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Development of an Optimized Synthetic and Purification Process of S-2367 (Velneperit), a Novel Neuropeptide Y (NPY) Y5 Receptor Antagonist

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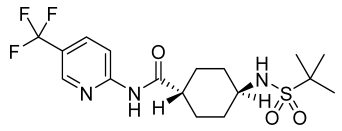
Supporting Information

ABSTRACT: We developed a simple synthetic route to S-2367 (Velneperit) (**1**) using *trans*-1-ethoxycarbonyl-4-aminocyclohexane hydrochloride salt (**12**) as a starting material. The key step was Na_2WO_4/H_2O_2 oxidation, and we found that it was accelerated in weakly basic conditions. The finding was useful to control one of the critical impurities: **14** in **10**. The new process was more efficient than the early process from the viewpoint of the number of reactions, yield, throughput, and EHS (environment, health, and safety) but a quality deviation occurred in the pilot manufacturing: **10** content in **1** was over the upper limit. The cause was presumed to be hydrolysis of **1** during the recrystallization step. After finding it, we developed two reliable purification processes. The first was slurry washing including clever polymorphic control using only acetone and water. The second was salt formation of **10** and rational building of the recrystallization procedure based on solubility to improve removal rate.

INTRODUCTION

Neuropeptide Y (NPY) is a 36-amino acid peptide neurotransmitter that is widely distributed in mammalian central and peripheral nervous systems. Thus far, five distinct subtypes of G protein-coupled NPY receptors, Y1, Y2, Y4, Y5, and Y6, are known. Among them, the Y5 receptor subtype is thought to play a role in meal initiation and the regulation of energy balance. Therefore, an antagonist of the NPY Y5 receptor is considered to have potential as an antiobesity drug.[1] S-2367 (**1**) (Figure 1), which was discovered by Shionogi Research



S-2367 (**1**)

Figure 1. Chemical structure of S-2367 (**1**).

Laboratories, is a novel, potent, and selective orally available NPY Y5 antagonist. It has been shown to have a significant effect on weight loss in clinical studies, suggesting its potential as a promising antiobesity drug.[2] In addition, it can ameliorate the glucose metabolism, reduce LDL cholesterol and uric acid levels, lower blood pressure, and improve liver function.[3,4] Therefore, the development of an optimized manufacturing process was required to make it available for commercial supply as well as clinical studies. Required process optimization included not only simplifying the synthetic route, reaction telescoping, and increasing yield, but also increasing the charged amount and selecting low-toxic and recoverable solvent because all of them affect the manufacturing cost and environmental impact. However, the changes caused a quality deviation. Herein, we discuss the summary of process improvement, a new finding on Na_2WO_4/H_2O_2 oxidation and purification strategies of **1** to solve the quality issue.

RESULT AND DISCUSSIONS

Summary of process improvement. In the pilot manufacturing for preclinical and early clinical studies, the synthesis of **1** was carried out using the starting material **5**.[5] Esterification of **5** using $SOCl_2$ in methanol gave methyl ester **6**. The coupling reaction of **6** with sulfinyl chloride **4**, which was synthesized by oxidation of di-*tert*-butyl sulfide **2** and chlorination reaction, produced sulfinamide **7**. Oxidation of **7** using H_2O_2/Mo catalyst, isomerization by NaOMe, and hydrolysis gave the intermediate **10**. The coupling reaction of **10** with **11** through acid chloride and recrystallization using acetone/water produced purified **1**, whose polymorph was form I (Scheme 1). The process could be tolerable for scale-up, but there was still room for improvement in synthetic route, yield, and productivity. The starting material was changed from **5** to *trans*-1-ethoxycarbonyl-4-aminocyclohexane hydrochloride salt (**12**), which was commercially available.[6] The change could remove esterification and isomerization from the manufacturing process.

