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Development of a Scalable Synthesis of the Small Molecule TGFβR1 Inhibitor BMS-986260

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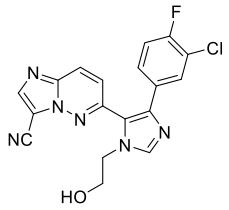
ABSTRACT: A scalable route to the small molecule TGFβR1 inhibitor **BMS-986260** (**1**) was developed. This alternative approach circumvented the purification of intermediates by column chromatography and provided access to multikilogram quantities of the key intermediate, **6**. The safety aspects of the synthetic approach to the other fragment of the API (TosMIC **10**) were critically evaluated, and a robust process for its large-scale synthesis was successfully demonstrated.

KEYWORDS: *TGFβR1 inhibitor, imidazo[1,2-b]pyridazine, TosMIC, AKTS software, Van Leusen imidazole synthesis*

INTRODUCTION

The imidazo[1,2-*b*]pyridazine scaffold has been successfully utilized in the discovery of a number of therapeutic agents.[1−10] Compound **1** (**BMS-986260**, Figure 1), an imidazo[1,2-*b*]pyridazine-containing molecule, was identified as a potent and selective TGFβR1 inhibitor.[11,12] As the molecule was gearing up to progress into development, we required a safe and robust process that could deliver significant quantities of the drug substance to fund the pre-clinical and early clinical needs of this program. Herein, we report the process development efforts to synthesize kilogram quantities of **1** that represented a significant improvement over the Medicinal Chemistry route.



BMS-986260
1

Figure 1. Structure of **1** (**BMS-986260**).

RESULTS AND DISCUSSION

First-Generation Synthesis of 1. The medicinal chemistry approach to **1** involved eight steps starting from 6-bromopyridazine-3-amine **2** (Scheme 1).[12] The imidazopyridazine intermediate **4** was obtained in two steps from pyridazine **2** via condensation with dimethyl formamide−dimethyl acetal (DMF−DMA) and subsequent base-mediated cyclization of the intermediate enamine **3** with bromoacetonitrile. Stille coupling of **4** with tributyl(vinyl)stannane followed by osmium tetroxide-mediated oxidative cleavage of the resultant vinyl compound **5** afforded the key aldehyde **6**. Treatment of aldehyde **6** with ethanolamine led to aldimine **7**, which was subjected to the Van Leusen imidazole synthesis[13] with the TosMIC reagent **10** (synthesized in two steps from aldehyde **8**) to furnish the desired API **1**.

While this approach allowed medicinal chemistry researchers to access small quantities of **1** for early evaluation, it was clear that the route needed modification prior to further scale up: (i) the use of tributyl(vinyl)stannane and osmium tetroxide had to be avoided during the synthesis of larger quantities of API because of the well-documented hazards of these reagents and their remnants;[14−18] (ii) the synthesis of TosMIC reagent **10** was low yielding and warranted improvement; and (iii) most of the intermediates in the medicinal chemistry approach were purified by column chromatography, which was clearly not the preferred purification method on a large scale. However, we also recognized that the existing chemistry to convert aldehyde **6** to API **1** could be scaled up with minor improvements in the isolation conditions. Thus, the primary focus of the next

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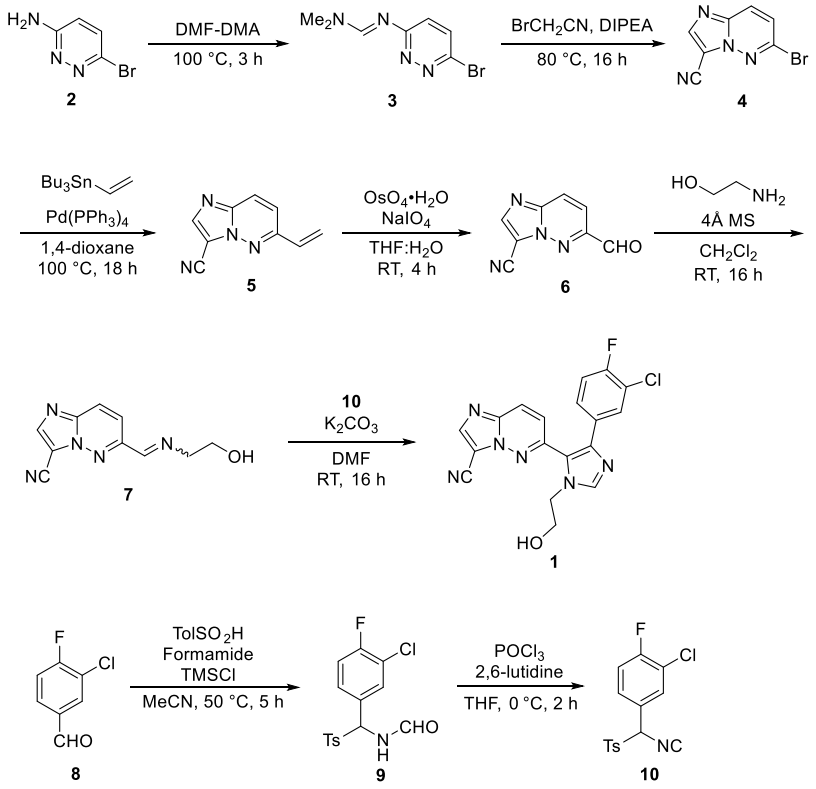
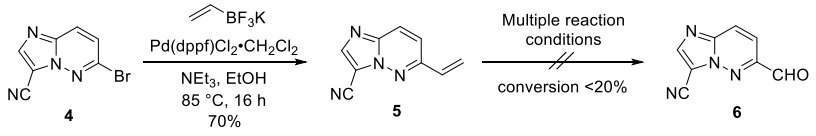
Scheme 1. First-Generation Synthesis of 1 (BMS-986260)



