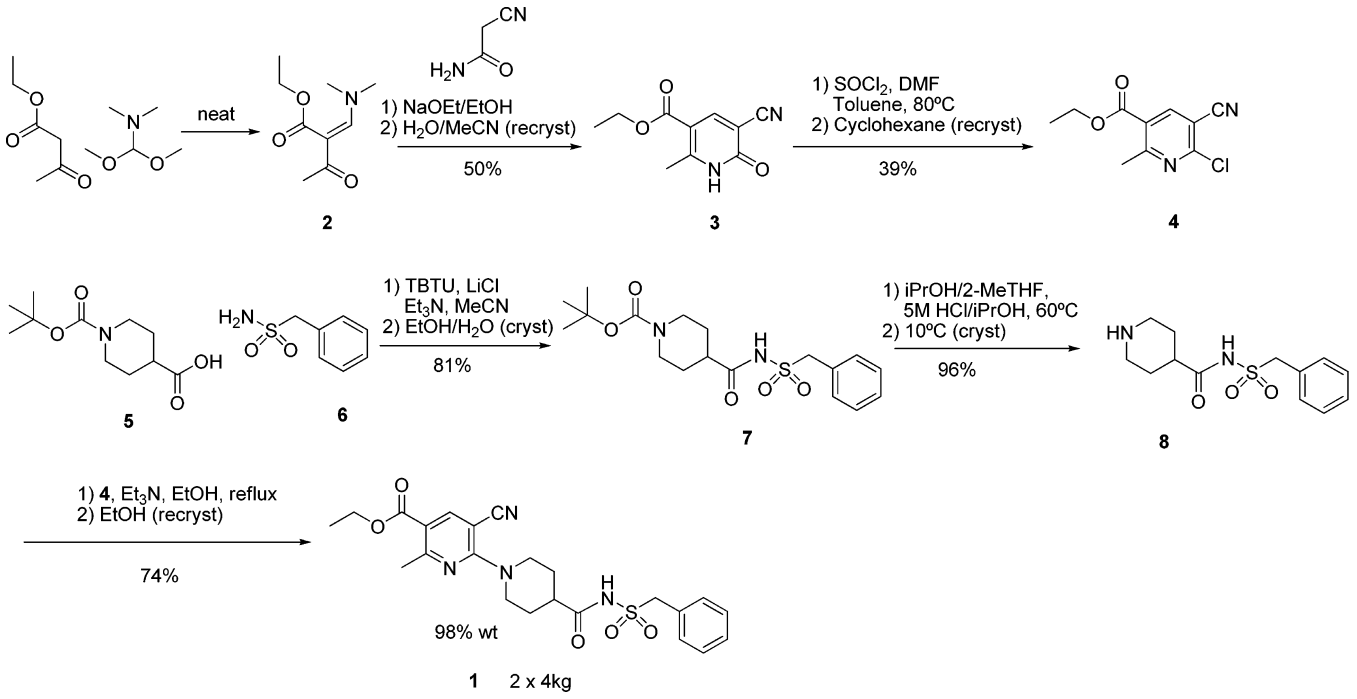
Scheme 2. Campaign 2



on a 10 L scale. Finally, isonipecotic amide **8** was coupled with 1 equiv 2-chloropyridine **4** (in the presence of triethylamine) by briefly heating up the reaction mixture to reflux. Upon cooling to ambient temperature and addition of aqueous potassium hydrogen sulfate, the crude product **1** oiled out and then precipitated from oily droplets. The purity was increased to >98% by treatment with charcoal and recrystallization from EtOAc to afford AZD1283 (**1**) for preclinical studies (polymorph I).[6] The orange color from 2-chloropyridine **4** persisted. In spite of considerable efforts, we were unable to identify the source of the color in any way. Attempts to further telescope the sequence from the coupling between Boc-isonipecotic acid **5** and benzylsulfonamide (**6**) to AZD1283, resulted in a final product that could not be precipitated. The chlorination could also be performed in EtOAc instead of toluene, but the final precipitation of AZD1283 (**1**) was difficult and generated larger amounts of byproducts.

First GMP Campaign, Campaign 2. The first GMP Campaign was based on Campaign 1 to supply material in time for initial clinical studies. Four kilograms of **1** was needed and based on Campaign 1, some key changes were necessary: (1) A recrystallization method was needed for chloropyridine **4** in order to avoid a strongly colored final compound; (2) an alternative to the Boc-deprotection in formic acid was essential to avoid the generation of foam; (3) a better crystallization method of the final product **1** was needed since it precipitated from oily droplet producing large particles. Analogously to Campaign 1, ethyl acetoacetate and DMF dimethyl acetal were reacted neat on a 15 kg scale and the methanol formed was distilled off under reduced pressure. After addition of cyanoacetamide to the intermediate enaminone **2** (in the presence of base), a better crystallization procedure was developed, precipitating pyridone **3** from acetonitrile/water in 67% yield. The material was recrystallized from acetonitrile/water affording **3** in 50% overall yield starting from ethyl acetoacetate and DMF dimethylacetal. 2-Chloropyridine **4** was prepared under Vilsmeier conditions, but contrary to Campaign 1, the product was crystallized and consequently was less colored. When scaling up the Vilsmeier reaction to 6−8 kg scale in a 100 L reactor, polymeric byproducts were formed. After completion of the reaction, the mixture was concentrated under reduced pressure and the viscous polymeric material caused the agitator to stop. On small scale these polymeric byproducts were only observed as a thin surface film. By repeatedly extracting the polymeric byproduct with toluene, the encapsulated product was dissolved leaving the polymeric material in the reactor. The crude product **4** was dissolved in ethanol and, upon controlled addition of water, crystallized in 67% yield. The material was dissolved in 95% ethanol, treated with activated carbon, and subsequently recrystallized from cyclohexane to give colorless 2-chloropyridine **4** in 39% yield starting from pyridone **3** (Scheme 2).

