

## Development of a Practical and Scalable Synthesis of a Potent p38 Mitogen-Activated Protein Kinase Inhibitor

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## S Supporting Information

**ABSTRACT:** Process research and development of a practical and scalable synthetic method toward a potent inhibitor of p38 mitogen-activated protein kinase **1** is described. The medicinal chemistry synthetic method had several issues in scale-up synthesis. In contrast, the synthetic method described here does not require purification by column chromatography for all steps, and the formation of impurities is suppressed well. Aminopyrazole ring formation was achieved by reaction between a new chiral amine building block **7** and bromoketone unit **4** as a key reaction. This highly efficient and scalable process was successfully demonstrated in the large-scale synthesis of **1**·HBr.

## ■ INTRODUCTION

p38 mitogen-activated protein (MAP) kinase inhibitors have been shown to effectively block the production of cytokines such as interleukin-1 (IL-1), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and IL-6. Inhibitors of p38 MAP kinase therefore have significant therapeutic potential for the treatment of autoimmune and inflammatory diseases, such as rheumatoid arthritis (RA), multiple sclerosis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease (IBD).<sup>1</sup> (R)-6-[2-(4-Fluorophenyl)-6-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl]-2-(2-tolyl)-2,3-dihydropyridazin-3-one monohydrobromide (**1**·HBr) (Figure 1) has been identified as a potent p38 MAP

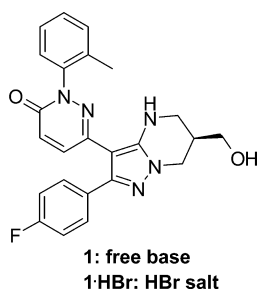


Figure 1. Structure of **1**.

kinase inhibitor.<sup>1a</sup> We were recently required to execute the first scale-up synthesis of **1**. In the medicinal chemistry synthetic route, the final product **1** was prepared by chiral column chromatography of the racemate **rac-1** (Scheme 1),<sup>1a</sup> meaning that scale-up synthesis using this methodology would be difficult. In our new synthetic route, compound **1** was constructed from the two key intermediates, thiosemicarbazide unit **8** derived from chiral amine building block **7**<sup>2</sup> and bromoketone unit **4** (Scheme 2). Here, we describe the development of a practical and scalable synthetic method capable of being operated on a 17 kg scale for the first GMP delivery of **1**·HBr.

## ■ RESULTS AND DISCUSSION

The total synthesis of compound **1** on a small scale was recently reported (Scheme 1).<sup>1a</sup> Many issues with this synthesis had to be overcome to achieve successful scale-up, as described below.

The SiO<sub>2</sub> column chromatography purification required in many steps should be avoided.

Final chiral product **1** was separated using chiral column chromatography, which was accomplished at a 260 g scale separation level. However, separation on a larger scale would be difficult because of the difficulty of chiral separation and cost performance.

The use of TBDMS-Cl should be avoided from the point of view of economics.

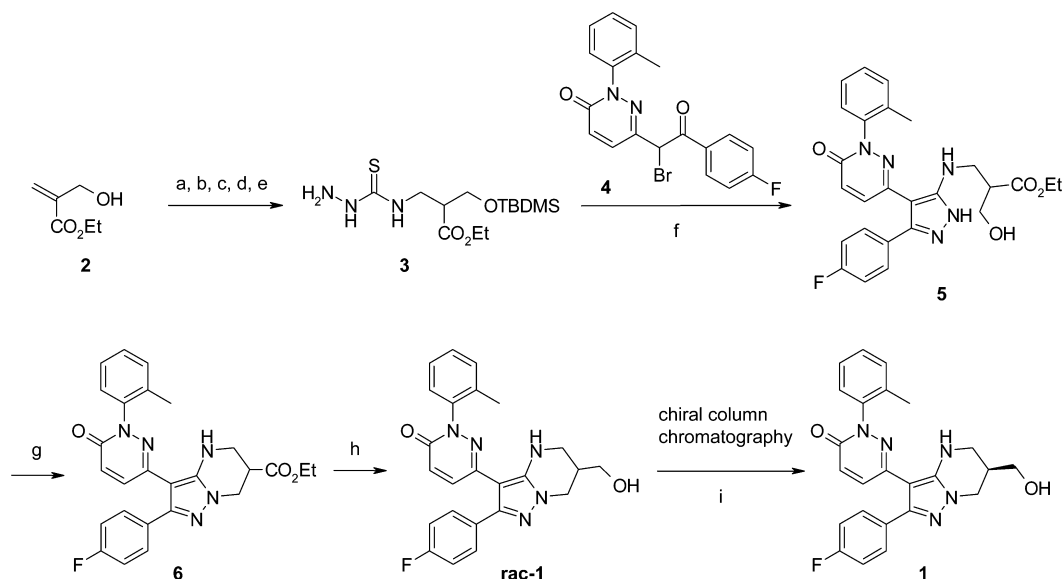
The overall yield was low [3.0% from ethyl 2-(hydroxymethyl)acrylate (**2**) in nine steps].

**New Synthetic Strategy for **1**.** Against this background, we experienced strong demand for the development of a scalable production process for **1** with a higher overall yield that does not require column chromatography purification. We describe our synthetic strategy for compound **1** in Scheme 2. The key reaction is aminopyrazole ring formation using thiosemicarbazide **8**, which was derived from chiral amine **7** and bromoketone unit **4**. A useful synthesis method for chiral building block **7** has already been described by our group.<sup>2</sup> The synthesis method of bromoketone unit **4** has already been reported,<sup>1a</sup> and it was prepared from 3-chloro-6-methylpyridazine (**9**) and ethyl 4-fluorobenzoate (**10**). We describe the development of a practical and scalable synthesis method for **1** below.

**Optimization of Bromoketone Unit **4** Synthesis.** The synthesis of bromoketone **4** is shown in Scheme 3. In the medicinal chemistry method, **4** was prepared from commercially available **9** and **10** in 33% yield in six steps.<sup>1a</sup> This method required a purification via SiO<sub>2</sub> column chromatography. We

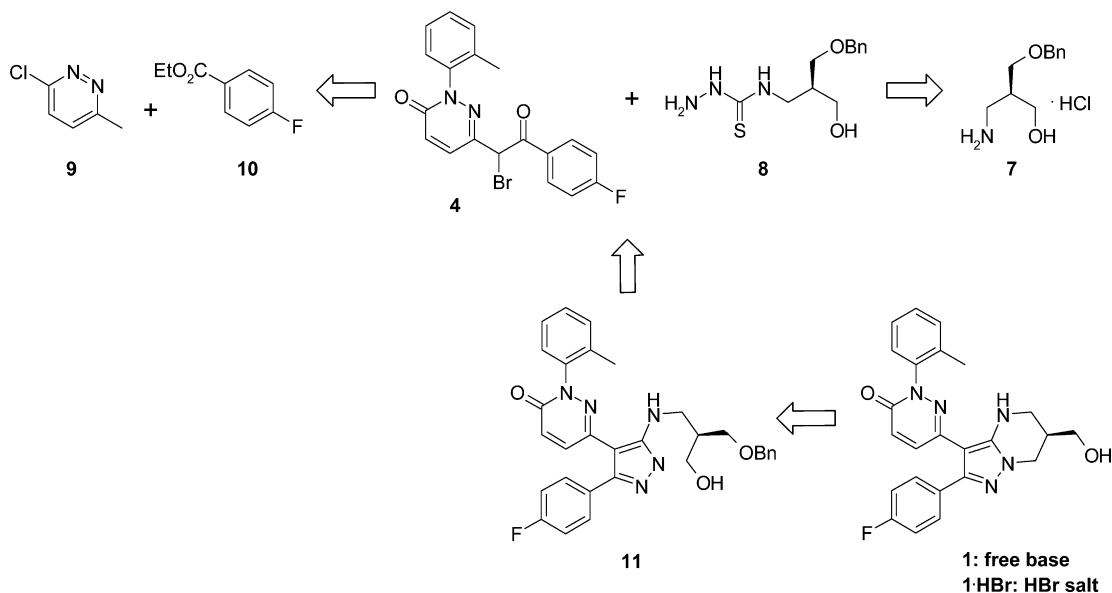
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Scheme 1. Medicinal Chemistry Synthetic Route for 1<sup>a</sup>

