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Article

Development of a Recycling Process for an Industrial-Scale Production of Tipifarnib

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ABSTRACT: Current production of tipifarnib involves a late-stage chiral resolution where the mother liquor containing ~2/3 of the product is disposed of as waste. As part of an effort to develop an efficient recycling process, a $NaNO_2$-mediated racemization was initially devised and successfully implemented at kilogram scale. However, formation of a new hard-to-purge impurity and concerns about potential *N*-nitrosamine contamination prompted exploration of a $NaNO_2$-free process. Additional experimentation with acidic conditions at elevated temperatures afforded a highly efficient, robust recycling process that was seamlessly incorporated into the original process. The resulting production output of tipifarnib increased over 60%, and waste disposal was dramatically decreased.

KEYWORDS: *green chemistry, recycle, racemization, N-nitrosamine, sodium nitrite, tipifarnib*

INTRODUCTION

Green chemistry is defined as the design of chemical products and processes that reduce or eliminate the generation of hazardous substances and utilize renewable sources of raw materials. The overarching goals of green chemistry, namely, more resource-efficient and inherently safer design of molecules, materials, products, and processes, can be pursued in a wide range of contexts.[1] Since its conception in the 1990s, the concepts and practices of green chemistry have been increasingly adopted in the chemical industries.[2] The pharmaceutical and biotechnology industry also recognizes the importance of sustainability and embraces the general concepts,[3] with notable examples of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) and ACS Green Chemistry Institute Pharmaceutical Roundtable that represent >40 major pharmaceutical and biotechnology company members. Still, practical applications performed at the industrial scale are relatively scarce,[4] probably due to a number of factors unique to the pharmaceutical and biotechnology industry, such as technical feasibility, cost benefit, quality control, scalability, regulatory compliance, and time line. For instance, pharmaceutical products tend to be high value, low volume, and highly regulated, and their production requires stringent quality control for human use. Therefore, the significant efforts necessary for development of "greener" processes are often deemed economically unjustifiable. How to balance the sustainability and social responsibility with the economic reality is a perpetual question that process chemistry professionals must address.

Herein, we share the development of an industrial-scale recycling process through racemization that returns the waste stream containing ~2/3 of the potential product back to the final product at kilogram scale. The first-generation $NaNO_2$-mediated process demonstrated the technical feasibility, but the use of $NaNO_2$ created concerns about potential *N*-nitrosamine contamination.[5] In addition, a new impurity associated with $NaNO_2$ was generated and hard to purge that would complicate the regulatory path forward for commercialization. A second-generation, $NaNO_2$-free process was then devised and optimized to ensure regulatory compliance through stringent impurity control. In the end, the robust and economical recycling process was successfully incorporated into the original process and scaled up for the current Good Manufacturing Practice (cGMP) production of final active pharmaceutical ingredient (API) qualified for human use. We believe a similar recycling through racemization process could be applied to other analogous compounds.

RESULTS AND DISCUSSION

Tipifarnib is a farnesyltransferase inhibitor that blocks the activity of the farnesyltransferase enzyme by inhibiting prenylation of the CAAX tail motif, which ultimately prevents Ras from binding to the membrane and rendering it inactive.[6] Originally developed by Johnson & Johnson for various indications including AML,[7] tipifarnib was more recently developed using a precision medicine approach and has demonstrated promising clinical activity[8] for the treatment of a variety of solid tumors and blood cancers.[9]

The original synthetic route for the production of tipifarnib drug substance is shown in Scheme 1.[10] Whereas this robust process is capable of producing tipifarnib at kilogram scale, the main drawback is a low-yielding chiral resolution step 2, where