Scheme 2. Attempts to Synthesize 6 from 4

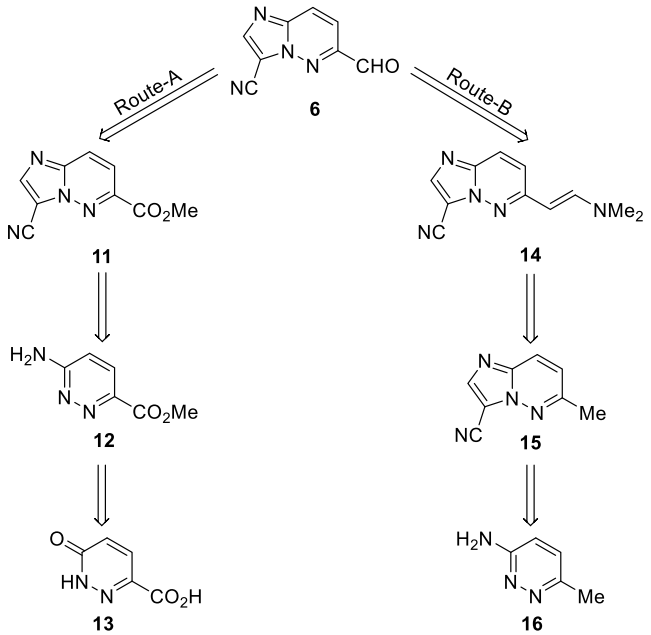


generation efforts was twofold—to develop a robust synthesis of aldehyde **6**, which avoids the pitfalls of the medicinal chemistry route, and to streamline the process toward the synthesis of the TosMIC component **10**.

While initial attempts to circumvent the use of tin by replacing the Stille coupling reaction with a Suzuki coupling reaction in the conversion of **4** to **5** seemed to be encouraging,[19] the substitution of the OsO_4-mediated oxidative cleavage of **5** to **6** with more benign alternatives (such as ruthenium chloride in the presence of bulk oxidants)[20−22] was not successful (Scheme 2). Similarly, several direct formylation conditions (either metal-mediated formylations, or metalation/formylation conditions) attempted on bromide **4** provided poor yields (<20%) of the desired aldehyde **6**. This prompted us to explore de novo routes to **6**, vide infra.

Second-Generation Synthesis of Aldehyde 6. We envisioned that the imidazopyridazine aldehyde **6** could be synthesized via two approaches, namely, route A and route B (Scheme 3). Route A involved the formation of pyridazine ester **12** from 6-oxo-1,6-dihydropyridazine-3-carboxylic acid **13**. Subsequent cyclization to form the imidazopyridazine ring followed by ester reduction would furnish aldehyde **6**. Alternatively, 6-methylpyridazin-3-amine **16** could be converted to the imidazopyridazine core **15**. Enamine (**14**) formation via homologation of the benzylic methyl group in **15** followed by oxidative cleavage of the enamine functionality would produce aldehyde **6** (route B, Scheme 3). Both of these routes were evaluated in parallel and our results are summarized herein.

Scheme 3. Retrosynthetic Analysis of Aldehyde 6



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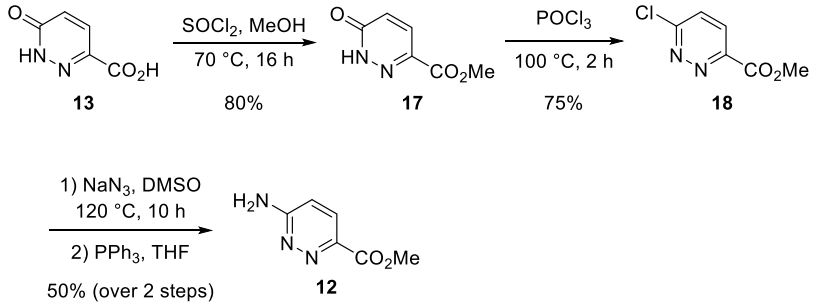
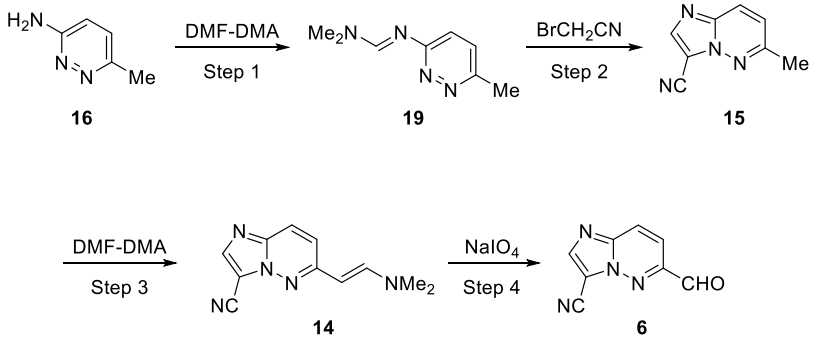
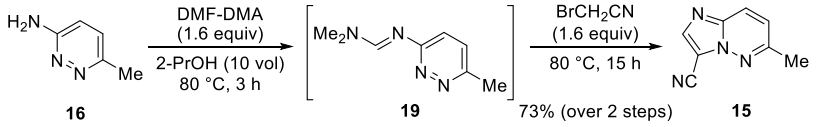
Scheme 4. Synthesis of Intermediate 12 (Route A)



Scheme 5. Proof-of-Concept for Route B



Scheme 6. Telescoped Synthesis of 15



Route A. Commercially available 6-oxo-1,6-dihydropyridazine-3-carboxylic acid **13** was converted to the corresponding methyl ester **17** via treatment with $SOCl_2$/MeOH (Scheme 4). Chlorination of **17** with neat $POCl_3$ provided the aryl chloride **18**. Our attempts to convert **18** to the corresponding amine **12** by treatment with an ammonia surrogate (such as benzophenone imine or LiHMDS) under Buchwald−Hartwig conditions provided very little conversion (<5%) to the desired product. This transformation has been reported in the literature using sodium azide at 120 °C followed by a Staudinger reduction using PPh_3.[23] While we were able to successfully reproduce these conditions on a laboratory scale, we were unable to accomplish this reaction under milder conditions.[24,25] Our inability to effect the amination under benign conditions, the hazards associated with handling azides especially at elevated temperatures, and the success we attained in our simultaneous efforts on route B (vide infra) prompted us to halt further work on route A.

Route B. The key transformation in the synthesis of aldehyde **6** via route B was the conversion of the methyl group at the 6-position of the imidazopyridazine **15** to enamine **14**. Compound **15** was synthesized in two steps from commercially available 6-methylpyridazin-3-amine **16** by treatment with DMF−DMA followed by cyclization of the intermediate amidine **19** with bromoacetonitrile (Scheme 5).[26] Treatment of **15** with DMF−DMA provided enamine **14**, which was oxidatively cleaved with sodium periodate to furnish aldehyde **6**.[27−29] We were able to rapidly achieve proof-of-concept on this route, which enabled our route-selection efforts. The next section describes the development of this synthetic route into a scalable process.