<sup>a</sup>Reagents and conditions: (a) imidazole, TBDMSCl, CH<sub>2</sub>Cl<sub>2</sub>, rt (99% yield); (b) BnNH<sub>2</sub>, EtOH, 50 °C, SiO<sub>2</sub> column chromatography (38% yield); (c) Pd(OH)<sub>2</sub>, H<sub>2</sub> (3 atm), EtOH (100% yield); (d) *O*-phenyl chlorothionoformate, saturated aqueous NaHCO<sub>3</sub>, toluene, rt, SiO<sub>2</sub> column chromatography (63% yield); (e) hydrazine monohydrate, EtOH, 40 °C, SiO<sub>2</sub> column chromatography (75% yield); (f) compound 4, AcOH, EtOH, 60 °C (54% yield); (g) MsCl, Et<sub>3</sub>N, CH<sub>3</sub>CN, 100 °C, SiO<sub>2</sub> column chromatography (79% yield); (h) LiBH<sub>4</sub>, THF, SiO<sub>2</sub> column chromatography (82% yield); (i) chiral column chromatography separation (48% yield).

Scheme 2. New Synthetic Strategy for 1

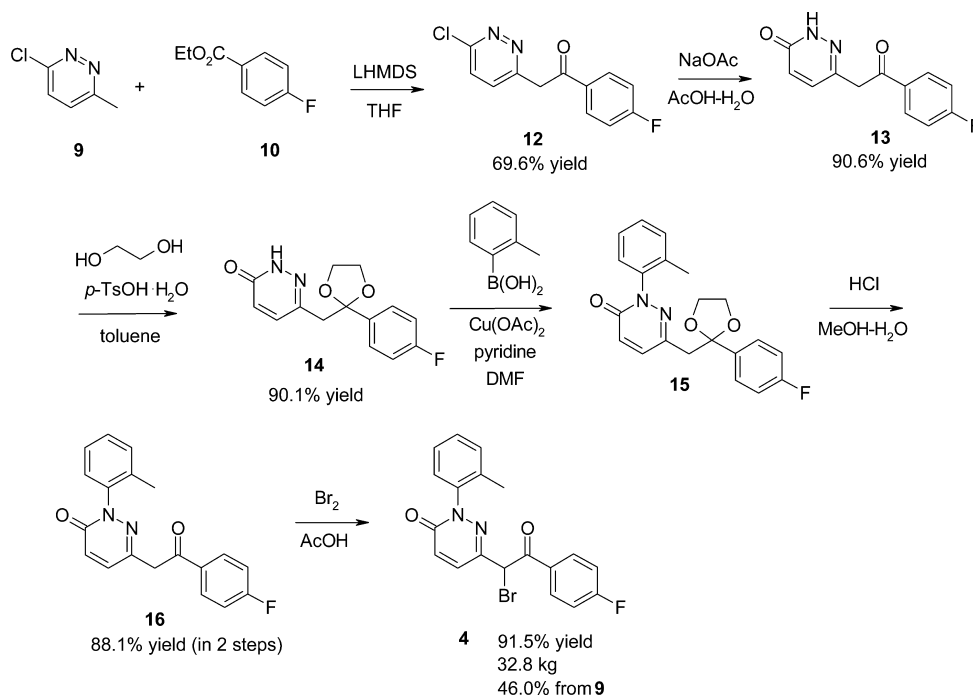


therefore investigated a robust synthesis method that did not require SiO<sub>2</sub> column chromatography purification. First, the reaction of 3-chloro-6-methylpyridazine **9** and ethyl 4-fluorobenzoate **10** was tested in the presence of various kinds of bases (Table 1). All of the bases tested gave complete conversion of **9**, but the use of sodium hexamethyldisilazane (NaHMDS), potassium hexamethyldisilazane (KHMDs), *t*-BuONa, *t*-BuOK, or NaOEt resulted in high levels of unknown impurities.<sup>3</sup> The order of the rate of reaction was roughly as follows: Li > Na > K. The use of LHMDS gave the best results for this reaction (**12**, 69.6% isolated yield).

Subsequent reaction of the chloropyridazine **12** was performed in aqueous acetic acid with NaOAc to give pyridazine

**13** in 91% yield. Subsequent ketal protection of **13** with ethylene glycol<sup>4</sup> gave the desired protected compound **14** in the presence of a catalytic amount of TsOH·H<sub>2</sub>O in toluene solvent. Chan–Evans–Lam coupling with commercially available 2-methylphenylboronic acid<sup>5</sup> was accomplished using pyridine and Cu(OAc)<sub>2</sub> in DMF at 25 °C under an atmosphere of air. The medicinal chemistry synthetic method required SiO<sub>2</sub> column chromatography at this stage. In contrast, our procedure did not require this chromatography but rather used optimization of the post-treatment sequence. Details of the phase separation procedure are provided in the Experimental Section. After the deketalization of **15** in the presence of aqueous HCl in MeOH,<sup>6</sup> highly pure **16** was obtained in 88% yield. Meanwhile, the direct

Scheme 3. Synthesis of Bromoketone Unit 4

Table 1. Base Screening for the Preparation of 12<sup>a</sup>

entry	base	HPLC (%) <sup>b</sup>	
		12	impurities <sup>c</sup>
1	LHMDS	84	8
2	NaHMDS	75	17
3	KHMDS	72	21
4	<i>t</i> -BuONa	66	27
5	<i>t</i> -BuOK	62	30
6	NaOEt	47	49

<sup>a</sup>Base, 2.1 equiv; reaction temperature, 0 °C; reaction time, 1 h; solvent, THF. <sup>b</sup>Determined by HPLC method A (see the Experimental Section). <sup>c</sup>The different bases generated the same kinds of many impurities, and the total quantity is given.

synthesis of 16 from 13 was attempted without protection. However, the desired reaction did not occur, and many small impurities were observed via HPLC. In the  $\alpha$ -bromination of 16, pyridinium tribromide was used as a bromination reagent in the medicinal chemistry route but carried the risk of an unstable supply of suitable quality. As an alternative, the reaction was accomplished using bromine in good yield. Consequently, we were able to prepare 32.8 kg of bromoketone unit 4 on a large scale without column chromatography. The yield of bromoketone

unit 4 from starting material 9 was 46.0%, which was an improvement of 12.8% compared with that of the medicinal chemistry method.

**Preparation of Thiosemicarbazide Unit 8 (Scheme 4).** Attempts to improve the impurity profile of the conversion of 7 to 8 are summarized in Table 2.

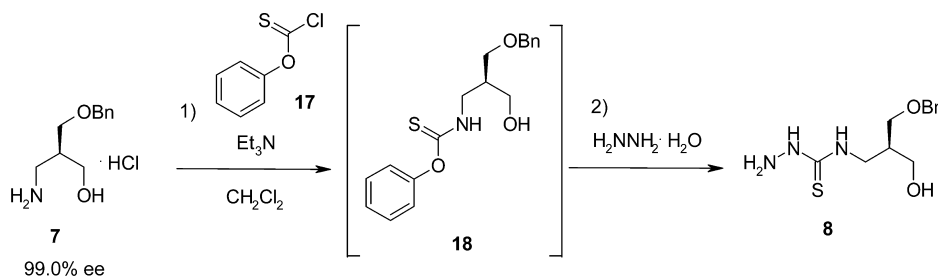
Thiocarbamate intermediate 18 was synthesized from the reaction between chiral amine unit 7 and *O*-phenyl chlorothionoformate (17) with Et<sub>3</sub>N as a base. When the reaction was performed at 25 or −10 °C, unacceptable levels of cyclic impurity 19 and dimer 20 (Figure 2) were observed (see Table 2, entries 1 and 2). After

Table 2. Preparation of Thiosemicarbazide Unit 8<sup>a</sup>

entry	conditions (equiv)	temperature (°C), time (h)	HPLC (%) <sup>b</sup>	
			19	20
1	Et <sub>3</sub> N (2.5), 17 (1.3)	25, 1	7	2
2	Et <sub>3</sub> N (2.5), 17 (1.3)	−10 to −5, 1	2	5
3	TMS-Cl (2.0), Et <sub>3</sub> N (4.5), then added 17 (1.0)	−10 to −5, 2	0.1	not detected

<sup>a</sup>Conversion, >95%; solvent, CH<sub>2</sub>Cl<sub>2</sub>. <sup>b</sup>Determined by HPLC method C (see the Experimental Section). Impurities 19 and 20 were observed before the addition of hydrazine hydrate.

