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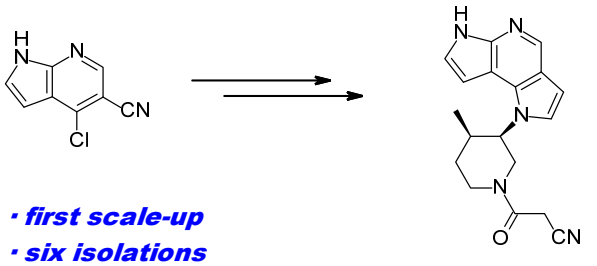
A Practical and Scalable Method for Manufacturing JAK Inhibitor ASP3627

Shun Hirasawa,[†,] Takashi Kikuchi,[†] and Souichirou Kawazoe[†]*

Process Chemistry Labs., Pharmaceutical Technology, Astellas Pharma Inc., 160-2 Akahama, Takahagi-shi, Ibaraki 318-0001, Japan

TOC GRAPHIC



- *first scale-up*
- *six isolations*
- *54.6% overall yield*
- *telescoping process*
- *Pd scavenging by L-cysteine*

JAK inhibitor
ASP3627
30 kg

ABSTRACT

ASP3627 (**1**) is a potent Janus kinase inhibitor discovered and developed by Astellas Pharma Inc. Here, we report the development of a practical and scalable method for manufacturing ASP3627 featuring a six-reaction telescoping process consisting of DIBAL reduction, hydrolysis, Wittig reaction, cyclization, and a two-step sequence to remove the SEM group. In addition, a simple palladium removal procedure using L-cysteine is described. This method was used to successfully perform the first multi-kilogram synthesis of ASP3627, producing 30 kg with high purity in excellent overall yield.

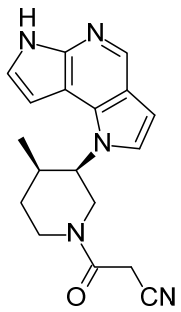
KEYWORDS

JAK inhibitor, telescoping process, palladium, L-cysteine, S_NAr reaction, SEM protection.

INTRODUCTION

Janus kinase (JAK) inhibitors are widely known to be useful in the treatment of immune and inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and transplant rejection.[1] Several JAK inhibitors (e.g., tofacitinib[2] and ruxolitinib[3]) have been approved by the U.S. Food and Drug Administration (FDA) and a number of others are under development. ASP3627 (**1**),[4] a tricyclic dipyrrolopyridine derivative, was discovered by Astellas Pharma Inc. as a highly potent JAK inhibitor with good oral bioavailability,[5] and is a promising candidate for the treatment of acute and chronic rejection in cardiac transplantation.[6] While a discovery synthetic approach appears to be suitable for large-scale synthesis of ASP3627, there are a number of problems associated with manufacturing 30 kg of an active pharmaceutical ingredient (API). This article describes the challenges we encountered in the process of developing a practical, scalable and reproducible manufacturing process for the first scale-up synthesis of ASP3627.

Figure 1. ASP3627 (**1**), a highly potent JAK inhibitor.



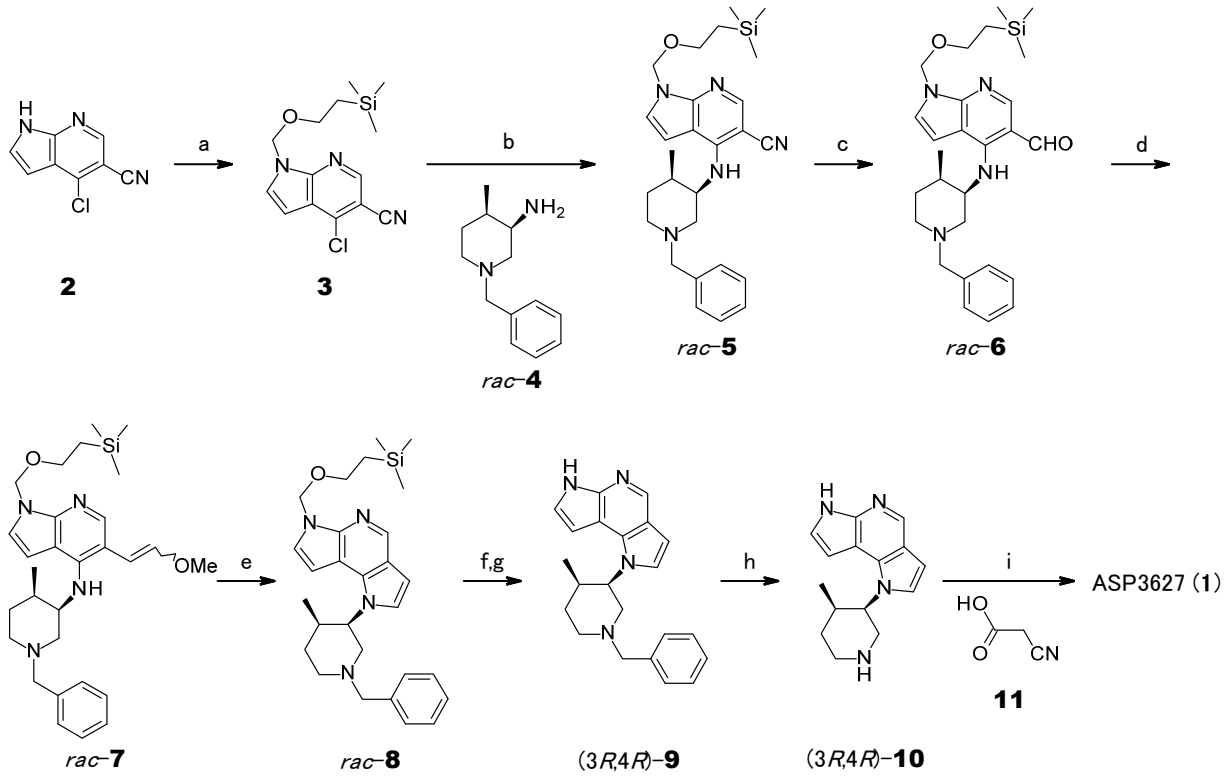
ASP3627 (1)

RESULTS AND DISCUSSION

Medicinal chemistry synthetic route

Synthesis of ASP3627 via the discovery route is shown in Scheme 1.[5] Protection of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (**2**)[7] with SEMCl gave **3**. S_NAr reaction of **3** with racemic 1-benzyl-4-methylpiperidin-3-amine (**4**)[8] yielded *rac*-**5** under a high reaction temperature (180 °C). The cyano moiety of *rac*-**5** was transformed to a pyrrole ring using the following sequence: DIBAL reduction, hydrolysis, Wittig reaction to give an *E*/*Z* mixture of *rac*-**7**, and two-step cyclization with acid via a dimethyl acetal intermediate to give *rac*-**8**. Subsequently, the SEM group of *rac*-**8** was removed using a two-step sequence, followed by enantiomeric separation using chiral column chromatography to yield (3*R*,4*R*)-**9**. Debenzylation of (3*R*,4*R*)-**9** using $Pd(OH)_2$/C and ammonium formate gave (3*R*,4*R*)-**10**. Condensation of (3*R*,4*R*)-**10** and cyanoacetic acid (**11**) was performed using EDC·HCl and HOBt to give ASP3627 (**1**) in good overall yield (33% yield/11 reactions).

Scheme 1. Synthesis of ASP3627[a] via the discovery route (from ref 5).



[a] Reagents and conditions. (a) SEMCl, NaH, THF, DMF, rt, 3 h, column chromatography, 88%; (b) **4**, DIPEA, NMP, 180 °C, 2 h, column chromatography, 91%; (c) DIBAL in *n*-hexane, THF, 0 °C, 1 h; MeOH, −78 °C; then 1 M aq HCl, 0 °C, 20 min, column chromatography, 82%; (d) $MeOCH_2P^+Ph_3Cl^-$, NaHMDS, THF, 0 °C, 30 min; then **6**, rt, 13 h, column chromatography; (e) AcCl, MeOH, 80 °C, 0.5 h; then H_2O, 80 °C, 1 h, column chromatography, 83% from *rac*-**6**; (f) TFA, CH_2Cl_2, rt, overnight; ethylenediamine, 1 M aq NaOH, CH_2Cl_2, rt, 2 h, 74%; (g) enantiomeric separation using chiral column chromatography; (h) $Pd(OH)_2/C$, ammonium formate, MeOH, 80 °C, 0.5 h, column chromatography, 95%; (i) **11**, EDC·HCl, HOBt, Et_3N, DMF, 50 °C, 2 h, column chromatography, 87%.

