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Synthetic Process Development of BMS-599793 Including Azaindole Negishi Coupling on Kilogram Scale

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Supporting Information

ABSTRACT: A new approach to the synthesis of **1** (DS003, BMS-599793), a small-molecule HIV entry inhibitor, is described. The initial medical chemistry route has been modified by rearranging the sequence of synthetic steps followed by replacement of the Suzuki coupling step by the Negishi conditions. Acylation of the resulting azaindole **7** under the Friedel−Crafts conditions is studied using monoesters of chlorooxalic acid in the presence of aluminum chloride. Polymorphism of **1** is also investigated to develop conditions suitable for preparation of the desired Form **1** of the target compound. The new route is further optimized and scaled up to establish a new process that is applied to the synthesis of kilogram quantites of the target active pharmaceutical ingredient.

INTRODUCTION

1 (DS003, BMS-599793) is a small-molecule entry inhibitor that interferes with HIV infection by binding to the gp120 protein.[1] The International Partnership for Microbicides (IPM) licensed **1** from Bristol-Myers Squibb (BMS) with the goal to develop it as a topical microbicide for use in resource-poor countries. Microbicides are vaginal dosage forms of potent inhibitors of HIV that women can use to prevent sexual transmission of HIV from male partners. At the time of licensing, a synthesis developed by the BMS medicinal chemistry group was provided (Scheme 1). Milligram quantities of **1** were prepared at BMS during the course of the discovery program. This discovery route utilized a Stille coupling reaction in the last step of the synthesis, yielding **1** containing excessive levels of residual tin that proved difficult to remove. In addition, the Stille reaction[2] required a pyrazine tributyltin reagent (**6**) that is toxic, expensive, unpleasant to use, and not readily available in larger quantities. Given these synthetic liabilities, the medicinal chemistry process was not suitable for scale-up and preparation of preclinical material. A new synthesis process was required to address these deficiencies. Our efforts to develop such a process are described herein.

RESULTS AND DISCUSSION

Step Sequence Change. In the initial approach to address the high residual metal level in **1** an attempt was made to rearrange the synthetic steps and to perform the Stille coupling as the first, rather than the last, step of the sequence as shown in Scheme 2. This approach worked well synthetically and provided the desired product with an overall yield comparable to that obtained by following the original med-chem route. However, despite the fact that three synthetic steps followed the Stille coupling step to reach **1**, the final material still contained residual levels of tin in the 40 ppm range. This result demonstrated the need for further research to identify a better alternative to the Stille reaction.

Alternative Coupling Conditions. At the initial stage the coupling reaction of azaindole **2** was explored using a pyrazine Grignard reagent derived from iodopyrazine **8**[3] (Scheme 3). Transmetalation of the Grignard to form a zinc intermediate and its reaction with **2** was performed under standard conditions for Negishi coupling[4] using a palladium catalyst. These conditions afforded the desired coupled product **7** in yields of over 60%.

The Suzuki reaction[5] was also briefly investigated using the pyrazine Grignard to form the corresponding pyrazine boronic acid derivatives. However, a number of reaction conditions that were tried produced impure mixtures. Application of pinacol diborane afforded a relatively clean pinacol boronate derivative, but its Suzuki reaction with **2** proved to be rather slow. No coupled product was observed when the reaction was run at 100 °C, and at 140 °C only a small amount of **7** was observed. In view of these results and the early positive result with the Negishi reaction, further research focused on the optimization of the Negishi chemistry.

Negishi Reaction. The pyrazine Grignard reagent was prepared via an exchange reaction of iodopyrazine **8**[3] using commercially available *n*-butylmagnesium chloride in THF at −20 °C to −10 °C. Only isopropyl magnesium chloride was examined as an alternative, but the outcome was less clean. Temperatures of −20 °C to −10 °C were found optimal for the

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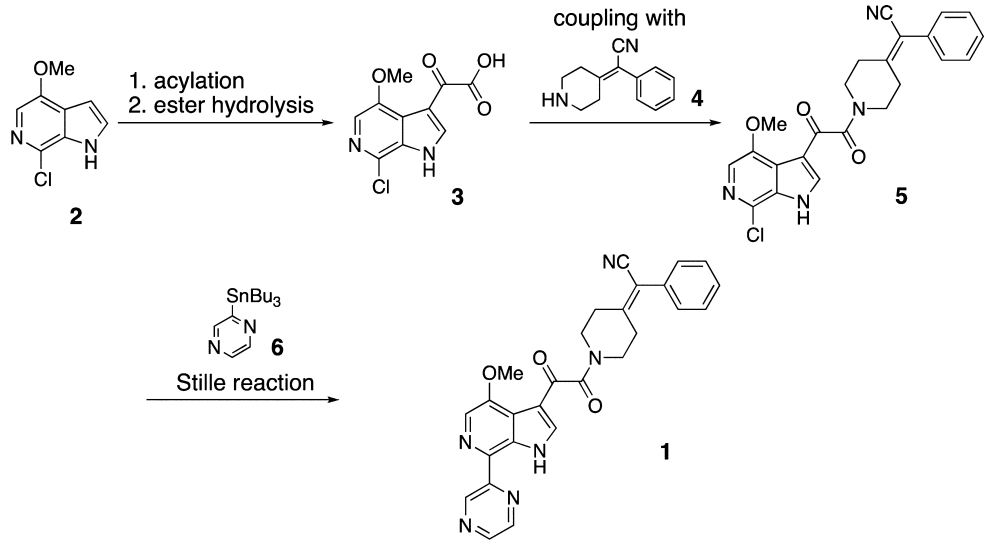
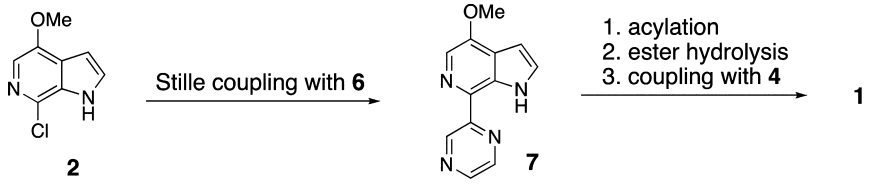
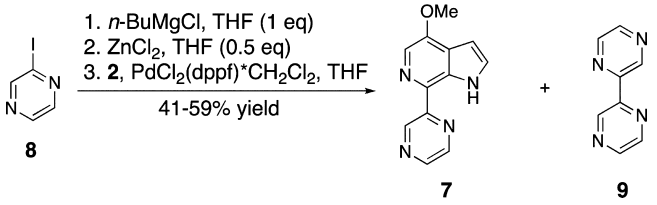
Scheme 1. Med-chem synthesis of 1



