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# Rapid Development of a Commercial Process for Linrodostat, an Indoleamine 2,3-Dioxygenase (IDO) Inhibitor

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**ABSTRACT:** The process development and the kilogram-scale synthesis of linrodostat (BMS-986205, **1**) are described. The synthesis features several highly efficient telescoped processes and the use of Evans auxiliary to install a methyl-bearing stereocenter. The target was prepared in 12 steps with 7 isolations in an overall yield of 31%.

**KEYWORDS:** *$S_NAr$, chiral auxiliary, TCFH, methylation, sulfolane*



## INTRODUCTION

Cancer is a devastating disease with approximately 1.7 million new cases being diagnosed every year in the United States alone. It is estimated that ∼40% of people will receive a diagnosis of cancer over the course of their lifetime.[1] While an absolute cure remains elusive, the advances in the field of immuno-oncology and the increasing number of drugs available offer new promise to patients. Indoleamine 2,3-dioxygenase (IDO) inhibitors are a potential new tool in the expanding approaches to combat this deadly disease. IDO-1 is an enzyme that converts tryptophan to the known immunosuppressant kynurenine and is often found overexpressed in a variety of tumor types.[2] The development of linrodostat (BMS-986205, **1**), an IDO inhibitor, for use in combination with immuno-oncology drugs, is potentially an important milestone in the evolution in the battle against cancer.[3]

## RESULTS AND DISCUSSION

To support the clinical development of **1**, along with enabling the potential commercial manufacture of this compound, an efficient and robust route was required. While a few alternative routes were considered, there were a number of practical advantages with optimizing and developing the approach used to discover the molecule, shown in a retrosynthetic fashion below (Figure 1).[4] The key steps in this sequence are the installation of the methyl-bearing stereocenter in **2**, the formation of a carboxylic acid fragment of **3** from ketone **5a**, and the construction of the carbon−carbon bond between the cyclohexyl and quinoline fragments. Evaluation of the initial processes suggested that there were no insurmountable roadblocks with the general synthetic approach preventing it from being used commercially (i.e., cost, safety, robustness, etc.). Thus, to develop this asset quickly, we strategically focused our efforts on improving this synthetic approach from a discovery synthesis into a commercially viable process.

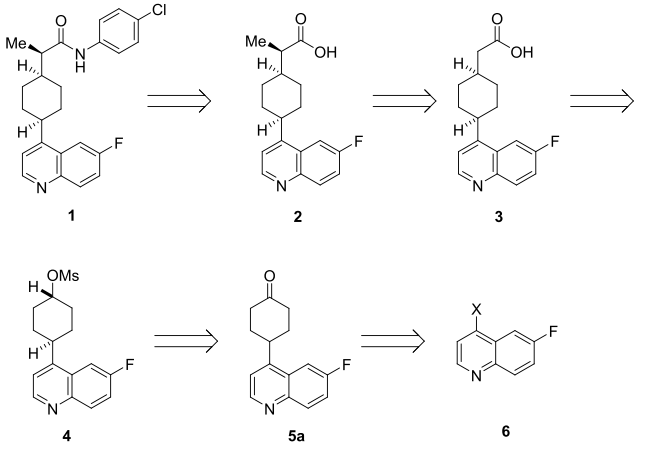


**Figure 1.** Retrosynthetic analysis of **1**.

**Synthesis of the Mesylate (4).** The original approach implemented to produce the first 100 kg of **4** is shown below in Scheme 1 (reaction conditions and yields listed in Scheme 1 are after initial optimization conducted to support early deliveries). Tertiary alcohol **8** was prepared via lithium halogen exchange of 4-bromo-6-fluoroquinoline (**6**, X = Br) followed by the addition of ketone **7**. Alcohol elimination, alkene hydrogenation, and ketal deprotection afforded ketone **5a** over

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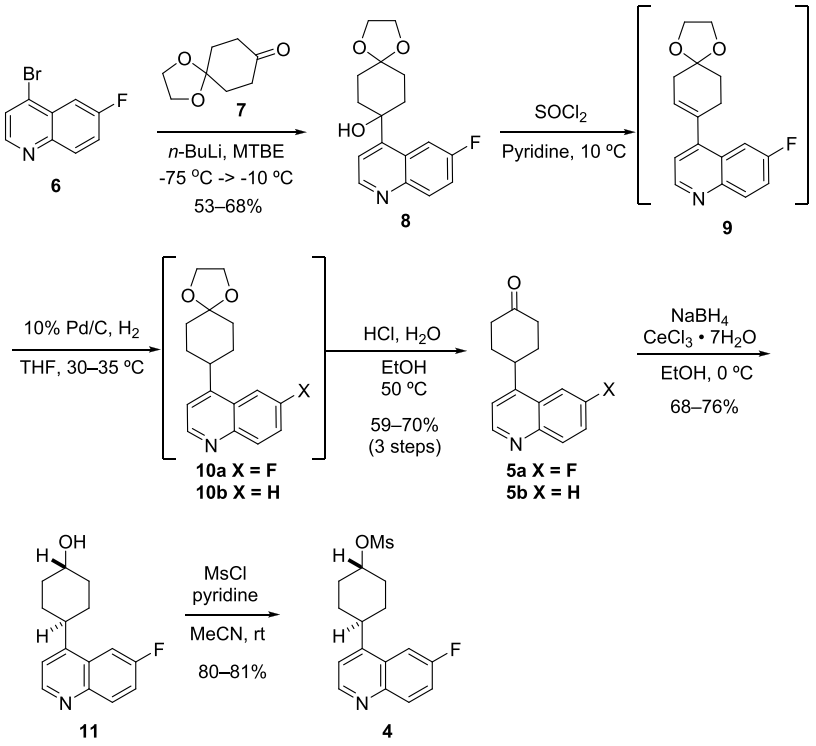
**Scheme 1. Initial Synthesis of Mesylate 4 (Reaction Conditions and Yields after Optimization)**




three steps. Diastereoselective ketone reduction followed by mesylation produced **4**.