SEMCl = 2-(trimethylsilyl)ethoxymethyl chloride; DIPEA = *N*,*N*-diisopropylethylamine; NMP = 1-methyl-2-pyrrolidinone; DIBAL = diisobutylaluminium hydride; NaHMDS = sodium bis(trimethylsilyl)amide; TFA = trifluoroacetic acid; EDC·HCl = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride; HOBt = 1-hydroxybenzotriazole.

Large-scale synthesis

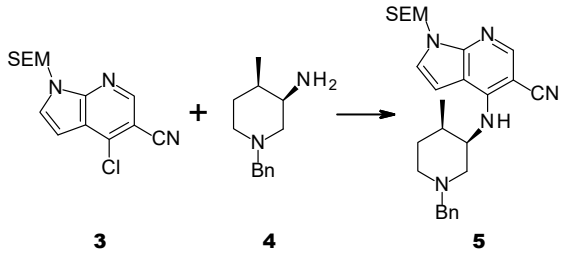
We determined that the discovery synthetic approach was suitable for the first scale-up synthesis of ASP3627 for two reasons: (1) starting material **2** was readily available in high purity and, because chiral amine (3*R*,4*R*)-**4** was commercially available, the enantiomeric separation process could be avoided; and (2) all reactions in the discovery route had good yields (11 reactions in 33% yield). However, a number of difficulties were also associated with manufacturing multi-kilograms of ASP3627, namely: (1) a high reaction temperature (**3** → **5**); (2) inefficient workup procedures and complicated processes for DIBAL reduction, hydrolysis, Wittig reaction, cyclization and deprotection (**5** → **9**; see Table 2, entry1 and Table 3, entry 1); (3) multiple column chromatography purifications; (4) removal of residual palladium from **10** using column chromatography; (5) low solubility of ASP3627 in various solvents; and (6) the need to avoid a number of reagents and solvents, namely NaH with DMF, TFA, and CH_2Cl_2. Given that Wittig product **7** with SEM protection dissolved easily in *n*-heptane, we expected that triphenylphosphine oxide, the byproduct of the Wittig reaction, would be removed by crystallization with *n*-heptane. Therefore, SEM protection was necessary in our scale-up synthetic strategy. The challenges we encountered in solving these problems for manufacturing 30 kg of ASP3627 are described in detail below.

*1) Synthesis of (3R,4R)-**5***

In SEM protection of starting material **2**, NaHMDS was used as a substitute for NaH, which was adopted in the discovery conditions to give **3**. NaH should be avoided for the scale-up because it generates hydrogen as a byproduct. Additionally, NaH is known to cause a thermal runaway reaction with DMF.[9] In the S_NAr reaction of **3** with commercially available chiral amine

(3*R*,4*R*)-**4**, the discovery conditions required a high reaction temperature (180 °C). In contrast, a steam heating system, which is commonly used in scale-up manufacturing, requires a lower reaction temperature (<120 °C). After optimizing the base, solvent, and temperature (Table 1), we concluded that Na_2CO_3 in sulfolane at 120 °C was the best reaction condition (entry 12). This step may be a good candidate for future flow reactions given that the reaction time at 120 °C is still long (>18 h) for a batch process. Subsequently, development of an efficient crystallization purification method was required to control the quality of (3*R*,4*R*)-**5** due to the production of a number of byproducts. Because most of the impurities appeared to be more polar than (3*R*,4*R*)-**5**, as shown in Figure S1, we expected that crystallization with a highly polar solvent such as alcohol and water would be sufficient for their removal. After solubility and crystallization studies with various solvents, we found that crystallization in aqueous EtOH efficiently produced (3*R*,4*R*)-**5** with high quality (99.3 HPLC area percent purity (A%)) as expected (Figure S2). Quality control for (3*R*,4*R*)-**5** production was important for the subsequent telescoping process.

Table 1. Optimization of the S_NAr reaction of **3** with **4**



entry	base	solvent	temp	HPLC A%[a]		isolated yield
				5	**3**	
1[b]	DIPEA	NMP	180 °C	N/A	N/A	91%
2[c]	DIPEA	NMP	130 °C	73.4	9.4	N/A
3[c]	pyridine	NMP	130 °C	41.0	11.6	N/A
4[c]	DBU	NMP	130 °C	37.0	0.2	N/A
5[c]	NMM	NMP	130 °C	60.2	18.8	N/A
6[c]	Et_3N	NMP	130 °C	43.1	20.5	N/A
7[c]	Cs_2CO_3	NMP	130 °C	38.0	0.3	N/A
8[c]	K_2CO_3	NMP	130 °C	80.7	0.3	N/A
9[c]	Na_2CO_3	NMP	130 °C	87.5	0.2	N/A
10[d]	Na_2CO_3	NMP	120 °C	85.9	0.9	85%[e]
11[d]	Na_2CO_3	DMSO	120 °C	80.9	0.8	78%[e]
12[d]	Na_2CO_3	sulfolane	120 °C	84.9	0.4	88%[e]
13[d]	Na_2CO_3	DMAc	120 °C	70.6	1.4	N/A

[a] Except for the solvent peak. [b] Discovery conditions (ref 5): *rac*-**4** (1.1 equiv), DIPEA (3.0 equiv), NMP, 180 °C, 2 h, column chromatography. [c] (3*R*,4*R*)-**4** (1.2 equiv), base (3.0 equiv), 130 °C, overnight. [d] (3*R*,4*R*)-**4** (1.2 equiv), base (1.2 equiv), 120 °C, 7−20 h. [e] Crystallization with EtOH/H_2O (7/3). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; NMM = 4-methylmorpholine; DMSO = dimethyl sulfoxide; DMAc = *N*,*N*-dimethylacetamide.

*2) Transformation from (3R,4R)-**5** to (3R,4R)-**9** using the telescoping process*

In the transformation from (3*R*,4*R*)-**5** to (3*R*,4*R*)-**9**, we determined that the telescoping process would be effective for avoiding an inefficient workup and complicated process.

In general, the telescoping process has many advantages for scale-up synthesis.[10] However, it is typically very challenging to control the quality of the product and to ensure reproducibility of the process without isolating the intermediates. To develop a reproducible and robust telescoping process, we focused on the following: (1) preparation of (3*R*,4*R*)-**5** with high quality (see purification of (3*R*,4*R*)-**5** above); (2) optimization of each reaction, the workup conditions, and whole process; and (3) efficient crystallization of (3*R*,4*R*)-**9** to remove impurities that accumulate across the reactions.

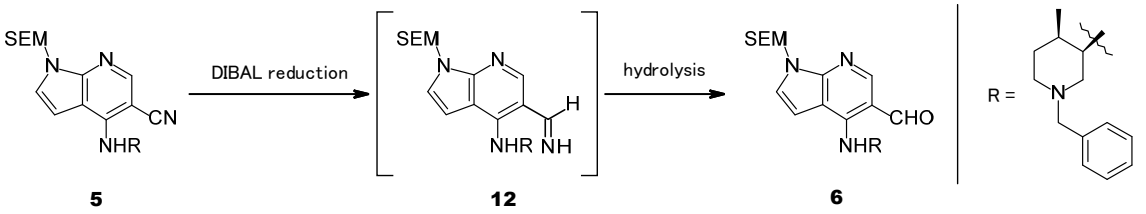
The procedure described in the previous section yielded high quality (3*R*,4*R*)-**5**. We subsequently attempted to optimize the process. In the transformation from (3*R*,4*R*)-**5** to (3*R*,4*R*)-**7**, the workup conditions needed to be optimized. Specifically, Al-related impurities generated from DIBAL and triphenylphosphine oxide generated from the Wittig reagent needed to be efficiently removed without column chromatography. The discovery conditions required filtration of the Al-related impurities and subsequent column chromatography (Table 2, entry 1). Table 2 shows the findings from our attempts to remove Al-related impurities. After DIBAL reduction and quenching with MeOH, Al-related impurities were efficiently removed by washing with aqueous Rochelle salt. Under these extraction conditions, separation of the two layers was sufficient for scale-up synthesis. Subsequently, hydrolysis with aqueous HCl, followed by neutralization with aqueous NaOH gave (3*R*,4*R*)-**6** (Table 2, entry 2). That washing with aqueous Rochelle salt after hydrolysis resulted in poor separation of layers suggested that the order in which these processes were performed was very important for ease of operation and reducing the

reaction time (Table 2, entry 3). In the Wittig reaction (**6** → **7**), removal of the byproduct triphenylphosphine oxide is typically a serious problem.[11] We developed an efficient purification method that employed crystallization with *n*-heptane. The residual amount of triphenylphosphine oxide was reduced from 3.9 A% to 0.2 A% using this crystallization process. This removal method can be applied to any products that dissolve in *n*-heptane.[12] In the case of intermediate **7**, the SEM group probably enhanced its solubility in *n*-heptane. Therefore, SEM protection was necessary in our synthetic strategy to purify the Wittig product by crystallization of the byproduct.