In Campaign 2, the coupling of Boc-isonipecotic acid **5** and benzylsulfonamide (**6**) was carried out in acetonitrile (THF used in Campaign 1). After completion of reaction, the solvent was swapped to isopropyl acetate and, after workup, the product crystallized from ethanol/water to afford Boc protected **7** in 81% yield. Two batches were prepared affording 9 kg of **7** in total. Using formic acid for Boc removal of **7** became increasingly problematic on scale due to foaming, but could be replaced with 5 M HCl/iPrOH. It was observed that the product **8** had a low solubility in 2-MeTHF and reaction conditions were found where the deprotection of **7** took place in a mixture of iPrOH and 2-MeTHF (3:1) at 55−60 °C and upon cooling **8** crystallized in 98% yield on a 6 kg scale. During Campaign 1, the final crystallization of **1** was sluggish. At first, **1** formed oily droplets together with inorganic salts and then precipitated. As a result particles several millimeters across in diameter were formed and it was challenging to get the material out of the reactor. Like Campaign 1, the coupling of **4** and **8** was performed in refluxing ethanol in the presence of triethylamine. After reaching 95% conversion, the mixture was cooled to 50 °C and upon acidification with an aqueous solution of *ortho*-phosphoric acid (instead of potassium

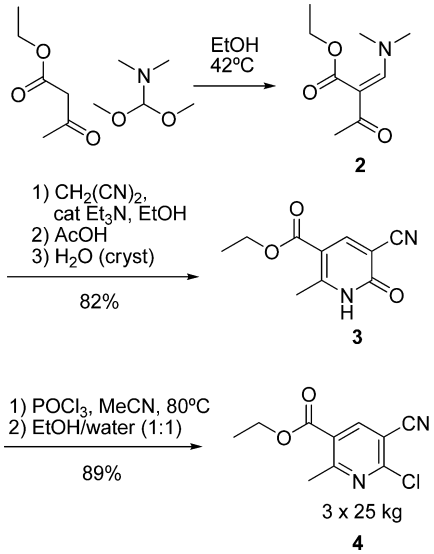
dx.doi.org/10.1021/op400288v | *Org. Process Res. Dev.* 2013, 17, 1543−1551

hydrogen sulfate), the product **1** precipitated without initially oiling out. Treatment with activated charcoal and recrystallization from ethanol gave the stable polymorph II[6] of AZD1283 (**1**) in a good yield and more than 99% purity. A total amount of 8 kg of **1** was prepared in this manner to support phase I clinical studies.

Second GMP Campaign, Campaign 3a, Prestudy, and Common Intermediates. For Campaign 3a it was estimated that more than 60 kg of API was needed. In parallel with the Campaign 2 manufacture, a prestudy was carried out with the aim to identify the best route for Campaign 3a and onwards. As a result of the large amounts needed for clinical studies and stressed timelines, the main criteria for the route to AZD1283 were as follows: robustness, manufacturability, and low cost of API. When taking the criteria into account, 5 different synthetic routes were identified and investigated (Figure 2): the Campaigns 1 and 2 route, the pyridine acid route, the pyridine amide route, the enamine acid route, and the enamine amide route.

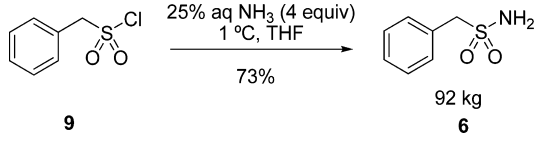
The selected routes to AZD1283 (**1**) have some intermediates in common, such as the 2-chloropyridine **4** and the benzylsulfonyl chloride or amide. A route to the pyridone **3** and 2-chloropyridine **4** was developed in collaboration with Almac[7] and was recently published.[4] It was found that when malononitrile was used as the starting material, instead of cyanoacetamide, a robust and scaleable procedure emerged producing colorless 2-chloropyridine **4** (Scheme 3). In this manner, three 25 kg batches of **4** were produced.

Scheme 3. Malononitrile route to 2-chloropyridine (4)[4]



Benzylsulfonamide (**6**) for Campaign 3a was outsourced to SAFC,[8] who prepared **6** from benzylsulfonyl chloride (**9**) via ammonolysis (Scheme 4). The reaction between benzylsulfonyl chloride (**9**) and ammonia[9] was tested in THF, dichloromethane, and acetonitrile with 2−12 equiv of 25% ammonium hydroxide solution added at −10 to +10 °C. Both addition of aqueous ammonia to the benzylsulfonyl chloride (**9**) and reverse addition were tested and it was found that addition of **9** in a THF solution to excess aqueous ammonia not only minimized the formation of benzylsulfonic acid from 3% to less than 1%, but also reduced the level of other byproducts.