Next we tried to develop a telescoped process using toluene and water. The solvent of the coupling reaction could be changed from dimethylformamide (DMF) to toluene/water but following oxidation of **13** did not proceed well, probably because **13** was distributed in the toluene layer but oxidant was

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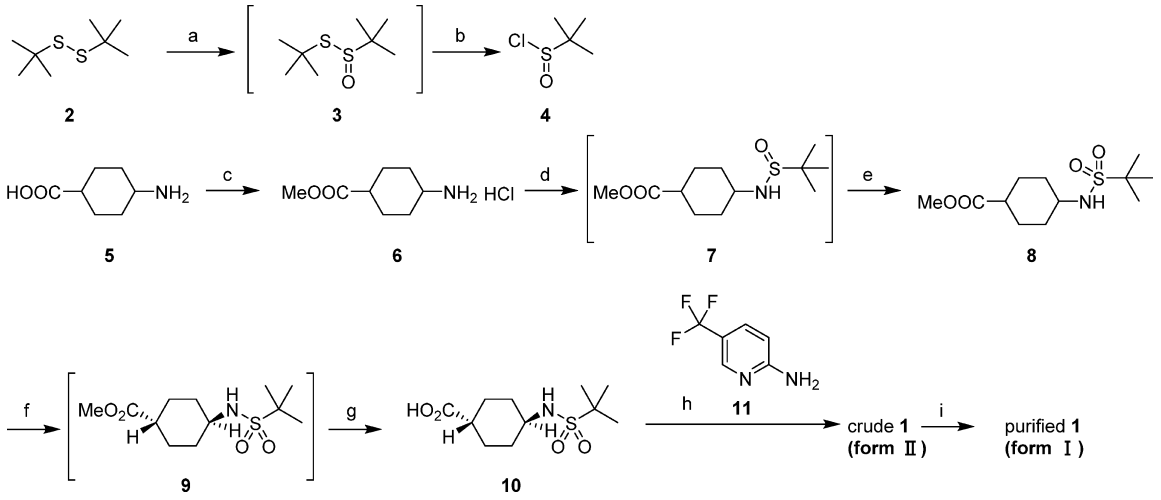
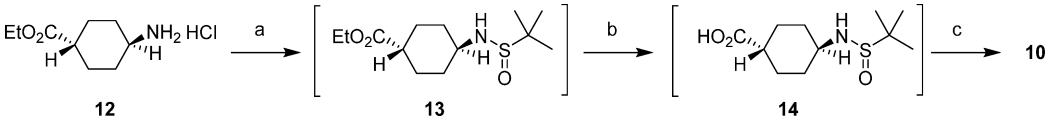
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 1. Synthetic Route to S-2367 (1) for Preclinical and Early Clinical Studies[a]



[a]Reagents and conditions: (a) H_2O_2, AcOH; (b) Cl_2, 87% (2 steps;) (c) $SOCl_2$, MeOH, washing by MeCN, 93%; (d) **4**, Et_3N, DMF; (e) H_2O_2, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ cat., water, recrystallization by AcOEt and cyclohexane, 81% (2 steps); (f) NaOMe, toluene, and MeOH; (g) water, 90% (containing 1.5 area % of *cis*-**10**), (2 steps); (h) $SOCl_2$, DMF cat., toluene → **11**, pyridine (i) recrystallization using acetone and water, 87% (2 steps).

Scheme 2. Improved Synthetic Route to the Intermediate 10[a]



[a]Reagents and conditions: (a) **4**, Et_3N, toluene, H_2O; (b) NaOH; (c) H_2O_2, $Na_2WO_4\cdot 2H_2O$ cat., H_2O, 95% (3 steps).

in water. Hence, we exchanged the order of oxidation and hydrolysis. Hydrolysis of **13** and oxidation of **14** proceeded quantitatively. Moreover, the workup procedure could be simplified: aqueous and organic impurities were removed by the extraction after the coupling reaction and the hydrolysis, respectively. After oxidation, **10** could be isolated by neutralization crystallization with aqueous H_2SO_4 in 95% yield (Scheme 2).

With regard to the final step, the amidation reaction conditions were not changed, but the washing liquid of the filtrated crude **1** cake was changed from 2-propanol to 50 v/v % acetone/water to unify the solvents used in the overall synthesis. That would reduce the tasks such as receiving test and storage of 2-propanol in commercial manufacturing. We also tried to reduce the bottleneck volume of the solvent dissolving crude **1** during the recrystallization to increase the charged amount. The solubility of **1** (form I and II) in various ratios of acetone/water is shown in Figure 2. As the highest solubility was obtained with acetone/water = 95 v/v %, the dissolving solvent was changed from 14 V of 100 v/v % acetone to 10.95 V of 95 v/v % acetone/water. Though crude **1** was form II, obtaining the desired polymorph form I was not difficult because form II was quickly transformed to form I in various ratios of acetone/water. Even if the seed of form II was added during the recrystallization, it was dissolved and form I was precipitated.