Scheme 2. Modified med-chem route with Stille coupling as the first step



Scheme 3. Negishi coupling



exchange reaction. At higher temperatures, the addition of a butyl group to pyrazine was observed, probably via the reaction of *n*-butyl halide formed in the Grignard exchange reaction. The stoichiometry was critical in that excess *n*-butyl magnesium chloride would compete with pyrazine in the subsequent coupling reaction and consume expensive azaindole. In addition, this scenario produced a process impurity that was relatively difficult to remove. The optimized conditions used exactly one equivalent of the Grignard reagent.

The next step involved transmetalation of the Grignard reagent with zinc chloride. The zinc chloride stoichiometry has a large effect on the species produced at this point, and the reactivity of those species.[6] When a 1:1 ratio of zinc to magnesium was used, zinc chloride was added to the Grignard reagent at −10 °C and the mixture was allowed to warm to room temperature and stirred for 1 h under a nitrogen atmosphere. The zinc species with one aryl ligand and one halide ligand that were formed this way were effective in the Negishi reaction. Even better results were observed with diaryl zinc species formed using a 0.5 equiv of zinc chloride versus pyrazine Grignard. Under such conditions a good reaction rate and full consumption of the azaindole were observed within about 6 h at 60 °C. The reactive zinc species exist as a suspension and should be used within several hours of preparation. Attempts to filter this mixture to remove insoluble materials resulted in an unreactive solution.

The amount of iodopyrazine, and thus how much diaryl zinc reagent is produced, has a significant effect on the conversion of this Negishi reaction. Typically, 3 equiv of iodopyrazine versus **2** were used, resulting in 1.5 equiv of the diaryl zinc species after Grignard formation and transmetalation with zinc chloride. Experiments were conducted with less iodopyrazine and it was found that with a ratio of 2:1 (iodopyrazine to azaindole), the Negishi reaction would still go to completion. Those reactions were conducted through a portionwise addition of the suspension of zinc species to the reaction mixture containing azaindole **2** and palladium catalyst. With ratios of less than 2 equiv of starting iodopyrazine the azaindole was not completely consumed. With ratios in excess of 2 equiv, the azaindole was completely consumed, but this was accompanied by the formation of dimer **9** at low levels (usually <0.6%).[7] When completed, the Negishi reaction was subjected to aqueous workup and the crude product **7** was initially isolated as the hydrochloride salt. The poor aqueous and organic solubility of this salt facilitated easy removal of all reaction byproducts. The hydrochloride salt was neutralized with aqueous sodium carbonate and extracted into DCM. DCM was removed and the material precipitated from methanol to afford **7** in approximately 60% yield and over 99% purity by HPLC.

The Negishi reation was successfully optimized and scaled up to provide over 2 kg of **7** in several batches (Table 1).

Acylation of Azaindole 7. Acylation of azaindole **7** was achieved by adding the substrate to a mixture of aluminum chloride in the mixed solvent system of DCM and nitromethane, ∼4:1 v/v (Scheme 4).[8] Methyl chlorooxalate was

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Table 1. Analysis of kilo-lab scale batches of 7

batch	**2** used (kg)	**7** obtained (kg)	yield (%)	purity by HPLC (%)
1	0.4	0.205	41	98.9
2	0.4	0.210	42	99.0
3	0.4	0.291	59	99.4
4	0.4	0.282	57	99.4
5	0.4	0.294	59	99.4
6	1.5	0.995	54	99.6