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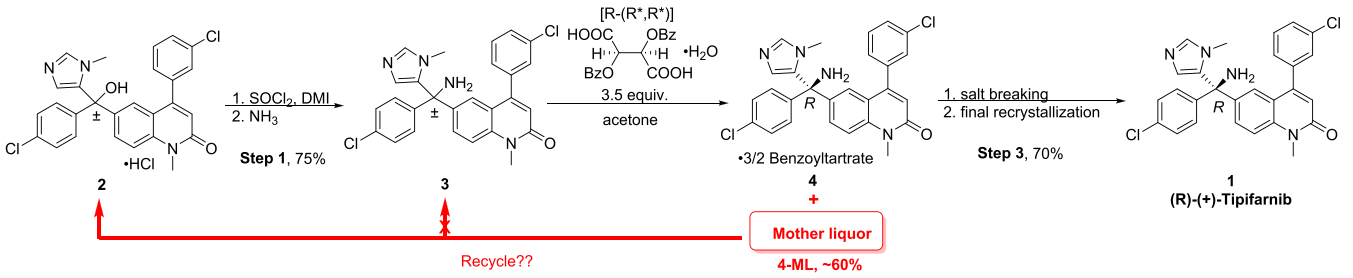
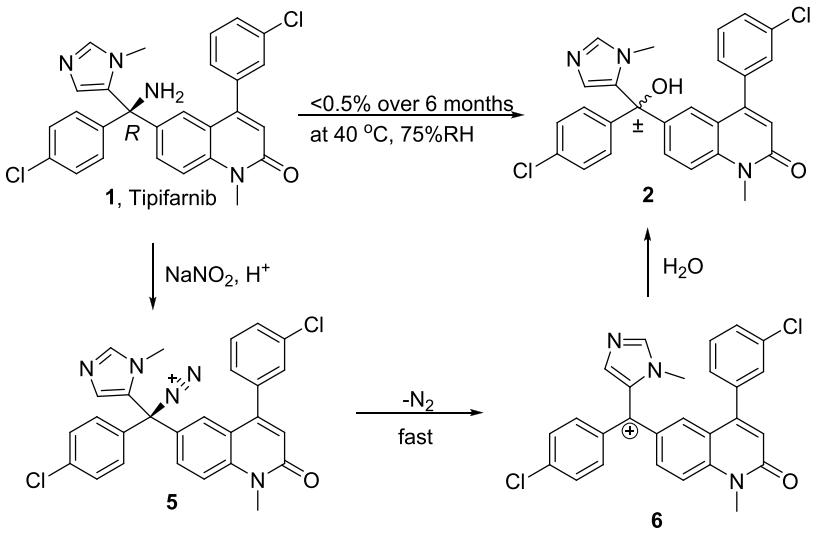
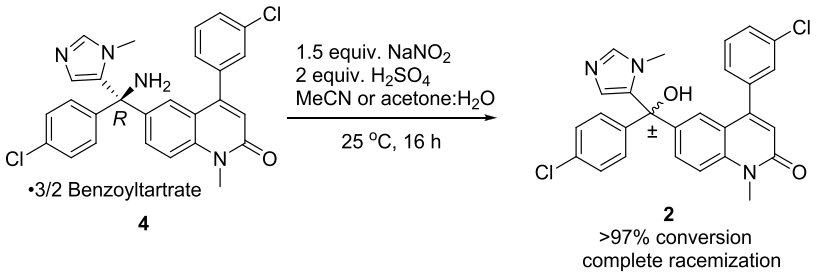
Scheme 1. Original Synthesis of R-(+)-Tipifarnib



Scheme 2. Racemization of Tipifarnib through $NaNO_2$-Mediated Diazotization



Scheme 3. $NaNO_2$-Mediated Conversion of 4 to 2



~2/3 of advanced intermediate **3** was disposed as waste. Evidently, recycling the undesired enantiomer through racemization would be economically attractive and environmentally appealing.[11]