In step 1, the reaction of 6-methylpyridazin-3-amine **16** with DMF−DMA proceeded smoothly in toluene to afford the desired amidine **19**. While clean conversion to **19** was achieved in the reaction, the noncrystalline nature of **19** created problems during isolation. In our initial attempts, treatment of crude **19** with bromoactonitrile and $NaHCO_3$ in 2-propanol led to imidazopyridazine **15**, which was isolated by the addition of water (antisolvent), and recrystallized using MTBE.

We sought to streamline this process further by addressing two main concerns namely, the noncrystalline nature of **19**, and the need to recrystallize **15**. Gratifyingly, the amidine formation reaction (step 1) worked well in 2-propanol,[30,31] paving the way for the development of a one-pot telescoped process.[32] At the end of the step 1 reaction, bromoacetonitrile was charged into the reaction mixture, and heated to 80 °C to achieve the cyclization reaction. Interestingly, this reaction proceeded in the absence of an external base, and the product crystallized out upon the addition of aqueous $NaHCO_3$. This two-step, one-pot telescoped process worked well on a multikilogram scale to furnish compound **15** as a crystalline solid in 73% yield and >99 area % purity by HPLC (Scheme 6).

The next step in the sequence was synthesis of enamine **14** via homologation of the Me group at the 6-position. Based on the literature precedent for these kinds of reactions, *N*,*N*-diisopropylethylamine was used as the base in the presence of 5 equiv of DMF−DMA.[33] Under these conditions, the reaction stalled at 67 area % product after 15 h at 115 °C (Figure 2). We screened several bases (n-Bu_3N, 2,6-lutidine, DABCO, and DBU, 5 equiv each) in an attempt to push the reaction to

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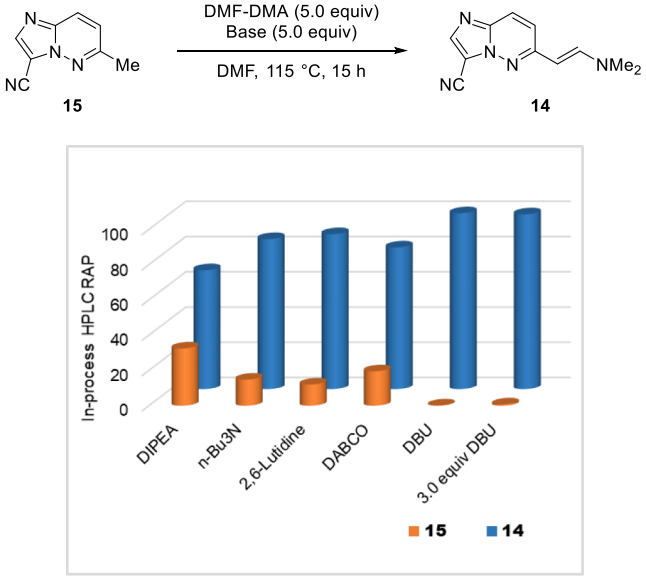
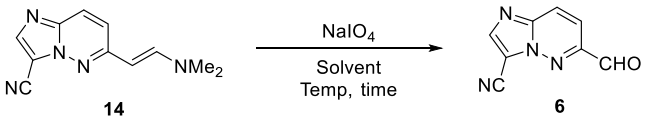


Figure 2. Step 3 conversions as a function of base used.

completion. While the reaction proceeded to ca. 80% conversion with most of the other bases, the reaction with DBU provided 99 area % of product **14** after 15 h even with only 3 equiv of the base. After completion of the reaction, the crude product was precipitated by the addition of aqueous NH_4Cl. The crude product was dissolved in 2-MeTHF and treated with neutral alumina to remove color and insoluble inorganics. Addition of *n*-heptane as the antisolvent furnished exclusively the E-isomer **14** in 71% yield and >98 area % purity.

Our initial proof-of-concept conditions to synthesize small quantities (<5 g) of aldehyde **6** by the sodium periodate-mediated oxidative cleavage of enamine **14** involved the use of THF−H_2O as the solvent system at ambient temperature.[34−37] The reaction produced ∼75 area % of the product by HPLC analysis (Table 1, entry 1), but was accompanied by a significant number of small peaks in the chromatogram. In addition, differential scanning calorimetry (DSC) studies on the reaction mixture indicated a significant thermal event with an onset of ∼66 °C, and an energy release of 470 J/g (Figure 3A). We attempted to lower the reaction temperature to 0−5 °C in order to provide a wider safety margin to carry out the reaction, but a significant amount of starting material remained unreacted (Table 1, entry 2). We, therefore, screened alternative solvent systems in an effort to increase both the conversion as well as the onset temperature, and a few representative conditions are presented in Table 1. While the conversions were low to modest in most of the solvents screened (Table 1, entries 3−7),[38] it was gratifying to note that methanol provided ∼83 area % product at ambient temperature (Table 1, entry 8).[28] Interestingly, the addition of 10% v/v water to the methanol reaction pushed the reaction to 96 area % product (Table 1, entry 9). The addition of water facilitated the reaction presumably by increasing the solubility of $NaIO_4$ in the reaction medium.

Table 1. Screening of Oxidative Cleavage of Enamine 14 Using $NaIO_4$



entry	equiv of $NaIO_4$	solvent (vol)	temp (°C)	time (h)	in-process area % 6	in-process area % 14
1	3.0	THF/water (10:10)	23	1	74.6	0
2	3.0	THF/water (10:10)	0−5	3	67.9	18.8
3	1.5	2-MeTHF/water (20:5)	0−5	3	76.5	2.6
4	1.5	MeCN/water (20:5)	0−5	3	40.9	1.5
5	2.0	DMF (20)	23	1	0	100
6	2.0	2-PrOH (20)	23	1	0	100
7	2.0	EtOH (20)	23	1	20.3	75.5
8	2.0	MeOH (20)	23	2	83.2	2.7
9	**2.0**	**MeOH/water (30:3)**	**23**	**2**	**96.1**	**0.2**

DSC studies with $NaIO_4$ (in the absence of substrate **14**) revealed a substantially lower energy release under the aqueous MeOH conditions (99.7 J/g, Figure 3D) than the aqueous THF conditions (555 J/g, Figure 3C). Furthermore, the reaction mixture (with substrate **14**) in aqueous methanol exhibited a significantly higher onset of decomposition (∼178 °C), and a relatively low decomposition energy (267 J/g) by DSC (Figure 3B) in comparison to the aqueous THF conditions (Figure 3A), providing a wider thermal window for carrying out the reaction.