then added and the reaction was allowed to proceed to completion. Once complete, the reaction was quenched with ammonium acetate, and the product was isolated by an extractive workup. Although optimization efforts focused on reaction temperatures and aluminum chloride and methyl chlorooxalate stoichiometry, the main issue with this step in the synthesis was the formation of unwanted acid **11** produced from the hydrolysis of the desired intermediate **10a**. While **11** is the product of the subsequent step, it translates to a yield loss in this step, thus the need to reduce its levels. Compound **11** could not be recovered from the aqueous layer and prolonged reaction times used to complete the conversion of **7** into **10**, also led to the formation of **11**. Therefore, it was critical to ensure that the hydrolysis reaction could be suppressed to a low level, allowing large scale manufacturing with the associated longer processing time cycles. Attempts to suppress the hydrolysis reaction by varying the aluminum chloride and methyl chorooxalate amounts were explored but, ultimately, it was found that the reaction temperature was a critical parameter effecting hydrolysis. When run at 0 °C, the acylation step would proceed at a reasonable rate, consuming almost all of **7** in about 15 h with, typically, less than 3% of the hydrolysis product **11** formed. The hydrolysis reaction would level off at 1−2% and stay at that level for many hours. When run at ambient temperature, the acylation would again proceed to completion, but the extent of hydrolysis would increase over time. The results of these laboratory scale experiments are presented in Figure 1, compare (a) versus (b) and (c).

Lowering the aluminum chloride charge to 6 equiv resulted in the acylation reaction stalling after 85−90% conversion (see Figure 1d). Increases in the aluminum chloride charge would increase the rate without affecting the level of hydrolysis (when run at 0 °C), but the ultimate percent conversion was unaffected by an increase in aluminum chloride.

Variations in the acylating agent included the use of oxalyl chloride, ethyl chlorooxalate, and isopropyl chlorooxalate. Only a few percent of product formation was observed with oxalyl chloride. The acylation proceeded more slowly with ethyl or isopropyl chlorooxalate when compared to that with methyl chlorooxalate. Finally, the optimal conditions for the synthesis of acylated intermediate **10** utilized 4 equiv of methyl chloroxalate, 8 equiv of aluminum chloride, and a reaction temperature of 0 °C.

Although the acylation reaction using methyl chlorooxalate worked well in the lab, it was still challenging to control the undesired hydrolysis on a larger scale. In addition, the considerably lower cost of ethyl chlorooxalate as compared to its methyl analogue encouraged further exploration of the reaction. As it turned out, good yields of the ethyl ester **10b** could be obtained by simply extending reaction times to over 8 h while increasing temperature to 5 °C. The results of multiple kilo-lab batches run with ethyl chlorooxalate are summarized in Table 2.

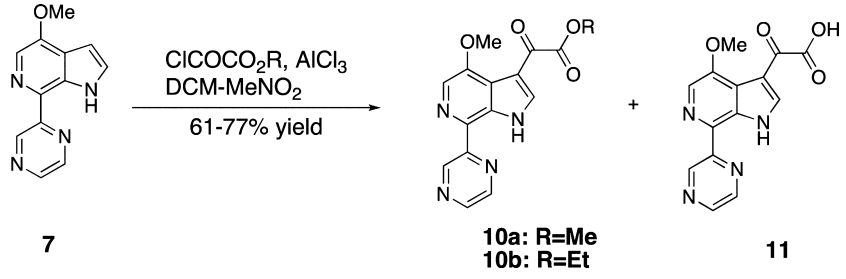
Hydrolysis of Azaindole Ester 10. The penultimate step in the synthesis includes hydrolysis of acylated azaindole **10** into carboxylic acid **11** (Scheme 5). This step was performed on laboratory scale using **10a** and aqueous potassium carbonate in methanol. Once the reaction was complete, methanol was removed and the mixture diluted with water and extracted with MTBE to remove neutral impurities. The precipitate obtained after the mixture was acidified to pH ∼1 was isolated by filtration to provide the target product **11** in 95% yield and >99% purity by HPLC.

The laboratory-scale hydrolysis conditions were applied in the kilo-lab using ethyl ester **10b** as a substrate. However, the workup was further simplified by eliminating the methanol evaporation and MTBE extraction steps. Instead, when the hydrolysis was complete, the reaction mixture was diluted with water and acidified to pH ∼1 with hydrochloric acid, and then the precipitate was collected by filtration. This procedure was used to produce 1.2 kg of **11** in 96% yield in a single batch. The obtained product had 99.4% purity by HPLC and was used in the final step of the synthesis without further purification.

Coupling with Piperidine 4. The final step of the synthesis of **1** involved *O*-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) -mediated coupling of carboxylic acid **11** with piperidine **4** in DMF to afford **1** (Scheme 6). Ethanol was added to the reaction mixture and the precipitated product isolated by filtration. In the laboratory-scale experiments **1** was obtained in approximately 70% yield and >99% purity. However, 16 ppm of Pd, 400 ppm of iron, and 100 ppm of zinc impurities were also found, requiring that this liability to be addressed before larger-scale production could be attempted.