The chiral center of tipifarnib is a triaryl-substituted quaternary carbon bearing a primary amine with no other adjacent functional groups, which renders direct racemization back to racemic **3** rather difficult.[12] Our cue came from the stability study on enantiomerically pure **1**, where a trace amount of **2** was observed as a degradant over the long-term storage (Scheme 2). Chiral high-performance liquid chromatography (HPLC) analysis showed complete racemization of the quaternary carbon center, presumably via hydrolysis of the achiral, planar carbocation intermediate **6**. However, this degradation in the solid state was rather slow, with <0.5% conversion observed over 6 months of storage at 40 °C/75% RH (relative humidity). Facile formation of active intermediate **6** would be a requisite for the racemization to be synthetically useful. $NaNO_2$-mediated diazotization of aromatic amine (Sandmeyer reaction)[13] is well documented in the literature. In comparison, diazonium salts of aliphatic amines such as compound **5** tend to lose N_2 too rapidly, making the method much less synthetically useful and thus rarely reported in the literature.[14] However, in our case, we envisioned that a high reactivity of intermediates **5** and **6** might be employed toward our advantage to achieve the racemization to afford **2** through a facile hydrolysis.

Indeed, when enantiopure dibenzoyltartrate salt **4** was subjected to 1.5 equiv of $NaNO_2$ with 2 equiv of H_2SO_4 in the presence of water, a facile conversion to **2** and complete racemization were achieved in high yield at room temperature, as shown in Scheme 3.

Encouraged by the above result, the mother liquor **4-ML** was then utilized as the input material for the racemization. It was found that an additional H_2SO_4 was not required, presumably because benzoyltartaric acid present in the mother

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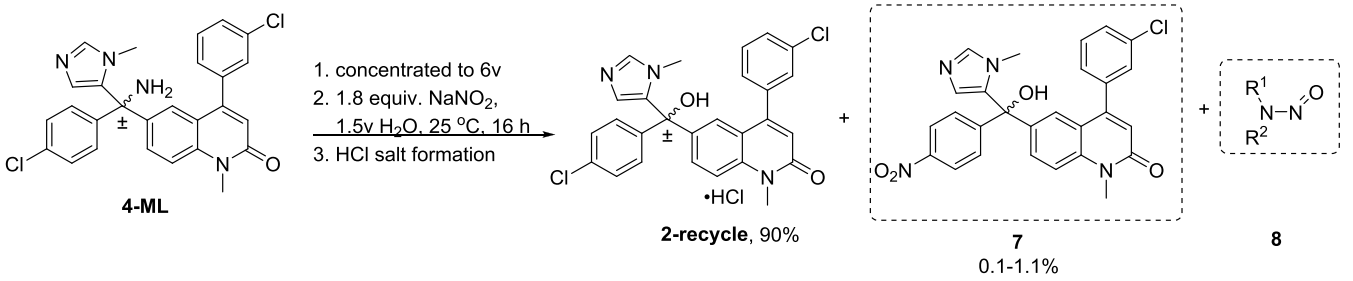
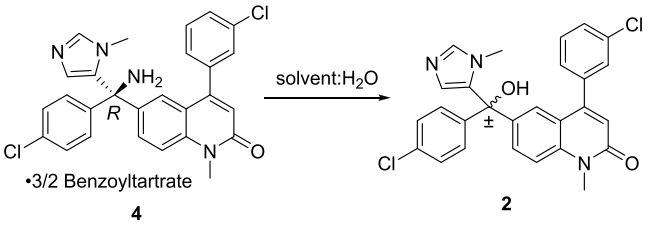
Scheme 4. $NaNO_2$-Mediated Racemization Process of 4-ML