There were a number of challenges with the original reaction conditions. The coupling of **7** with **6** required cryogenic conditions and suffered from low and variable yields (37–47%). The hydrogenation of the cyclohexene **9** was prone to reductive removal of the fluorine, and the resulting des-fluoro impurity **5b** did not readily purge in the downstream steps. The deprotection and conversion to ketone **5a** did not consistently go to completion (60% isolated yield), and the reduction to alcohol **11** was only mildly selective, forming the desired trans isomer in an approximately 5:1 ratio. Mesylate **4** was not stable under the crystallization conditions and afforded decreasing yields upon any scale-up. A number of modifications were quickly investigated to improve yield and robustness to enable an early scale-up of mesylate **4** (Scheme 1).

In the original procedure to form alcohol **8**, a mixture of 1.2 equiv of quinoline **6** and 1.05 equiv of *n*-BuLi was first mixed in diethyl ether, followed by the addition of ketone **7** as the limiting reagent. In the revised procedure, the reaction solvent was switched to methyl *tert*-butyl ether (MTBE), and 2.5 equiv of *n*-BuLi were added to a mixture of quinoline **6** and 2.5 equiv of ketone **7**. The in-process yield significantly increased to 86% in the revised procedure. Interestingly, this created some practical challenges, as now there was so much product in solution, it was no longer soluble during the workup procedure causing it to precipitate during phase splits. Because of this, on the first implementation, large amounts of alcohol **8** were left behind in the equipment and representative isolated yields of **8** ranged from 53 to 68%. Ten batches afforded in total 373 kg of **8** with an 88.3–94.6 high-performance liquid chromatography (HPLC) area percent purity. Although additional optimization of the workup conditions had the potential to further improve yields, enough product was prepared to meet our material demands and so additional development was not conducted.

The conversion of alcohol **8** to olefin **9** was performed by charging 5 equiv of thionyl chloride to a mixture of **8** and using pyridine as the solvent. Originally, the reaction was performed at −10 °C; however, it was discovered that there was no significant impact by running at 10 °C. A modified wash protocol using aqueous acetic acid was implemented to remove pyridine (see the Experimental Section). Six batches afforded 279 kg in total of olefin **9** in an 83–97% yield and with an 85.9–93.4 HPLC area percent purity.

The original Pd-catalyzed reduction to **10a** was conducted in ethanol and went to completion in 5–6 days. A kicker charge of a 10% Pd/C catalyst would be charged after 40 h. Aside from the impractically long reaction times, a more significant challenge was the tendency to over-reduce and generate a des-fluoro impurity **10b**. This was of particular concern as the des-fluoro impurity had very poor purging downstream. Batches of **5a** containing even trace (≥0.15 HPLC area percent) amounts of **5b** could potentially impact active pharmaceutical ingredient (API) quality. To address this, the reaction conditions were rapidly investigated using high-throughput screening. It was found that running with 10 mol % Pd/C in tetrahydofuran (THF) with 0.15–0.20 MPa of $H_2$ was very effective and minimized over-reduction to the des-fluoro impurity **5b** to <0.03%. The catalyst was filtered off, and the crude solution was used directly in the next step after solvent swapping to ethanol. The process afforded, in four batches, a total of 280 kg of **10a** in near-quantitative yield and with a 90.3–95.0 HPLC area percent purity.

The ethanol solution of **10a** was treated with 3 N aqueous hydrochloric acid and warmed to 50 °C. Upon reaction completion, the mixture was subjected to an extractive workup, concentrated, and crystallized from petroleum ether. One challenge to be addressed was that any residual ethylene glycol present would cause ketal **10a** to reform during the concentration of the mixture, thus decreasing the overall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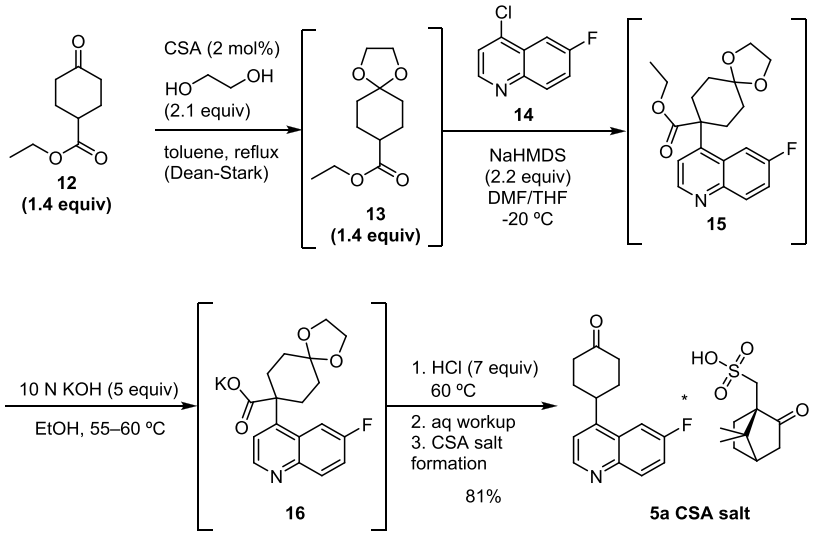
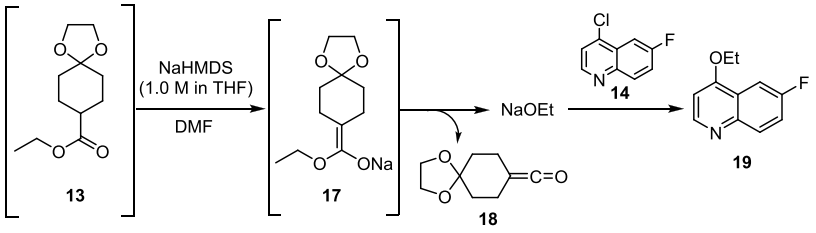
**Scheme 2. Revised Synthesis of 5a (Optimized Conditions)**




**Scheme 3. Proposed Route to $S_NAr$ Impurity 19**




yield. The process afforded, in two batches, a total of 169 kg of ketone **5a** in a 71−72% yield and a 91.8−93.3 HPLC area percent purity.

The reduction of **5a** with 1.5−2.0 equiv of sodium borohydride in ethanol proceeded to completion within 20 h at 0 °C; however, the original selectivity was poor, affording only a 5:1 trans/cis isomeric ratio. The addition of cerium(III) chloride heptahydrate improved the selectivity to >13:1 and allowed for the reaction to complete in <1 h.[5] Crystallization from dichloromethane (DCM) and methyl *tert*-butyl ether afforded good purging of undesired cis isomer with <2% detected in the isolated product. The process afforded, in two batches, a total of 118 kg of alcohol **11** in a 68−76% yield and a 91.1−93.0 HPLC area percent purity.