While the aqueous methanol conditions provided high conversions, the isolation of pure aldehyde **6** proved challenging primarily because of its high solubility in aqueous media. In general, aqueous solutions of reducing agents such as sodium thiosulfate and sodium bisulfite are used to quench residual oxidizing agents. However, under these conditions, it was extremely difficult to extract the product from the aqueous phase because of the high solubility of aldehyde **6** in water.[39] We addressed this challenge by developing a nonaqueous workup protocol wherein upon reaction completion, the reaction mixture was filtered to remove insoluble inorganics (such as excess $NaIO_4$ and its byproducts). The filter cake was separately quenched with aqueous $Na_2S_2O_3$ and discarded. The product-rich filtrate was treated with excess solid $Na_2S_2O_3$, and the residual inorganic solids were separated by filtration and discarded. The methanol in the filtrate was replaced with methylene chloride, and the solution was treated with neutral alumina and filtered. The filtrate was concentrated, and the product was crystallized from toluene/*n*-heptane (1:2) to provide **6** in 56% yield and ∼96 area % purity on a multikilogram scale.

Large-Scale Synthesis of TosMIC 10. The medicinal chemistry synthesis of TosMIC **10** was accomplished in two steps starting from 3-chloro-4-fluorobenzaldehyde **8** (Scheme 1).[12] The first step involved treatment of benzaldehyde **8** with formamide, chlorotrimethylsilane (TMSCl), and 4-methylbenzenesulfinic acid ($TolSO_2H$) in acetonitrile to yield the substituted formamide **9**. After purification by column chromatography, intermediate **9** was dehydrated using $POCl_3$ in the presence of 2,6-lutidine to produce the TosMIC reagent **10** in 47% overall yield from **8**.

As we considered increasing the yield and throughput in this sequence, one obvious area for improvement was the avoidance of purification by column chromatography. Furthermore, $TolSO_2H$ was prepared by acidification of the corresponding commercially available sodium salt (sodium *p*-toluenesulfinate,

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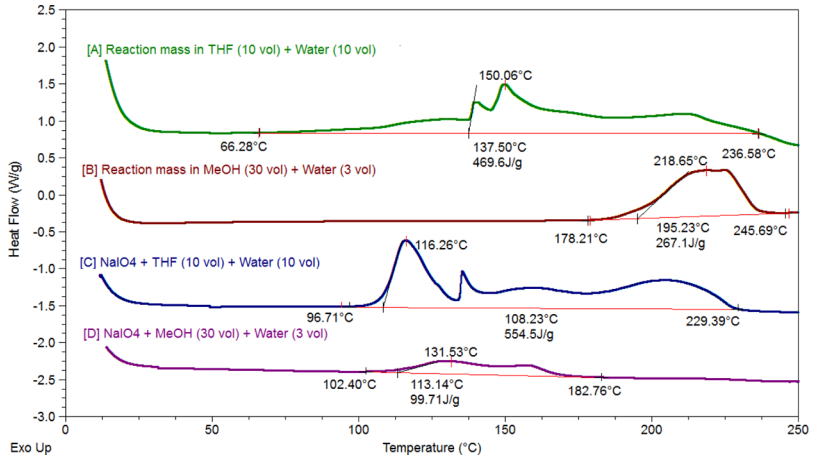
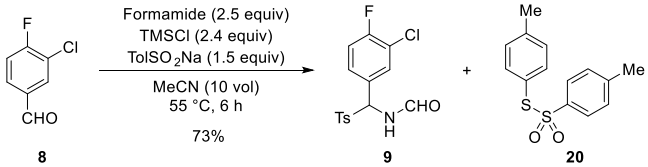


Figure 3. DSC thermograms of: (A) reaction mass in THF/water; (B) reaction mass in MeOH/water; (C) $NaIO_4$ in THF/water; and (D) $NaIO_4$ in MeOH/water.

$TolSO_2Na$) using HCl and isolated prior to use in the first step.[40] We determined that the reaction proceeded smoothly even with $TolSO_2Na$, and thus we were able to circumvent the extra protonation step. Upon completion of the reaction under these modified reaction conditions (Scheme 7), the crude

Scheme 7. Synthesis of TosMIC Precursor 9

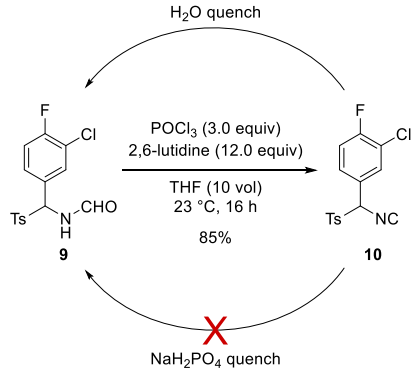


product was precipitated by the addition of water, but was found to be contaminated with ca. 15 area % of byproduct **20**. Compound **20** presumably arises out of a disproportionation of $TolSO_2Na$, and was purged effectively by slurrying the crude product with MTBE. This protocol worked very well on a multikilogram scale to furnish **9** in 73% yield and >92 area % purity by HPLC.

The dehydration reaction to prepare TosMIC **10** from **9** worked best when using 3 equiv of $POCl_3$ in the presence of 2,6-lutidine (12 equiv). Of the bases surveyed, 2,6-lutidine performed best, and the reactions routinely proceeded to >90 area % product by HPLC. While the reaction itself worked well, we encountered two major challenges during work up and isolation:[41,42] (1) TosMIC **10** was prone to hydrolysis (to give precursor **9**) during the addition of water to quench the excess $POCl_3$ at the end of the reaction (the pH at the end of the water addition was ~5.5), and (2) isolated TosMIC **10** exhibited a sharp exothermic event by DSC (T_{onset} 94 °C, $\Delta H = -425$ J/g), suggesting that its decomposition could be autocatalytic,[43] which necessitated certain controls during workup, isolation, and drying. Both of these issues needed to be addressed prior to scale up.