liquor was sufficient to promote the reaction. A racemization process (Scheme 4) was therefore developed consisting of (1) concentrating the acetone mother liquor solution at 50 °C under vacuum to ∼6v; (2) charging water (1.5v) and $NaNO_2$ (1.8 equiv) and stirring at room temperature for 16 h. N_2 off-gassing was observed; (3) after workup, concentrated HCl was added to afford **2-recycle** as the HCl salt. Safety evaluation, mostly differential scanning calorimetry (DSC) evaluation, was also performed to demonstrate the scalability of this robust process, and kilogram-scale production was successfully conducted. However, during the scale-up campaign, a new impurity **7** was observed in small amounts. Impurity **7** did not exist in the original synthesis, and the *nitro* group presented a structural alert for potential mutagenicity per *in silico* assessment. Albeit the negative Ames test result, a good control strategy of impurity **7** was evidently necessary to incorporate the recycling step into the original one. Extensive optimization of the racemization step was conducted, but impurity **7** was inevitably present in the range of 0.1−1.1%. We then turned our attention to hopefully controlling it in the subsequent steps (**2** → **3** → **4**). Unfortunately, it was found that impurity **7** was not effectively purged, rather enriched through the steps. Lack of control of impurity **7** presented two significant hurdles for incorporating this recycling process: (1) *in vivo* toxicology qualification of impurity **7** and (2) separate specifications for the recycled material, which would render the recycling process economically unviable. While we were working on the $NaNO_2$-mediated racemization process, the news on *N*-nitrosamine contamination of Valsartan in 2018 and later Zantac in 2019[15] broke out that resulted in multiple high-profile recalls and later a new FDA guideline for tighter regulation of *N*-nitrosamine in 2020.[5] Use of a stoichiometric amount of $NaNO_2$ would no doubt raise questions on the potential formation of *N*-nitrosamine like impurities **8**. Coupled with the lack of an effective control strategy of impurity **7**, the $NaNO_2$-mediated process was abandoned.

Upon closer examination of the racemization mechanism shown in Scheme 2, we reasoned that it might be feasible to form intermediate **6** through direct acid-catalyzed cationization, instead of $NaNO_2$-mediated diazotization, owing to the three cation-stabilizing aromatic rings adjacent to the quaternary carbon. To our pleasant surprise, when enantiopure dibenzoyltartrate salt **4** was heated in pure water (Table 1, entry 1) for 18 h, an 86% conversion to **2** with complete racemization was observed. Addition of 2 equiv of HCl (entry 2) had no impact on the reaction rate and conversion, consistent with the previous observation in the $NaNO_2$-mediated conditions. For entries 1 and 2, both reactions stalled after 18 h, which we attributed to the heterogeneity of the reaction mixture due to the poor solubility of compounds **4** and **2** in pure water even at an elevated temperature. A number

Table 1. Investigation of $NaNO_2$-Free Racemization



entry	solvent/acid	temp/°C	reaction time/h	conversion[a]/%
1	6v H_2O	50	18	86
2	6v H_2O/2 equiv HCl	50	18	86
3	6v:1v MeCN/H_2O	80	3	79
			6	89
			24	93
			48	94
4	6v:1v MEK/H_2O	80	3	46
			6	67
			24	97
5	6v:1v acetone/H_2O	60	3	33
			6	46
			24	83
			48	93
6	6v:1v DMF/H_2O	80	3	41
			6	55
			24	83
			48	92

[a]Complete racemization was observed based on the chiral HPLC analysis of the final sampling point.

of organic solvents were then explored to generate homogeneous reaction solutions, and the results were summarized in entries 3−6. Among the four solvents investigated, MeCN and MEK afforded more rapid reaction and fewer impurities.

Impacts of water volume for both MeCN and MEK systems were further investigated. Data summarized in Table 2 showed that increasing the water volume from 1v to 3v had a limited impact on the conversion for both solvent systems. MeCN demonstrated faster reaction rate, whereas MEK afforded an improved impurity profile.[16]

We then investigated both solvent systems on the mother liquor (**4-ML**) recovered from the real-world production. The recovered mother liquor was an acetone solution (typically ∼15v) containing ∼1:3 mixture of R/S enantiomers. In addition, the remaining (∼2.0 equiv) resolution reagent (i.e., benzoyltartrate) and degradants such as benzoic acid were present. The large volume of acetone in the mother liquor was first reduced down to ∼3v, and precipitation of some solids (a