The original small-scale procedure to prepare mesylate **4** involved running the reaction in acetonitrile with 2 equiv of pyridine and 1.5 equiv of methanesulfonyl chloride. The mixture was initially heterogeneous and would become homogeneous over time, with the reaction taking between 10 and 16 h to reach completion. The original workup included a wash with saturated ammonium chloride; however, it afforded variable effectiveness in removing the pyridine. This was attributed to variability in the pH of the aqueous solution after the reaction quench. To alleviate the variability, a pH 4 citric acid wash was implemented that was effective in minimizing product loss while affording efficient pyridine removal. The crystallization involved heating the crude mesylate in water to 100 °C, adding methanol until it fully dissolved, and then cooling. It was quickly discovered that mesylate **4** was not stable under these conditions and resulted in the elimination of the mesylate to form the alkene. An alternative crystallization was developed, in which **4** was dissolved in dichloromethane and hexanes were added at 25 °C until crystallization was achieved. This proved to be a much more robust process and led to minimal epimerization and elimination of the mesylate. The process afforded, in two batches, a total of 116 kg of mesylate **4** in an 80−81% yield and a 90.4−96.6 HPLC area percent purity (>99:1 trans/cis ratio).

While the original route to ketone **5a** was successful in supplying initial quantities, there were some potential challenges implementing this approach in the commercial space including cost, the need for specialty equipment, and robustness. We were pleased when proof of concept for an alternative route to ketone **5a** was identified (Scheme 2). The key transformation involved nucleophilic aromatic substitution ($S_NAr$) coupling between 4-chloro-6-fluoroquinoline (**14**) and protected keto-ester **13**. Relatively straightforward functional group manipulations could then provide **5a**. There were several general features of this alternative approach, which made it more attractive. The fragment coupling did not require expensive metal catalysts[6] or cryogenic conditions.[7] The risk of generating the des-fluoro impurity **5b** was also obviated, as the cyclohexene reduction was no longer required.

Protected keto-ester **13** was produced from (−)-(*R*)-camphorsulfonic acid (CSA)-catalyzed ketalization under the Dean−Stark conditions. Aqueous workup and azeotropic distillation of the keto-ester **13**/toluene stream set the stage for the key $S_NAr$ coupling with 4-chloro-6-fluoroquinoline (**14**). Screening efforts for the $S_NAr$ coupling found that sodium hexamethyldisilazide (NaHMDS) was a uniquely effective base. If alternative counterions (LiHMDS or KHMDS) were used or if the temperature was raised to greater than −10 °C, the ester enolate **17** would decompose to the proposed ketene intermediate **18** with concomitant $S_NAr$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by the ethoxide anion to form **19** (Scheme 3). Thus, the reaction temperature range was established to be between −25 and −15 °C. The polar, aprotic cosolvent system dimethylformamide (DMF)/tetrahydofuran (THF) promoted the coupling, and the reaction was tolerant of toluene as a cosolvent introduced with the protected keto-ester. An aqueous workup was performed to quench the stream and remove dimethylformamide. Subsequently, the solution was solvent-swapped to ethanol. Aqueous potassium hydroxide in ethanol was a simple, inexpensive approach to saponify the ester of **15**. After the hydrolysis was complete, the process stream was transferred to a solution of aqueous hydrochloric acid held at 60 °C for decarboxylation and ketal hydrolysis. The reverse addition allowed for controlled carbon dioxide off-gassing. After reaction quench and aqueous workup, the free base of **5a** was in hand. Attempts to isolate the free base of **5a** revealed a propensity to oil out during crystallization. However, salt formation with CSA allowed for robust isolation of **5a** CSA salt.

There were several learnings during the first scale-up of this chemistry. Acid-catalyzed trans-esterification of ethylene glycol and **13** to form **20** was observed at up to 12 HPLC area percent (Figure 2) during the atmospheric pressure Dean−Stark distillation (boiling point = 111 °C) to form **13**. This impurity is inconsequential to the downstream chemistry as it reacts during the $S_NAr$ step and is subsequently hydrolyzed to **16**; however, we wanted to ensure robust control of the process. It was found that trans-esterification by ethylene glycol only occurred at high temperature in the presence of water, and therefore the degree of trans-esterification is dependent on the rate of water removal during the Dean−Stark distillation. While switching to the less acidic pyridinium *p*-toluenesulfonate catalyst was effective at controlling **20** on a lab scale, a simple solution was to run the reaction with a slight vacuum to lower the batch temperature (80−380 mbar, 45−85 °C). The vacuum distillation mitigated the sensitivity of the process to water content and resulted in excellent control of **20** (<0.5 HPLC area percent).

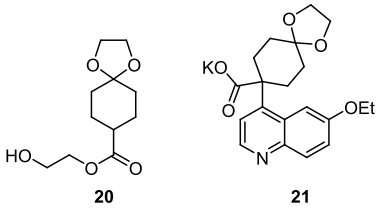



**Figure 2.** Impurities observed during the production of ketone **5a**.

In addition, up to 2.5 HPLC area percent of ethoxy impurity **21** was observed in the hydrolysis step reaction mixture (Figure 2). The ethoxy impurity has a modest purge in downstream steps, and our desire was to better control the impurity at this stage. For future scale-up, the hydrolysis reaction temperature was lowered from 70 to 55−60 °C, which minimized **21** formation and reduced the potential risk of additional impurity generation during any extended holds. After optimization, **5a** CSA salt was produced on a scale at a 130 kg batch size in an 81% yield and a 93−98 HPLC area percent purity.

With improved access to ketone **5a**, we focused our efforts on the subsequent steps. While the isolation of **5a** as the CSA salt was hugely advantageous in preventing oiling out during crystallization, freebasing was desired before the reduction was conducted. It was found that by salt-breaking a suspension of **5a** CSA salt in ethyl acetate with aqueous sodium carbonate, followed by aqueous workup and azeotropic distillation, afforded a stream which performed as expected in the reduction to form alcohol **11** (Scheme 4). One of the challenges with this chemistry was the reduction of the quinoline ring and the formation of impurity **22** (Figure 3).