Scheme 4. Synthesis of Thiosemicarbazide Unit 8



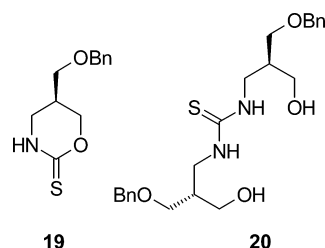


Figure 2. Structures of impurities.

completion of the conversion of **7**, the levels of **19** continued to increase at 25 °C. The slow addition of **17** gave a higher level of formation of dimer **20**. In contrast, attempts to directly convert impurity **19** with hydrazine hydrate to **8** failed. As an alternative method, in situ double protection of amine and alcohol with TMS-Cl was attempted to prevent formation of these impurities (entry 3), which resulted in the complete suppression of their formation. Further, after the removal of *O*-TMS with citric acid in MeOH, desired compound **8** was obtained in good yield (typically 80%). However, this method required inefficient protection and deprotection that should be avoided. Accordingly, we screened the reaction solvent to optimize this reaction and thereby obviate the need for this problematic TMS protection methodology (Table 3).

Table 3. Solvent Screening<sup>a</sup>

entry	solvent	HPLC (%) <sup>b</sup>		
		7	19	20
1	CH <sub>3</sub> CN	1.2	3.4	0.2
2	<i>i</i> -PrOAc	3.7	5.9	27
3	EtOH	1.2	not detected	not detected

<sup>a</sup>**21**, 1.05 equiv; Et<sub>3</sub>N, 2.1 equiv; reaction temperature, −5 to 0 °C; reaction time, 0.5–1 h. <sup>b</sup>Determined by HPLC method C (see the Experimental Section).

As a result of this, EtOH was selected as the optimal solvent, and the formation of impurities was completely suppressed because of the low solubility of intermediate **18** in EtOH (entry 3). The use of CH<sub>3</sub>CN or *i*-PrOAc produced unfavorable stirring conditions because of the Et<sub>3</sub>N·HCl formed by the reaction (entries 1 and 2) and gave higher levels of impurities. After treatment with hydrazine hydrate, thiosemicarbazide compound **8** could be crystallized as a salt of hydrochloric acid. However, crystallization was unnecessary from the point of view of the quality of this compound. Thiosemicarbazide compound **8** was used in the next step without isolation and purification. The yield of this step was typically 86%.

**Aminopyrazole Ring Formation (Scheme 5).** In the medicinal chemistry route, aminopyrazole ring formation was performed in an AcOH/EtOH solvent at 60 °C (Table 4, entry 1). However, the reaction profile on HPLC analysis in this case was characterized by its slowness, with the reaction incomplete at 3 days, at which time the levels of intermediates **22** and **23** remained at 12% (entry 1). Further, the isolated yield of desired compound **11** was low (typically 39%). To increase this yield, we screened other conditions. Liquid chromatography–mass spectrum studies during this reaction indicated a tendency for the very rapid formation of amination intermediate **21** with liberation of 1 equiv of HBr and cyclization, which was completed in EtOH at 25 °C. Subsequent dehydration was accelerated by the addition of AcOH or warming of the reaction mixture to around 40 °C, and an almost

1:1 ratio of thiadiazine **22** and **23** was observed on HPLC analysis. The subsequent desulfurization (sulfur extrusion) of thiadiazine **22** and **23** was not accelerated under these conditions. From these results, it was determined that the subsequent desulfurization reaction was rate-limiting. To improve the sulfur extrusion reaction, basic conditions were attempted, for example, reaction in the presence of KOH, NaOEt, NaHCO<sub>3</sub>, and Et<sub>3</sub>N (entries 2–5, respectively).<sup>7b–d,i</sup> As a result, the sulfur extrusion proceeded faster than in the absence of base, but new, unidentified impurities were formed, which resulted in a poor HPLC profile. Alternatively, acidic conditions were investigated, for example, reaction with an aqueous solution of HBr, HCl, or HBr with AcOH.<sup>1a,7e,f,h</sup> However, these conditions did not provide a good reaction profile, with a large amount of deprotected impurity **24** observed on HPLC (entries 6–8). Because the enantiopurity was decreased by the formation and residual amount of **24**, the formation of **24** should be suppressed during the reaction. To improve the reaction profile, the reaction was attempted in the presence of a weak acid, including KH<sub>2</sub>PO<sub>4</sub> (entry 9) and PPTS (entry 10). Results showed that the addition of aqueous KH<sub>2</sub>PO<sub>4</sub> buffer (pH 4.1), which buffered the HBr generated during this reaction, worked well and gave a good reaction profile on HPLC. The suppression of the impurities by buffering the reaction mixture with aqueous KH<sub>2</sub>PO<sub>4</sub> demonstrates that the pH is critical during sulfur extrusion. Consequently, the yield of the reaction was improved from 39% to typically 83%, and the formation of **24** was suppressed well (<1%). Impurity **24** was completely purged into the filtrate during precipitation of **11**. This robust procedure was demonstrated on a large scale, with 30.6 kg of desired compound **11** prepared in 71.0% yield in two steps (see the Experimental Section).