Alternative coupling conditions were explored for the final synthetic step. HOBT was substituted for HATU, but this reagent led to a complex mixture of products. Conversion of **11** to the corresponding acid chloride using oxalyl chloride in DCM[9] and subsequent reaction with **4** in the presence of iPr_2NEt afforded **1** in only 20% yield. Some effort was made to

Scheme 4. Acylation of azaindole 6



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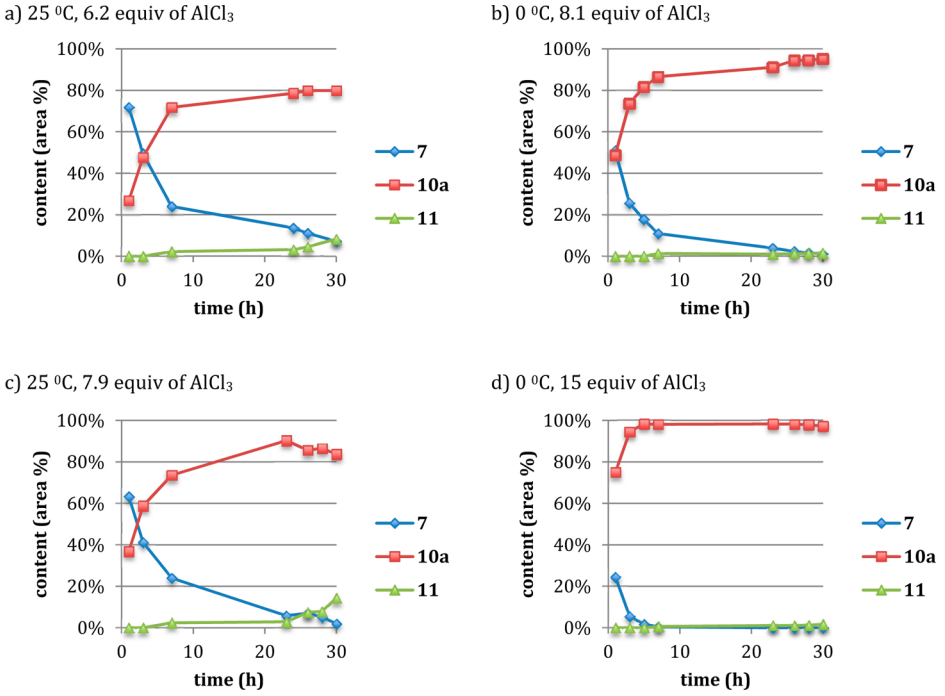
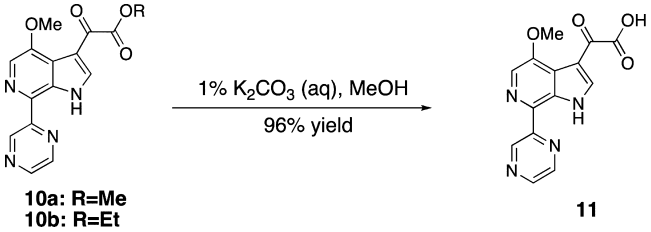


Figure 1. Acylation of 7 with methyl chlorooxalate (2 equiv) in the presence of aluminum chloride.

Table 2. Analysis of kilo-lab scale batches of acylated azaindole 10b

batch	7 used (kg)	**10b** obtained (kg)	yield (%)	purity by HPLC (%)
1	0.11	0.116	73	99.53
2	0.40	0.398	69	99.70
3	0.38	0.334	61	99.89
4	0.37	0.412	77	99.34
5	0.45	0.474	73	99.60

Scheme 5. Hydrolysis of azaindole ester 10

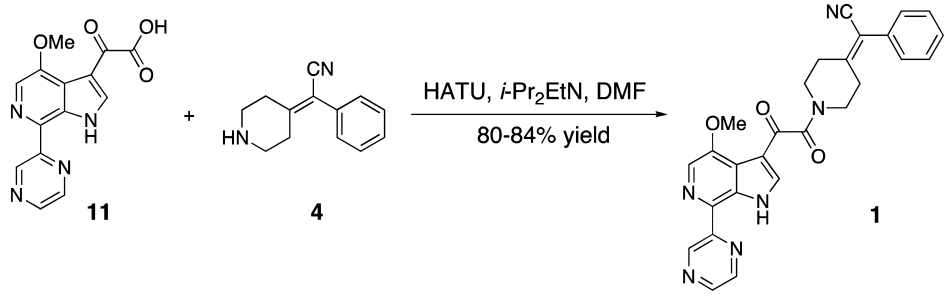


react methyl ester **10a** directly with **4** to afford **1**, without going through the intermediate acid **11**. Thus, **4** was treated with NaHMDS, KHMDS, or NaO^{t}Bu in THF followed by addition of compound **10a**. Although reported[10] to be successful on similar systems, this transformation did not work in our case.

In addition to a potential excessive level of heavy metals in **1** carried over from the Negishi reaction, the kilo-lab runs were faced with some residual yellow-to-brown discoloration carried over from the Friedel–Crafts acylation step. To address the color issue the workup procedure after the final coupling reaction was modified to include treatment with active carbon. Thus, the solid material obtained after precipitation of the product with ethanol was redissolved in DCM[11] and treated with Darco KB at 35 °C. After filtration through a Celite bed, the DCM solution was washed with 5% aqueous ammonium chloride to remove residual DMF. Following the solvent swap to *n*-heptane the precipitated product was collected by filtration. Unfortunately, the crystalline form of **1** (Form 2) obtained this way was different from the desired Form 1 targeted for manufacturing of the drug product and for the preclinical toxicology studies.