Scheme 4. Synthesis of benzylsulfonamide (6)



Using this approach, 139 kg of benzylsulfonyl chloride (**9**) was converted to benzylsulfonamide (**6**). It was difficult to control the crystallization of **6**, which precipitated immediately on cooling, but after diluting the solids with more toluene and stirring the suspension overnight at 65 °C, a second cooling step afforded an excellent product quality and yield.

Evaluation of the Campaigns 1 and 2 Route. The Campaigns 1 and 2 route was improved by substituting TBTU/LiCl/Acetontrile with EDC/2-MeTHF[10] and as such had the potential to become a robust route since all the problematic steps could be improved. The conversions in all steps were good and the synthesis short. On the negative side, during Campaign 2 the pyridone **3** and the 2-chloropyridine **4** were flagged as potentially genotoxic intermediates and the route also had the highest cost of API, since the two most expensive starting materials, Boc-protected isonipecotic acid **5** and benzylsulfonamide (**6**), were used early in the synthesis.

Evaluation of the Pyridine Acid and Pyridine Amide Routes. 2-Chloropyridine **4** is the starting point of both the pyridine acid and the pyridine amide route. The pyridine acid route is similar to the original Medicinal Chemistry route,[1,5] but with the improved route to the 2-chloropyridine **4**,[4] it was found that this route could be dramatically improved and AZD1283 (**1**) crystallized without the need for chromatography. The S_NAr reaction between 2-chloropyridine **4** and isonipecotic acid could be performed in ethanol in the presence of triethylamine and the subsequent coupling with benzylsulfonamide (**6**) could be accomplished using EDC/DMAP or CDI in NMM or 2-MeTHF (Scheme 5). Alternatively, the coupling could be performed via the acid chloride, although it was tricky to reproduce.

The pyridine amide route is very similar, except that isonipecotic amide is used instead of isonipecotic acid and the last step consists of sulfonylation of the resulting pyridine amide. Similar to the pyridine acid route, chloropyridine **4** could be coupled with the isonipecotic amide in ethanol and triethylamine. Sulfonylation with benzylsulfonyl chloride **9**[11] was done in THF in the presence of sodium *tert*-amylate at low temperature (it was found that the reaction temperature had to be less than −25 °C). By comparison of the pyridine acid/amide routes to the Campaigns 1 and 2 route, they are of similar length, but with a lower cost of API (no protecting group used). In the case of the pyridine acid route via CDI/EDC coupling, potentially genotoxic **4** was used early in the synthesis and the sequence is robust. Via the acid chloride, the final step was unexpectedly tricky and in need of more investigation. The pyridine amide route required low temperature in the final step, reducing the manufacturability.

Evaluation of the Enamine Acid and Enamine Amide Routes. In the last two routes, which were considered, the pyridine ring was build with the isonipecotic acid moiety in place (Scheme 6).

Initial experiment showed that it was possible to build the pyridine ring system with isonipecotic acid/amide in place. For both routes ethanol was added to malononitrile affording the corresponding enamine HCl salt.[12] In the enamine acid route,

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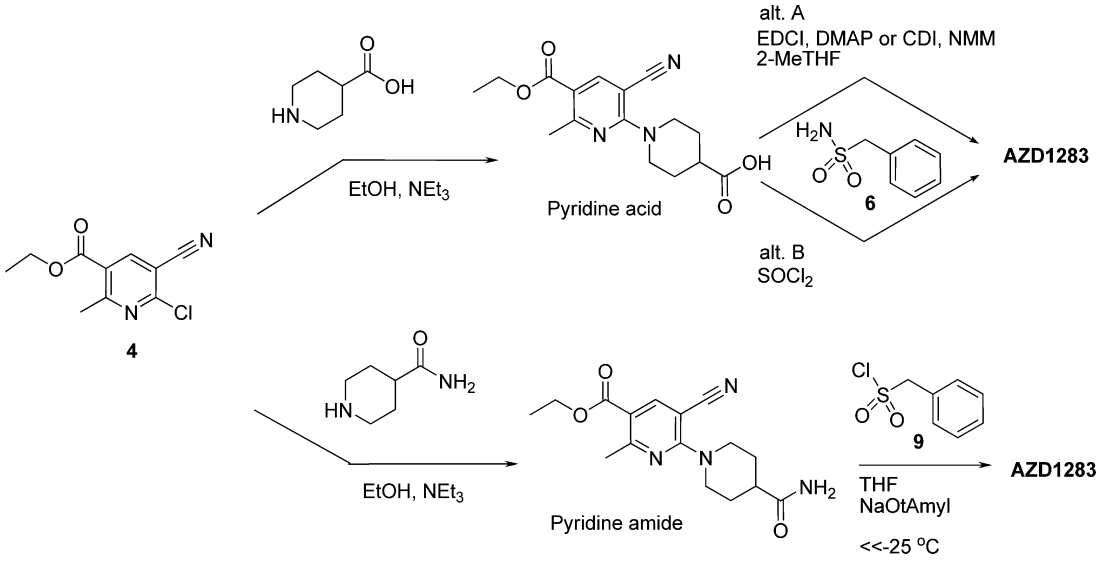
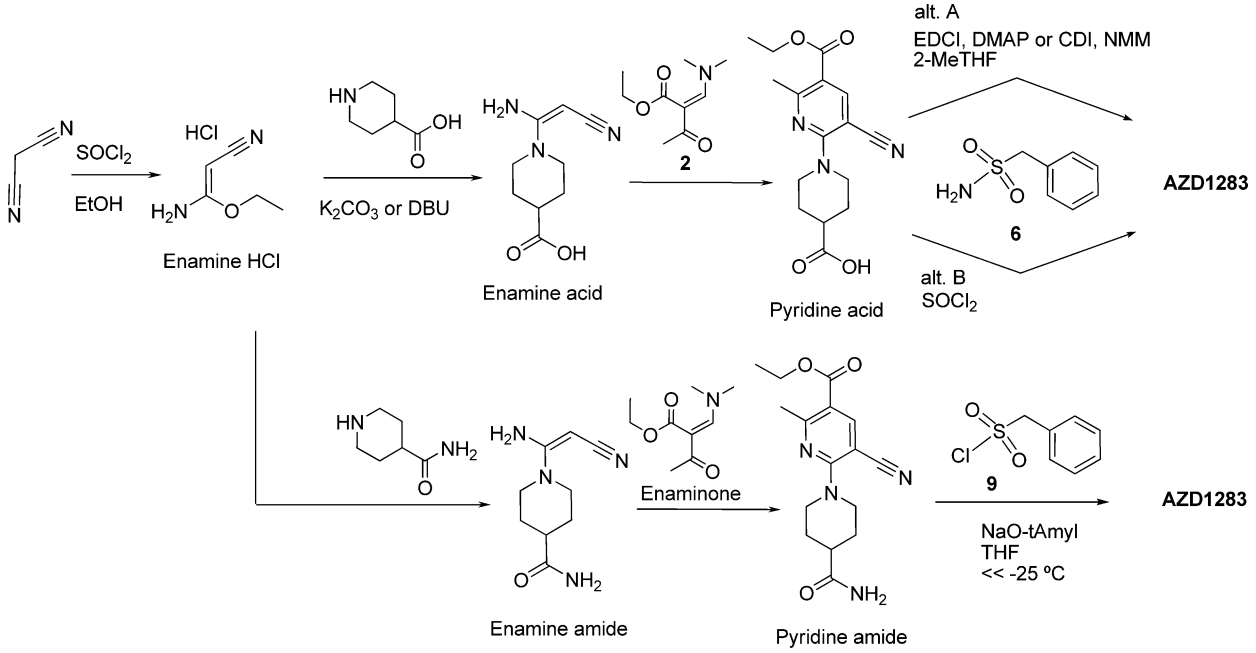
Scheme 5. Pyridine acid and pyridine amide route