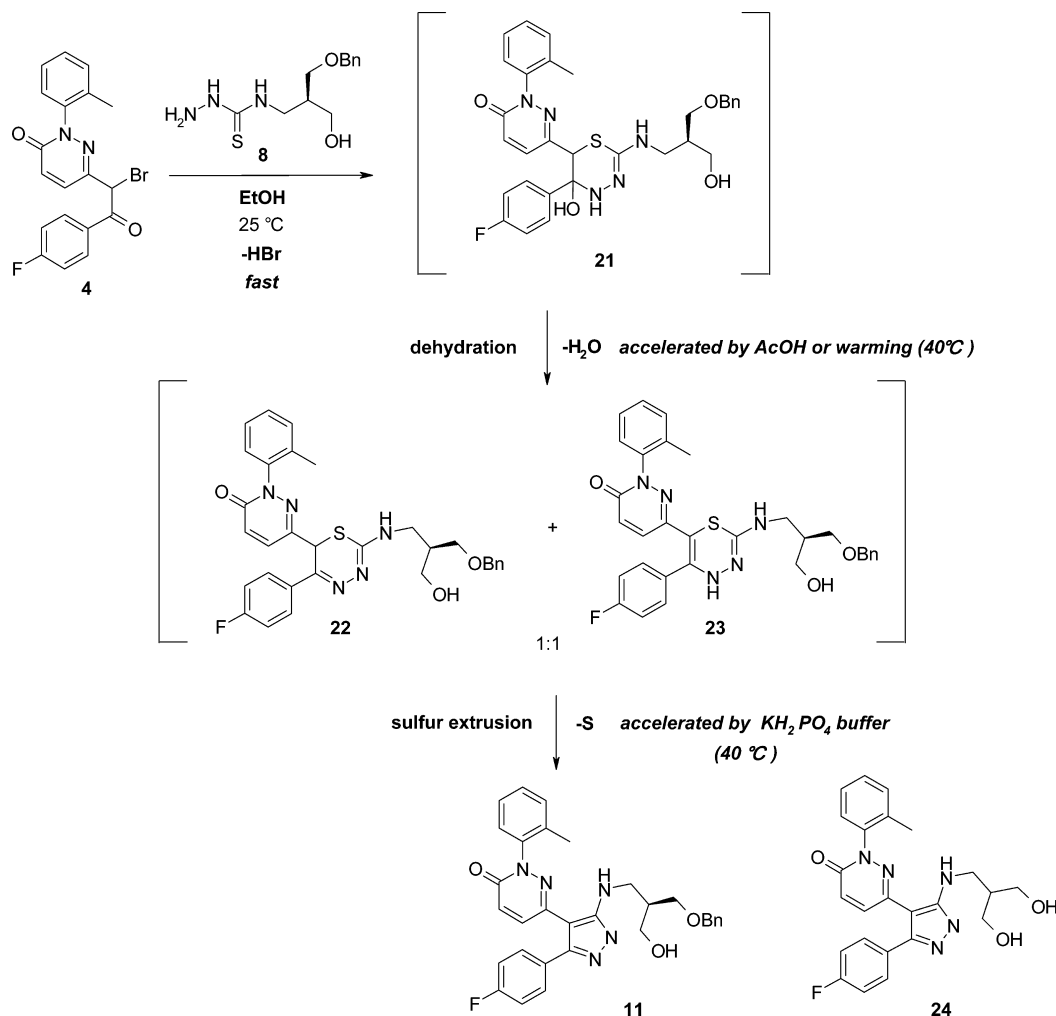
**Tetrahydropyrazolopyrimidine Ring Formation.** For formation of the tetrahydropyrazolopyrimidine ring, Et<sub>3</sub>N and MsCl were used in the medicinal chemistry method. However, this produced a complicated reaction because of the replacement of mesylate with chloride (Scheme 6 and Table 5, entry 1).<sup>8</sup> Whereas the conversion of mesylate **25** to **27** was fast, that of chloride **26** to **27** was very slow and not completed despite continuous reaction for 48 h at 80 °C. Moreover, this reaction was not reproducible. Because this issue would likely interfere with an efficient scale-up, a base screen was performed (Table 5).

The use of K<sub>2</sub>CO<sub>3</sub> or NaHCO<sub>3</sub> did not give full conversion (entries 3 and 4). In contrast, the use of pyridine worked well, with the formation of intermediate **26** suppressed completely. The isolated yield of **27** was typically 85%. In a pilot plant-scale synthesis, 25.0 kg of compound **27** was obtained (85.1% yield).

**Preparation of Final Product 1·HBr (Scheme 7).** In the final stage, debenzoylation of primary alcohol **27** with hydrochloric acid in EtOH at 60 °C was performed, and the desired free base **1** (22.0 kg) was prepared in 98.6% yield in the first scale-up synthesis. The subsequent salt formation was performed in aqueous HBr in *n*-propanol in good yield. Details of the procedure are described in the Experimental Section. Using this newly developed synthetic method, 16.7 kg of final product **1·HBr** was synthesized with a purity of 98.9% in a highly practical and scalable way. The overall yield from 3-chloro-6-methylpyridazine (**9**) was 19.6%. The enantiomer was detected at 0.27% at the release testing of drug substance **1·HBr**, with this being the same level of enantiopurity that was seen for the key intermediate chiral amine **7**.

## CONCLUSION

In summary, we developed a practical and scalable synthetic route for the potent p38 MAP kinase inhibitor **1**. Aminopyrazole

Scheme 5. Aminopyrazole Ring Formation<sup>1a,7</sup>Table 4. Aminopyrazole Ring Formation<sup>a</sup>

entry	additive, temperature (°C), time (h)	HPLC (%) <sup>c</sup>				
		4 and 8	11	intermediate 22 and 23	impurity 24	unknown impurities
1	AcOH (6 v/w), 60, 72	<1	53	12	11	23
2	KOH, <sup>b</sup> 40, 24	<1	30	1	not detected	68
3	NaOEt, <sup>b</sup> 40, 24	<1	29	4	not detected	66
4	NaHCO <sub>3</sub> , <sup>b</sup> 40, 24	<1	74	6	not detected	19
5	Et <sub>3</sub> N, <sup>b</sup> 40, 24	<1	71	7	not detected	21
6	aqueous HBr, <sup>b</sup> 40, 8	<1	41	4	41	13
7	HBr/AcOH, <sup>b</sup> 40, 8	<1	37	5	49	8
8	aqueous HCl, <sup>b</sup> 40, 8	<1	39	3	55	2
9	aqueous KH <sub>2</sub> PO <sub>4</sub> , <sup>b</sup> 40, 24	<1	90	2	<1	6
10	PPTS, <sup>b</sup> 40, 24	<1	81	7	3	8

<sup>a</sup>8, 1 equiv; EtOH, 6 v/w. <sup>b</sup>One equivalent of additive was added after the formation of 22 and 23. <sup>c</sup>Determined by HPLC method C (see the Experimental Section).

ring formation was achieved by reaction of a key chiral amine unit 7 that was synthesized from a triol compound using an enantioselective lipase reaction<sup>2</sup> and bromoketone unit 4. The formation of impurities 19 and 20 was controlled well at low levels during preparation of the thiosemicarbazide unit. Finally, this process was performed on a large scale, and we prepared 16.7 kg of final product 1·HBr for the first GMP delivery. The overall yield was 19.6% from 3-chloro-6-methylpyridazine (9) and 16.1% from 2-(hydroxymethyl)-1,3-propanediol.<sup>2</sup> This yield represented a

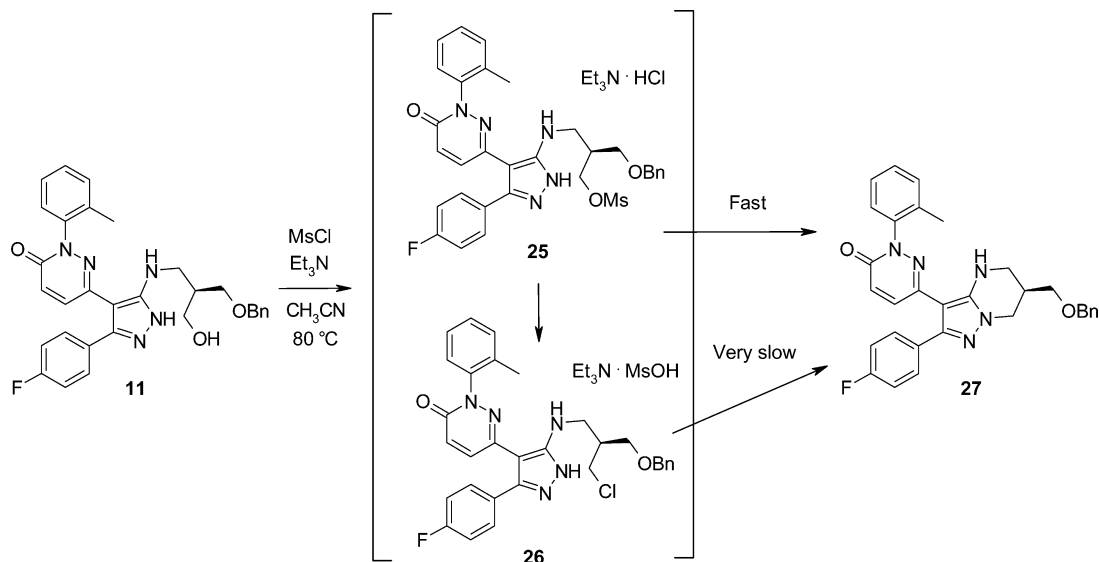
significant increase in comparison to that of the medicinal chemistry method, which required chiral separation of racemate using chiral column chromatography in the final stage (3.0% overall yield).