In the cyclization and deprotection sequence for transformation from (3*R*,4*R*)-**7** to (3*R*,4*R*)-**9**, we attempted to develop a process that solved the following problems: (1) inefficient two-reaction sequence via dimethyl acetal intermediate **13** for cyclization; (2) a complicated workup requiring column chromatography; and (3) the use of 18 equiv of TFA, a corrosive acid, and CH_2Cl_2, which has a negative environmental impact, for deprotection (Table 3, entry 1). Table 3 shows the optimization of the cyclization and deprotection processes. We found that aqueous HCl/MeOH or DME conditions yielded **8** in one reaction (Table 3, entries 2 and 3). Moreover, in the subsequent reaction, the first step of deprotection was conducted in "one pot" by adding another 12 equivalents of aqueous HCl to the reaction mixture to yield the alcohol intermediate (3*R*,4*R*)-**14**. The resulting product contained triphenylphosphine derived from the Witting reagent, which needed to be removed because residual triphenylphosphine would poison the palladium catalyst used in the next step.[13] To remove triphenylphosphine, phase split was attempted using *n*-heptane. As expected, most of the triphenylphosphine was purged into the *n*-heptane layer and (3*R*,4*R*)-**14** was obtained in the aqueous layer. After the subsequent crystallization of (3*R*,4*R*)-**9**, the amount of triphenylphosphine was successfully reduced (0.6

A%) such that it would not affect the next debenzylation step. Addition of aqueous NaOH to the aqueous layer containing (3*R*,4*R*)-**14** progressed the second step of deprotection to give crude (3*R*,4*R*)-**9** (Table 3, entry 3).

Table 2. Optimization of workup process of DIBAL reduction and hydrolysis reaction.

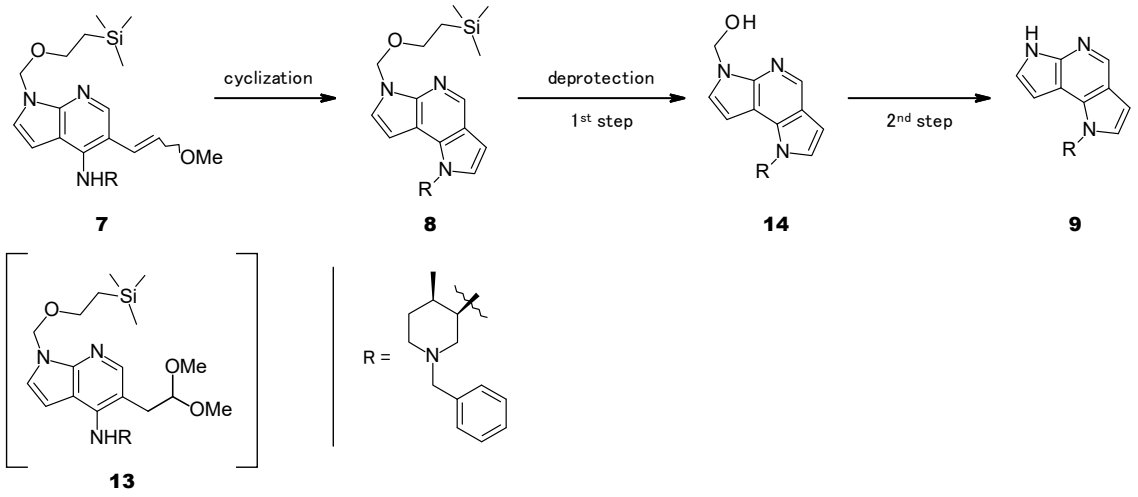


5 **12** **6**

entry	DIBAL reduction		hydrolysis		yield of **6**
	reaction	workup	reaction	workup	
1[a]	1 M DIBAL/*n*-hexane (2.5 equiv), THF, 0 °C, 1 h	add MeOH	1 M aq HCl, 0 °C, 20 min	1. neutralize with 1 M aq NaOH, then filter 2. extract with EtOAc 3. wash with water 4. dry over $MgSO_4$ 5. column chromatography	82%
2	1 M DIBAL/toluene (2.5 equiv), THF, −50 °C, then 0 °C, 1 h	1. add MeOH 2. wash with aq Rochelle salt (good separation)	3 M aq HCl, rt, 45 min	1. neutralize with 5 M aq NaOH 2. separate 3. wash with aq NaCl and water	99%
3	1 M DIBAL/toluene (2.5 equiv), THF, −60 °C, then 0 °C, 1 h	add MeOH	3 M aq HCl, rt, 3.5 h	1. neutralize with 3 M aq NaOH 2. add aq Rochelle salt (bad separation) 3. extract with CPME 4. wash with aq NaCl and water	90%

[a] Discovery conditions (ref 5). CPME = cyclopentyl methyl ether.

Table 3. Optimization of cyclization and removal of SEM.



entry	cyclization		deprotection	
	reaction	workup	first step	second step
1[a]	1. AcCl (3.0 equiv), MeOH, 80 °C, 0.5 h 2. H_2O, 80 °C, 1 h	1. concentrate 2. add aq $NaHCO_3$ 3. extract with EtOAc 4. wash with aq NaCl 5. dry over $MgSO_4$ 6. column chromatography 83% yield from **6**	1. TFA (18 equiv), CH_2Cl_2, rt, overnight 2. concentrate 3. add aq $NaHCO_3$ 4. extract with IPA/$CHCl_3$ 5. wash with aq NaOH (×2) and aq NaCl 6. dry over $MgSO_4$	1. ethylenediamine (3.0 equiv), 1 M aq NaOH, CH_2Cl_2, rt, 2 h 2. add water 3. extract with IPA/$CHCl_3$ 4. wash with aq NaCl 5. dry over $MgSO_4$ 6. slurry wash with IPA/IPE 74% yield
2	concd aq HCl (3.4 equiv), MeOH (5 vol), 50 °C, 6 h, IPC[b]: **8**/**7** = 82.4/0.8	1. add aq $NaHCO_3$ 2. extract with EtOAc 3. wash with aq NaCl 4. concentrate	6 M aq HCl (15 equiv), DME (5 vol), 50 °C, 18 h, IPC[b]: **14**/**8** = 78.0/0.2	add 5 M aq NaOH (18 equiv), 75 °C, 0.5 h, IPC[b]: **9**/**14** = 76.1/0.5
3	6 M aq HCl (3.0 equiv), DME (5 vol), 50 °C, 4.5 h, IPC[b]: **8**/**7** = 84.5/0.4	none	add 6 M aq HCl (12 equiv), 50 °C, 21 h, IPC[b]: **14**/**8** = 81.9/0.2, then wash with *n*-heptane	add 5 M aq NaOH (18 equiv), 75 °C, 0.5h, IPC[b]: **9**/**14** = 80.5/0.6

[a] Discovery conditions (ref 5). [b] HPLC A%. DME = 1,2-dimethoxyethane; IPA = 2-propanol; IPE = diisopropyl ether.

Despite developing a practical synthetic method for the production of crude (3*R*,4*R*)-**9**, a large number of impurities were observed. Therefore, we developed the workup process below to obtain pure (3*R*,4*R*)-**9**. First, to remove highly polar water-soluble impurities, the reaction mixture was diluted with EtOAc and washed with aqueous NH_4Cl followed by water at 50 °C. This improved the quality from 80.5 A% to 84.2 A%. Second, the crystallization conditions were developed after completing the solubility and crystallization experiments using various solvents. Finally, pure (3*R*,4*R*)-**9** (94.9 A%) was obtained by performing the crystallization process under aqueous EtOH conditions in 81.9% yield with 9.1% loss to the mother liquor. As described above, the six-reaction telescoping process—DIBAL reduction, hydrolysis, Wittig reaction, cyclization, and two-step removal of the SEM group—was successfully completed without the need for column chromatography purification. The whole process of this six-reaction sequence was optimized for the following: (1) selection of the appropriate order of hydrolysis and Al removal; (2) removal of triphenylphosphine in the back-extractable intermediate; and (3) one pot reaction in the same solvent as that used for the cyclization and deprotection. In addition, we set appropriate in-process controls (IPCs) to control the quality of all intermediates. The criteria for IPCs are described in the experimental section.