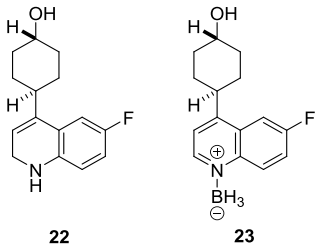
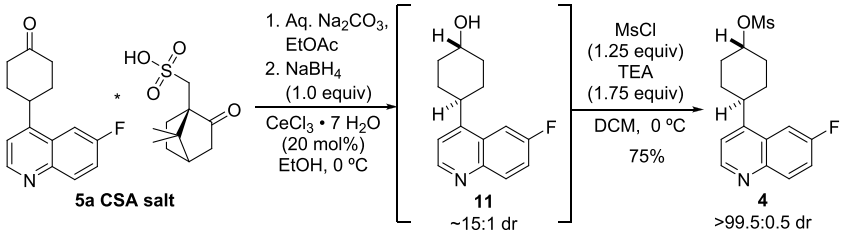



**Figure 3.** Impurities observed during the ketone reduction step.

Lowering the cerium(III) trichloride heptahydrate catalyst loading (from 30 to 20 mol %) and sodium borohydride charge (from 2 to 1 equiv) minimized the reduction impurity **22** from a 1 HPLC area percent down to <0.15 HPLC area percent. After the reduction is complete, the reaction stream is quenched with aqueous citric acid. In some scale-up batches, a borane complex **23**[8] of the desired product (Figure 3) was present, which carried forward into the isolated mesylate **4**. While this impurity was well tolerated in the downstream chemistry, we wanted to better understand and minimize its formation. It was found that aging the aqueous citric acid quench at 20−25 °C effectively broke up the borane complex. An added challenge was the relative insolubility of alcohol **11** in most solvent systems; however, dichloromethane (DCM) was found to be an excellent solvent for **11**, which allowed for an effective aqueous workup.

We thought we could leverage the improved diastereoselectivity resulting from the cerium(III) trichloride heptahydrate additive in the reduction and avoid the isolation of alcohol **11**. Telescoping of the process directly to mesylate **4** would potentially afford significant improvements to the

**Scheme 4. Revised Synthesis of Mesylate 4**



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**Scheme 5. Initial Lab Conditions for Synthesis of Carboxylic Acid 3**

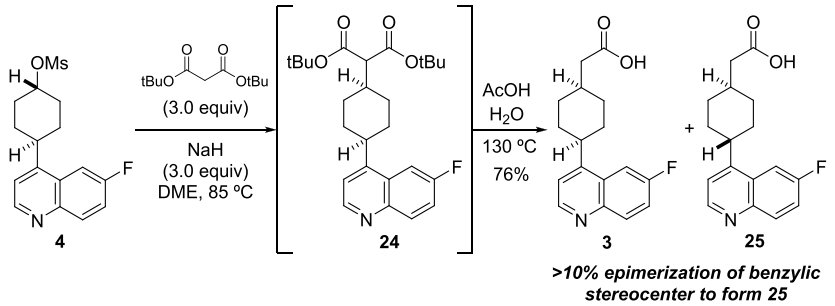
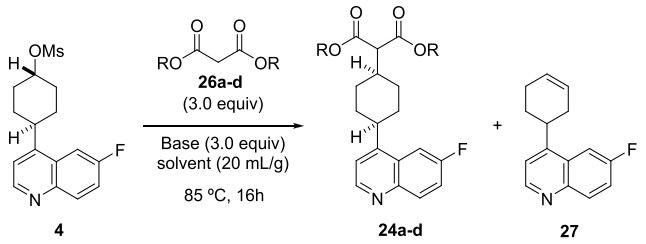



**Table 1. Screening for Malonate $S_N2$ of 4**




| entry | malonate (R=) (**26a–d**) | solvent | base | elimination impurity area percent (**27**) | product area percent (**24a–d**) | conversion (%) |
|---|---|---|---|---|---|---|
| 1 | $-C(CH_3)_2-$ (**26a**) | THF | NaO*t*Bu | 0 | 0 (**24a**) | ND |
| 2 | Me (**26b**) | THF | NaO*t*Bu | 2.7 | 37.7 (**24b**) | 44.2 |
| 3 | Et (**26c**) | THF | NaO*t*Bu | 2.8 | 56.7 (**24c**) | 72.5 |
| 4 | *t*Bu (**26d**) | THF | NaO*t*Bu | 1.8 | 81.9 (**24d**) | 94.9 |
| 5 | *t*Bu (**26d**) | THF | LiO*t*Bu | 1.9 | 13.0 (**24d**) | 13.7 |
| 6 | *t*Bu (**26d**) | THF | KO*t*Bu | 2.4 | 84.1 (**24d**) | 99.3 |
| 7 | *t*Bu (**26d**) | NMP | NaO*t*Bu | 13.3 | 36.6 (**24d**) | 49.0 |
| 8 | *t*Bu (**26d**) | DME | NaO*t*Bu | 1.6 | 78.8 (**24d**) | 88.1 |
| 9 | *t*Bu (**26d**) | dioxane | NaO*t*Bu | 1.3 | 89.2 (**24d**) | 98.8 |
| 10 | *t*Bu (**26d**) | *t*AmOH | NaO*t*Bu | 2.5 | 90.1 (**24d**) | 99.7 |
| 11 | *t*Bu (**26d**) | toluene | NaO*t*Bu | 2.2 | 95.5 (**24d**) | 99.4 |
| 12 | *t*Bu (**26d**) | toluene | NaO*t*Pent | 2.2 | 96.2 (**24d**) | 99.7 |

overall yield by minimizing losses to mother liquor. After the workup of the sodium borohydride reduction, the stream of **11** in dichloromethane was azeotropically dried to remove water. The mesylation was then conducted using triethylamine and methanesulfonyl chloride. Aqueous workup followed by crystallization in tetrahydrofuran/*n*-heptane produced the desired mesylate **4**. The optimized telescoped process improved the two-step overall yield from 54–62 to 75% and resulted in the isolated product in >99.5:0.5 trans/cis ratio. The process was scaled up to 190–360 kg, producing **4** with a 97.8–99.3 HPLC area percent purity.