Polymorphism of 1. To better understand polymorphism of **1** and to develop a procedure to convert Form 2 to Form 1 a brief polymorphism study was conducted. After full characterization of both forms it was determined that Form 2 has a monotropic relationship to Form 1. Both forms were shown to

Scheme 6. Final coupling of carboxylic acid 11 with piperidine 4



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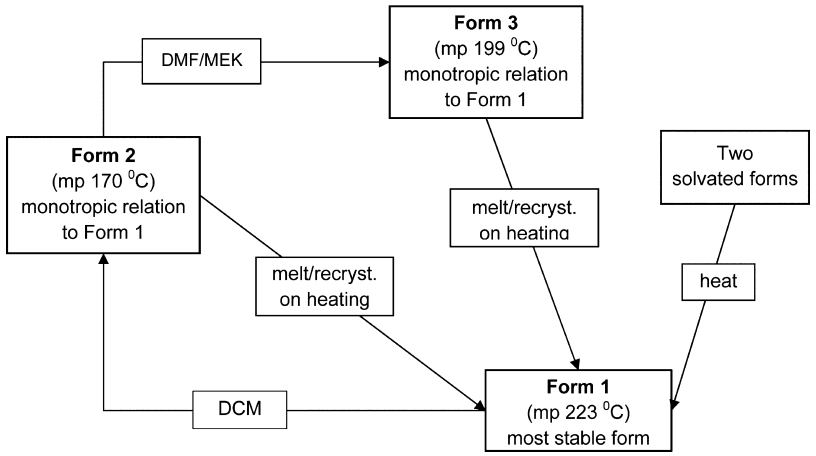

Figure 2. Polymorphic relationships of **1**.

be stable at elevated temperatures and humidities when present as a single form. However, a mixture of Forms 1 and 2 was seen to gradually convert to Form 1 over time when exposed to elevated temperatures and humidities.

A polymorph screen was carried out to try to identify other forms of **1**, as well as conditions under which they would be formed. Despite many attempts it was not possible to make suitable amorphous material, so, maturation of amorphous solid in a range of solvents could not be carried out. Therefore the polymorph screen was carried out using several sovent evaporation or antisolvent addition methods. As a result three polymorphic forms and two solvated forms (a mono-DMSO solvate and a hemi-dioxane solvate) were identified and characterized. Relationships between these forms are summarized in Figure 2.

To develop a reliable procedure to convert Form 2 to Form 1 a series of slurry experiments was performed using a range of Class III solvents at ambient, 30 °C, and 60 °C temperatures (Table 3). Thirteen solvents were successful in producing the Form 1 material, but three of these caused a significant reduction in crystallinity. Of the remaining ten solvents, four required prolonged slurrying for the conversion to occur, which was not suitable for large-scale use. Of the six solvents that were successful in producing Form 1 material after one day of slurrying, four needed temperatures of 60 °C. From the two solvents: *n*-propanol and 3-methyl-1-butanol, that efficiently converted Form 2 to Form 1 in less than 1 day at 30 °C, the former was selected for use on a preparative scale.

To speed up the polymorphic conversion in the kilo-lab a slurry of Form 2 in *n*-propanol was heated to 90 °C, and 1 h at this temperature was sufficient to achieve complete conversion of Form 2 to the desired Form 1. After cooling, filtration, and drying of the solid, 1.856 kg of the desired Form 1 of **1** was obtained in two batches (Table 4). On the basis of the largest batch size performed, the overall yield of the four-step process was 32% with purity of the final material exceeding 99.5%. In addition, the process executed in the kilo-lab provided **1** containing less than 1 ppm each of palladium, iron and zinc, and less than 3 ppm of each magnesium and aluminum. This material was used in formulation studies and in preclinical toxicology evaluation of **1**.

Table 3. Conversion of Form 2 to Form 1 by slurrying in selected solvents at ambient temperature, 30 °C, and 60 °C for 1 or 7 days

	complete conversion after	
solvents used	7 days[a]	1 day[a]
acetone	D	–
anisole	C	C
n-butanol	A[b]	–
sec-butanol	A	C
n-butyl acetate	C	–
sec-butyl acetate	C	–
cumene	A	C
ethanol	C	–
3-methyl-1-butanol	B	B
methyl isobutyl ketone	B[b]	C
n-pentanol	C[b]	C[b]
n-propanol	A	B
isopropanol	B	C

[a]A - all temperatures; B - 30 and 60 °C; C - 60 °C only; D - 30 °C only. [b]Partial loss of crystallinity.

Table 4. Analysis of kilo-lab scale batches of the target 1

batch	**11** used (kg)	**1** obtained (kg)	yield (%)	purity by HPLC (area %)
1	0.700	0.903	80	99.58
2	0.705	0.953	84	99.60

CONCLUSIONS

A robust synthesis of **1**, which does not involve tin reagents, has been developed. This improved process was scaled up to yield kilogram quantities of **1**. The Stille coupling step was moved from the last step of the med-chem synthesis route to the first step of the new process, and has been further replaced by the Negishi conditions to eliminate the tributyltin-based reagent that was used previously. The protocol for the acylation step to produce ester **10** was optimized, and inexpensive ethyl-chlorooxalate was introduced to allow for kilogram-scale runs without concern over ester hydrolysis. Conversion of ester **10** into **1** was accomplished in two steps including ester hydrolysis followed by HATU-mediated coupling with piperidine **4**. On the basis of a polymorphism study of **1**, an efficient procedure was established for the conversion of the undesired polymorphic Form 2 of **1** produced in the process, to the most stable Form 1 of **1**. The new process allows for the

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synthesis of kilogram quantities of **1** in 30−35% overall yield starting from azaindole **1**. The final product is obtained with high purity of over 99.5% and heavy metal impurities meeting standard ACH guidelines.