Scheme 6. Enamine acid and enamine amide routes



the enamine was substituted with isonipecotic acid in the presence of potassium carbonate or DBU and in the enamine amide route, with isonipecotic amide.[13] These products in turn were reacted with enaminone **2** to yield the final intermediates: pyridine acid and pyridine amide. The pyridine acid could be coupled with benzylsulfonamide (**6**) to afford AZD1283 (**1**) using EDC/DMAP or CDI in NMM or 2-MeTHF or via the acid chloride in pyridine/toluene. For the enamine amide route, the pyridine amide could be reacted with benzylsulfonyl chloride (**9**) in THF at low temperature. The lengths of the enamine acid/amide routes are comparable to previously discussed alternatives, but have lower cost of API than the Campaigns 1 and 2 route (no protection group used). When adding isonipecotic acid/amide to enamine **2**, the use of potassium carbonate as a base caused some concerns about the huge amount of salt waste and the reaction was difficult to work up when using DBU (byproducts). The enamine acid route using thionyl chloride in the last step shared similar concerns with the pyridine acid route, being tricky to reproduce. The enamine amide route required low temperatures for the final step. In general, the stability of the enamine intermediates, and thereby the robustness of the sequences, was unknown, and much more development work is needed.

Second GMP Campaign, Campaign 3a. The pyridine acid route was selected for further development and scale-up due to the low cost of API, but also as the most secure route alternative with the highest probability for good manufacturability and robustness in all steps. In addition, both of the potential genotoxic compounds (pyridone **3** and 2-chloropyridine **4**) were used early in the synthesis. In Campaign 3, the solvent for the S_NAr substitution of **4** with isonipecotic acid was changed from EtOH to iPrOH to minimize the formation of

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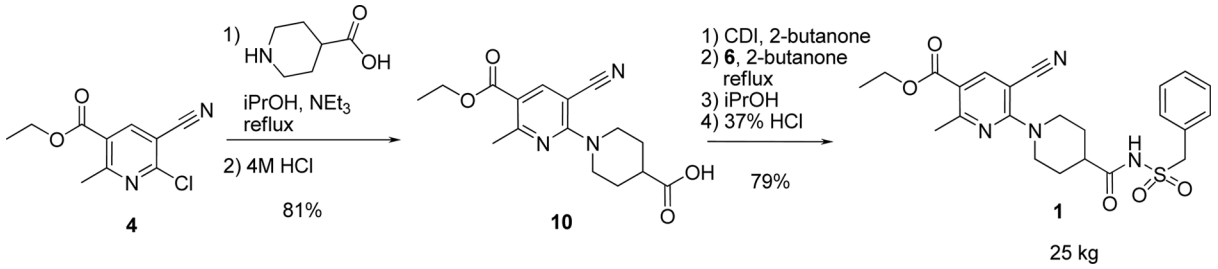
Scheme 7. Campaign 3a