## EXPERIMENTAL SECTION

**General.** Starting materials, reagents, and solvents were obtained from commercial suppliers and used without further purification. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in the



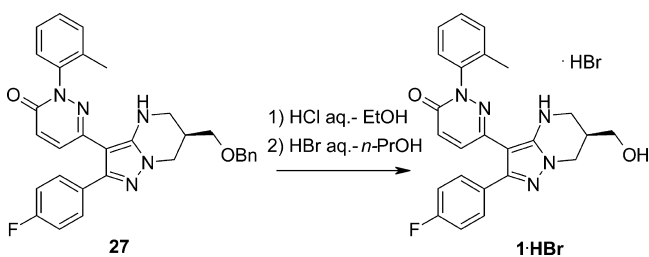
## Scheme 6. Tetrahydropyrazolopyrimidine Ring Formation

Table 5. Base Screening<sup>a</sup>

entry	base	HPLC (%) <sup>b</sup>		
		11	27	intermediate 26
1 <sup>c</sup>	Et <sub>3</sub> N	not detected	10	81
2	pyridine	<0.1	93	not detected
3	K <sub>2</sub> CO <sub>3</sub>	20	75	<0.1
4	NaHCO <sub>3</sub>	45	40	not detected

<sup>a</sup>MsCl, 2.2 equiv; base, 5 equiv; CH<sub>3</sub>CN, 10 v/w; reaction temperature, 60 °C; reaction time, 5–15 h. <sup>b</sup>Determined by HPLC method C (see the Experimental Section). <sup>c</sup>The reaction was not reproducible.

## Scheme 7. Preparation of Final Product 1·HBr



specified deuterated solvent. Chemical shifts of <sup>1</sup>H NMR spectra are reported in parts per million on the  $\delta$  scale from an internal standard of residual solvent (DMSO-*d*<sub>6</sub>, 2.50 ppm) or TMS. Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; dd, doublet doublet; t, triplet; m, multiplet; br, broad), coupling constant (hertz), and integration. Chemical shifts of proton-decoupled <sup>13</sup>C NMR spectra are reported in parts per million from the central peak of DMSO-*d*<sub>6</sub> (39.5 ppm) on the  $\delta$  scale. Mass spectra were measured using UPLC/SQD-LC/MS, JEOL JMS-GC mate II, Waters ZQ 2000, and JEOL JMS-LX2000 instruments. IR spectra were measured using the KBr disk method (JP16). KF were measured using the JP method. HPLC was performed using a Hitachi D-2500 or D-7500 system. HPLC methods are described below.

**HPLC Method A.** Waters XTERRA RP18, 5  $\mu$ m, 4.6 mm  $\times$  250 mm column, elution with 0.05 M aqueous K<sub>2</sub>HPO<sub>4</sub>/CH<sub>3</sub>CN (1/1), over 20 min, 1.0 mL/min, at 40 °C, with UV detection at

270 nm: 3-chloro-6-methylpyridazine (9), 3.2 min; 12, 5.9 min; 13, 3.2 min; 14, 3.6 min; toluene, 9.4 min; 2-methylphenylboronic acid, 3.8 min; *o*-cresol, 5.2 min; 15, 8.1 min; 16, 6.5 min.

**HPLC Method B.** YMC-Pack ODS-A, 5  $\mu$ m, 4.6 mm  $\times$  150 mm column, elution with 0.01 M aqueous KH<sub>2</sub>PO<sub>4</sub>/CH<sub>3</sub>CN (4/6), over 20 min, 1.0 mL/min, at 40 °C, with UV detection at 270 nm: 16, 3.7 min; 4, 6.0 min.

**HPLC Method C.** YMC-Pack ODS-A, 5  $\mu$ m, 4.6 mm  $\times$  150 mm column, elution with 0.01 M aqueous KH<sub>2</sub>PO<sub>4</sub>/CH<sub>3</sub>CN (1/1), over 30 min, 1.0 mL/min, at 40 °C, with UV detection at 220 nm: 7, 1.5 min; intermediate 18 (thiocarbamate compound), 7.7 min; *O*-phenyl chlorothionoformate (17), 15 min; 8, 2.2 min; phenol, 2.7 min; 11, 5.7 min; 4, 11 min; intermediate 21, 3.5 min; intermediate 22, 7.4 min; intermediate 23, 7.6 min; 27, 17 min; pyridine, 2.2 min; 1, 2.7 min.

**HPLC Method D.** Waters Xterra RP18, 5  $\mu$ m, 4.6 mm  $\times$  150 mm column, elution A; 0.01 M aqueous KH<sub>2</sub>PO<sub>4</sub> (adjusted to pH 3.0 with aqueous H<sub>3</sub>PO<sub>4</sub>), elution B; CH<sub>3</sub>CN, over 70 min, 1.0 mL/min, at 25 °C, with UV detection at 220 nm.

The gradient program was as follows (1, 12 min):

time (min)	elution A	elution B
0 to 20	70	30
20 to 60	70 to 20	30 to 80
60 to 70	20	80

**HPLC Method E.** DAICEL CHIRALCEL OJ-H, 5  $\mu$ m, 4.6 mm  $\times$  250 mm column, elution with *n*-hexane/MeOH/*i*-PrOH (5/4/3), over 60 min, 0.5 mL/min, at 40 °C, with UV detection at 228 nm: 1, 14 min; enantiomer of 1, 18 min.

**2-(6-Chloropyridazin-3-yl)-1-(4-fluorophenyl)ethan-1-one (12).** A solution of 3-chloro-6-methylpyridazine 9 (23.5 kg, 183 mol) and ethyl 4-fluorobenzoate 10 (32.3 kg, 192 mol) in THF (47 L) was cooled to −8 °C. To the batch was added LHMDs (28% in THF, 229 kg, 384 mol) at −8 to 6 °C and the mixture aged for 1 h; then HPLC analysis indicated <2% 9 remained (HPLC method A). The batch was then poured into an aqueous solution of HCl [35 wt % HCl (83.9 kg) and water (353 L)] at 0–30 °C and washed with THF (23.5 L). The resulting slurry was aged for 16 h at 20 °C, filtered, and washed with *i*-PrOH (47 L) and then water (70.5 L). Loss to the filtrate was 13%. The wet cake was dried in

vacuo at 50 °C to afford the desired **12** at 98.5% purity via HPLC method A (31.9 kg, 69.6% yield): MS (ESI, positive mode)  $m/z$  251.0; MS (ESI, negative mode)  $m/z$  249.0;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.15–8.20 (2H, m), 7.93 (1H, d,  $J$  = 8.8 Hz), 7.79 (1H, d,  $J$  = 8.8 Hz), 7.38–7.45 (2H, m), 4.85 (2H, s);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  194.8, 166.5, 164.0, 158.3, 155.2, 132.8 ( $J_{\text{CF}}$  = 3.0 Hz), 131.6 ( $J_{\text{CF}}$  = 44.8 Hz), 131.1 ( $J_{\text{CF}}$  = 40.2 Hz), 129.3 ( $J_{\text{CF}}$  = 161 Hz), 128.2 ( $J_{\text{CF}}$  = 8.9 Hz), 115.8 ( $J_{\text{CF}}$  = 21.8 Hz), 44.6. Anal. Calcd for  $\text{C}_{12}\text{H}_8\text{ClFN}_2\text{O}$ : C (57.50%), H (3.22%), N (11.18%), F (7.58%). Found: C (57.33%), H (3.11%), N (11.32%), F (7.77%). Water: 0.3% (KF).