EXPERIMENTAL SECTION

General. Chloroazaindole **2**, piperidine **4**, and iodopyrazine **8** used in the work described here were custom-made in kilogram quantities by Z.D. Chemipan, Warsaw, Poland.

HPLC method used for monitoring laboratory-scale experiments (see Table 5 for gradient elution): Column: Phenomenex Jupiter C18 300A, 4.6 mm × 250 mm, 5 μm of particle size. Flow rate: 1.5 mL/min. Injection volume: 10 μL. Detection: UV, 220 nm. Column temp.: 30 °C. Run time: 56 min. Mobile phase A: 0.025% TFA in water. Mobile phase B: 0.025% TFA in ACN. Gradient elutions are listed in Table 5).

Table 5. Gradient elution

time (min)	A (%)	B (%)
0	90	10
15	10	90
17	10	90
18	90	10
22	90	10

Retention times: compound **1**: 10.8 min, compound **2**: 6.9 min, compound **4**: 6.7 min, compound **7**: 5.5 min, compound **9**: 4.9 min, compound **10a**: 6.3 min, compound **11**: 4.1 min.

4-Methoxy-7-(pyrazin-2-yl)-1*H*-pyrrolo[2,3-*c*]pyridine (7, *kilo-lab scale process*). To a solution of iodopyrazine **8** (721 g, 3.5 mol) in THF (8.4 L) at −18 °C was added *n*-BuMgCl (2 M in THF, 1.75 L, 3.5 mol) over 30−60 min. While the temperature was maintained at −18 to −20 °C, $ZnCl_2$ (0.5 M in THF, 3.5 L, 1.75 mol) was added over 30−60 min, and the mixture was warmed up to 25 °C in 2 h. Chloroazaindole **1** (210 g, 1.15 mol) and $PdCl_2(dppf)*CH_2Cl_2$ (100 g, 0.122 mol) were added, and mixture was heated at 58 °C for 8 h when HPLC analysis showed >20:1 ratio of the product **7** to the azaindole **2**. The reaction mixture was cooled to 0 °C and quenched with NH_4Cl (6 N aqueous, 2.5 L). The inorganic salts were filtered off and washed with THF (420 mL). The combined organic solutions were treated with aqueous HCl (1.2 L of conc HCl plus 7 L of water). The mixture was stirred at 25 °C for 1 h, and the precipitated hydrochloride of azaindole **7** was filtered and washed with ethyl acetate (2.1 L). The solids were suspended in DCM (8 L), aqueous sodium carbonate (10%, 4 L) was added, and the mixture was stirred for 2 h at 25 °C. The precipitated salts were removed by filtration, and the organic phase was separated and concentrated to ∼0.4 L volume. Methanol (1.5 L) was added, and the solvents were distilled off until a volume of ∼0.5 L was reached. The process of methanol addition and solvent distillation was repeated two more times, and the mixture was stirred at 25 °C for 1 h. The precipitate was filtered, washed with methanol (0.3 L), and dried to give 158 g (60.2% yield) of the azaindole **7** (99.5% pure by HPLC).[12] ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.08 (s, 3H), 6.64 (d, J = 2.8 Hz, 1H), 7.56 (t, J = 2.4 Hz, 1H), 8.03−8.05 (m, 1H), 8.64 (d, J = 2.4 Hz, 1H), 8.74−8.75 (m, 1H), 9.62 (d, J = 1.6 Hz, 1H), 11.78 (br, s, 1H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (s, 3H), 6.70 (dd, J = 2.6 Hz, 3.0 Hz, 1H), 7.36 (dd, J = 2.6 Hz, 3.0 Hz, 1H), 8.48−8.51 (m, 2H), 9.80 (d, J = 1.6 Hz, 1H), 10.88 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 99.5, 120.5, 124.5, 126.9, 131.5, 133.2, 142.2, 142.5, 143.5, 150.9, 152.4; LC/MS: m/e 227 $(M + H)^+$.

Methyl 2-(4-methoxy-7-(pyrazin-2-yl)-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)-2-oxoethanoate (10a, *laboratory scale process*). To a solution of dichloromethane and nitromethane (4:1, 200 mL) cooled with ice−water bath, was added portionwise $AlCl_3$ (22.3 g, 168 mmol) followed by azaindole **7** (4.75 g, 21.0 mmol). **CAUTION**: mixtures of CH_3NO_2 and $AlCl_3$ are potentially hazardous. Conduct a proper safety evaluation before running this chemistry. The internal temperature was raised from 1 to 6 °C and then lowered back to 1 °C. Methyl chlorooxalate (3.9 mL, 41.1 mmol) was added into the solution dropwise in ∼5 min. The resulting homogeneous solution was stirred at 0 °C for 10 min and then put in a cold room (∼0 °C) for 15 h without stirring. Analysis by HPLC after 15 h showed the ratio of **7**:**10a**:**11** to be 0:92:3. The reaction solution was poured into cold 25% aqueous NH_4OAc solution (500 mL), and the organic layer was separated. The aqueous layer was extracted with DCM (300 mL, then 2 × 150 mL), and the combined organic layers were washed with brine (2 × 300 mL) and dried (Na_2SO_4). Removal of solvents in vacuo gave ester **10a** as a solid (4.85 g, 74% yield), which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 4.10 (s, 3H), 8.15 (s, 1H), 8.35 (d, J = 3.3 Hz, 1H), 8.57−8.60 (m, 2H), 9.81 (d, J = 1.2 Hz, 1H), 11.7 (br s, 1H). Analysis by ICP-MS showed 1535 ppm Fe, 103 ppm Zn.