*3) Synthesis of **1** and removal of Pd*

Debenzylation of (3*R*,4*R*)-**9** was conducted by employing Pearlman's catalyst ($Pd(OH)_2/C$), H_2, and HCl. After optimizing the amount of HCl, we found that the reaction was highly reproducible using two equivalents of HCl. This result indicates that the protonation of two nitrogens of pyrrolopyridine and piperidine with two equivalents of acid suppressed the

poisoning of palladium and improved reproducibility. Meanwhile, residual palladium up to 560 ppm remained present in (3*R*,4*R*)-**10** when left untreated. According to the ICH Q3D guideline, the Permitted Daily Exposure (PDE) for oral exposure to palladium is 100 μg/day.[14] The amount of residual palladium in the API must therefore be strictly controlled to ensure that it is below the acceptable level. Although approximately 85% of residual palladium could be removed in subsequent steps, this was not sufficient to meet the criterion. Our efforts to remove palladium are shown in Table 4. We found that palladium could be efficiently removed using a combination of activated carbon and 2,4,6-trimercapto-*s*-triazine (TMT)[15] (Table 4, entry 2), a combination of activated carbon and L-cysteine[15a,16] (Table 4, entry 3), or L-cysteine alone without activated carbon (Table 4, entry 4). When activated carbon was used, the additive had to be filtered out before crystallization of (3*R*,4*R*)-**10** (Table 4, entries 1−3). Further, addition of carbon into the reactor is undesirable for cleaning of the reaction vessel under Good Manufacturing Practice (GMP) and there is a risk of carbon contamination. In contrast, use of only L-cysteine (Table 4, entry 4) did not require additional operations like filtration to remove the additive because L-cysteine was dissolved in the crystallization solvent and purged into the filtrate. We therefore adopted the use of only L-cysteine. The resulting simple procedure developed to remove residual palladium is shown in Figure 2. Although *N*-acetylcysteine is known to work as a Pd scavenger in the crystallization,[15a,17] to our knowledge, the method of removing Pd to the mother liquor using L-cysteine has never been reported.

Condensation of (3*R*,4*R*)-**10** and cyanoacetic acid (**11**) was performed using EDC·HCl and HOBt·H_2O to yield crude **1**.[18] However, an impurity that was thought to be the overreacted compound was observed in the reaction mixture. Addition of aqueous HCl to the reaction mixture successfully hydrolyzed this impurity to give the desired compound **1** as expected.

For the final purification, we investigated the solubility of **1** and found that it was very low in a number of solvents except for DMF and DMSO. However, we determined that DMF and DMSO should be avoided for the following reasons: (1) DMF is categorized as a Class 2 solvent in the ICH Q3C guideline;[19] and (2) recrystallization of **1** using aqueous DMSO deteriorated the solution's filterability, and the level of residual DMSO in the API was unacceptably high. Although free form **1** had low solubility, the HCl salt of **1** dissolved easily in aqueous HCl/EtOH. After the polish filtration, aqueous NaOH was added to produce a slurry of free form **1**. Following filtration and drying, ASP3627 (**1**) was obtained with high quality (≥99.0 A%, residual EtOH: 0.2%).[20]

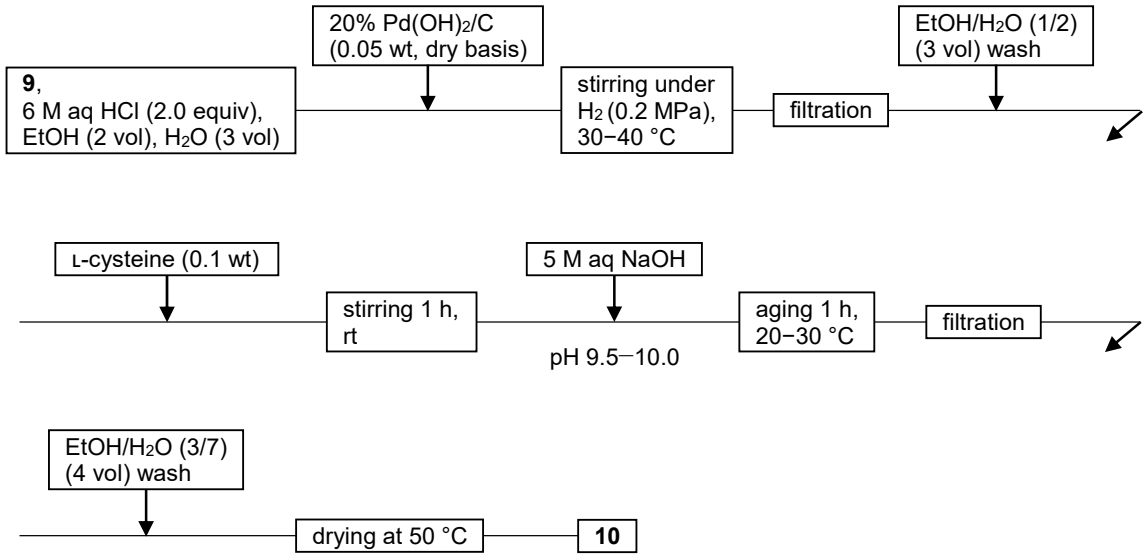
Ultimately, the target compound was prepared using six isolations in an overall yield of 52.9% at the lab-scale.

Table 4. Removal of Pd from **10**.[a]

entry	Pd initial	additive	removal of additive	Pd residue	adsorption
1	560 ppm	activated carbon (0.1 wt)	filtration	160 ppm	71.4%
2	560 ppm	activated carbon (0.1 wt), TMT (0.1 wt)	filtration	30 ppm	94.6%
3	560 ppm	activated carbon (0.1 wt), L-cysteine (0.1 wt)	filtration	8.8 ppm	98.4%
4	560 ppm	L-cysteine (0.1 wt)	none	17 ppm	97.0%

[a] Reagents and conditions. **10** (0.3 g), additive, 6 M aq HCl (2.0 equiv), EtOH/H_2O (3/5), rt, 1 h, followed by filtration of additive (entries 1−3), neutralization, then crystallization with aq EtOH.

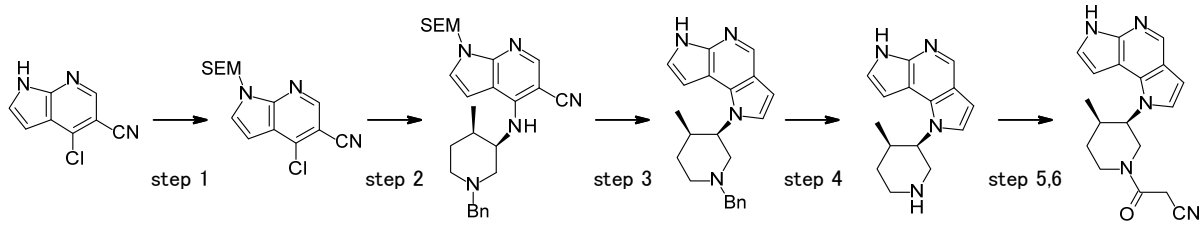
Figure 2. Scale-up procedure for (3*R*,4*R*)-**10**.



Scale-up synthesis

We used the optimized methods described above to demonstrate the first multi-kilogram synthesis of ASP3627 (**1**). The scaled-up manufacturing process effectively reproduced the lab experiments to prepare 30 kg of **1** with high purity (99.2 A%) in excellent overall yield (54.6%) (Table 5).

Table 5. Scale-up synthesis of **1**.



step	reaction	lab experiments		first scale-up synthesis			
		yield (%)	purity (HPLC A%)	yield (%)	purity (HPLC A%)	start (kg)	target (kg)
1	SEM protection	84.1	97.9	86.9	98.0	36.0	54.2
2	S_NAr reaction	90.7	99.3	92.3	99.5	52.0	74.2
3	six-reaction telescoping	81.9	94.9	80.8	96.8	69.0	40.4
4	removal of Bn	96.4	97.1	95.1	98.0	39.7	27.9[a]
5[b]	condensation	90.3	98.8	91.0; 90.9	98.7; 98.8	13.6; 13.6	15.7; 15.7
6	recrystallization	97.2	99.3	97.4	99.2	31.1	30.3
overall		52.9		54.6			

[a] Residual palladium: 5 ppm. [b] Step 5 for the first scale-up procedure was performed in two batches at the same scale.