the corresponding diester of **10** (Scheme 7). Using ethanol resulted in 0.6% diethyl ester of **10**, whereas using iPrOH only resulted in 0.2% ethyl isopropyl diester of **10**. It was also found that 2 equiv of base were needed for the reaction to work well (1 equiv for the formed HCl and 1 equiv to deprotonate the carboxylic acid) and a small excess of isonipecotic acid was necessary to ensure that all 2-chloropyridine **4** was consumed. Triethylamine could be added at both ambient and high temperature, but to have control over the energy release, the base was added slightly below reflux temperature. In this manner 18 kg of 2-chloropyridine **4** was reacted with 1.03 equiv of isonipecotic acid and after refluxing for 4.5 h, all starting material had been consumed. On lab scale it was observed that rapid addition of 1.05 equiv of aqueous HCl caused the product to crash out. The crystallization behaved much better if the reaction mixture was seeded after 55% of the aqueous HCl had been added (if less aqueous HCl added, the seed crystals dissolved). After aging the crystallization mixture, the remaining aqueous HCl could be added during 2.5 h. After cooling, the pyridine acid **10** was filtered off and washed with iPrOH−water mixtures. In order to get rid of triethylammonium chloride, the first wash contained mainly iPrOH (5:1 wt/wt iPrOH−water), whereas the second and third washes contained more water to get rid of excess HCl (1:4 wt/wt iPrOH−water). Due to the water in the wash, the filter cake was voluminous and the drying time long. After Campaign 3a it was found that the third wash could be performed with iPrOH at lower temperature (0 °C instead of 10 °C), improving the yield and shortening the drying time. It was also observed that the solids could be dried at 60 °C instead of 40 °C, without affecting the purity of **10**. The largest observed impurity was the addition of isonipecotic acid to **10** (added to the isonipecotic acid part, MW 428).

A screen of different coupling conditions was carried out for the final coupling between pyridine acid **10** and benzylsulfonamide (**6**). Using thionyl chloride for the coupling was abandoned since a huge excess of pyridine as base/solvent was necessary and the subsequent coupling did not produce good results. The coupling was also tested with EDC, CDI, and isobutyl chloroformate. CDI[14] was chosen since it gave the highest yield and no base was needed (addition of a base such as *N*-methyl morpholine or pyridine only resulted in lower yields). A range of solvents were screened for the coupling, such as 2-butanone, MIBK, THF, 2-MeTHF, acetonitrile, DMSO, NMP, and DMI, and the best result were obtained with 2-butanone, NMP, and DMI—2-butanone was chosen for Campaign 3a since it had a lower boiling point and no potential SHE issues. Both pyridine acid **10** and CDI forms slurries in 2-butanone, but since the slurry of **10** in 2-butanone was more homogeneous than CDI in 2-butanone, it was decided that the slurry of **10** should be added to the slurry of CDI. Thus on a 20 kg scale, pyridine acid **10** was added to a mixture of CDI in 2-butanone, affording the corresponding acyl imidazole. Initially the reaction was performed at 45−50 °C, but was later lowered to 20−25 °C, since it gave better results. For the final coupling of the acyl imidazole of **10** with **6**, the reaction rate increased with increased temperature, but at temperatures above 110 °C in THF/MIBK, considerable side reactions were seen and decomposition of **1** started to occur. With 2-butanone and a reflux temperature of 82 °C, a fast conversion was observed on lab scale with limited byproduct formation. In the beginning of the development work, an excess of 1.3 equiv of benzylsulfonamide (**6**) was used with a reaction time around 1 h. Lowering the excess of **6** to 1.2 equiv gave similar results, but when 1.1 equiv was used a significantly longer reaction time was needed (22 h). With 1.05 equiv of **6** the reaction did not progress beyond 70% conversion. Both EtOH and iPrOH were tested as antisolvents, but with EtOH the product oiled out in several experiments. Changing to iPrOH improved the process, no oiling out was observed, and the solubility properties improved. For the development work, a ratio of 65:35 2-butanone−iPrOH (v/v) was chosen and the reaction mixture was clear filtered at 80 °C. Upon cooling, AZD1283 (**1**) precipitates from this solvent mixture. Generated imidazole also precipitates, either by cocrystallization or incrustation in the formed crystals, but by addition of HCl/iPrOH the formed imidazole hydrochloride remains in the mother liquid. Only a minor excess of HCl can be added since AZD1283 (**1**) is not stable below pH 1. It was also noted that if the HCl/iPrOH mixture was added after the mixture had been seeded, the crystallization was interrupted and a clear solution obtained. From that point on, the crystallization was uncontrollable. A possible reason for this could be the higher solubility of **1** in slightly basic media. By adding part of the HCl/iPrOH mixture prior to seeding and reducing the crystallization temperature from 65 to 60 °C, the kinetics for the nucleation was favored over those of dissolution. After aging for 1 h, the remaining HCl/iPrOH was added and the crystallization temperature lowered to 0 °C. This protocol gave robust crystallization, affording AZD1283 (**1**) (polymorph II)[6] with a purity above 99.5%, even in the presence of a large excess of benzylsulfonamide (**6**) (1.45 equiv) and up to 20% of hydrolyzed **1** (decomposition product of **1**). The only impurity of concern from the reaction, imidazole, could be removed by aqueous wash. Taking all these details into account, we converted pyridine acid **10** into AZD1283 (**1**) on a 20 kg scale in 83% yield.