**Synthesis of the Carboxylic Acid (3).** The initial lab-scale conditions for the synthesis of carboxylic acid **3** used sodium hydride, di-*tert*-butyl malonate, and dimethoxyethane (DME)[9] to conduct nucleophilic substitution ($S_N2$) displacement of mesylate **4**, followed by deprotection/decarboxylation using aqueous acetic acid. Unfortunately, there were a number of immediate concerns around the original reaction conditions. The use of sodium hydride was deemed not practical; there were safety concerns with using dimethoxyethane on scale, and there were robustness concerns due to epimerization leading to >10% of the trans isomer **25** during the decarboxylation step (Scheme 5). Improved conditions were highly desired for long-term commercial production.

Initial screening to find mild and selective $S_N2$ displacement conditions surveyed base, solvent, and malonate ester structure (Table 1). Non-nucleophilic tertiary alkoxides (e.g., LiO*t*Bu, NaO*t*Bu, KO*t*Bu) were safe, scalable, and effective replacements for NaH[10] and were the focus of additional screening experiments. Surveying a variety of malonates revealed an interesting trend (entries 1–4). The less hindered malonates, like Meldrum's acid and dimethylmalonate, showed little to no reactivity, while more hindered malonates showed higher reactivity. The low reactivity observed with dimethylmalonate could be a function of the low solubility of the sodium enolate in THF, whereas the poor reactivity of Meldrum's acid is likely a function of its decreased nucleophilicity relative to acyclic malonates.[11] Investigation of the nature of the alkoxide base in combination with di-*tert*-butyl malonate showed that potassium and sodium *tert*-butoxides were superior to lithium *tert*-butoxide in THF (entries 4–6). The choice to move forward with sodium was driven by the fact that the potassium base led to a heterogeneous reaction, which could have the potential for scale dependence.

During the base and malonate ester screening, it became apparent that stereoselectivity for the formation of the cis isomer was uniformly high (<1% trans isomer), despite the elevated temperatures. The greater challenge was maximizing conversion while suppressing elimination byproduct **27**. Solvent screening was undertaken for the reaction of sodium *tert*-butoxide and di-*tert*-butyl malonate (entries 4 and 7–11). Dioxane, *tert*-amyl alcohol, and toluene all gave good reaction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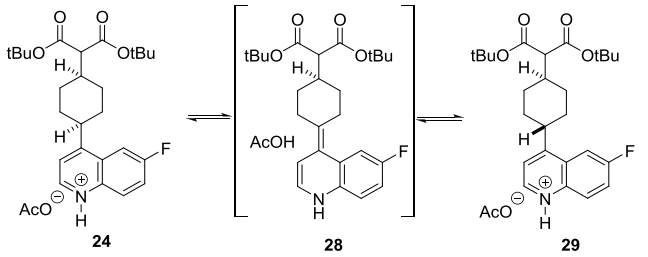
performance, and toluene was chosen as the optimal solvent. In the end, sodium *tert*-pentoxide was selected as the base since it gave a slightly improved in-process purity profile when compared to sodium *tert*-butoxide (compare entries 11 and 12).

With a method for the formation of malonate **24** in hand, we moved forward to investigate the deprotection/decarboxylation step. We hoped to use this toluene stream directly in the next step to streamline the process.[12] Examination of the original conditions with acetic acid revealed significant levels of epimerization (Scheme 6). We hypothesized that epimerization was occurring through the quinolinium salt of **24**. Using a weak acid (p$K_a$ of AcOH = 4.8)[13] generated a salt with a fairly basic counterion, which could lead to epimerization of the benzylic position through **28**. If this were true, the use of a stronger acid with a less basic counterion could suppress the undesired epimerization. Switching to methanesulfonic acid (MSA, p$K_a$ = −2.6) showed a dramatic improvement consistent with our hypothesis. However, it introduced a new practical complication. Phase separation was observed, presumably due to the poor solubility of the quinolinium salt in toluene. HPLC analysis showed no starting material or product remained in the toluene phase, and samples of the lower layer rapidly solidified upon cooling to room temperature, presenting a challenge for sampling at scale.

**Scheme 6. Proposed Mechanism for Epimerization of 24**



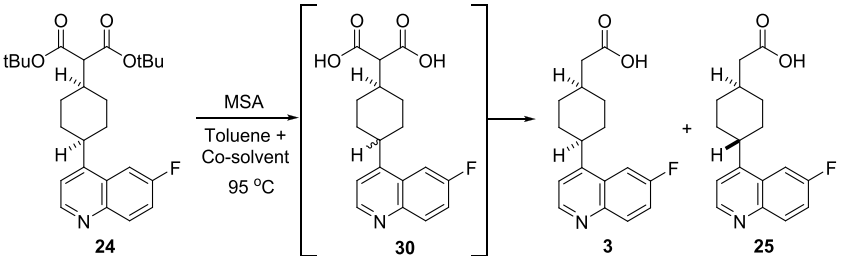

A screen of cosolvents was undertaken to render the reaction monophasic or at least to prevent solidification on cooling (Table 2). Although adding water or dioxane initially appeared promising, it did not mitigate the issues, and in the end, it was found that the addition of polar aprotic solvents provided a better option. Although the addition of *N*-methyl-2-pyrrolidone (NMP) gave a homogeneous reaction, it promoted an unacceptable amount of epimerization. Sulfolane was finally selected, despite the fact that the mixture became biphasic on cooling, since it prevented the formation of solids, did not lead to significant amounts of epimerization, and afforded shorter reaction times. This solvent was quite attractive since it is known to be thermally and chemically stable while avoiding many of the issues associated with the use of the closely related and more well-known solvent dimethyl sulfoxide (DMSO).[14]

With preliminary reaction conditions for the two-step telescope defined, the only issue that remained was the isolation of carboxylic acid **3** from the crude reaction stream. This was initially accomplished through neutralization of the decarboxylation stream with sodium acetate, thereby precipitating the sodium carboxylate form of **3**. Initial attempts at charging aqueous sodium acetate resulted in the precipitation of very sticky solids. A reverse charge of the postdecarboxylation aqueous stream to a solution of sodium acetate was developed for initial scale-up, resulting in a slurry with fewer processing issues. However, two aspects of the crystallization remained, which were less than ideal. The first is that following the reverse charge, additional solid sodium acetate was required to further adjust the pH and maximize yield. This was unsatisfactory as the addition of solid sodium acetate to the crystallizing stream had the potential liability of potency issues due to trapping of solids in the product crystal matrix. Additionally, due to the nature of the extremely rapid precipitation, there was virtually no purging of impurities in the isolation, which led to isolated **3** in a ∼95 HPLC area percent.