The comparison of the early process with the improved process is shown in Table 1. The overall yield from the starting material was increased from 59% to 83%. The number of chemical reactions was reduced from 6 to 4. The types of solvents and their quantity could also be reduced. The new process was better from the viewpoint of EHS (environment, health, and safety) because dimethylformamide (DMF), which is relatively toxic and difficult to recover, could be substituted

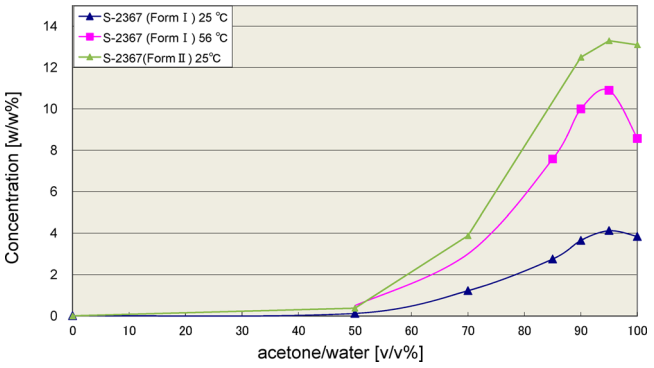


Figure 2. Solubility of **1** (form I and form II) in acetone/water.

Table 1. Early Process vs Improved Process

items	early process	improved process
Lot scale (yield of **1** for one batch)	11 kg	348 kg
Overall yield[a]	59%	83%
Purity of purified **1**	99.5–99.9% (2 lots)	99.6–100.6% (6 lots)
Chemical reactions[a]	6	4
Types of sovents[a]	7	3
Relative total quantity of solvent[a]	1	0.2
Relative maximum volume in the final step	1	0.8

[a]From the starting material **5** or **12** to purified **1**

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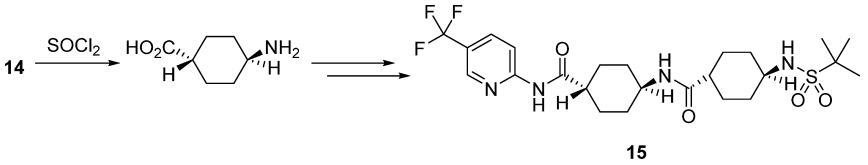
Scheme 3. Fate of Impurity 14 in the Amidation Reaction



by toluene and water.[7] Furthermore, the relative maximum volume of the final step was reduced; that is, production capacity was increased.

Acceleration effect in weakly basic condition and safety evaluation on Na_2WO_4/H_2O_2 oxidation. The key step of the improved process was oxidation of **14** because residual **14** in the intermediate **10** was quantitatively converted to the impurity **15** with low removal rate in the following steps. Residual **14** had to be controlled by not more than 0.04 w/w % in oxidation reaction to meet our target quality of **1** (Scheme 3). It could be achieved by extending reaction time and increasing the amount of H_2O_2 and/or catalyst, but they might increase the processing time and the material cost. At first we changed the catalyst from $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ to $Na_2WO_4\cdot 2H_2O$ because the latter was more inexpensive. As a result of investigation, we found the interesting new knowledge that the oxidation reaction in the weakly basic condition of pH 9.0−9.5 was faster than that under nearly neutral conditions (Table 2).

Table 2. Optimization of pH in Na_2WO_4/H_2O_2 Oxidation

entry	pH	residual **13** (w/w %) after addition of H_2O_2	residual **13** (w/w %) after stirring for 2.5 h
1	8.0	1.80	0.07
2	9.0	1.27	0.00
3	9.5	0.77	0.00
4	10.0	2.14	0.03