■ CONCLUSION

Large scale synthesis routes to AZD1283 (**1**) have been developed and material manufactured to support preclinical and clinical studies in scale-up Campaigns 1, 2, and 3a. In Campaign 1, 0.5 kg non-GMP AZD1283 (**1**) was produced in six steps starting from ethyl acetoacetate and DMF dimethyl acetal. The

dx.doi.org/10.1021/op400288v | *Org. Process Res. Dev.* 2013, 17, 1543−1551

overall yield was 50% starting from 2-chloropyridine **4**, Boc-isonipecotic acid **5**, and benzylsulfonamide (**6**). The Campaign 1 material appeared as an orange solid and the synthesis was in need of better workup procedures. One synthetic step was not scaleable (Boc-deprotection performed in formic acid). In Campaign 2, using the same synthetic sequence, improved workup procedures were developed as well as a scaleable Boc-deprotection process using HCl/iPrOH. Campaign 2 generating 8 kg of colorless GMP material for phase I clinical studies in 58% overall yield starting from **4**, **5**, and **6**. Prior to the next round of scale-up, Campaign 3a, a thorough prestudy was performed to identify the most suitable route based on robustness, manufacturability, and low cost of API. Five routes were selected and investigated and the pyridine acid route was selected (Figure 2). In the pyridine acid route, isonipecotic acid is coupled with 2-chloropyridine **4** to give pyridine acid **10**, which is coupled with benzylsulfonamide (**6**) to afford AZD1283 (**1**). The route was developed and scaled up to yield 20 kg batches of AZD1283 (**1**) in a 64% overall yield starting from **4**, **6**, and isonipecotic acid. Campaign 1 afforded polymorph I and Campaigns 2 and 3 yielded polymorph II.[6] The synthesis of benzylsulfonamide (**6**) and 2-chloropyridine **4** were outsourced and optimized procedures are included for **6**. Optimized procedures for **4** have recently been published.[4] During Campaign 3a it was found that pyridone **3** and 2-chloropyridine **4** were not genotoxic after all and we also found a thermodynamically more stable polymorph of AZD1283 (**1**), being formed after 4−5 days at 0 °C in 2-butanone (more stable at 0 to 65 °C, polymorph II more stable at 65 to 80 °C). If seeded the transformation of polymorph II into the more stable polymorph takes less than 24 h at 0 °C in 2-butanone. A total of six polymorphs were observed.

EXPERIMENTAL SECTION

Commercially available solvents and reagents were used without purification. All reaction and operations were conducted under an inert nitrogen atmosphere and, unless otherwise noted, temperature describes the mantle temperature of the reactor. Thin-layer chromatography was made on silica gel 60 F_{254} (Merck KGaA, Darmstadt). LC analyses were performed using a Waters 600 instrument, C8 kromasil 100 column (50 × 4.6 mm, d_f = 5 μm), mobile phase 0.1 M NH_4OAc buffer/acetonitrile. HRMS analyses were performed using a Micromass LCT mass spectrometer. ^{1}H NMR measurements were performed on a Varian Mercury VX 400 spectrometer, operating at a ^{1}H frequency of 400 MHz or on Varian UNITY plus 400, 500, and 600 spectrometers, operating at ^{1}H frequencies of 400, 500, and 600 MHz, respectively. Chemical shifts are given in ppm with the solvent as internal standard. Coupling constants are given in Hz. Purity is measured by %area in LC and %wt by Quantitative NMR. When %wt is noted the yields have been corrected.

Campaign 2. *tert-Butyl 4-[(benzylsulfonyl)carbamoyl]-piperidine-1-carboxylate (**7**).* A reactor was charged with 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (**5**) (4.5 kg, 98.6 wt %, 19.4 mol), 1-benzylsulfonamide (**6**) (3.44 kg, 1.05 equiv), LiCl (0.21 kg, 0.25 equiv), TBTU (6.56 kg, 1.05 equiv), and then AcCN (27 L). The reaction mixture was cooled to 15 °C and triethylamine (8.78 kg, 4.5 equiv) was added. For the coupling, the temperature was increased to 25 °C. In order to reach full conversion more TBTU (1.25 kg, 0.2 equiv) was added after 2.5 h. After 17 h, the reaction mixture was concentrated under reduced pressure at 40 °C (25 L distilled off) and isopropyl acetate (23 L) was added. The solvents were distilled off under reduced pressure at 40 °C (23 L distilled off, all acetonitrile removed). Isopropyl acetate (22 L) was added and then 1 M HCl (45 L). The organic phase was washed with 1 M HCl (3 × 45 L) and concentrated under reduced pressure at 40 °C to a crude residue. EtOH (15 L) added and the mixture concentrated under reduced pressure at 40 °C (13 L distilled off). EtOH (26 L) was added and at 40 °C, water (25 L) was added until crystallization was induced. The product mixture was cooled to 5 °C over 4 h, and after 12 h, the solids were filtered off. The mother liquid was concentrated under reduced pressure at 40 °C (12 L distilled off) and water (20 L) added until crystallization was induced. Cooled to 5 °C and after 2 h, the solids were filtered off. The combined solids were washed with cold EtOH (0 °C, 7 L) and dried under reduced pressure at 40 °C to 6.0 kg (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.43 − 1.76 (m, 4H), 2.26 (tt, J = 3.8, 11.3, 1H), 2.67 (s, 2H), 4.04 (d, J = 13.3, 2H), 4.6 (s, 2H), 7.21 − 7.45 (m, 5H), 8.69 (s, 1H). ^{13}C NMR (151 MHz, CD_3OD) δ 28.7 (3C), 29.0 (2C), 43.8, 44.0 (2C), 59.1, 81.2, 129.8 (2C), 130.0, 130.4, 131.9 (2C), 156.3, 176.3. HRMS (ESI): [M]+ m/z Calcd for $C_{18}H_{26}N_2O_5S$ 382.1562; Found 382.1563.