An alternate workup and crystallization sequence was developed, which involved using aqueous potassium hydroxide to basify the crude decarboxylation stream. At basic pH, a majority of the impurities that do not contain a carboxylic acid moiety partition to the upper toluene layer and are discarded during the phase split. This phase split affords in-process purity of up to ∼99 HPLC area percent. The pH is then adjusted using the slow addition of aqueous acetic acid, promoting slow crystal growth and more controlled particle formation. An isolated product purity of >99 HPLC area percent is consistently achieved by this method.

The finalized process used sodium *tert*-pentoxide, di-*tert*-butyl malonate in toluene to complete the $S_N2$, decarbox-

**Table 2. Cosolvent Screening for Synthesis of 3**




| cosolvent | homogeneous reaction mixture | time to full conversion (h) | cis/trans ratio (3:25) |
|---|---|---|---|
| $H_2O$ | no | 16 | 99.9:0.1 |
| dioxane | no | 16 | 100:0 |
| DMF | no | 16 | 84:16 |
| DMAc | no | 16 | 73:27 |
| NMP | yes | 16 | 85:15 |
| sulfolane with 3% water[15] | yes, above 85 °C | 3 | 99.9:0.1 |



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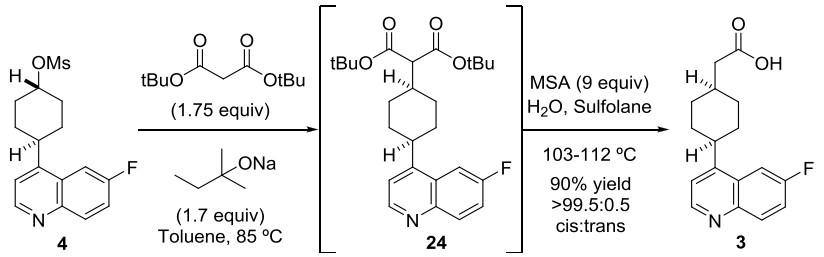
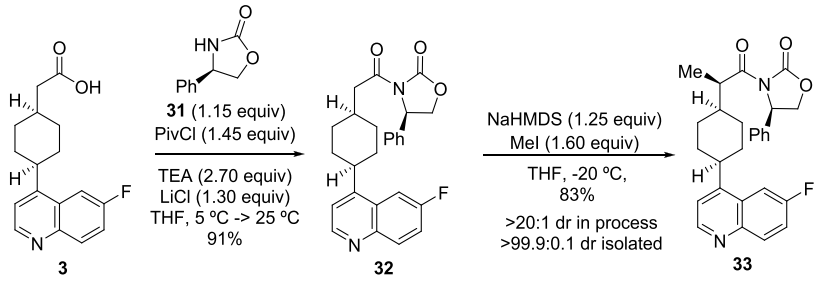
**Scheme 7. Final Conditions for Synthesis of Carboxylic Acid 3**




**Scheme 8. Diastereoselective Methylation Sequence (Optimized Conditions and Yields)**



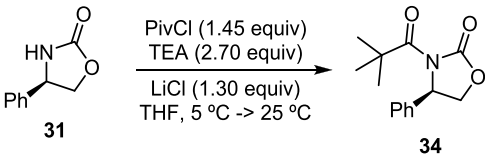

ylation in the presence of methanesulfonic acid and sulfolane (containing up to 3 wt % water), workup with an aqueous potassium hydroxide phase split, and isolation via aqueous acetic acid (Scheme 7). The process was scaled up to 199 kg, and the average yield was 90% with a 99.5 HPLC area percent purity.

**Introduction of a Methyl-Bearing Stereocenter.** To introduce the methyl group in an asymmetric fashion, we decided to continue with the existing chemistry, leveraging a diastereoselective alkylation using the Evans auxiliary (Scheme 8). The original reaction conditions to install the auxiliary used pivaloyl chloride (1.20 equiv) and triethylamine (2.50 equiv) in THF to generate a mixed anhydride intermediate, followed by the introduction of the (*R*)-4-phenyloxazolidin-2-one auxiliary **31** (1.25 equiv) and Lewis acid lithium chloride (1.25 equiv) to produce the imide product **32**.[16] Alternative activation of the carboxylic acid by oxalyl chloride was also briefly investigated. While the reaction conditions showed some promise, the product isolated from this process was of lower purity than that of the pivaloyl chloride process (96 vs >99 HPLC area percent). Therefore, the original activator, pivaloyl chloride, was retained. A screen of Lewis acids was conducted, and lithium chloride afforded the best conversion and selectivity for activating the mixed anhydride intermediate toward nucleophilic attack by auxiliary **31**. Initial scale-up showed reaction stalling, which required a kicker charge of pivalolyl chloride to reach full conversion. It was thought that the reagent stoichiometry could be optimized to avoid stalling for future campaigns.

The quench protocol was also changed to improve product quality. Aqueous ammonium chloride, the original quench solution, led to the formation of pivalamide from excess pivaloyl chloride. Pivalamide would generate impurities in the methylation step and impact quality downstream (impurity **37** in Table 3). It was found that the process stream was basic enough (pH = 8 after water addition) that a simple water quench was effective. The revised quench produced pivalic acid, which could be removed to the aqueous washes. Isopropyl acetate (IPAc) was added to solubilize the product and allowed for the aqueous workup. A solvent swap from the reaction solvent THF to the crystallization solvent IPAc was then conducted prior to crystallization. The **32**/IPAc stream was initially heated to 70 °C to dissolve the product, cooled, seeded, and charged with *n*-heptane as antisolvent.