The result was unexpected for us because it was reported that oxidation of 2-octanol using Na_2WO_4/H_2O_2 did not proceed under basic conditions, probably due to the decomposition of H_2O_2.[8] The reason was not clarified, but the interesting finding made it possible to control residual **14** in **10** without extending reaction time and increasing the amount of H_2O_2 and/or catalyst. Besides, safety evaluation of the reaction was done. To avoid the combustion, at least either one of three elements of combustion (oxygen, heat, and fuel) must be removed. As oxygen gas was continuously released by decomposition of H_2O_2 in the reaction, we removed flammable toluene before the reaction (partial toluene vapor pressure/atmospheric pressure ≤0.012). Furthermore, reaction heat could be controlled by addition of H_2O_2 (Figure 3), and the maximum temperature attainable by the synthesis reaction (MTSR; 87.6 °C) was lower than the boiling point of water (100 °C) (total reaction heat; 332 kJ/mol, process temperature; 25 °C adiabatic temperature; 62.6 °C). They suggested that the reaction could be performed safely.

Deviation in the pilot manufacturing. In the pilot manufacturing the impurity **10** in purified **1** was 0.08 w/w % ∼ 0.09 w/w %, which did not meet the specification of not more than 0.06 w/w %. It was controlled at 0.03 w/w % ∼ 0.04 w/w % in the previous pilot manufacturing for the clinical studies, and the flask experiment conducted using the improved process. Since it seemed that the cause lay in the amidation reaction and/or the recrystallization step, we investigated them

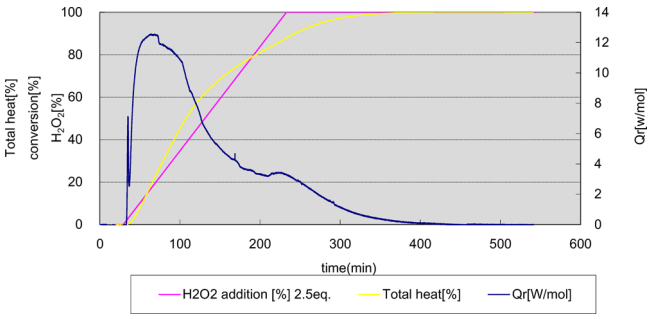


Figure 3. Heat flow of oxidation reaction (total 332 kJ/mol).

in detail.[9] The formation of acid chloride and the amidation reaction was controlled by the IPT (In Process Test),[10] and they indicated that the reactions had successfully proceeded. The impurity **10** content in crude **1** was 0.05−0.10 w/w % (7 lots), which was equivalent to that in the preliminary flask experiment. These results suggested that the process before obtaining crude **1** was not the cause of the impurity exceeding the specification limit. Next, we examined the material balance of **10** in the recrystallization step and found purified **1** and the mother liquor included 0.08 w/w % and 0.10 w/w % of **10**, respectively, which suggested that the absolute quantity of **10** increased during the recrystallization step. It was probably due to the hydrolysis of **1**. We therefore compared the increase in the amount of **10** in the crude **1** in 95 v/v % acetone/water to 100% acetone, and the result showed that the increase in the former was about five times higher than that in the latter (Figure 4). This suggested that the increase of **10** by hydrolysis

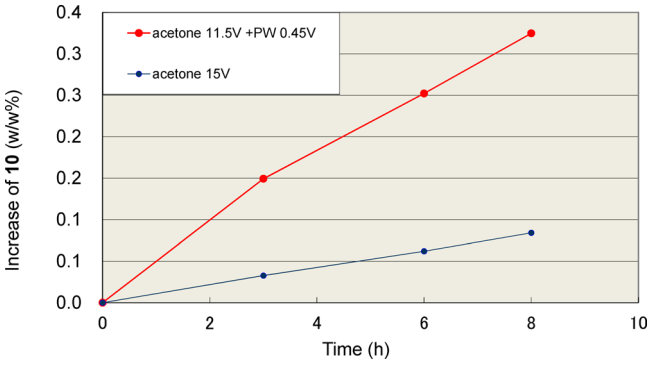


Figure 4. Stability of crude **1** dissolved in acetone and acetone/water at 55 °C.

during the dissolving step was the cause of the deviation. We did not pay attention to the hold time of the dissolution and could not find the issue in the flask experiment conducted before the pilot manufacturing.