**6-[2-(4-Fluorophenyl)-2-oxoethyl]-2,3-dihydropyridazin-3-one (13).** A solution of **12** (31.7 kg, 127 mol), AcOH (133 kg), NaOAc (10.9 kg, 133 mol), and water (31.7 kg) was heated to 100–108 °C, and the batch was aged for 5 h; then HPLC analysis indicated <1% **12** remained (HPLC method A). Water (256.3 L) was then added to the batch at 38–80 °C; the resulting slurry was heated to 82 °C, and the resulting solution was cooled to 0–5 °C and aged for 19 h. The batch was then filtered, and the residue was washed with water (127 L). Loss to the filtrate was 6%. The wet cake was dried in vacuo at 50 °C to afford the desired **13** at 97.0% purity via HPLC method A (26.6 kg, 90.6% yield): MS (ESI, positive mode)  $m/z$  233.1; MS (ESI, negative mode)  $m/z$  231.0;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.9 (1H, s), 8.09–8.15 (2H, m), 7.36–7.44 (3H, m), 6.87 (1H, d,  $J$  = 9.7 Hz), 4.43 (2H, s);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  195.2, 166.5, 163.9, 160.3, 142.7, 135.3, 132.8 ( $J_{\text{CF}}$  = 3.0 Hz), 131.2 ( $J_{\text{CF}}$  = 9.7 Hz), 129.1, 115.9, 115.7, 43.7. Anal. Calcd for  $\text{C}_{12}\text{H}_9\text{FN}_2\text{O}_2$ : C (62.07%), H (3.91%), N (12.06%), F (8.18%). Found: C (62.21%), H (3.99%), N (11.92%), F (8.33%). Water: 0.1% (KF).

**6-[2-(4-Fluorophenyl)-1,3-dioxolan-2-yl]methyl]-2,3-dihydropyridazin-3-one (14).** A batch of **13** (26.4 kg, 114 mol), *p*-toluenesulfonic acid monohydrate (2.16 kg, 11.4 mol), and ethylene glycol (35.3 kg, 569 mol) in toluene (264 L) was heated to 105–111 °C and aged for 12 h; then HPLC analysis indicated <7% **13** remained (HPLC method A). During the reaction, the resulting water was removed at atmospheric pressure by azeotropic distillation. The batch was then cooled to 20 °C and concentrated in vacuo. To the residue was added acetonitrile (264 L), and the mixture was concentrated in vacuo. To the residue were then added acetonitrile (132 L) and an aqueous solution of NaOH [NaOH (0.64 kg) and water (15.1 L)] and water (264 L) at <20 °C. The resulting slurry was cooled to 0–30 °C and aged for 16 h. The batch was then filtered and washed with water (52.8 L). Loss to the filtrate was 7%. The wet cake was dried in vacuo at 50 °C to afford the desired **14** at 98.5% purity via HPLC method A (28.3 kg, 90.1% yield): MS (GC, positive mode)  $m/z$  277.1; MS (ESI, negative mode)  $m/z$  275.2;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.74 (1H, s), 7.35–7.42 (2H, m), 7.28 (1H, d,  $J$  = 9.7 Hz), 7.12–7.20 (2H, m), 6.77 (1H, d,  $J$  = 9.7 Hz), 3.88–3.95 (2H, m), 3.68–3.75 (2H, m), 3.11 (2H, s);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  163.0, 160.6, 160.2, 142.7, 137.8 ( $J_{\text{CF}}$  = 3.0 Hz), 135.1, 128.6, 127.7, 127.6, 114.9, 114.7, 108.3, 64.4, 44.3. Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{FN}_2\text{O}_3$ : C (60.87%), H (4.74%), N (10.14%), F (6.88%). Found: C (60.61%), H (4.99%), N (10.01%), F (6.77%). Water: 0.2% (KF).

**6-[2-(4-Fluorophenyl)-1,3-dioxolan-2-yl]methyl]-2-(2-tolyl)-2,3-dihydropyridazin-3-one (15).** To the mixture of 2-methylphenylboronic acid (30.4 kg, 224 mol), **14** (28.1 kg, 102 mol), and pyridine (32.2 kg, 407 mol) in DMF (169 L) was added anhydrous  $\text{Cu}(\text{OAc})_2$  (2.77 kg, 15.3 mol), and the batch was stirred for 37 h at 25 °C under an atmosphere of air; then HPLC analysis indicated <3% **14** remained (HPLC method A). To the batch were then added isopropyl acetate (225 L), water (281 L), and filter aid

(Radiolite, 14.1 kg). The suspended substance was removed during filtration. After filtration of the batch, the resulting cake was washed with isopropyl acetate (56 L). After phase separation, the organic layer was washed twice with an aqueous solution of NaOH [NaOH (11.2 kg) and water (281 L)]. *o*-Cresol derived from 2-methylphenylboronic acid was purged into aqueous layers. The resulting organic layer was washed with an aqueous solution of HCl [35 wt % HCl (28.1 kg) and water (259 L)] and concentrated in vacuo using a vacuum pump to afford the desired **15** at 92.4% purity via HPLC method A, which was used in the next step without isolation or purification: MS (ESI, positive mode)  $m/z$  367.2;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.46 (1H, d,  $J$  = 9.7 Hz), 7.31–7.40 (4H, m), 7.22–7.30 (1H, m), 7.12–7.20 (2H, m), 7.04 (1H, d,  $J$  = 7.5 Hz), 6.98 (1H, d,  $J$  = 9.7 Hz), 3.95–4.02 (2H, m), 3.73–3.77 (2H, m), 3.17 (2H, s), 1.84 (3H, s);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  163.1, 160.7, 158.5, 143.2, 140.7, 137.6, 137.5, 135.0, 134.3, 130.5, 129.3, 128.7, 127.7, 127.6, 127.1, 126.5, 114.8 ( $J_{\text{CF}}$  = 21.6 Hz), 108.4, 64.5, 44.4, 16.6.

**6-[2-(4-Fluorophenyl)-2-oxoethyl]-2-(2-tolyl)-2,3-dihydropyridazin-3-one (16).** To the residue of **15** was added MeOH (142 L). To the resulting solution was added 35 wt % HCl (21.2 kg, 204 mol), and the mixture was aged for 8 h at 25 °C; then HPLC analysis indicated <2% **15** remained (HPLC method A). The batch was then seeded (2.8 g) at 25 °C, and water (141.5 L) was added at 25 °C. The resulting slurry was cooled to 2 °C and aged for 13 h. The batch was then filtered and washed with a MeOH (28.1 L)/water (28.1 L) solution. Loss to the filtrate was 1%. The wet cake was dried in vacuo at 50 °C to afford the desired **16** at 98.5% purity via HPLC method A (28.9 kg, 88.1% yield from **14** in two steps): MS (ESI, positive mode)  $m/z$  323.1; MS (ESI, negative mode)  $m/z$  321.1;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.08–8.13 (2H, m), 7.52 (1H, d,  $J$  = 9.7 Hz), 7.35–7.42 (4H, m), 7.28–7.34 (1H, m), 7.24 (1H, d,  $J$  = 7.4 Hz), 7.08 (1H, d,  $J$  = 9.7 Hz), 4.51 (2H, s), 2.02 (3H, s);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  195.0, 166.5, 163.9, 158.6, 143.3, 140.8, 135.1, 134.3, 132.7 ( $J_{\text{CF}}$  = 3.0 Hz), 131.2 ( $J_{\text{CF}}$  = 9.7 Hz), 130.5, 129.8, 128.7, 127.2, 126.6, 115.9, 115.7, 43.7, 16.8. Anal. Calcd for  $\text{C}_{19}\text{H}_{15}\text{FN}_2\text{O}_2$ : C (70.80%), H (4.69%), N (8.69%), F (5.89%). Found: C (70.51%), H (4.79%), N (8.61%), F (5.69%). Water: 0.1% (KF).