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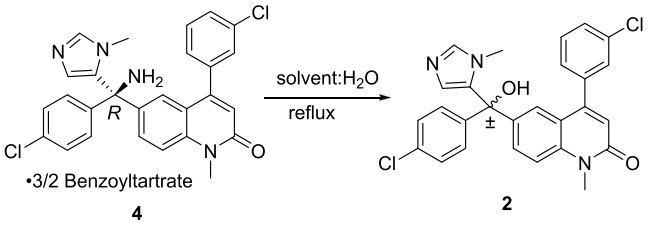
Table 2. Investigation of Water Volume



entry	solvent	reaction time/h	conversion/%
1	6v:1v MeCN/H_2O	3	79
		6	89
		24	93
		48	94
2	6v:3v MeCN/H_2O	3	89
		6	94
		24	96
		48	96
3	6v:1v MEK/H_2O	3	46
		6	67
		24	97
4	6v:3v MEK/H_2O	3	49
		6	68
		24	93
		48	98

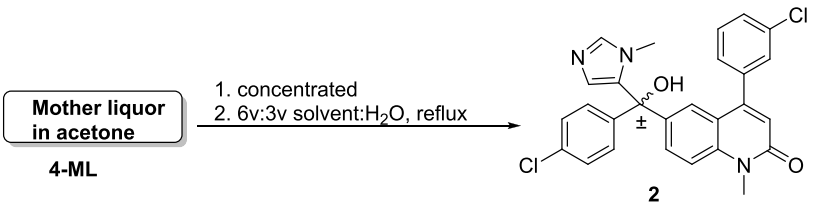
mixture of product and resolution reagents) was observed. MeCN (6v) or MEK (6v) along with 3v of water was added to dissolve all solids to form a biphasic solution that were heated to the reflux temperature. Additional acid additive (H_2SO_4) was also investigated, and the results are listed in Table 3. Consistent with the previous data, extra acid (H_2SO_4) had no apparent impact (entries 2 and 4) and MeCN as solvent afforded faster reaction rate. However, in the end, MEK was chosen as the preferred solvent due to (1) slightly improved reaction impurity profile; (2) MEK being a class 3 solvent vs MeCN a class 2 solvent according to the ICH Q3C guideline; (3) MEK belongs to the same chemical class of solvents as acetone that was the solvent in the mother liquor as well as in the subsequent HCl salt formation of compound **2** (Scheme 5); and (4) MEK has lower water miscibility than MeCN, which was advantageous to effect cleaner phase separation in the workup.

With the above results, we selected the reflux condition in 6v MEK and 3v H_2O with no acid additive for further scale-up to produce racemized **2** in excellent yield and purity. Compared with **2** from the original process, the only difference was one single impurity generated in step 1 that was carried over from **4-ML**. Importantly, when racemized **2** was subjected to step 1, essentially identical **3** as the normal process was produced and no new impurities were observed. Therefore, for intermediates **3** and **4**, no distinction between normal and recycled materials was necessary and the identical specifications were used for release. To the end, the recycling process was seamlessly incorporated into the original production process, as outlined in Scheme 5. In addition, every recycling cycle would generate a new batch of mother liquor, which in turn could be subjected to recycling. Indeed, we repeated this recycling cycle three times and **4** was still well within the predetermined specifications, which further demonstrated the robustness of the recycling process. Ultimately, the regular and recycled **4** was carried over to produce tipifarnib API qualified for human use, with the overall output increased by >60% and waste disposal significantly reduced.

CONCLUSIONS

A recycling process for a greener and industrial-scale production of tipifarnib was successfully developed. Initially,

Table 3. Racemization of Mother Liquor 4-ML



entry	solvent/additive	reaction time/h	conversion/%
1	MeCN	2	94
		4	99
		6	100
		8	100
2	MeCN/0.5 equiv H_2SO_4	2	96
		4	99
		6	100
		8	100
3	MEK	2	63
		4	85
		6	95
		8	96
		16	100
4	MEK/0.5 equiv H_2SO_4	2	68
		4	84
		6	97
		8	97