Purification by solvent-mediated polymorphic transformation to remove acid component enclosed in crude 1. It was an option that the dissolving solvent was reverted to 100% acetone but the throughput was poor, and the risk of

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deviation from the specification limit could not be completely removed because residual **10** content varied in the flask experiments. Considering these points, we decided to build the process that can reliably remove **10** using 95 v/v % acetone/water. The dissolution of crude **1** in 95 v/v % acetone/water was highly acidic (about pH 1) because crude **1** included 0.02−0.14 equiv of HCl and/or H_2SO_3 derived from $SOCl_2$, and it was thought to cause acidic hydrolysis.[11] We considered that removing the residual acid would decrease the hydrolysis. At first, we tried purging the acidic gas from the reaction mixture by nitrogen and increasing the amount of pyridine, but they were not effective. Increasing the amount of washing liquid of the filtrated crude **1** cake could reduce the rate of hydrolysis but not stop it completely. From these insights, we assumed that the acid component would be enclosed in the crystal, which meant that crude **1** had to be dissolved to remove acid. As additional operation should be minimized, it was unwise to repeat the recrystallization process. On the other hand, solvent-mediated polymorphic transformation by slurrying consists of the dissolution of the unstable form and the nucleation and growth of stable form. By the method, crude **1** was expected to be dissolved by a small amount of solvent keeping low temperature and concentration, which would prevent hydrolysis. Since the crude **1** was form II, we searched the effective solvent for transformation of form II to form I and found that it was realized by slurrying in the mixture of acetone and water for a short time.[12] This led to sufficient removal of the residual acid enclosed in the crystal and improved the stability of the dissolution (Figure 5). However, the polymorph type of crude

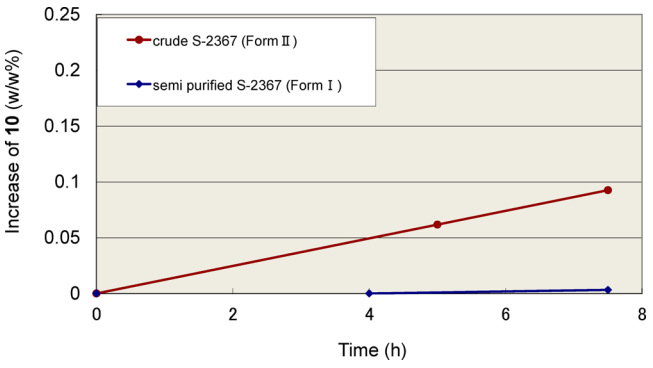

Figure 5. Stability of crude and semipurified **1** dissolved in acetone/water at 55 °C.

1 washed by 50% acetone/water changed from form II to form I within 2 days at room temperature. Since it was crucial to maintain the polymorph form before the slurry washing, we investigated the other washing liquids to extend the lifetime of form II and found washing it with purified water allowed it to be maintained for at least 12 days at room temperature. By the clever polymorph control using only acetone and water, the purified **1** including 0.00% of **10** could be produced in the pilot manufacturing.

*Dramatic improvement of removal rate of **10** by salt formation and rational building of the recrystallization procedure based on its solubility.* Toward commercial supply, we tried to eliminate the solvent-mediated polymorph transformation because it could increase the costs of operation and facility installation. As the hydrolysis was caused by the residual acid, we tried neutralizing crude **1** dissolution in 95 v/v % acetone/water. This was expected to lead to stable dissolution and prevention of hydrolysis of **1**. Furthermore, the removal rate of **10** of the recrystallization step was expected to be improved because the cause of the fluctuation in the removal rate from 36% to 73% in the flask experiments was considered to be the possible weak interaction of acid **10** with the basic pyridyl group of **1**; the salt formation could prevent this (Figure 6). Monitoring of the pilot manufacturing showed that excess

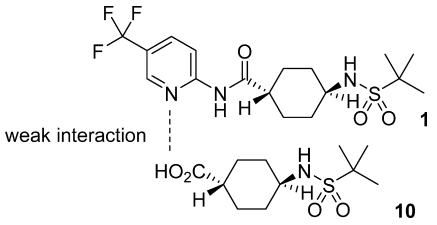

Figure 6. Possible interaction of **1** and **10**.