In the initial scale-up, it was discovered that the Evans auxiliary **31** was difficult to purge since it has low solubility in the crystallization system. An improved control strategy was needed in this step as the auxiliary **31** could impact conversion in the subsequent methylation. Fortunately, we could take advantage of the slower side reaction between the Evans auxiliary and pivaloyl chloride. The deliberate pivalation of excess Evans auxiliary **31** to form **34** (Scheme 9) provided

**Scheme 9. Formation of Pivaloyl Auxiliary 34**




improved product purity as **34** purges well in the crystallization. Reaction DoEs and statistical modeling led to optimized reagent charges (1.45 equiv pivaolyl chloride, 2.70 equiv triethylamine, 1.30 equiv lithium chloride, 1.15 equiv auxiliary **31**) that achieved high conversion of both carboxylic acid **3** and the excess Evans auxiliary **31**.

With the upstream changes in the reaction conditions, the crystallization was simplified as an antisolvent crystallization with seeding, which avoided the previously required need for multiple cooling ramps and antisolvent charges to minimize **31** entrapment in the product. The optimized reaction and crystallization conditions were implemented on up to 230 kg scale and produced **32** in a 91% yield and >99.8 HPLC area percent purity with no detectable levels of auxiliary **31**.

With the imide installed, it was now possible to perform the diastereoselective methylation to form **33** (Scheme 8). A variety of alkylating agents (MeI, $Me_2SO_4$, MeOTs, MeOTf, $Me_2CO_3$, and $Me_4NI$) and bases (LiHMDS, NaHMDS, and


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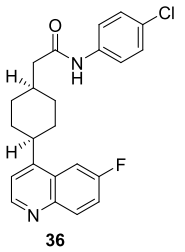
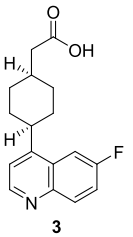
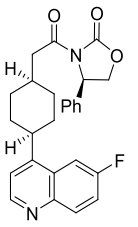
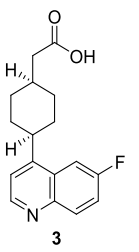
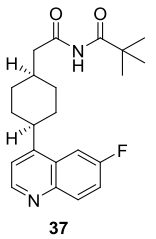
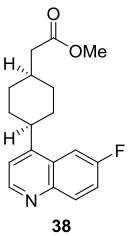
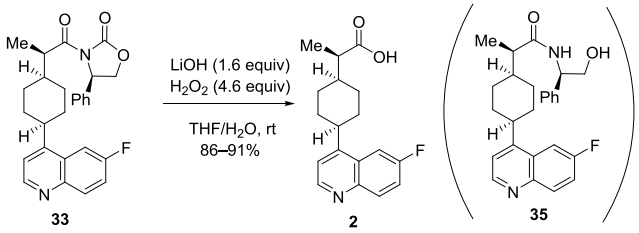
**Table 3. Des-Methyl Impurities in API 1, Penultimate 2, and Prepenultimate 33 Steps**

| API 1 Impurity | Penultimate 2 Impurity | Pre-Penultimate 33 Impurities |
|---|---|---|
|  36 |  3 |  32  3  37  38 |

KHMDS) were explored, but the conditions from the original synthesis appeared to be optimal (methyl iodide and NaHMDS).[17] At −40 °C, a 1 M solution of NaHMDS in THF was added to a slurry of **32** in THF to form the corresponding sodium enolate. The addition of methyl iodide delivered **33** with ∼30:1 diastereomeric ratio. These conditions were effective at gram scale; however, a number of challenges became apparent when the reaction was initially scaled up. First, as stress experiments and IR studies indicated, the in situ-generated sodium enolate of **32** decomposes over time. Second, quenching the reaction at low temperature by the addition of an aqueous ammonium chloride solution resulted in a heterogeneous mixture along with significant decomposition of **33** to its ring-opened impurity **35**, which is also an impurity observed in the next step (Scheme 10). There was no

**Scheme 10. Synthesis of Penultimate 2 and Ring-Opened Impurity 35**




background reaction between methyl iodide and **32** under the reaction conditions, which enabled in situ generation of the enolate in the presence of methyl iodide. Charging NaHMDS last mitigates the challenge of enolate instability, and the new reaction conditions also provide a cleaner reaction profile. The quench was changed to acetic acid, which minimized product degradation. The initial crystallization used isopropyl alcohol/water and was effective at purging the diastereomer and most process-related impurities to acceptable levels.

One of the particular challenges with this chemistry was the low tolerance for residual starting material **32** in the isolated **33**. There is a very limited purging of **32** in the isopropyl alcohol/water crystallization. In the next chemical step, **32** is hydrolyzed to generate the des-methyl compound **3** where poor purging is also observed during crystallization. In the API step, impurity **3** is converted to the corresponding des-methyl API impurity **36** and is also poorly purged during isolation (Table 3). Due to the limited purging capability of the des-methyl analogues in the last three steps of the synthesis, a very high conversion was required and the initial control strategy was to target a reaction conversion of ≥99.80%. During early process development, it was challenging to consistently achieve this high conversion requirement. Moreover, when reactions stalled, kicker charges of reagents were sometimes ineffective to consume the residual starting material. This led to a deeper study of the reaction and crystallization operations.

It was noted that stalled reactions oftentimes remained as a heterogeneous solution, whereas completed reactions were consistently homogeneous. In addition, two different polymorphs of undissolved **32** were observed at various times in the process. The solids of **32** introduced to the reaction were a neat form that could fully dissolve in THF at room temperature given sufficient time. Once the THF solution was cooled, a fine precipitate developed. These fine solids were found to be a THF solvate form. The physical properties of the two forms are different—the THF solvate is of smaller and more uniform particle size than the neat form. We hypothesized that the stalled reactions were never homogeneous at room temperature; hence, there was a mixture of neat form and THF solvate form at the reaction temperature. The neat form was not able to fully dissolve in the reaction mixture during the NaHMDS addition and reaction age, which led to reaction stalling.