CONCLUSION

We developed a practical, scalable, and highly reproducible method for the synthesis of ASP3627 that features the following: (1) elimination of the need for a high reaction temperature to synthesize (3*R*,4*R*)-**5** by setting appropriate reaction conditions, (2) a challenging and efficient six-reaction telescoping process, (3) no column chromatography purification, (4) a simple palladium removal method using L-cysteine, (5) a robust debenzylation reaction condition using two equivalents of HCl, and (6) recrystallizaion of a low solubility API by neutralization. This method was used to successfully perform the first scale-up synthesis of ASP3627, producing 30 kg with high quality in 54.6% overall yield over six steps.

EXPERIMENTAL SECTION

General methods

Unless otherwise noted, all reactions were performed under a nitrogen atmosphere. All reagents and solvents purchased from suppliers were used as received unless otherwise noted. (3*R*,4*R*)-**4** was obtained commercially from a custom synthesis supplier. NMR spectra were recorded on a Bruker ADVANCE III HD500. Chemical shifts (δ) are reported in ppm in reference to the residual solvent signal (δ 2.50 for ^{1}H NMR in DMSO-d_6, δ 39.52 for ^{13}C{^{1}H} NMR in DMSO-d_6, and δ 77.16 for ^{13}C{^{1}H} NMR in $CDCl_3$). High-resolution mass spectra were obtained on a Thermo Scientific EXACTIVE Plus. Elemental analyses were performed on a Elementar Vario MICRO cube and DIONEX ICS-3000-I. IR spectra were recorded on a SHIMADZU IRAffinity-1S.

HPLC conditions

Method A. YMC-Pack ODS-A (5 μm, 12 nm), 150 × 4.6 mm I.D., eluent: 0.01 M aqueous KH_2PO_4/MeCN = 25/75, flow rate: 1.0 mL/min, temperature: 40 °C, detection: UV at 254 nm. Retention time: 2.1 min for **2**, 6.7 min for **3**, 20.6 min for **5**, 16.9 min for **12**, 18.3 min for **6**, 5.3 min for **9**.

Method B. YMC-Pack ODS-A (5 μm, 12 nm), 150 × 4.6 mm I.D., eluent: 0.02 M aqueous K_2HPO_4 (pH 7.0)/MeCN = 25/75, flow rate: 1.0 mL/min, temperature: 40 °C, detection: UV at 254 nm. Retention time: 18.3 min for **6**, 2.3 min for triphenylphosphine oxide, 20.3 min for (*Z*)-**7**, 22.4 min for (*E*)-**7**, 24.8 min for **8**, 4.2 min for **14**, 9.4 min for triphenylphosphine, 5.3 min for **9**.

Method C. YMC-Pack Pro C18 (5 μm, 12 nm), 150 × 4.6 mm I.D., eluent A: 0.02 M aqueous K_2HPO_4 (pH 7.0), eluent B: MeCN, flow rate: 1.0 mL/min, temperature: 40 °C, detection: UV at 254 nm. Gradient: 0 → 5 min, A/B = 75/25; 5 → 15 min, A/B = 75/25 → 30/70; 15 → 40 min, A/B = 30/70. Retention time: 19.8 min for **9**, 4.0 min for **10**.

Method D. YMC-Pack Pro C18 (5 μm, 12 nm), 150 × 4.6 mm I.D., eluent A: 0.02 M aqueous K_2HPO_4 (pH 7.0), eluent B: MeCN, flow rate: 1.0 mL/min, temperature: 40 °C, detection: UV at 254 nm. Gradient: 0 → 12 min, A/B = 75/25; 12 → 20 min, A/B = 75/25 → 50/50; 20 → 40 min, A/B = 50/50. Retention time: 4.0 min for **10**, 21.9 min for overreacted compound, 10.0 min for **1**.

Method E. CHIRALPAK IC (5 μm), 250 × 4.6 mm I.D., eluent: 0.02 M aqueous NH_4HCO_3 (pH 9.0)/MeCN = 67/33, flow rate: 1.0 mL/min, temperature: 25 °C, detection: UV at 222 nm. Retention time: 15.2 min for **1**, 17.6 min for *ent*-**1**.

*4-Chloro-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**3**).* A 500 L reactor-1 was charged with **2** (36.0 kg, 203 mol) and DMF (170.1 kg, 5 vol). NaHMDS (38.1% in THF, 107.3 kg, 1.1 equiv, 223 mol) was added to the resulting slurry at ≤10 °C, and the mixture was stirred for ≥30 min at 0−10 °C. Following the addition of SEMCl (37.2 kg, 1.1 equiv, 223 mol) over ≥30 min at 0−10 °C, the reaction mixture was stirred for ≥1 h at 0−10 °C (IPC: **2** ≤ 1.0 A% by HPLC Method A). The reaction mixture was transferred to a 2000 L reactor-2 and quenched with aqueous NH_4Cl (prepared from 72.0 kg (2 wt) of NH_4Cl and 360 L (10 vol) of water), and EtOAc (97.4 kg, 3 vol) and Radiolite (18.0 kg, 0.5 wt) were added at ≤30 °C. The mixture was stirred for ≥1 h at 20−30 °C, filtered, and the wet cake was washed with EtOAc (64.9 kg, 2 vol). The filtrate was transferred to a 1500 L reactor-3. The biphasic mixture was separated. The organic layer was washed with aqueous NH_4Cl (prepared from 36.0 kg (1 wt) of NH_4Cl and 360 L (10 vol) of water) (×2) at 10−30 °C, transferred to a 500 L reactor-4 and reactor-3 was rinsed with EtOAc (20.0 kg, 0.6 vol). The mixture was concentrated under vacuum at 50 °C to ≤108 L (3 vol). EtOH (113.6 kg, 4 vol) was added to the residue and the mixture was concentrated under vacuum at 50 °C to ≤108 L (3 vol). More EtOH (113.6 kg, 4 vol) was added to the residue and the mixture was concentrated under vacuum at 50 °C to 97−119 L (3 vol). EtOH (113.6 kg, 4 vol) was again added, the mixture was warmed to 45−55 °C, and stirred for ≥1 h. The solution was cooled to 20−30 °C (approximately 10 °C/ h), and stirred for ≥1 h. Water (108 L, 3 vol) was added over ≥30 min at 20−30 °C. The slurry was aged for ≥2 h, cooled to −5 to 5 °C (approximately 10 °C/h), aged for ≥5 h (IPC: **3** ≤ 4 g/L by HPLC Method A), and then filtered. The wet cake was washed with cooled aqueous EtOH (prepared from 73.9 kg (2.6 vol) of EtOH and 47 L (1.3 vol) of water), dried at 50 °C (internal temperature) for ≥1 h under reduced pressure (IPC: loss on drying (LOD) ≤ 1.0%) to give **3**[5]

(54.2 kg, 176 mol, 86.9% yield) as a pale yellow solid. HPLC purity: 98.0 A% (specification: ≥95.0 A% by HPLC Method A). ^{1}H NMR (DMSO-d_6, 500 MHz): δ –0.13 (s, 9H), 0.80 (t, 2H, J = 8.0 Hz), 3.51 (t, 2H, J = 8.0 Hz), 5.66 (s, 2H), 6.74 (d, 1H, J = 3.7 Hz), 7.97 (d, 1H, J = 3.7 Hz), 8.70 (s, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz): δ –1.5, 17.1, 65.8, 73.0, 99.7, 101.5, 115.7, 118.8, 133.0, 137.3, 146.6, 148.5. HRMS–ESI (m/z): $[M + H]^+$ calcd for $C_{14}H_{19}N_3OClSi$, 308.0980; found, 308.0981. Anal. Calcd for $C_{14}H_{18}N_3OClSi$: C, 54.62; H, 5.89; N, 13.65; Cl, 11.52. Found: C, 55.00; H, 5.99; N, 13.66; Cl, 11.11. IR (ATR, cm^{-1}): 3088, 2955, 2926, 2220, 1589, 1346, 1248, 1233, 1070, 858, 833, 737, 698. DSC (onset): 66.4 °C.