base was needed since the residual acid included in crude **1** varied from 0.02 to 0.14 equiv due to the inconsistent washing of the cake; 0.2 equiv of base was used to deal with the highest amount of the residual acid. The pK_a of the conjugated acid of the base used for the neutralization needed to be more than 6 for completion of the salt exchange, since the calculated pK_a of **10** was 4.2. However, the strong base sodium hydroxide could not be used because its excess use caused basic hydrolysis of **1**. Then we examined several weak bases (Table 3). $NaHCO_3$

Table 3. Salt Formation and Increase Amount of 10

entry	compd	pK_a	Increase of **10** (w/w %)[a]
1	compound **10**	4.2	
2	$NaHCO_3$	6.35	0.04
3	sodium acetate	4.76	0.02
4	sodium lactate	3.86	0.00
5	ammmonia	9.25	0.01

[a]Crude **1** and 0.2 equiv of base in 95% acetone/water were heated at 55 °C for 6 h.

(pK_a of carbon dioxide at 25 °C; 6.35) also caused slight basic hydrolysis, but the removal rate was improved to 80% due to the completion of salt formation (Entry 2). Sodium acetate (pK_a of acetic acid at 25 °C; 4.76) and sodium lactate (pK_a of lactic acid at 25 °C; 3.86) made the crude **1** dissolution stable, but the pK_a was not sufficient for salt formation and the generated acid could be a new impurity (Entries 3 and 4). Ammonia (pK_a of the conjugate acid; 9.25) made the dissolution stable, probably because any excess was volatilized though its pK_a was high (Entry 5). We hesitated to use it because of acute aquatic toxicity with a long-lashing effect. Considering these points, we chose $NaHCO_3$ for further examination. In the pilot manufacturing the variant which could critically influence the stability was the acid content in crude **1** because it was difficult to strictly control the cake washing. The stabilities of crude **1** including various equivalents of residual acid dissolved in 95% acetone/water with 0.2 equiv of $NaHCO_3$ are shown in Figure 7. The dissolution including more acid did not show decomposition, but a slight amount of basic hydrolysis was observed using crude **1** with less acid. After the salt formation could eliminate the possibility of intermolecular interaction, the driving force of separation was the difference of the respective solubility. The solubility of form I at 58 °C and the sodium salt of **10** and the concentration

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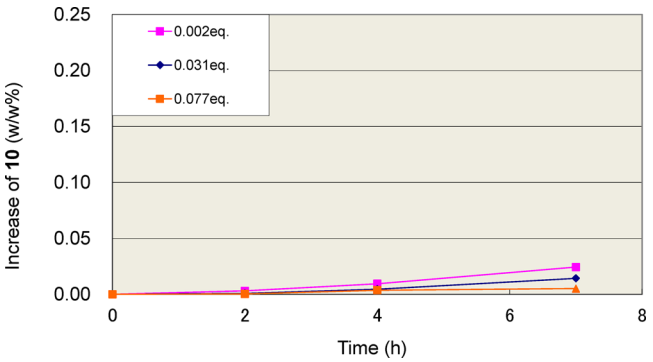

Figure 7. Stability of crude **1** (influence of residual acid).

transition of the modified process are shown in Figure 8. In the existing process purified **1** was precipitated from the dissolution

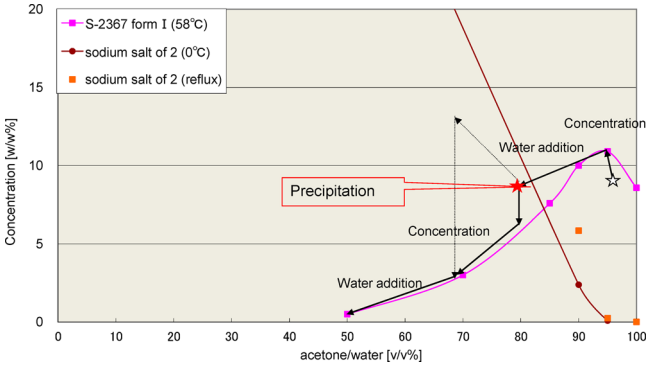

Figure 8. Modified concentration transition of the recrystallization process.

in 95% acetone/water during the concentration but the solubility of the sodium salt in the ratio was low. The process could cause the precipitation of **10** salt, and it could be enclosed in the crystal of **1**. To improve the removal effect, the precipitation point of form I was set at 80 v/v % acetone/water in which the solubility of sodium salt of **10** was sufficiently large. The first concentration was performed under the solubility of form I to certainly prevent the precipitation. After that water was added to 80% acetone/water of supersaturation concentration where visible nucleation of form I occurred. Then concentration, water addition, and cooling were followed. By the changes, the removal rate of **10** was dramatically and reproducibly increased to more than 83%. Using the recrystallization procedure, we could produce purified **1** with no **10** at an average 94.7% yield (348 kg/lot, 6 lots). The rational building of the recrystallization procedure led to the highly reliable control of impurity **10** without increasing maximum volume.