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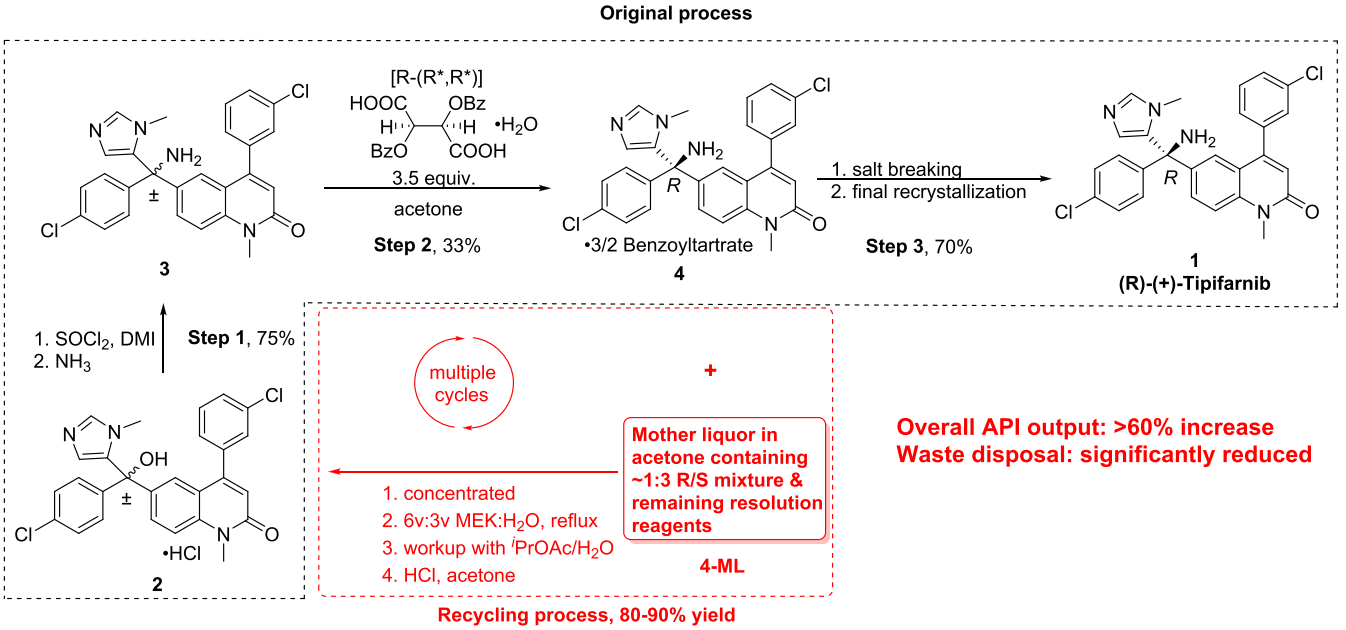
Scheme 5. Integrated Production Process of Tipifarnib



a $NaNO_2$-mediated process was devised, but introduction of impurity **7** and concerns about potential *N*-nitrosamine contamination necessitated an alternative approach. Careful understanding of the racemization mechanism led to a streamlined recycling process that was seamlessly incorporated into the original process, and the resulting process was both environmentally friendly and economically advantageous. We expect this recycling through the racemization process applicable to analogous compounds that have a chiral quaternary carbon center bearing a primary amine.