*4-{[(3R,4R)-1-Benzyl-4-methylpiperidin-3-yl]amino}-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**5**).* A 500 L reactor-1 was charged with **3** (52.0 kg, 169 mol), (3*R*,4*R*)-**4** (41.4 kg, 1.2 equiv, 203 mol), and sulfolane (524.2 kg, 8 vol). Na_2CO_3 (21.5 kg, 1.2 equiv, 203 mol) was added to the resulting solution, and the reaction mixture was warmed to 115−125 °C and stirred for ≥18 h (IPC: **3** ≤ 1.0 A% by HPLC Method A). The reaction mixture was cooled to 10−30 °C, transferred to a 2000 L reactor-2, diluted with EtOAc (469.0 kg, 10 vol), and quenched with aqueous NaCl (prepared from 15.6 kg (0.3 wt) of NaCl and 780 L (15 vol) of water). The biphasic mixture was separated. The organic layer was washed with aqueous NaCl (prepared from 10.4 kg (0.2 wt) of NaCl and 520 L (10 vol) of water) and aqueous NaCl (prepared from 104.0 kg (2 wt) of NaCl and 520 L (10 vol) of water) at 10−30 °C. The resulting solution was transferred to a 1500 L reactor-3 and reactor-2 was rinsed with EtOAc (20.0 kg, 0.4 vol). The solution was concentrated under vacuum at 50 °C to ≤156 L. EtOH (164.1 kg, 4 vol) was added to the residue and the mixture was concentrated under vacuum at 50 °C to ≤156 L (3 vol). More EtOH (164.1 kg, 4 vol) was added the residue and the mixture was concentrated

under vacuum at 50 °C to 146−166 L (3 vol). EtOH (205.1 kg, 5 vol) was again added to the residue, the mixture was cooled to −5 to 5 °C, seeded with (3*R*,4*R*)-**5** (1.0 g), and aged for ≥1 h. Water (156 L, 3 vol) was added over ≥30 min, the slurry was aged for ≥1 h at −5 to 5 °C, warmed to 40−50 °C, and aged for ≥1 h. The slurry was cooled to −5 to 5 °C (approximately 10 °C/h), aged for ≥5 h (IPC: **5** ≤ 5 g/L by HPLC Method A), and then filtered. The wet cake was washed with cooled aqueous EtOH (prepared from 114.9 kg (2.8 vol) of EtOH and 62 L (1.2 vol) of water), dried at 50 °C (internal temperature) for ≥1 h under reduced pressure (IPC: LOD ≤ 1.0%) to give (3*R*,4*R*)-**5** (74.2 kg, 156 mol, 92.3% yield) as a pale yellow solid. HPLC purity: 99.5 A% (specification: ≥97.0 A% by HPLC Method A). ^{1}H NMR (DMSO-d_6, 500 MHz): δ –0.13 (s, 9H), 0.77 (t, 2H, J = 8.0 Hz), 0.83 (d, 3H, J = 6.7 Hz), 1.42–1.56 (m, 2H), 1.81–1.93 (m, 1H), 2.05–2.16 (m, 1H), 2.27 (d, 1H, J = 10.6 Hz), 2.73–2.87 (m, 2H), 3.43 (d, 1H, J = 13.4 Hz), 3.47 (t, 2H, J = 8.0 Hz), 3.56 (d, 1H, J = 13.4 Hz), 4.39–4.47 (m, 1H), 5.53 (s, 2H), 6.31 (d, 1H, J = 9.9 Hz), 6.84 (d, 1H, J = 3.8 Hz), 7.17 (t, 1H, J = 7.3 Hz), 7.24 (t, 2H, J = 7.5 Hz), 7.35 (d, 2H, J = 7.3 Hz), 7.43 (d, 1H, J = 3.8 Hz), 8.19 (s, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz): δ –1.5, 17.1, 17.4, 28.8, 33.7, 51.8, 52.6, 57.4, 61.6, 65.4, 72.5, 84.2, 101.3, 104.3, 118.5, 125.9, 126.9, 128.1, 128.5, 138.3, 147.5, 149.4, 149.8. HRMS–ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{27}H_{38}N_5OSi$, 476.2840; found, 476.2842. Anal. Calcd for $C_{27}H_{37}N_5OSi$: C, 68.17; H, 7.84; N, 14.72. Found: C, 68.74; H, 7.98; N, 14.73. $[\alpha]_D^{23}$ – 27.7 (*c* 1.00, EtOH). IR (ATR, cm^{-1}): 3339, 2951, 2922, 2818, 2199, 1591, 1557, 1524, 1512, 1225, 1080, 858, 833, 712, 698. DSC (onset): 75.2 °C.

1-[(3R,4R)-1-Benzyl-4-methylpiperidin-3-yl]-1,6-dihydrodipyrrolo[2,3-b:2',3'-d]pyridine (***9***). A 1500 L reactor-1 was charged with (3*R*,4*R*)-**5** (69.0 kg, 145 mol) and THF (368.0 kg, 6 vol). The

resulting solution was cooled to −65 to −45 °C, and DIBAL (17% in toluene, 300.4 kg, 2.5 equiv, 363 mol) was added at −65 to −45 °C. The reaction mixture was warmed to −5 to 5 °C, and stirred for ≥1 h (IPC: **5** ≤ 0.3 A% by HPLC Method A). The reaction was cooled to −65 to −45 °C, quenched with MeOH (27.3 kg, 0.5 vol), and transferred to a 5000 L reactor-2. Aqueous Rochelle salt (prepared from 207.0 kg (3 wt) of Rochelle salt and 690 L (10 vol) of water) was added to the solution at ≤10 °C. The biphasic mixture was stirred vigorously for ≥1 h at 15−25 °C and separated to give (3*R*,4*R*)-**12** in toluene solution (the organic layer).

Aqueous HCl (prepared from 162.8 kg (1599 mol) of concd aqueous HCl and 414 L (6 vol) of water) was added to the toluene solution of (3*R*,4*R*)-**12**, and the reaction mixture was stirred for ≥3 h at 15−25 °C. The pH of the aqueous layer was adjusted to 8−9 by adding 5 M aqueous NaOH (359.8 kg, 1497 mol) at 15−25 °C. The biphasic mixture was separated. The organic layer was washed with aqueous NaCl (prepared from 69.0 kg (1 wt) of NaCl and 345 (5 vol) L of water) (×2) at 15−25 °C, transferred to a 1500 L reactor-3, and reactor-2 was rinsed with THF (20.0 kg, 0.3 vol). The solution was concentrated under vacuum at 50 °C to ≤138 L (2 vol). Toluene (298.8 kg, 5 vol) was added to the residue and the mixture was concentrated under vacuum at 50 °C to ≤138 L (2 vol). More toluene (298.8 kg, 5 vol) was added to the residue and the mixture was concentrated under vacuum at 50 °C to 128−148 L (2 vol, IPC: residual water ≤ 0.10%). THF (184.0 kg, 3 vol) was added to the residue to give (3*R*,4*R*)-**6** in THF solution.

A 1500 L reactor-4 was charged with (methoxymethyl)triphenylphosphonium chloride (74.6 kg, 1.5 equiv, 218 mol) and THF (184.0 kg, 3 vol). The resulting slurry was stirred, cooled to −20 to −10 °C, and NaHMDS (38.7% in THF, 137.5 kg, 2.0 equiv, 290 mol) was added over ≥30 min at −20 to −10 °C. The mixture was stirred for ≥1 h, the THF solution of (3*R*,4*R*)-**6** was added over ≥30 min at −20 to −10 °C, and reactor-3 was rinsed with THF (122.7 kg, 2 vol). The reaction

mixture was warmed to 15−25 °C and stirred (IPC: **6** ≤ 1.0 A% by HPLC Method B). The reaction was quenched with aqueous NH_4Cl (prepared from 69.0 kg (1 wt) of NH_4Cl and 345 L (5 vol) of water), transferred to a 5000 L reactor-5, and reactor-4 was rinsed with THF. The biphasic mixture was separated at 0−30 °C. The organic layer was washed with aqueous NaCl (prepared from 69.0 kg (1 wt) of NaCl and 345 L (5 vol) of water) at 0−30 °C, transferred to a 1500 L reactor-6, and reactor-5 was rinsed with *n*-heptane (13.7 kg, 0.3 vol). The mixture was concentrated under vacuum at 50 °C to ≤207 L (3 vol). *n*-Heptane (236.0 kg, 5 vol) was added to the residue and the mixture was concentrated under vacuum at 50 °C to ≤207 L (3 vol). More *n*-heptane (236.0 kg, 5 vol) was added to the residue and the mixture was concentrated under vacuum at 50 °C to 197−217 L (3 vol). *n*-Heptane (424.8 kg, 9 vol) was again added to the residue at 45−55 °C. The slurry was cooled to −5 to 5 °C (approximately 10 °C/h), aged for ≥10 h, warmed to approximately 50 °C, stirred for 3 h, cooled to approximately 30 °C (IPC: triphenylphosphine oxide ≤ 0.7 A%, by HPLC Method B), and then filtered. The wet cake was washed with *n*-heptane (188.8 kg, 4 vol). The filtrate was transferred to a 2000 L reactor-7 and concentrated under vacuum at 50 °C to ≤138 L (2 vol). DME (297.7 kg, 5 vol) was added to the residue and the mixture was concentrated under vacuum at 50 °C to 128−148 L (2 vol). More DME (238.2 kg, 4 vol) was added to the residue to give an *E*/*Z* mixture of (3*R*,4*R*)-**7** in DME solution.