CONCLUSION

An optimized process to manufacture **1** could be developed. The telescopic process to synthesize **10** was realized by changing the starting material, coupling reaction conditions, and the order of oxidation and hydrolysis reaction from the early process. Then we found the interesting knowledge that Na_2WO_4/H_2O_2 oxidation could be accelerated in weakly basic conditions, and it was useful to control the residual **14** in **10**. Changing the dissolving solvent from acetone to 95 v/v % acetone/water in the recrystallization step reduced the bottleneck volume but caused the increase of residual **10** in purified **1** in the pilot manufacturing. After finding it, we developed two reliable purification processes. The first was slurry washing including clever polymorphic control using only acetone and water. The second was salt formation of **10** to improve stability and build a rational recrystallization process based on solubility by excluding the possibility of ionic interaction of **1** and **10**. The latter process led to reliable control of the impurity **10** without increasing maximum volume.

EXPERIMENTAL SECTION

All experiments were run under a nitrogen atmosphere. Solvents and reagents were obtained from commercial sources and used without further purification. High performance liquid chromatographic (HPLC) analysis was carried out using a Shimadzu LC-10ADVP. Reaction heat was measured using Mettler Toledo RC1e. ^{1}H NMR spectra were recorded on a 300 MHz Varian FT spectrometer. XRPD was measured using Rigaku RINT TTR III. Melting points were measured with Rigaku Industrial Corporation Thermo plus DSC8230S. Infrared spectra were recorded with Thermo Fisher Scientific MAGNA560. The solvent composition after distillation was simulated using CHEMCAD 5.3.0

Preparation of the intermediate 10 by the improved process. To the reactor water (660 kg) were charged **12** (330 kg, 1589 mol) and toluene (828 kg) after the nitrogen purge. The mixture was adjusted to 15 °C (internal temperature), and triethylamine (354 kg, 3495 mol) was charged. To the mixture was charged slowly **4** (232 kg 1652 mol) in toluene (285 kg). After stirring for 1 h, the reaction mixture was adjusted to 25 °C and the aqueous layer was removed. To the toluene layer were added water (653 kg) and 25% aq NaOH (636 kg, 3972 mol) at 25 °C. Then it was heated to 45 °C, stirred for 2 h, and cooled to 25 °C. After the toluene layer was removed, the aqueous layer was concentrated to remove residual toluene and ethanol. To the aqueous solution was added 20 w/w % aq H_2SO_4 to adjust the pH 9.0. After the addition of catalyst $Na_2WO_4{\cdot}2H_2O$ (5.2 kg, 16 mol) was charged slowly 35% H_2O_2 aqueous solution (309 kg, 3178 mol) at 25 °C, and the mixture was stirred for 2.5 h. Then 13.2 w/w % aq H_2SO_3 (1365 kg) was added to quench the reaction. It was heated to 40 °C, and 20% aq H_2SO_4 was charged to adjust the pH 2.5. The slurry was cooled to 25 °C and stirred for 30 min. The precipitated intermediate **10** was filtered, washed with water, and dried in vacuum (397 kg, 95%). **10** is already known, and the ^{1}H NMR data corresponded to that reported.[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (d, 1H, J = 9 Hz), 3.67 (s, 3H), 3.27 (m, 1H), 2.00−2.32 (m, 5H), 1.49−1.62 (m, 2H), 1.39 (s, 3H), 1.16−1.32 (m, 2H).