Ethyl 2-(4-Methoxy-7-(pyrazin-2-yl)-1*H*-pyrrolo[2,3-*c*]-pyridin-3-yl)-2-oxoethanoate (10b, *kilo-lab scale process*). To a solution of dichloromethane (7 L) and nitromethane (1.9 L) at 5 °C was added in portions $AlCl_3$ (930 g, 7.0 mol), followed by ethyl chlorooxalate (193 mL, 1.73 mol) and azaindole **7** (194 g, 0.86 mol). **CAUTION**: mixtures of CH_3NO_2 and $AlCl_3$ are potentially hazardous. Conduct a proper safety evaluation before running this chemistry. The reaction mixture was stirred at 5 °C for 8 h and progress monitored by HPLC. When the analysis indicated complete disappearance of the starting material, the mixture was slowly added to a solution of ammonium acetate (4.75 kg) in water (15 L) cooled to 0 °C. The organic layer was separated, and the aqueous layer was extracted with DCM (2 × 3 L). The combined organic layers were concentrated in vacuo to ∼0.4 L volume. Methanol (1.0 L) was added, and the solvents were distilled off until a volume of ∼0.5 L was reached. The process of methanol addition and solvent distillation was repeated one more time, and the mixture was stirred at 25 °C for 1 h. The precipitate was filtered off, washed with methanol (0.2 L), and dried to give 170 g (60.75% yield) of the azaindole **10b** (99.6% pure by HPLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 1H), 4.07 (s, 3H), 4.42 (q, J = 7.2 Hz, 1H), 8.08 (s, 1H), 8.31 (d, J = 3.2 Hz, 1H), 8.54−8.57 (m, 2H), 9.76 (d, J = 1.2 Hz, 1H), 11.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 56.5, 62.1, 114.3, 121.3, 124.1, 131.8, 133.6, 136.2, 142.2, 143.3, 143.5, 151.1, 151.5, 164.2, 180.8.

2-(4-Methoxy-7-(pyrazin-2-yl)-1*H*-pyrrolo[2,3-*c*]-pyridin-3-yl)-2-oxoethanoic Acid (11) by Hydrolysis of 10a. To a suspension of ester **10a** (10.00 g, 32.1 mmol) in methanol (150 mL) at room temperature was added aqueous K_2CO_3 (1 M, 150 mL, 150 mmol). The reaction mixture was stirred for 1 h when complete hydrolysis of **10a** was indicated by HPLC analysis. Methanol was removed under vacuum, and the remaining mixture was diluted with water to 1.2 L and

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washed with MTBE (2 × 400 mL). Aqueous phase was acidified with HCl (2 M, 185 mL, 370 mmol) to pH = 1, and the gray precipitate was filtered off and dried to give 9.29 g of acid **11** (97% yield). Analysis by ICP-MS showed 143 ppm Fe, 96 ppm Zn.

2-(4-Methoxy-7-(pyrazin-2-yl)-1*H*-pyrrolo[2,3-*c*]-pyridin-3-yl)-2-oxoethanoic Acid (11) by Hydrolysis of 10b *(kilo-lab scale process)*. A reactor was charged with ester **10b** (1.61 kg, 4.93 mol), methanol (1.5 L) and aqueous K_2CO_3 (1 M, 6.5 L). The reaction mixture was heated to 40 °C and stirred for 1 h when complete hydrolysis of **10b** was indicated by HPLC analysis. Water (15 L) was added, and the mixture was acidified to pH ∼1 with 2 N hydrochloric acid. The precipitate was filtered off, washed with water (12 L), and dried to give 1.416 kg of acid **11** (96% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.04 (s, 3H), 8.21 (s, 1H), 8.32 (d, J = 1.6 Hz, 1H), 8.68 (d, J = 2.4 Hz, 1H), 8.74 (dd, J = 1.6, 2.4 Hz, 1H), 9.59 (d, J = 1.6 Hz, 1H), 12.64 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 56.5, 113.2, 121.5, 124.3, 132.6, 132.9, 138.6, 142.9, 143.5, 144.0, 151.0, 151.3, 166.9, 183.1.