The problem of hydrolysis of **10** during the aqueous quench of the excess $POCl_3$ was addressed by a systematic screening of bases. While carbonate bases led to frothing and some hydrolysis, it was found that a 10% aqueous NaH_2PO_4 quench at 0−15 °C suppressed the hydrolysis (Scheme 8). Stability studies indicated that the mixture after the NaH_2PO_4 quench (pH 7−8) was stable for 9 h. Beyond that time, product **10** was

Scheme 8. Synthesis of TosMIC 10



slowly hydrolyzed to starting material **9** (Scheme 8). After an extractive workup (EtOAc/H_2O) and charcoal treatment, the product was isolated as a pale brown solid in 85% yield and 97.5 area % purity by crystallization from *n*-heptane in the temperature range 15−25 °C. Because of the safety concerns associated with the isolation of TosMIC **10** (vide infra), we attempted to telescope the crude solution after the charcoal treatment into the subsequent Van Leusen reaction with aldimine **7**. The poor yields obtained in this approach suggested that the purity of TosMIC **10** was critical for the success of the final Van Leusen reaction, and therefore, we focused our efforts on defining safe operating parameters for the isolation of **10**.

While TosMIC **10** was isolable, the low onset temperature (94 °C) necessitated a study of the decomposition kinetics of the material in order to establish a safe operating window for concentration and drying operations on scale. Kinetic analysis of the heat data obtained from a series of dynamic DSC runs using the AKTS software predicted the ADT24 to be 50 °C. As suspected, the AKTS model also predicted significant decomposition under isothermal conditions (above 50 °C) beyond 40 h (Figure 4). Furthermore, TosMIC **10** also exhibited a strong autocatalytic behavior as evidenced by the long induction time to decomposition. On the basis of these studies, we decided to restrict the maximum operating temperature to 45 °C during concentration and drying. The AKTS model also predicted the self-accelerating decomposition temperature to be 29 °C. Therefore, the compound was stored at 2−8 °C, and processed to the next step within two weeks.

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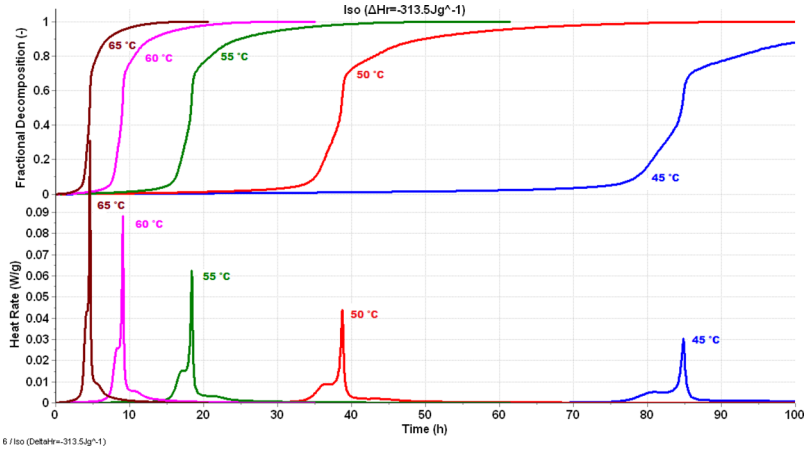
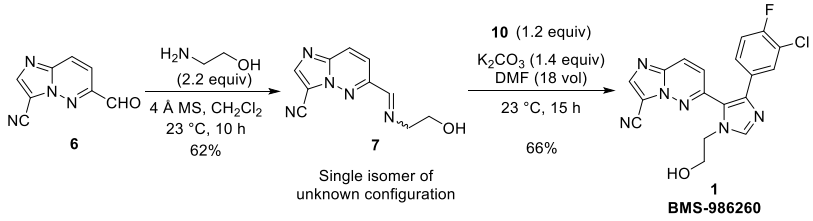
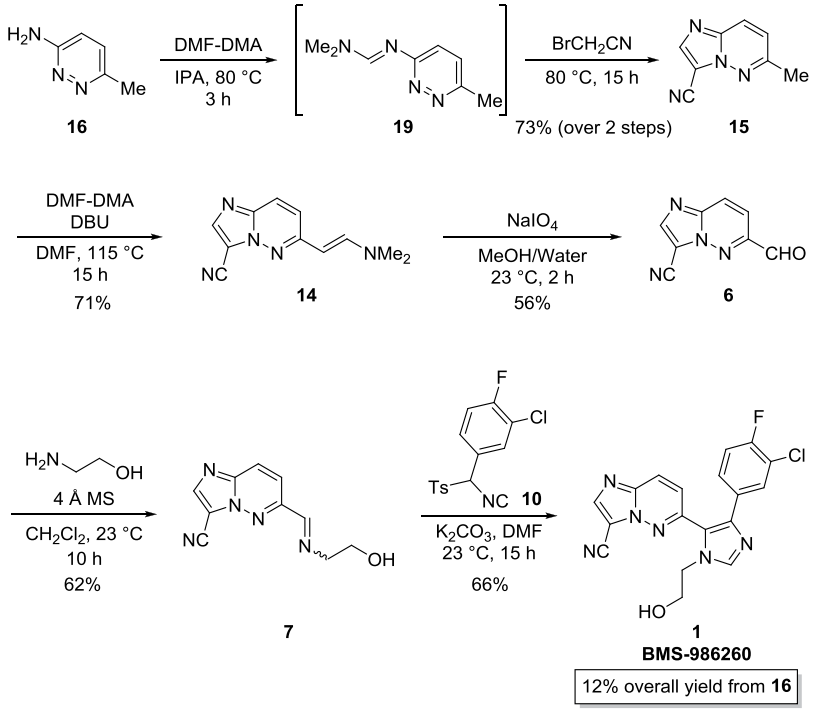


Figure 4. Predicted decomposition of TosMIC **10** under isothermal conditions using AKTS software.

Scheme 9. End Game



Scheme 10. Summary of the Second-Generation Route to 1



During this period, no significant loss of purity or potency was observed by HPLC analysis.

End Game. With both aldehyde **6** and TosMIC **10** in hand, we turned our attention to the assembly of the API. Aldehyde **6** was converted to the corresponding aldimine **7** via a reaction with 2-aminoethanol in the presence of 4 Å molecular sieves (Scheme 9). The reaction furnished a single imine isomer of an undetermined configuration, and the product was isolated in >99.9 area % purity after crystallization from CH_2Cl_2/*n*-heptane (2:3).

Aldimine **7** was treated with TosMIC **10** in the presence of K_2CO_3 in DMF to effect the Van Leusen imidazole synthesis reaction.[12] The reaction proceeded cleanly at ambient temperature. A detailed safety evaluation revealed that the reaction was accompanied by a modest adiabatic temperature rise of 35 °C, and the total heat was released at a steady rate over ∼7−8 h.