Preparation of purified 1 by the improved process. 10 (475 kg, 1804 mol) was charged with a catalytic amount of DMF (2.6 kg, 36 mol) and toluene (1604 kg). The resulting slurry was heated to about 50 °C, and then thionyl chloride (236 kg, 1984 mol) was dropped slowly. After the reaction mixture was stirred about 30 min, it was cooled to 30 °C. Next, pyridylamine (**11**) (322 kg, 1984 mol) and pyridine (314 kg, 3968 mol) dissolved in toluene were added, and the resulting slurry was stirred about 1 h. After the reaction was completed, purified water (1425 L) was added. The crude **1**, whose polymorph was form II, was filtered and washed with purified water. Half the amount of crude **1** was used in the following step. To crude **1** and acetone (3040 kg) was added sodium

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

bicarbonate (15 kg, 180 mol) dissolved in purified water (165 L), and the resulting mixture was adjusted to 55 °C (internal temperature) and stirred for about 1 h. The precipitating salt was filtered and washed with acetone (290 kg). Then acetone was distilled until the internal volume was reduced to 4023 L, and then purified water (735 L) was added. The slurry was distilled until the internal volume was reduced to 3032 L, purified water (1011 L) was added, and the reaction mixture was cooled to 10 °C (internal temperature) and stirred for 60 min. The purified **1** was filtered, washed with 50 v/v % of acetone/water, and dried in vacuum (348 kg; 94.7%). S-2367 (**1**) is already known, and the ^{1}H NMR data corresponded to that reported.[2] ^{1}H NMR (300 MHz, DMSO-d^6) δ 10.84 (1H, s), 8.69 (1H, s), 8.28 (1H, d, J = 8.7 Hz), 8.10−8.18 (1H, m), 6.79 (1H, d, J = 8.4 Hz), 3.00−3.15 (1H, m), 2.40−2.54 (1H, m), 1.82−2.00 (4H, m), 1.25−1.75 (4H, m), 1.27 (9H, s), melting point; 224.6 °C, crude S-2367 (form II) 2θ = 12.5 ± 0.2, 14.3 ± 0.2, 16.8 ± 0.2, 17.8 ± 0.2, 18.4 ± 0.2, 19.0 ± 0.2, 21.6 ± 0.2, purified S-2367 (form I) 2θ = 10.2 ± 0.2, 14.5 ± 0.2, 16.8 ± 0.2, 17.1 ± 0.2, 17.7 ± 0.2, 18.3 ± 0.2, 19.1 ± 0.2, 20.2 ± 0.2, 20.8 ± 0.2, 26.5 ± 0.2, melting point; 219.6 °C.

■ ASSOCIATED CONTENT

Supporting Information

XRPD of form I and form II. 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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(9) The whole procedure of the step was as follows. To the reactor were charged **10**, DMF (0.02 equiv), and toluene (4 V). The resulting slurry was heated to 50 °C, and then thionyl chloride (1.1 equiv) was charged slowly. After the reaction mixture had been stirred for 30 min, it was cooled to 30 °C. To the reaction mixture was charged a solution of **11** (1.1 equiv) and pyridine (2.2 equiv) in toluene, and then this was stirred for 30 min. After the reaction was completed, purified water (3 V) was added. The crystallized crude **1**, whose polymorph was form II, was filtered and washed with 50% acetone/water (2 V) and purified water (2 V). The obtained crude **1** was dissolved in acetone (10.5 V) and purified water (0.45V) at 55 °C, filtered to remove the foreign matter, and flushed with acetone (1 V). Next, acetone was removed by distillation, and the residue was adjusted to 5 wt %. To this was added purified water (5 V) at 55 °C, and the obtained slurry was cooled to 10 °C and stirred for 60 min. The purified **1** was filtered, washed with 50 v/v % of acetone/water, and dried in vacuum.

(10) The reaction mixtures were quenched by methanol and analyzed using HPLC (215 nm).

(11) The quantity of the included acid was determined as follows. 1.00 g of wet crude **1** was measured accurately, which was dissolved in 30 mL of 95% acetone/water. To the solution was added dropwise 0.001 N sodium hydoroxide solution. The end point of neutralization was determined by pH meter. The number of equivalents was calculated based on dried crude S-2367.

(12) It was monitored by the concentration transition of mother liquor and the specific peak strength 1686 cm^{-1} of form II and 1708 cm^{-1} of form I in the infrared spectrum. Sugata, Y.; Ide, Y.; Sakata, T.; Omura, S. WO2009136617A1.

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