2-(1-(2-(4-Methoxy-7-(pyrazin-2-yl)-1*H*-pyrrolo[2,3-*c*]-pyridin-3-yl)-2-oxoethanoyl)piperidin-4-ylidene)-2-phenylethanenitrile (1, *laboratory scale process*). A flask was charged with acid **11** (9.29 g, 31.2 mmol), DIPEA (12.9 mL, 78 mmol), **4** (7.18 g, 36.3 mmol) and DMF (95 mL) subsequently. HATU (13.66 g, 35.9 mmol) was added to the reaction mixture over 10 min, which was accompanied by increase of internal temperature from 19 to 27 °C. After the reaction mixture was stirred at 25 °C for 3.5 h, the HPLC analysis showed complete disappearance of acid **11**. Ethanol (950 mL) was added, and the resulting suspension was heated at reflux for 1 h. The mixture was then cooled to 25 °C, and **1** was isolated by filtration and washed with ethanol (50 mL). The material was dried under vacuum at 50 °C to afford 10.58 g (71% yield) of **1** as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58−2.65 (m, 2H), 2.91−2.99 (m, 2H), 3.48−3.51(m, 1H), 3.68−3.78 (m, 2H), 3.95−3.99 (m, 1H), 4.11 (s, 3H), 7.27−7.46 (m, 5H), 8.16 (d, J = 5.1 Hz, 1H), 8.21−8.25 (m, 1H), 8.60 (s, 2H), 9.82 (d, J = 3.9 Hz, 1H), 11.75 (br s, 1H). LC/MS: m/e 479.3 $(M + H)^+$. Analysis by ICP-MS showed 16 ppm Pd, 79 ppm Fe, 102 ppm Zn. This material was found to be a mixture of two polymorphs: Form 1 and Form 2.

2-(1-(2-(4-Methoxy-7-(pyrazin-2-yl)-1*H*-pyrrolo[2,3-*c*]-pyridin-3-yl)-2-oxoethanoyl)piperidin-4-ylidene)-2-phenylethanenitrile (1, *kilo-lab scale process including polymorph conversion*). A reactor was sequentially charged at 25 °C with DMF (4 L), acid **11** (705 g, 2.36 mol), piperidine **4** (668 g, 2.85 mol, 1.2 equiv), and DIPEA (1.8 L, 4.5 equiv). To the clear solution was added a solution of HATU (1.080 kg, 2.85 mol, 1.2 equiv), and the mixture was stirred at 25 °C until HPLC analysis indicated complete disappearance of acid **11**. Ethanol (48 L) was added, and the mixture was stirred for 1 h. The precipitate was collected by filtration, washed with ethanol (10 L), and dried by purging nitrogen for 4 h. The crude product was dissolved in DCM (80 L), Darco KB (2.3 kg) was added, and the mixture was stirred at 30 °C for 1 h. Darco KB was removed by filtration through a bed of Celite, and the clear solution was washed with a 5% aqueous solution of ammonium chloride (41 L). The DCM solution was concentrated to a volume of ∼3 L by vacuum distillation, heptane (21 L) was added, and the mixture was concentrated again to a volume of ∼3 L. This step was repeated one more time using 10 L of heptane. The resulting suspension was filtered; the precipitate was washed with heptane (3.5 L) and dried under vacuum to give **1** as a pure Form 2 polymorph. This material was suspended in *n*-propanol (15 L), and the mixture was stirred for 1 h at 90 °C. After the mixture was cooled to ambient temperature, the precipitate was filtered, washed with *n*-propanol (8 L), and dried under vacuum at 65 °C to give 0.953 kg of **1** (84% yield) and 99.6% purity by HPLC. This material was a pure Form 1 polymorph. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (t, J = 5.8 Hz, 1H), 2.65 (t, J = 5.9 Hz, 1H), 2.94 (t, J = 5.8 Hz, 1H), 2.99 (t, J = 5.9 Hz, 1H), 3.51 (t, J = 5.8 Hz, 1H), 3.72 (t, J = 5.8 Hz, 1H), 3.78 (t, J = 6.0 Hz, 1H), 3.98 (t, J = 6.0 Hz, 1H), 4.12, 4.12 (two s, 3H), 7.29−7.47 (m, 5H), 8.16, 8.18 (two s, 1H), 8.23, 8.25 (two d, J = 3.1 Hz, 1H), 8.60−8.63 (m, 2H), 9.83, 9.84 (two d, J = 1.4 Hz, 1H), 11.76, 11.78 (two br s, 1H); ^{13}H NMR (100 MHz, $CDCl_3$) δ 30.3, 31.0, 33.7, 34.3, 41.7, 42.0, 46.0, 46.3, 56.8, 111.4, 115.0 (2C), 117.7 (2C), 120.9, 124.2, 128.9 (2C), 129.0, 129.1 (2C), 131.9, 132.6 (2C), 133.9 (2C), 136.6, 142.2, 143.4, 143.7 (2C), 151.1, 151.3, 154.8, 166.4, 166.5, 185.6. Anal. Calcd for $C_{27}H_{22}N_6O_3$: C, 67.77; H, 4.63; N, 17.56. Found: C, 67.84; H, 4.64; N, 17.56.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR of **1**, DSC and XRPD traces of Form 1 and Form 2 of **1**. 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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(7) If needed, dimer **9** could be removed by crystallization of the crude product from hexane−ethyl acetate.

(8) Although we are aware of a potential hazard associated with using aluminum chloride and nitromethane, no observations of hazardous results were seen over hundreds of experiments under a variety of conditions. These data fulfilled our safety requirements at this scale for a fit-for-purpose process. Future experiments will explore ways to eliminate nitromethane and/or to establish reaction-condition limits for larger-scale preparations.

(9) This acid chloride formation step was not a clean reaction and caused partial decomposition of **10**.

(10) Private communication from BMS.

(11) The use of DCM at this stage of the process is necessary because of very low solubility of **1** in many organic solvents.

(12) The lab trial material prepared this way contained 1669 ppm Fe and 83 ppm Zn when tested by ICP-MS.

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