*4-[(Benzylsulfonyl)carbamoyl]piperidinium hydrochloride (**8**).* A reactor was charged with *tert*-butyl 4-[(benzylsulfonyl)-carbamoyl]piperidin-1-carboxylate (**7**) (6.0 kg, 15.7 mol), iPrOH (30 L) and 2-MeTHF (8.5 L). The temperature was increased to 60 °C and 5 M HCl in iPrOH (8 L) was added during 2 h. The addition vessel was washed with 2-MeTHF (2 L). After 2 h the reaction mixture was cooled to 10 °C over 5 h. The product crystallized from the cold reaction mixture and was filtered off and washed with 2-MeTHF (10 L). The product was dried at 40 °C under reduced pressure to 4.78 kg (96% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.66−1.92 (m, 4H), 2.79 (d, J = 9.9, 2H), 3.22 (d, J = 12.6, 2H), 3.35 (s, 1H), 4.68 (s, 2H), 7.21−7.33 (m, 2H), 7.33−7.44 (m, 3H), 9.05 (s, 1H), 9.23 (s, 1H), 11.72 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 24.3 (2C), 39.1, 41.9 (2C), 57.5, 128.6 (2C), 128.7, 129.0, 130.7 (2C), 173.6. HRMS (ESI): [M]+ m/z Calcd for $C_{13}H_{18}N_2O_3S$ 282.1038; Found 282.1038.

*AZD1283: Ethyl 6-{4-[(benzylsulfonyl)carbamoyl]-piperidin-1-yl}-5-cyano-2-methylpyridine-3-carboxylate (**1**).* A reactor was charged with ethyl 6-chloro-5-cyano-2-methyl-nicotinate (**4**) (3.0 kg, 86 wt %, 11.5 mol), 4-[(benzylsulfonyl)-carbamoyl]piperidinium chloride (**8**) (4.6 kg, 96 wt %, 1.2 equiv) and EtOH (30 L). Triethylamine (5.2 kg, 4.5 equiv) was added and the reaction mixture was refluxed for 2 h. The mixture was cooled to 50 °C and a solution of *ortho*-phosphoric acid (4 kg in 15 L of water) was added to the reactor. The resulting slurry was stirred for one hour and then cooled to 0 °C over 5 h. The crystalline product was filtered off and washed with cold EtOH (0 °C, 20 L). The product was dried under reduced pressure at 40 °C to 5.1 kg crude product (94%). The crude product was treated with activated charcoal (350 g) in THF (25 L) at reflux for 5 h. The filtrate was concentrated under reduced pressure at 60 °C to a volume of 12.5 L. Cooled to 10 °C and upon addition of EtOH (25 L) the product precipitated. After 3 h, the solids were filtered off and washed twice with cold EtOH (10 °C, 7.5 and 10 L). The product was dried under reduced pressure at 40 °C to 4.1 kg of polymorph II[6] (98 wt %, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.1), 1.59 − 1.8 (m, 4H), 2.26 − 2.37 (m, 1H), 2.60 (s, 3H,), 2.94 − 3.06 (m, 3H), 4.19 (q, 2H, J = 7.1), 4.48 − 4.57 (m, 4H), 7.11 − 7.31 (m, 5H), 8.03 (s, 1H), 8.22 (s, 1H).

dx.doi.org/10.1021/op400288v | Org. Process Res. Dev. 2013, 17, 1543−1551

^{13}C NMR (101 MHz, $CDCl_3$) δ 14.3, 25.7, 27.7 (2C), 42.8, 46.4 (2C), 58.8, 61.0, 89.2, 115.0, 117.9, 127.8, 129.0 (2C), 129.5, 130.6 (2C), 147.7, 158.3, 164.4, 164.6, 173.0 . HRMS (ESI): [M]+ m/z Calcd for $C_{23}H_{26}N_4O_5S$ 470.1624; Found 470.1598 .

Campaign 3. *Benzylsulfonamide (**6**).* A reactor was charged with 25% aqueous ammonia (209 kg, 3068 mol) and cooled to 1 °C. A solution of benzylsulfonyl chloride **9** (139 kg, 729 mol) in THF (312 kg) was slowly added over 1 h (max reaction temperature 9 °C) and the addition vessel was washed with THF (21 kg). The temperature was increased to 22 °C and stirred for 8 h (less than 0.2% starting material left). The lower aqueous phase was removed and MTBE (217 kg) added. A small amount of additional aqueous phase was removed (5 L) and the organic phase was washed twice with brine (116 and 83 kg) and then with water (84 L). The organic phase was concentrated under reduced pressure at 45 °C (400 L removed) and then cooled to 21 °C. The solution was filtered and the temperature increased to 43 °C. Toluene (417 kg) was added maintaining a temperature of 40−45 °C. The solution was concentrated under reduced pressure at 80 °C (250 L removed). The product precipitated immediately on cooling instead of slowly crystallizing and therefore more toluene (40 L) was added and the mixture stirred at 65 °C overnight. The solution was slowly cooled to 20 °C over 5 h and stirred at this temperature for additional 3 h. The product was filtered off, washed with toluene (249 kg), and dried under reduced pressure at 38 °C to 91.8 kg (73.2%, UV purity 99.95% at 210 nm).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (s, 2H), 4.66 (s, 2H) and 7.36−7.47 (5H, m). ^{1}C NMR (150.9 MHz, DMSO- d_6) δ 60.2, 127.8, 128.2 (2C), 130.7 (2C), 130.8. HRMS (ESI): $[M]^-$ m/z Calcd for $C_7H_8NO_2S$ 171.0354; Found 171.0337.