**(RS)-6-[1-Bromo-2-(4-fluorophenyl)-2-oxoethyl]-2-(2-tolyl)-2,3-dihydropyridazin-3-one (4).** To a solution of **16** (28.8 kg, 89.4 mol) in AcOH (181 kg) was added  $\text{Br}_2$  (15.04 kg, 94.1 mol) at 25 °C, and the mixture was aged for 4 h at the same temperature; then HPLC analysis indicated <1% **16** remained (HPLC method B). To the batch were added toluene (346 L) and water (173 L). The resulting organic layer was concentrated in vacuo. To the residue was added isopropyl acetate (173 L) while the mixture was heated to 87 °C. The resulting solution was cooled to 30 °C, and diisopropyl ether<sup>9</sup> (346 L) was added at 30 °C. The slurry was cooled to 2 °C and aged for 12 h. The batch was then filtered and washed with diisopropyl ether (28.8 L, precooled to 2 °C). Loss to the filtrate was 4%. The wet cake was dried in vacuo at 50 °C to afford the desired **4** at 99.2% purity via HPLC method B (32.8 kg, 91.5% yield): MS (ESI, positive mode)  $m/z$  401.0 (d, 403.0); MS (ESI, negative mode)  $m/z$  399.0 (d, 401.1);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.12–8.17 (2H, m), 7.80 (1H, d,  $J$  = 9.7 Hz), 7.34–7.42 (4H, m), 7.29–7.33 (1H, m), 7.19–7.23 (2H, m), 7.08 (1H, s), 1.87 (3H, s);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  196.0, 166.3, 163.8, 158.6, 146.6, 140.5, 134.3, 132.0, 131.9, 131.3, 131.0, 130.6, 128.9, 127.2, 126.6, 115.8, 115.6, 74.1, 16.6. Anal. Calcd for  $\text{C}_{19}\text{H}_{14}\text{BrFN}_2\text{O}_2$ : C (56.88%), H (3.52%), N (6.98%), F (4.74%), Br (19.91%). Found: C (56.71%), H (3.71%), N (6.69%), F (4.69%), Br (19.82%). Water: 0.1% (KF).

**(R)-4-[3-(Benzyloxy)-2-(hydroxymethyl)propyl]-thiosemicarbazide (8).** To a solution of **7** (18.5 kg, 79.8 mol) in EtOH (146 kg) was added triethylamine (17.0 kg, 168 mol) at 25 °C. The solution was cooled to –5 °C, and *O*-phenyl chlorothionformate (14.5 kg, 84.0 mol) was added at –5 to 1.5 °C, and then the mixture was aged for 1 h; then HPLC analysis indicated <1% **7** remained (HPLC method C). To the batch was then added hydrazine monohydrate (4.40 kg, 87.9 mol) at –3 °C, and the mixture was heated to 40 °C and aged for 16 h; then HPLC analysis indicated <1% intermediate **18** remained (thiocarbamate compound, HPLC method C). The reaction mixture was used in the next step without isolation.

An analytical sample of **8** was purified by crystallization as the HCl salt from *i*-PrOH (10 v/w) and diisopropyl ether (20 v/w) in 80% yield: MS (FAB, positive mode)  $m/z$  270.1; MS (FAB, negative mode)  $m/z$  268.1;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  10.01 (2H, br), 8.59 (1H, br), 7.20–7.37 (5H, m), 4.47 (2H, s), 4.02 (1H, br), 3.41–3.55 (7H, m), 2.01–2.04 (1H, m). Anal. Calcd for  $\text{C}_{12}\text{H}_{19}\text{N}_3\text{O}_2\text{S}\cdot\text{HCl}$ : C (47.13%), H (6.59%), N (13.74%), S (10.48%), Cl (11.59%). Found: C (47.13%), H (6.58%), N (13.72%), S (10.41%), Cl (11.46%).

**(R)-6-(5-[[3-(Benzyloxy)-2-(hydroxymethyl)propyl]-amino]-3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-(2-tolyl)-2,3-dihydropyridazin-3-one (11).** The reaction mixture of the previous step was cooled to 28 °C, and then **4** (32.0 kg, 79.8 mol) and EtOH (15.3 kg) were added. The batch was heated to 40 °C, and to the resulting solution was added an aqueous solution of  $\text{KH}_2\text{PO}_4$  [ $\text{KH}_2\text{PO}_4$  (10.9 kg, 80.1 mol) and water (55.5 kg)] at 36–42 °C. The reaction mixture was aged for 22 h; then HPLC analysis indicated <1% intermediate **21** and <2% intermediate **22** and **23** remained (HPLC method C). During the reaction, the pH was around 4. The reaction mixture was then cooled to 30 °C and filtered, and the residue was washed with EtOH (28.6 kg). The filtrate was concentrated in vacuo to 110 L. To the residue were added MEK (150 kg) and water (187.0 kg), and the resulting aqueous layer was re-extracted with MEK (74.5 kg). The collected organic layer was washed with an aqueous solution of NaOH [NaOH (7.4 kg) and water (185 kg)] and then an aqueous solution of NaCl [NaCl (9.25 kg) and water (185 kg)]. To the organic layer was added toluene (81.7 kg), and the mixture was concentrated in vacuo to 70 L. To the residue was added toluene (81.9 kg), and the mixture was concentrated in vacuo to 70 L. To the resulting residue were added isopropyl acetate (33.4 kg) and toluene (162 kg), and the mixture was heated to 100 °C. The resulting solution was cooled to 65 °C and seeded (1.85 g) at 65 °C. The batch was cooled to –4 °C and aged for 41 h. The slurry was filtered and washed with isopropyl acetate (16.1 kg, precooled to 10 °C). The wet cake was dried in vacuo at 50 °C to a constant weight to afford the desired **11** at 96.8% purity via HPLC method C (30.6 kg, 71.0% yield from **7**): MS (ESI, positive mode)  $m/z$  540.3; MS (ESI, negative mode)  $m/z$  538.2;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  12.3 (1H, br), 7.50–7.55 (2H, m), 7.28–7.40 (8H, m), 7.22–7.27 (3H, m), 7.05 (1H, d,  $J$  = 9.8 Hz), 6.92 (1H, d,  $J$  = 9.8 Hz), 5.50 (1H, br), 4.51 (1H, br), 4.26 (2H, s), 3.27–3.41 (4H, m), 3.18–3.26 (2H, m), 2.09 (3H, s), 1.87–1.93 (1H, m);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  157.7, 141.2, 138.5, 134.3, 132.5, 132.4, 130.9, 130.7, 130.6, 130.5, 130.1, 130.0, 128.7, 128.2, 128.1, 127.5, 127.3, 127.2, 127.1, 127.0, 126.7, 115.9 (two carbons), 115.8, 115.7, 72.1, 59.8, 42.2, 42.1, 41.4, 17.0. Anal. Calcd for  $\text{C}_{31}\text{H}_{30}\text{FN}_5\text{O}_3$ : C (69.00%), H (5.60%), N (12.98%), F (3.52%). Found: C (68.83%), H (5.78%), N (13.00%), F (3.46%). Water: 0.1% (KF).

**(R)-6-{6-[(Benzyloxy)methyl]-2-(4-fluorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidin-3-yl]-2-(2-tolyl)-2,3-dihydropyridazin-3-one (27).** To a solution of **11** (30.4 kg, 56.3 mol) in acetonitrile (238.3 kg) were added pyridine (22.3 kg, 282 mol) and methanesulfonyl chloride (14.2 kg, 124 mol) at 22–25 °C, and then the mixture was heated to 60 °C. The batch was aged for 5 h at 60 °C; then HPLC analysis indicated <1% **11** remained (HPLC method C). Water (152.8 kg) was then added at 60 °C, and the solution was cooled to 40 °C and aged for 1 h. Water (153.7 kg) was then added at 40 °C, and the resulting slurry was cooled to 20 °C and aged for 12 h. The slurry was filtered and washed twice with water (30.4 kg). The wet cake was dried in vacuo at 50 °C to afford the desired **27** at 98.2% purity via HPLC method C (25.0 kg, 85.1% yield): MS (ESI, positive mode)  $m/z$  522.3;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.46–7.52 (2H, m), 7.31–7.38 (8H, m), 7.20–7.30 (3H, m), 7.08 (1H, d,  $J$  = 9.8 Hz), 6.92 (1H, d,  $J$  = 9.8 Hz), 6.00 (1H, br), 4.50 (2H, s), 4.16 (1H, dd,  $J$  = 12.3, 5.1 Hz), 3.86 (1H, dd,  $J$  = 12.3, 8.0 Hz), 3.50 (2H, d,  $J$  = 6.7 Hz), 3.34–3.39 (1H, m), 3.08 (1H, t,  $J$  = 9.1 Hz), 2.40–2.45 (1H, m), 2.09 (3H, s);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  163.0, 160.6, 157.8, 146.5, 144.6, 141.4, 141.1, 138.3, 134.5, 133.1, 130.4, 130.3, 130.2, 130.1, 130.0, 129.8, 128.6, 128.2, 127.4, 127.3, 127.2, 126.6, 115.4, 115.2, 94.0, 72.1, 69.1, 46.9, 40.9, 32.1, 17.1. Anal. Calcd for  $\text{C}_{31}\text{H}_{28}\text{FN}_5\text{O}_2$ : C (71.38%), H (5.41%), N (13.43%), F (3.64%). Found: C (71.13%), H (5.68%), N (13.20%), F (3.46%). Water: 0.1% (KF).