EXPERIMENTAL SECTION

$NaNO_2$-Mediated Racemization. In a 30 L reactor, the mother liquor solution in acetone from the regular production campaign (~15v, containing ~1.445 kg of R/S mixture of **3** based on the assay) was concentrated to ~6v, and water (2.16 L, 1.5v) was added. $NaNO_2$ (175 g, 1.8 equiv) was charged, and the reaction solution was stirred at room temperature until complete reaction was monitored by HPLC analysis. ^{i}PrOAc (7.2 L, 5v) was added followed by a 10% NaOH aqueous solution to adjust the pH to ~10. The aqueous layer was extracted with ^{i}PrOAc (7.2 L, 5v) one more time. The organic layers were combined, and then concentrated hydrochloric acid (37 wt %, 1.5 equiv) was slowly charged. The precipitated solid was collected by filtration, washed with ^{i}PrOAc, and dried to afford compound **2** (HCl salt) in an ~90% yield. ^{1}H NMR (400 MHz, DMSO) δ: 9.17 (s, 1H), 7.63−7.70 (m, 2H), 7.46−7.55 (m, 3H), 7.39−7.42 (m, 3H), 7.29−7.31 (m, 1H), 7.22−7.24 (m, 2H), 7.17 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 1.5 Hz, 1H), 6.60 (s, 1H), 3.68 (s, 3H), 3.53 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ: 160.6, 148.7, 139.8, 138.2, 137.6, 137.5, 133.5, 130.7, 128.9, 128.7, 128.7, 128.5, 127.7, 121.4, 118.6, 115.8, 75.0, 35.6, 29.5. MS: $C_{27}H_{21}Cl_2N_3O_2$ $[M + H]^+$: calcd: 490.1; found: 490.2.

Impurity **7** was isolated from 30 gm of crude **2** free base (containing ~1% based on HPLC analysis) via preparatory HPLC as a yellow solid. ^{1}H NMR (400 MHz, DMSO) δ: 8.19 (d, J = 8.8 Hz, 2H), 7.83 (s, 1H), 7.66 (m, 2H), 7.45−7.52 (m, 4H), 7.37 (s, 1H), 7.30 (d, J = 7.3 Hz, 1H), 7.17 (d, J = 6.8 Hz, 2H), 6.57 (s, 1H), 6.20 (s, 1H), 3.66 (s, 3H), 3.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ: 160.4, 152.2, 148.5, 146.6, 140.6, 139.4, 138.3, 138.2, 135.0, 133.3, 130.5, 130.0, 128.9, 128.7, 128.4, 128.0, 127.5, 124.7, 123.3, 121.2, 118.3, 115.4, 75.3, 33.2, 29.3. IR (cm^{-1}): 1640, 1578, 1520, 1348, 1264, 1068, 812, 731, 701. HRMS: $C_{27}H_{21}ClN_4O_4$ $[M + H]^+$: calcd: 501.1325; found: 501.1321.

$NaNO_2$-Free Racemization. The mother liquor solution in acetone recovered from the chiral resolution step (typically ~15v, containing ~1.64 kg of R/S mixture of **3** based on the assay) was concentrated to ~3v, and then MEK (7.3 kg, 6v) and process water (4.5 kg, 3v) were sequentially charged. The biphasic reaction mixture was heated to reflux until complete reaction was monitored by HPLC analysis and then cooled to room temperature. Process water (3.8 kg, 2.5v) was added followed by a 30 w/w% NaOH aqueous solution to adjust pH ~ 8. The aqueous layer was back-extracted with ^{i}PrOAc (6.0 kg, 4.5v) one more time. The organic layers were combined, washed with water (4.5 kg, 3v), and concentrated below 50 °C under reduced pressure to ~5.5v. ^{i}PrOAc (3.3 kg, 2.5v) was slowly charged, and the suspension was stirred at room temperature for 16 h. The precipitated solid (compound **2**, free base) was collected by filtration and washed with acetone (1.3 kg, 1.0v). The wet cake was collected, resuspended in acetone (6.0v), and then a concentrated HCl aqueous solution (37 wt %, 1.3 equiv) was charged slowly at room temperature. The precipitated solid was collected by filtration, rinsed with acetone (3.3 kg, 2.5v), and dried at 80 °C to afford **2** (HCl salt) as a white solid.

The same protocol was also performed on >1000 L mother liquor batches and repeated 3 times, and the product quality was still well within predetermined specifications. The typical yield was consistently at 80−90%.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00132.

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Characterization data and spectra of compounds **7** and **2** (PDF)

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Notes

The authors declare no competing financial interest.

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