Aqueous HCl (3.0 equiv, 436 mol, prepared from 44.5 kg of concd aqueous HCl and 37 L of water) was added to the *E*/*Z* mixture of (3*R*,4*R*)-**7** in DME solution, the reaction mixture was warmed to 45−55 °C, and stirred for ≥3 h (IPC: **7** ≤ 1.0 A% by HPLC Method B) to give (3*R*,4*R*)-**8** in aqueous DME solution.

Aqueous HCl (12.0 equiv, 1742 mol, prepared from 177.3 kg of concd aqueous HCl and 145 L of water) was added to the aqueous DME solution of (3*R*,4*R*)-**8** at 45−55 °C, and the reaction mixture was stirred for ≥19 h (IPC: **8** ≤ 1.0 A% by HPLC Method B). *n*-Heptane (94.4 kg, 2 vol) was added to the reaction mixture and the biphasic mixture was separated to give (3*R*,4*R*)-**14** in aqueous DME solution (the aqueous layer).

A 6000 L reactor-8 was charged with NaOH (104.4 kg, 18.0 equiv, 2610 mol), water (524 L, 7.6 vol), and DME (59.5 kg, 1 vol). The aqueous DME solution of (3*R*,4*R*)-**14** was added to the reaction mixture and the biphasic reaction mixture was stirred for ≥0.5 h at 70−80 °C (IPC: **14** ≤ 1.5 A% in organic layer by HPLC Method B). A 5000 L reactor-9 was charged with NH_4Cl (69.0 kg, 1 wt) and water (345 L, 5 vol). EtOAc (373.4 kg, 6 vol) was added to the solution and the mixture was stirred at 45−65 °C. The reaction mixture in reactor-8 was added to the biphasic mixture in reactor-9 at 45−65 °C and reactor-8 was rinsed with DME (29.8 kg, 0.5 vol). The biphasic mixture was separated. The organic layer was washed with water (345 L, 5 vol) at 45−65 °C, diluted with EtOAc (124.5 kg, 2 vol), and then washed with water (345 L, 5 vol) at 45−65 °C. The organic layer was transferred to a 1500 L reactor-10 and reactor-9 was rinsed with EtOAc (20.0 kg, 0.3 vol). The solution was concentrated under vacuum at 50 °C to ≤207 L (3 vol). EtOH (272.2 kg, 5 vol) was added to the residue and the mixture was concentrated under vacuum at 50 °C to ≤207 L (3 vol). More EtOH (272.2 kg, 5 vol) was added to the residue and the mixture was concentrated under vacuum at 50 °C to 197−217 L (3 vol). EtOH (435.5 kg, 8 vol) was again added to the residue, the mixture was warmed to 55−65 °C, and stirred for ≥1 h. The solution was cooled to 20−30 °C (approximately 10 °C/h) and stirred for ≥2 h. Water (345 L, 5 vol) was added to the slurry over ≥30 min at 20−30 °C, and the slurry was cooled to −5 to 5 °C (approximately 10 °C/h), aged for ≥3 h (IPC: **9** ≤ 5 g/L by HPLC Method B), and then filtered.

The wet cake was washed with cooled aqueous EtOH (prepared from 141.5 kg (2.6 vol) of EtOH and 90 L (1.3 vol) of water), dried at 50 °C (internal temperature) for ≥1 h under reduced pressure (IPC: LOD ≤ 1.0%) to give (3*R*,4*R*)-**9**[5] (40.4 kg, 117 mol, 80.8% yield) as a white solid. HPLC purity: 96.8 A% (specification: ≥94.0 A% by HPLC Method A). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.51 (d, 3H, J = 6.8 Hz), 1.58–1.70 (m, 2 H), 2.13–2.31 (m, 2H), 2.67 (dd, 1H, J = 11.8, 3.2 Hz), 2.84–2.94 (m, 1H), 3.04 (dd, 1H, J = 11.8, 3.8 Hz), 3.53 (d, 1H, J = 13.2 Hz), 3.59 (d, 1H, J = 13.2 Hz), 5.01 (q, 1H, J = 4.0 Hz), 6.61 (d, 1H, J = 3.3 Hz), 6.74–6.77 (m, 1H), 7.22 (tt, 1H, J = 7.2, 1.4 Hz), 7.28–7.37 (m, 5H), 7.99 (br s, 1H), 8.43 (s, 1H), 11.6 (br s, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 16.0, 30.2, 34.1, 52.2, 56.1, 56.8, 63.5, 97.6, 101.5, 105.1, 118.3, 121.3, 126.3, 127.3, 128.4, 129.1, 135.8, 137.7, 138.3, 145.2. HRMS–ESI (m/z): $[M + H]^+$ calcd for $C_{22}H_{25}N_4$, 345.2074; found, 345.2071. Anal. Calcd for $C_{22}H_{24}N_4$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.70; H, 7.08; N, 16.19. $[\alpha]_D^{23}$ – 28.5 (*c* 1.00, 0.1 M aq HCl). IR (ATR, cm^{-1}): 3111, 3028, 2926, 2808, 1612, 1582, 1452, 1350, 1327, 885, 837, 820, 731, 719, 698. DSC (onset): 185.0 °C.

1-[(3R,4R)-4-Methylpiperidin-3-yl]-1,6-dihydrodipyrrolo[2,3-b:2',3'-d]pyridine (***10***). A 500 L reactor-1 was charged with (3*R*,4*R*)-**9** (39.7 kg, 115 mol), EtOH (62.6 kg, 2 vol), and water (119 L, 3 vol). Aqueous HCl (2.0 equiv, 230 mol, prepared from 23.4 kg of concd aqueous HCl and 19 L of water) and 20% $Pd(OH)_2$/C (wetted with water, 2.0 kg, 0.05 wt, dry basis) were added to the resulting mixture. The reaction mixture was stirred for 6 h at 30−40 °C under a H_2 atmosphere (0.15−0.25 MPa) (IPC: **9** ≤ 1.0 A% by HPLC Method C). The reaction mixture was cooled to 20−30 °C, filtered, and the wet cake was washed with aqueous EtOH (prepared from 31.3 kg (1 vol) of EtOH and 79 L (2 vol) of water). The filtrate was transferred to a 500 L