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Furthermore, the reaction mixture at the end of the reaction as well as the product **1** were stable under the reaction conditions with no significant thermal events up to 200 °C.

After an extractive workup with CH_2Cl_2, a solvent exchange with MTBE led to the precipitation of the crude product. The isolated crude API **1** was dissolved in CH_2Cl_2, decolorized with activated charcoal, and crystallized using CH_2Cl_2/*n*-heptane (1:4) to furnish the API **1** in 99.8 area % purity (Scheme 9).[44]

CONCLUSION

An improved process for the large-scale synthesis of **BMS-986260** (**1**) was developed (Scheme 10). The modified route to the key aldehyde fragment **6** avoided the use of osmium tetroxide and vinyl(tributyl)tin. A systematic study of the safety aspects of the process to access the TosMIC coupling partner helped define the operating parameters for this step. The second-generation process described herein was a significant improvement over the first-generation route, and provided the API in 99.8% purity without recourse to chromatographic purification of any of the intermediates.

EXPERIMENTAL SECTION

General Information. All reagents, starting materials, and solvents (laboratory grade or anhydrous grade) were used as received. Purity was determined using reverse-phase HPLC. Chemical shifts (δ) for protons and carbon are reported in parts per million (ppm) referenced to tetramethylsilane (δ_H = 0.00, δ_C = 0.00) or to residual proton or carbon in the NMR solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.2 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.5 ppm).

6-Methylimidazo[1,2-*b*]pyridazine-3-carbonitrile (15). To a solution of 6-methylpyridazin-3-amine **16** (3.0 kg, 27.5 mol, 1.0 equiv) in 2-propanol (30 L) in a glass reactor, DMF−DMA (5.2 kg, 43.6 mol, 1.6 equiv) was charged in the temperature range 20−35 °C under a nitrogen atmosphere. The reaction was stirred in the temperature range 70−80 °C for 3 h. Once the reaction was deemed complete by HPLC (<2.0 area % of **16** remaining), 2-bromoacetonitrile (5.2 kg, 43.4 mol, 1.6 equiv) [**Caution**: lachrymator] was charged under a nitrogen atmosphere maintaining the temperature in the range 40−50 °C. The reaction was stirred in the temperature range 70−80 °C for 15 h. Upon reaction completion, the mixture was distilled to ∼9 L under vacuum at 55 °C, and then cooled to 20−25 °C. The mass was quenched with 10% aqueous $NaHCO_3$ (9 L), and further diluted with purified water (42 L). The mixture was cooled to 0−10 °C and stirred for 2 h. The resulting slurry was filtered, and the wet cake was washed with water (12 L). The filtered solid was deliquored under vacuum for 3 h, and dried in the temperature range 60−70 °C under vacuum for 14 h to afford 6-methylimidazo[1,2-*b*]pyridazine-3-carbonitrile **15** as a pale brown solid (3.2 kg, 99.3 HPLC area % purity, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.18 (s, 1H), 7.96 (d, 1H, J = 9.6 Hz), 7.17 (d, 1H, J = 9.2 Hz), 2.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 155.6, 142.0, 140.7, 126.5, 124.1, 111.2, 101.8, 21.6.

(*E*)-6-(2-(Dimethylamino)vinyl)imidazo[1,2-*b*]pyridazine-3-carbonitrile (14). To a solution of 6-methylimidazo[1,2-*b*]pyridazine-3-carbonitrile **15** (0.9 kg, 5.7 mol, 1.0 equiv) in DMF (9 L) in a glass reactor, DBU (2.6 kg, 17.1 mol, 3.0 equiv) and DMF−DMA (3.5 kg, 29.0 mol, 5.1 equiv) were added in the temperature range 20−25 °C under a nitrogen atmosphere. The reaction mixture was stirred in the temperature range 105−115 °C for 15 h. Upon reaction completion, the mass was cooled to 5−10 °C and 10% aqueous NH_4Cl (36 L) was added maintaining the temperature below 30 °C. The resulting slurry was allowed to granulate at 5−10 °C for 1 h, filtered, and the wet cake was washed with water (9 L). The wet solid was deliquored in the temperature range 20−25 °C under vacuum for 5 h. The solid was dissolved in 2-MeTHF (27 L), dried over Na_2SO_4 (4.5 kg), filtered, and washed with 2-MeTHF (5.5 L). The filtrate and washes were combined and treated with neutral alumina (2 kg) in the temperature range 20−25 °C. The alumina was removed by filtration through Celite, and the obtained cake was washed with 2-MeTHF (5 L). The combined filtrate was distilled under vacuum at <55 °C to ∼5 L, cooled to 20−25 °C, and *n*-heptane (36 L) was added over ∼0.5 h. The resulting slurry was stirred for 0.5 h at ambient temperature, and filtered. The wet cake was washed with *n*-heptane (5 L) and deliquored for 5 h. The filtered solid was dried in the temperature range 50−55 °C under vacuum for 14 h to afford (*E*)-6-(2-(dimethylamino)vinyl)imidazo[1,2-*b*]-pyridazine-3-carbonitrile **14** as a pale brown solid (0.86 kg, 98.5 HPLC area % purity, 71% yield). ^{1}H NMR (400 MHz, DMSO-d_6): 8.25 (s, 1H), 7.95 (d, 1H, J = 9.6 Hz), 7.62 (d, 1H, J = 13.6 Hz), 7.53 (d, 1H, J = 10.0 Hz), 5.17 (d, 1H, J = 13.6 Hz), 2.95 (s, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): 156.1, 147.8, 147.7, 140.3, 140.1, 124.9, 120.3, 111.7, 101.3, 90.7 (2C).