**(R)-6-[2-(4-Fluorophenyl)-6-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidin-3-yl]-2-(2-tolyl)-2,3-dihydropyridazin-3-one (1).** A mixture of **27** (24.8 kg, 47.5 mol) in EtOH (118.8 kg) was heated to 45 °C, and 35 wt % HCl (175.3 kg, 1682 mol) was added while the mixture was heated to 60 °C. The batch was aged for 1 day; then HPLC analysis indicated <1% **27** remained (HPLC method C). The batch was then cooled to 30 °C, and toluene (129.3 kg) was added. To the resulting aqueous layer was added an aqueous solution of 5 M NaOH (265.5 kg), and the pH was adjusted to 7.48. The resulting slurry was aged at 25 °C for 13 h. The slurry was filtered and washed with an EtOH (14.7 kg)/water (55.8 kg) solution and twice with water (148.8 kg). The wet cake was dried in vacuo at 50 °C to afford the desired **1a** at 95.6% purity via HPLC method C (20.22 kg, 98.6% yield): MS (ESI, positive mode)  $m/z$  432.2; MS (FAB, positive mode)  $m/z$  432.1; MS (FAB, negative mode)  $m/z$  430.1;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.47–7.51 (2H, m), 7.31–7.38 (4H, m), 7.20–7.25 (2H, m), 7.09 (1H, d,  $J$  = 9.8 Hz), 6.92 (1H, d,  $J$  = 9.8 Hz), 5.97 (1H, br), 4.83 (1H, t,  $J$  = 5.3 Hz), 4.12 (1H, dd,  $J$  = 12.3, 5.2 Hz), 3.82 (1H, dd,  $J$  = 12.3, 8.2 Hz), 3.46 (2H, t,  $J$  = 6.0 Hz), 3.30–3.38 (1H, m), 3.01–3.07 (1H, m), 2.15–2.30 (1H, m), 2.09 (3H, s);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  163.0, 160.6, 157.8, 146.5, 144.7, 141.5, 141.1, 134.5, 133.1, 130.4, 130.2, 130.1, 129.8, 128.6, 127.4, 126.6, 115.4, 115.2, 93.9, 60.6, 46.9, 40.8, 34.5, 17.1. Anal. Calcd for  $\text{C}_{24}\text{H}_{22}\text{FN}_5\text{O}_2$ : C (66.81%), H (5.14%), N (16.23%), F (4.40%). Found: C (66.74%), H (5.17%), N (16.27%), F (4.45%). Water: 0.2% (KF).

**(R)-6-[2-(4-Fluorophenyl)-6-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidin-3-yl]-2-(2-tolyl)-2,3-dihydropyridazin-3-one Monohydrobromide (1·HBr).** To the mixture of **1** (20.0 kg, 46.4 mol) in *n*-propanol (161.8 kg) was added 47 wt % aqueous HBr (12.0 kg, 69.5 mol), and the mixture was heated to 82 °C. The solution was then cooled to 50 °C and concentrated in vacuo to 40 L. To the residue was added *n*-propanol (79.0 kg), and the mixture was heated to 92 °C and then cooled to 30 °C. The batch was then transferred to another



vessel, and the vessel was washed with *n*-propanol (82.3 kg) and heated to 93 °C. The solution was filtered via a 1  $\mu$ m filter into another vessel, and the vessel was washed with *n*-propanol (16.2 kg). The filtrate was heated while being stirred to 91 °C, cooled to 64 °C, and seeded (2.0 g). The batch was cooled to 20 °C, aged for 6.5 h, heated to 60 °C, and aged for 1 h. The slurry was then cooled to 0 °C and aged for 24 h. The slurry was then filtered and washed with *n*-propanol (32 kg, precooled to 5 °C). The wet cake was dried in vacuo at 50 °C to afford the crude product **1** (18.5 kg, 77.9% yield). A batch of crude **1** (18.1 kg, 35.3 mol) in *n*-propanol (204 kg) was heated to 91 °C, and the solution was then filtered via a 1  $\mu$ m filter into another vessel and washed with *n*-propanol (14.6 kg). The batch was heated to 90 °C, and the solution was cooled to 66 °C. To the batch were then added 47 wt % aqueous HBr (2.98 kg, 17.7 mol, prefiltered via a 1  $\mu$ m filter) at 66 °C and *n*-propanol (7.28 kg, prefiltered via a 1  $\mu$ m filter), and the mixture was seeded (18.1 g) at 65 °C. The batch was aged for 24 h at 65 °C, cooled to 25 °C (rate of 10 °C/h), and aged for 1 h. To the slurry were then added 47 wt % aqueous HBr (2.98 kg, 17.7 mol, prefiltered via a 1  $\mu$ m filter) and *n*-propanol (7.28 kg, prefiltered via a 1  $\mu$ m filter) at 25 °C, and the mixture was aged for 1 h. The slurry was then cooled to 3 °C, stirred for 13 h, filtered, and washed with *n*-propanol (29.1 kg precooled to 5 °C and prefiltered via a 1  $\mu$ m filter). The wet cake was dried in vacuo at 50 °C to afford the desired **1**·HBr at 99.1% purity via HPLC method D (16.7 kg, 71.7% yield from **1**). The optical isomer was observed at 0.27% by chiral HPLC analysis (HPLC method E).

The overall yield from 3-chloro-6-methylpyridazine **9** was 19.6%, and 16.1% from 2-(hydroxymethyl)-1,3-propanediol.<sup>2</sup> MS (ESI, positive mode) *m/z* 432.2; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.50–7.55 (2H, m), 7.31–7.38 (4H, m), 7.26–7.30 (2H, m), 7.14 (1H, d, *J* = 9.8 Hz), 6.97 (1H, d, *J* = 9.8 Hz), 5.50 (1H, br), 4.17 (1H, dd, *J* = 12.2, 5.2 Hz), 3.88 (1H, dd, *J* = 12.2, 8.2 Hz), 3.45 (2H, d, *J* = 6.6 Hz), 3.37 (1H, dd, *J* = 12.2, 3.4 Hz), 3.07 (1H, dd, *J* = 12.2, 8.6 Hz), 2.20–2.32 (1H, m), 2.08 (3H, s); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  163.5, 161.1, 157.9, 145.7, 145.2, 141.0, 140.4, 134.5, 133.2, 130.6, 130.5, 130.4, 130.1, 128.7, 127.4, 126.7, 115.7, 115.5, 95.0, 60.4, 46.6, 40.6, 34.0, 17.2; IR (KBr, cm<sup>−1</sup>) 3301, 2873, 1654, 1624, 1490, 1243, 1171, 846; mp 220.6 °C (by DSC); heavy metals <20 ppm. Anal. Calcd for C<sub>24</sub>H<sub>22</sub>FN<sub>5</sub>O<sub>2</sub>·HBr: C (56.26%), H (4.52%), N (13.67%), Br (15.59%), F (3.71%). Found: C (56.27%), H (4.57%), N (13.67%), Br (15.65%), F (3.72%). Water: 0.09% (KF).

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

XRD chart of **1**·HBr and DSC and TG curves of **1**·HBr. 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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