*1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]-piperidine-4-carboxylic acid (**10**).* A reactor was charged ethyl 6-chloro-5-cyano-2-methylnicotinate (**4**) (17.6 kg, 78.1 mol), isonipecotic acid (10.4 kg, 80.5 mol) and iPrOH (83 kg). The temperature was increased to 80 °C and triethylamine (15.8 kg, 2.0 equiv) was added over 1 h. The reaction mixture was heated to reflux for 4.5 h to reach completion and then cooled to 45 °C. 12% Hydrochloric acid (14.4 kg) was added over 30 min. The mixture was seeded with **10** (124 g) and after 1 h, more 12% hydrochloric acid (11.3 kg) was added over 2.5 h. After additional 45 min the mixture was cooled to 8 °C over 5.5 h. After 4 h the product was filtered off and washed once with a cold 5:1 mixture (w/w) of iPrOH and water (10 °C, 43 kg) and then twice with a cold 1:4 (w/w) mixture of iPrOH and water (10 °C, 2 × 50 kg). The product was dried at 40 °C under reduced pressure to 21.4 kg (excl. seed, 94.1 wt %, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, 3H, J = 7.1), 1.8 − 1.96 (m, 2H), 2.02 − 2.16 (m, 2H), 2.62 − 2.78 (m, 4H), 3.25 − 3.38 (m, 2H), 4.32 (q, 2H, J = 7.1), 4.53 − 4.66 (m, 2H), 8.35 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.3, 25.7, 27.8 (2C), 40.6, 46.7 (2C), 60.9, 89.1, 114.8, 118.0, 147.7, 158.4, 164.4, 164.7, 180.0. HRMS (ESI): [M]+ m/z Calcd for $C_{16}H_{19}N_3O_4$ 317.1376; Found 317.1375.

*AZD1283: Ethyl 6-{4-[(Benzylsulfonyl)carbamoyl]-piperidin-1-yl}-5-cyano-2-methylpyridine-3-carboxylate (**1**).* A reactor at 25 °C was charged with 1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (**10**) (21.4 kg, 94.1 wt %, 63.5 mol) and 2-butanone (114 kg). After 45 min the solution of **10** was added to a mixture of 1,1-carbonyldiimidazol (12.4 kg, 1.20 equiv) and 2-butanone (33 kg) at 20 °C over 30 min (evolution of carbon dioxide). The reactor was rinsed with 2-butanone (16 L). After 1 h, 90% conversion. More 1,1-carbonyldiimidazole (1.72 kg, 0.17 equiv) in 2-butanone (4 kg) was added. After a total of 7 h 30 min more than 98% conversion. A solution of benzylsulfonamide (**6**) (13.2 kg, 1.21 equiv) in 2-butanone (33 kg) was added over 10 min and the addition vessel was rinsed with 2-butanone (8 kg). The temperature was increased to 90 °C and 2-butanone was distilled off until 8 relative volumes were left in the reactor (170 L). Thereafter the reactor content was refluxed for 17 h (full conversion). More 2-butanone (35 kg) was added to the hot reaction mixture, keeping the internal temperature above 80 °C, and then iPrOH (64 kg) was added, keeping the internal temperature above 70 °C. At 80 °C, the reaction mixture was clear filtered and the filter was washed with solution of 2-butanone (12 kg) and iPrOH (7 kg). The filtrate was cooled to 60 °C and a solution of 37% hydrochloric acid (9.8 kg) in iPrOH (18.1 kg) was added over 40 min, keeping the internal temperature at 60 °C. The mixture was seeded with AZD1283 (**1**) (0.24 kg of polymorph II) and after 1 h, a solution of 37% hydrochloric acid (16.0 kg) in iPrOH (29.6 kg) was added over 2 h, keeping the temperature at 60 °C. The reaction mixture was cooled to 0 °C over 10 h and stirred overnight (7 h). The product slurry was filtered and the product was washed with a cold 1:1 (w/w) mixture of 2-butanone and iPrOH (0 °C, 32 kg) and then with cold water (2 °C, 3 × 40 kg). The product was dried under reduced pressure at 40 °C to 24.7 kg of polymorph II[6] (excl. seed, 83% yield).

Analytical data as described under Campaign 2.

■ ASSOCIATED CONTENT

Supporting Information

Experimental methods. 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.

■ ACKNOWLEDGMENTS

We would like to thank Dr. Thomas Antonsson, Astrazeneca R&D for constructive criticism on the present paper. Jim Brennan, Veronica Profir, Emma Carlsson, and Stefan Berlin at Astrazeneca Process R&D are also acknowledged for their contributions to this work. The authors also thank SAFC for providing compound 6 on large scale.

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NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on November 22, 2013. The text "polymorph II" was corrected to "polymorph I" in the first section of the Results and Discussion. The corrected version was reposted on December 3, 2013.