6-Formylimidazo[1,2-*b*]pyridazine-3-carbonitrile (6). To a solution of (*E*)-6-(2-(dimethylamino)vinyl)imidazo[1,2-*b*]pyridazine-3-carbonitrile **14** (4.7 kg, 22.0 mol, 1.0 equiv) in MeOH (141 L) and water (15 L) in a C22-Hastelloy reactor, $NaIO_4$ (14.2 kg, 66.4 mol, 3.0 equiv) was charged slowly maintaining the internal temperature below 35 °C ($NaIO_4$ is a strong oxidant; adequate safety studies need to be completed prior to its use). The reaction mass was stirred for 2 h in the temperature range 20−25 °C. Upon reaction completion, the mixture was filtered, and washed with CH_2Cl_2 (38 L). The filtered solid contained inorganic residues including $NaIO_4$, and was quenched in a separate vessel using excess aqueous $Na_2S_2O_3$ solution, and discarded. The combined product-containing filtrate was quenched with solid $Na_2S_2O_3$ (2.8 kg) and was stirred for 0.5 h in the temperature range 20−25 °C. The slurry was filtered, and the filtered cake was washed with CH_2Cl_2 (38 L). The combined filtrate was distilled to ∼14 L under vacuum below 55 °C. CH_2Cl_2 (47 L) was added, and the mixture was distilled to ∼14 L. This operation was repeated one more time to remove residual MeOH (<1% by GC). The resulting slurry was dissolved in CH_2Cl_2 (118 L) in the temperature range 20−25 °C, and dried over Na_2SO_4 (23.5 kg). The inorganic solids were filtered, and the filtered cake was washed with CH_2Cl_2 (38 L). The combined filtrate was treated with neutral alumina (14.1 kg) in the temperature range 20−25 °C for 2 h, filtered through Celite, and the cake was washed with CH_2Cl_2 (38 L). The combined filtrate was distilled to ∼14 L under vacuum below 55 °C. Toluene (47 L) was added and the mixture was distilled to ∼35 L. The mass was cooled to 20−25 °C, and *n*-heptane (94 L) was added over a period of 0.5 h. The mixture was stirred for 0.5 h and filtered. The wet cake was washed with *n*-heptane (38 L), and deliquored in the temperature range 20−25 °C under vacuum for 1 h. The filtered solid was dried in the temperature range 55−60 °C under vacuum for 12 h to afford 6-formylimidazo[1,2-*b*]pyridazine-3-carbonitrile **6** as a pale brown solid (2.1 kg, 95.7 HPLC area % purity, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 10.15 (d, 1H, J = 0.8 Hz), 8.42 (s, 1H), 8.24 (dd, 1H, J = 9.6, 0.8 Hz), 7.89 (d, 1H, J = 9.2 Hz). ^{13}C

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NMR (100 MHz, $CDCl_3$): 188.3, 149.2, 143.6, 141.6, 127.3, 117.2, 109.1, 104.1.

***N*-((3-Chloro-4-fluorophenyl)(tosyl)methyl)-formamide (9).** To a solution of 3-chloro-4-fluoro-benzaldehyde **8** (1.8 kg, 11.4 mol, 1.0 equiv) in MeCN (14 L) in a glass reactor, formamide (1.3 kg, 28.9 mol, 2.5 equiv), $TolSO_2Na$ (3.0 kg, 17.0 mol, 1.5 equiv), and TMSCl (3.0 kg, 27.6 mol, 2.4 equiv) were charged in the temperature range 20−25 °C under a nitrogen atmosphere. The reaction mixture was heated to 45−55 °C and stirred for 5 h. Upon reaction completion, the mass was cooled to 20−25 °C and purified water (36 L) was added to the reaction mixture over a period of 1 h and stirred for another 1 h. The resulting slurry was filtered and the wet cake was washed sequentially with water (9 L) and *n*-heptane (36 L). The wet cake was deliquored under vacuum for 2 h. The filtered solid was reslurried in MTBE (18 L) at 0−10 °C for 2 h. The slurry was filtered and the wet cake was washed with MTBE (9 L) and deliquored under vacuum for 2 h. The filtered solid was dried in the temperature range 50−60 °C for 12 h to afford *N*-((3-chloro-4-fluorophenyl)(tosyl)methyl)formamide **9** as a white solid (2.9 kg, 92.0 HPLC area % purity, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.11 (s, 1H), 7.71 (d, 2H, J = 8.0 Hz), 7.53−7.46 (m, 2H), 7.33−7.25 (m, 3H), 7.12 (t, 1H, J = 8.4 Hz), 6.31 (d, 1H, J = 10.4 Hz), 2.41 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): 162.9 (d, J = 275.1 Hz), 160.2, 144.8, 133.3, 131.6 (d, J = 8.5 Hz), 129.7, 129.6, 129.2, 129.1, 126.7, 115.2 (d, J = 21.6 Hz), 69.4, 21.1. ^{19}F NMR (376 MHz, DMSO-d_6): −114.94.

2-Chloro-1-fluoro-4-(isocyano(tosyl)methyl)benzene (TosMIC) (10). To a solution of *N*-((3-chloro-4-fluorophenyl)-(tosyl)methyl)formamide **9** (1.6 kg, 4.7 mol, 1.0 equiv) in THF (12 L) in a glass reactor, $POCl_3$ (2.2 kg, 14.1 mol, 3.0 equiv) was charged at 0−10 °C under a nitrogen atmosphere over 15 min. A solution of 2,6-lutidine (6.0 kg, 56.4 mol, 12.0 equiv) in THF (3 L) was charged at 0−15 °C over a period of 15 min. The reaction mixture was stirred in the temperature range 20−25 °C for 16 h. Upon reaction completion, EtOAc (16 L) and 10% aqueous NaH_2PO_4 (13 L) were added sequentially to the reaction vessel maintaining the internal temperature between 0 and 15 °C. The mixture was allowed to warm to ambient temperature, and the layers were separated. The organic layer was washed sequentially with water (13 L) and 15% aqueous NaCl (13 L) in the temperature range 20−25 °C. The organic layer was dried over Na_2SO_4 (3.2 kg) and filtered. The filtrate was treated with activated charcoal (0.4 kg) and stirred in the temperature range 20−25 °C for 1 h. The slurry was filtered through Celite and washed with EtOAc (19 L). The combined filtrate was distilled to ∼14 L under vacuum maintaining the temperature below 35 °C (**Caution**: higher temperature leads to product decomposition, see the manuscript text for thermal hazards associated with **10**). *n*-Heptane (16 L) was then charged to the vessel, and the distillation was continued until a final volume of ∼14 L. The *n*-heptane addition and distillation sequence was repeated twice to ensure that the EtOAc levels at the end of the distillation were <0.5% v/v by GC. To the clear solution, *n*-heptane (16 L) and the 2-chloro-1-fluoro-4-(isocyano(tosyl)methyl)benzene **10** seed (32 g, 0.2 w/w % w.r.t. **9**) were charged sequentially, and the resulting slurry was allowed to granulate for 1 h at ambient temperature. The slurry was cooled to ambient temperature, and the solid was filtered. The wet cake was washed with *n*-heptane (8 L), and deliquored for 1 h to get the desired 2-chloro-1-fluoro-4-(isocyano(tosyl)methyl)benzene **10** as a light brown solid (1.3 kg, 97.5 HPLC area % purity, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.64 (dd, 2H, J = 6.8, 1.6 Hz), 7.38−7.35 (m, 3H), 7.26−7.23 (m, 1H), 7.16 (t, 1H, J = 8.4 Hz), 5.57 (s, 1H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 167.2, 159.5 (d, J = 252.8 Hz), 147.1, 130.9, 130.5, 130.0, 129.8, 128.5 (d, J = 8.0 Hz), 123.8 (d, J = 3.9 Hz), 122.0 (d, J = 18.3 Hz), 117.1 (d, J = 21.8 Hz), 75.1, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$): −110.99.