reactor-2 and L-cysteine (4.0 kg, 0.1 wt) was added. The mixture was stirred for ≥1 h at 20−30 °C. The pH of the solution was adjusted to 9.5−10.0 by adding 5 M aqueous NaOH (63.1 kg, 263 mol) at 20−30 °C. The slurry was aged for ≥1 h at 20−30 °C (IPC: **10** ≤ 2 g/L by HPLC Method C), and then filtered. The wet cake was washed with aqueous EtOH (prepared from 37.6 kg (1.2 vol) of EtOH and 111 L (2.8 vol) of water), dried at 50 °C (internal temperature) for ≥1 h under reduced pressure (IPC: LOD ≤ 1.0%) to give (3*R*,4*R*)-**10**[5] (27.9 kg, 110 mol, 95.1% yield) as a pale yellow solid. HPLC purity: 98.0 A% (specification: ≥94 A% by HPLC Method C). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.59 (d, 3H, J = 7.0 Hz), 1.51–1.60 (m, 1H), 1.67–1.75 (m, 1H), 2.27–2.54 (m, 2H), 2.70 (ddd, 1H, J = 12.2, 7.4, 3.7 Hz), 2.96 (ddd, 1H, J = 12.1, 7.3, 3.3 Hz), 3.08 (dd, 1H, J = 12.2, 3.7 Hz), 3.29 (dd, 1H, J = 12.3, 6.6 Hz), 4.89 (dt, 1H, J = 6.5, 4.1 Hz), 6.58 (d, 1H, J = 3.3 Hz), 6.71 (dd, 1H, J = 3.3, 1.6 Hz), 7.32 (t, 1H, J = 2.9 Hz), 7.76 (br s, 1H), 8.44 (s, 1H), 11.58 (br s, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz): δ 14.7, 30.9, 33.2, 43.2, 47.8, 55.7, 96.9, 100.7, 104.3, 117.7, 121.7, 125.1, 134.3, 137.2, 144.5. HRMS–ESI (*m*/*z*): [M + H]$^+$ calcd for $C_{15}H_{19}N_4$, 255.1604; found, 255.1603. Anal. Calcd for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 70.77; H, 7.24; N, 21.68. $[\alpha]_D^{23}$ − 159.0 (*c* 1.00, 0.1 M aq HCl). IR (ATR, cm^{-1}): 3310, 3109, 2899, 1614, 1352, 1339, 822, 716. DSC (onset): 84.3, 260.1 °C.

*Crude **1***. A 500 L reactor-1 was charged with (3*R*,4*R*)-**10** (13.63 kg, 53.6 mol) and DMF (128.8 kg, 10 vol). HOBt·H_2O (0.82 kg, 0.1 equiv, 5.4 mol) and cyanoacetic acid (**11**) (5.01 kg, 1.1 equiv, 58.9 mol) were added to the resulting slurry, followed by EDC·HCl (16.44 kg, 1.6 equiv, 85.8 mol) over ≥0.5 h, and the reaction mixture was stirred for ≥1 h at 20−30 °C (IPC: **10** ≤ 1.0 A% by HPLC Method D). Next, 1 M aqueous HCl (54.4 kg, 1.0 equiv, 53.3 mol) was added to the reaction mixture and the mixture was stirred for ≥1 h at 45−55 °C (IPC: overreacted

compound ≤ 1.0 A% by HPLC Method D). The pH of the solution was adjusted to 8.5 by adding 5 M aqueous NaOH (23.3 kg, 98.7 mol) at 45−55 °C. The slurry was aged for ≥1 h at 45−55 °C and water (72 L, 5.3 vol) was added over ≥1 h. The slurry was aged for ≥1 h at 45−55 °C, cooled to 20−30 °C (approximately 10 °C/h), aged for ≥12 h (IPC: **1** ≤ 3 g/L by HPLC Method D), and then filtered. The wet cake was washed with aqueous DMF (prepared from 12.9 kg (1 vol) of DMF and 14 L (1 vol) of water) and aqueous EtOH (prepared from 53.8 kg (5 vol) of EtOH and 68 L (5 vol) of water), and dried at 50 °C for ≥12 h under reduced pressure (IPC: LOD ≤ 1.0%) to give crude **1** (15.67 kg, 48.8 mol, 91.0% yield) as a pale yellow solid. HPLC purity: 98.7 A% (specification: ≥95 A% by HPLC Method D).

*3-{(3R,4R)-3-[Dipyrrolo[2,3-b:2',3'-d]pyridin-1(6H)-yl]-4-methylpiperidin-1-yl}-3-oxopropanenitrile (**1**).* A 200 L reactor-1 was charged with crude **1** (31.06 kg, 96.6 mol), EtOH (98.0 kg, 4 vol), water (41.9 kg, 1.35 vol), and 6 M aqueous HCl (17.62 kg, 1.0 equiv, 96.1 mol) at 0−30 °C. The resulting solution was transferred to a 500 L reactor-2 via a cartridge filter (≤1 μm) and reactor-1 was rinsed with aqueous EtOH (prepared from 49.0 kg (2 vol) of EtOH and 31 L (1 vol) of water). The solution was warmed to 45−55 °C. Next, 1 M aqueous NaOH (20.1 kg, 0.2 equiv, 19.3 mol) was added over ≥0.5 h and the mixture was stirred for ≥1 h at 45−55 °C. The pH of the mixture was adjusted to 8.5 by adding more 1 M aqueous NaOH (81.6 kg, 0.8 equiv, 78.5 mol). The slurry was stirred for ≥1 h and cooled to 20−30 °C (approximately 10 °C/h), stirred for ≥1 h (IPC: **1** ≤ 2 g/L by HPLC Method D), and then filtered. The wet cake was washed with aqueous EtOH (prepared from 122.5 kg (5 vol) of EtOH and 155 L (5 vol) of water) and water (311 L, 10 vol), and dried at 50 °C for ≥12 h under reduced pressure (IPC: residual EtOH ≤ 1.0%, DMF ≤ 0.088%) to give **1**[5] (30.25 kg, 94.1 mol, 97.4% yield) as a pale

yellow solid. HPLC purity: 99.2 A% (HPLC Method D), ≥99.80% ee (HPLC Method E). ^{1}H NMR (DMSO-d_6, 500 MHz, 6/4 mixture of rotamers): δ 0.62 (d, 1.8H, J = 7.0 Hz), 0.68 (d, 1.2H, J = 7.1 Hz), 1.61−1.76 (m, 1.0H), 1.83−1.92 (m, 1.0H), 2.38−2.48 (m, 1.0H), 3.36−3.43 (m, 0.6H), 3.51−3.58 (m, 0.4H), 3.58−3.67 (m, 1.0H), 3.70−3.78 (m, 0.4H), 3.78−3.87 (m, 1.0H), 3.97 (dd, 0.4H, J = 13.7, 8.1 Hz), 4.07 (d, 0.4H, J = 19.0 Hz), 4.09 (d, 0.6H, J = 18.8 Hz), 4.18 (dd, 0.6H, J = 13.4, 6.4 Hz), 4.30 (d, 0.6H, J = 18.9 Hz), 4.95−5.01 (m, 0.6H), 5.04−5.10 (m, 0.4H), 6.64 (d, 0.6H, J = 3.3 Hz), 6.67 (d, 0.4H, J = 3.3 Hz), 6.74−6.78 (m, 1.0H), 7.19 (d, 0.4H, J = 3.3 Hz), 7.28 (d, 0.6H, J = 3.3 Hz), 7.34 (t, 1.0H, J = 2.9 Hz), 8.46 (s, 0.6H), 8.48 (s, 0.4H), 11.64 (br s, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 125 MHz, 6/4 mixture of rotamers): δ 13.3, 14.2, 24.8, 25.2, 28.9, 29.1, 31.8, 32.4, 38.7, 43.4, 43.5, 46.3, 54.3, 55.0, 96.9, 97.0, 101.8, 101.9, 104.1, 104.2, 116.0, 116.2, 117.5, 117.7, 122.0, 122.1, 123.1, 123.7, 134.2, 134.4, 137.2, 137.2, 144.6, 144.6, 161.8, 162.1. HRMS–ESI (m/z): $[M + H]^+$ calcd for $C_{18}H_{20}N_5O$, 322.1662; found, 322.1661. Anal. Calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.31; H, 6.08; N, 21.70. $[\alpha]_D^{23}$ + 51.2 (c 0.750, 0.1 M aq HCl) (lit.[5] $[\alpha]_D^{25}$ + 50.1 (c 0.733, 0.1 M aq HCl)). IR (ATR, cm^{-1}): 3296, 2934, 2263, 1645, 1611, 1462, 1335, 1252, 1211, 1182, 885, 710. DSC (onset): 310.6 °C.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

xxx.

HPLC chromatograms of the SNAr reaction, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of compounds **3**, (3*R*,4*R*)-**5**, (3*R*,4*R*)-**9**, (3*R*,4*R*)-**10**, and ASP3627 (**1**).

AUTHOR INFORMATION

Corresponding Author

* E-mail: shun.hirasawa@astellas.com

Present Addresses

† Pharmaceutical Science & Technology Labs., Pharmaceutical Technology, Astellas Pharma Inc., 21 Miyukigaoka, Tsukuba-shi, Ibaraki 305-8585, Japan

ORCID

Shun Hirasawa: 0000-0002-1659-3424

Notes

The authors declare no competing financial interest.

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