6-(((2-Hydroxyethyl)imino)methyl)imidazo[1,2-*b*]-pyridazine-3-carbonitrile (7). To a solution of 6-formylimidazo[1,2-*b*]pyridazine-3-carbonitrile **6** (1.7 kg, 9.6 mol, 1.0 equiv) in CH_2Cl_2 (63 L) in a glass reactor, 2-aminoethanol (1.3 kg, 21.4 mol, 2.2 equiv) was added in the temperature range 20−25 °C under a nitrogen atmosphere and stirred for 1 h. 4 Å molecular sieves (3.3 kg) were added and the slurry was stirred for 10 h in the temperature range 20−25 °C under a nitrogen atmosphere. Upon reaction completion, activated charcoal (0.5 kg) was added, and the slurry was stirred for 1 h in the temperature range 20−25 °C. The slurry was filtered through Celite and washed with CH_2Cl_2 (2 × 16 L). The combined filtrate was distilled under vacuum below 55 °C to ∼16 L. The mass was cooled to 20−25 °C and *n*-heptane (25 L) was added slowly into the mass over about 1 h. The resulting slurry was stirred for 0.5 h and filtered. The wet cake was washed with *n*-heptane (2 × 16 L) and filtered. The wet solid was deliquored in the temperature range 20−25 °C under vacuum for 1 h, and dried in the temperature range 60−65 °C under vacuum for 15 h to afford 6-(((2-hydroxyethyl)imino)methyl)-imidazo[1,2-*b*]pyridazine-3-carbonitrile **7** as a yellow solid (1.3 kg, >99.9 HPLC area % purity, 62% yield). ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (s, 1H), 8.45 (s, 1H), 8.39 (d, 1H, J = 9.6 Hz), 7.98 (d, 1H, J = 9.6 Hz), 4.72 (br s, 1H), 3.83−3.80 (m, 2H), 3.74−3.72 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 158.8, 151.6, 143.3, 141.9, 127.3, 119.3, 110.9, 102.7, 63.4, 60.6.

6-(4-(3-Chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile (BMS-986260) (1). To a solution of 6-(((2-hydroxyethyl)imino)methyl)imidazo[1,2-*b*]pyridazine-3-carbonitrile **7** (1.2 kg, 5.6 mol, 1.0 equiv) in DMF (22 L) in a glass reactor, K_2CO_3 (1.1 kg, 8.0 mol, 1.4 equiv) and 2-chloro-1-fluoro-4-(isocyano(tosyl)methyl)benzene **10** (2.2 kg, 6.8 mol, 1.2 equiv) were added in the temperature range 20−25 °C under a nitrogen atmosphere. The mixture was stirred for 15 h in the temperature range 20−25 °C. Upon reaction completion, water (38 L) and CH_2Cl_2 (38 L) were added and the layers were separated. The aqueous layer was back-extracted with CH_2Cl_2 (38 L). The combined organic layers were washed sequentially with water (2 × 38 L) and 30% aqueous NaCl (2 × 38 L). The organic phase was distilled to ∼1.5 L under vacuum below 55 °C. MTBE (6 L) was added and the mixture was distilled to ∼1.5 L. This operation was repeated one more time to remove any residual CH_2Cl_2. The mixture was diluted with MTBE (27 L) and the resulting slurry was stirred in the temperature range 20−30 °C for 1 h. The mass was filtered and the wet cake was washed with MTBE (2 × 9 L). The wet solid was deliquored under vacuum for 1 h, and was dissolved in CH_2Cl_2 (55 L) in the temperature range 20−25 °C. Activated charcoal (0.4 kg) was added; the slurry was stirred for 1 h in the temperature range 20−25 °C, filtered through Celite, and the filtered cake was washed with CH_2Cl_2 (2 × 22 L). The combined filtrate was charged into a clean glass reactor through a 0.2 μm cartridge filter, and distilled under vacuum to ∼17 L. The solution was cooled to 20−25 °C, and *n*-heptane (70 L) was added over about 0.5 h. The resulting slurry was stirred in the temperature range 20−30 °C for 0.5 h and filtered. The wet cake was washed with *n*-heptane (2 × 9 L). The wet solid was deliquored under

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vacuum for 1 h, and dried in the temperature range 60−65 °C under vacuum for 20 h to afford 6-(4-(3-chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]-pyridazine-3-carbonitrile **1** as a white solid (1.4 kg, 99.8 HPLC area % purity, 66% yield). ^{1}H NMR (400 MHz, DMSO-d_6): 8.63 (d, 1H, J = 6.0 Hz), 8.35 (d, 1H, J = 9.6 Hz), 8.03 (s, 1H), 7.77 (dd, 1H, J = 7.2, 2.4 Hz), 7.48−7.42 (m, 1H), 7.42 (d, 1H, J = 5.2 Hz), 7.33 (t, 1H, J = 8.8 Hz), 4.97 (t, 1H, J = 5.6 Hz), 4.32 (t, 2H, J = 5.2 Hz), 3.76−3.73 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 157.1 (d, J = 245.9 Hz), 147.2, 142.6, 141.5, 140.6, 140.1, 132.2 (d, J = 3.7 Hz), 129.7, 128.5 (d, J = 7.2 Hz), 127.2, 124.6, 123.3, 120.2 (d, J = 17.8 Hz), 117.3 (d, J = 20.9 Hz), 111.0, 102.9, 61.0, 48.7. ^{19}F NMR (376 MHz, DMSO-d_6): −118.07.

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M.V. and S.R. contributed equally. The manuscript was written with contributions from all authors. All authors have given approval to the final version of this manuscript.

Notes

The authors declare no competing financial interest.

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