Two changes were implemented based on this hypothesis. First, the THF was increased to >10 L/kg and initially heated to 45 °C for 2 h to ensure complete dissolution of the neat form of **32**. Second, the reaction temperature was increased from −40 to −20 °C to enhance the solubility of **32**, which notably had a very minimal impact on the diastereoselectivity of the methylation. Under the new conditions, consistent conversion was obtained. In addition, kicker charges of reagents have now proven to be effective to promote additional conversion, if the reaction has stalled due to the variation of process conditions.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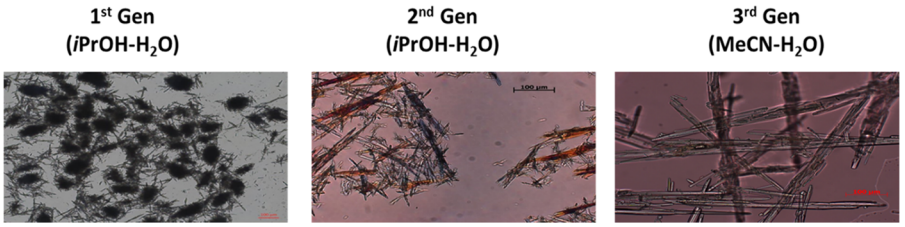


**Figure 4.** Comparison of isolated particles of **33** from different crystallizations.

Another unique challenge of this chemistry was that a higher level of des-methyl **3** was observed in the downstream chemistry than would be expected based on the levels of starting material **32** in the isolated product **33**. We suspected that this discrepancy was related to low levels of precursor impurities present in the isolated **33** that were being funneled to **3** in the subsequent hydrolysis step. Therefore, a systematic analysis was completed to identify all low-level impurities and address those that could be generating the challenge to remove impurity **3** (Table 3). Small levels of **3** (up to 0.05 HPLC area percent) were observed in nearly every batch of **33**, as **3** was generated during processing by the hydrolysis of **32** due to residual water in the methylation reaction. Imide impurity **37**, which can hydrolyze to **3** in the next step, was initially observed and was related to the presence of pivalamide in **32**. As previously discussed, revising the quench of pivaloyl chloride in the prior step **32** eliminated the presence of pivalamide and avoids the formation of **37**. Methyl ester **38** was observed sporadically and was found to come from residual methanol in the equipment train. Improved control of reactor cleaning eliminated **38**. With a greater understanding and controls that eliminated the risk of des-methyl precursors **37** and **38**, the long-term des-methyl control strategy was to set specifications on acid **3** and imide **32** in the isolated product **33**.

An improved crystallization was then sought to ensure excellent purging of acid **3** and imide **32**. The aforementioned first-generation isopropyl alcohol/water crystallization was capable of purging ≥90% **3**, but only provided ≤30% purging of **32**. We hypothesized that purging could be improved if we could address an uncontrolled agglomeration of **33** during self-nucleation and water addition (Figure 4). Seeding and heat cycles were implemented to control the crystal growth, which led to more uniform particles and significantly improved purging of imide **32** to 60%. While the second-generation isopropyl alcohol/water crystallization was promising, we were conducting parallel investigations on purging capabilities of alternative solvent systems. An acetonitrile/water crystallization was identified as a significant improvement over the isopropyl alcohol/water system. The new crystallization afforded complete rejection of **3** and purging of >85% imide **32**. The increased purging capability of this third-generation crystallization improved the tolerance for an unreacted starting material and enabled us to loosen the target reaction conversion from ≥99.80 to ≥99.50%. In addition, the new crystallization conditions reduced yield loss from 8 to 4% and led to more uniform needle-shaped crystals with improved filtration rates.

The finalized reaction and crystallization conditions for **33** have been demonstrated on up to 216 kg scale and led to an 83% yield with >99.9 HPLC area percent purity. These batches have also led to very low levels of the acid **3** and imide **32** impurities (typically <0.05 HPLC area percent each).

**Removal of the Auxiliary.** With the methyl-bearing stereocenter in place, we investigated the auxiliary removal to produce carboxylic acid **2**. It was found that, as reported in the literature,[18] lithium hydroxide and hydrogen peroxide offered high selectivity for the attack at the desired carbonyl group producing **2** (Scheme 10). Optimization of the conditions revealed that the amount of undesired ring-opened side product (**35**) could be minimized by employing higher levels of hydrogen peroxide and limiting the total amount of water present in the reaction mixture. It was found that 4.6 equiv of hydrogen peroxide could control the in-process level of **35** to a 2.5−3.0 HPLC area percent.

The original process also needed modification to improve overall efficiency. Upon reaction completion and quench with aqueous sodium bisulfite, the original process included a distillation to remove the THF, acetic acid charge to adjust the pH, and two extractions of the aqueous layer with 3:1 ethyl acetate (EtOAc)/THF. An additional four-solvent swap and a polish filtration were used to remove inorganics and crystallize the product. Filtration of the slurry resulted in the product with a typical HPLC area percent of 99.3 of **2**, 0.6 of impurity **35**, and up to 0.15 of Evans auxiliary **31**. It was later found during process development that the THF distillation after the quench, acetic acid charge, and subsequent extractions were superfluous. The sodium bisulfite reaction quench resulted in a consistent pH of 4.0−5.0 and resulted in a very efficient phase split with minimal product loss to the aqueous layer. *N*,*N*-Dimethylacetamide (DMAc) was then charged to the THF stream, aged for 1 h to precipitate any dissolved inorganics, polish-filtered, and then solvent swap was conducted to remove THF. Crystallization was induced via the addition of water at 70 °C without the requirement of seeds, followed by cooling to 20 °C. Product **2** is typically isolated in a 99.6 HPLC area percent purity with a 0.25−0.30 HPLC area percent of **35** and nondetectable levels of the Evans auxiliary **31**. The large crystals obtained had excellent filtration properties, and under normal drying conditions (50 °C under vacuum), they consistently dried to a KF of <0.1 wt %, which was an important requirement for the amide bond formation in the final step.

Also during process development, we were quite surprised to see a high level of oxygen off-gassing. While it is known that a background reaction between lithium hydroxide and hydrogen peroxide can slowly evolve oxygen, we observed more than was expected. In addition, the peracid that is directly formed in the reaction was only observed as a fleeting intermediate. This led us to investigate further, and ultimately, we found that the high rate of observed oxygen off-gassing was related to the reaction mechanism. The oxygen off-gassing was an issue that would need to be addressed to ensure the process could be run safely. The details of this investigation are described elsewhere.[19,20] We investigated several approaches in parallel: (1) incorporating a nitrogen sweep to the reactor to dilute oxygen to a safe


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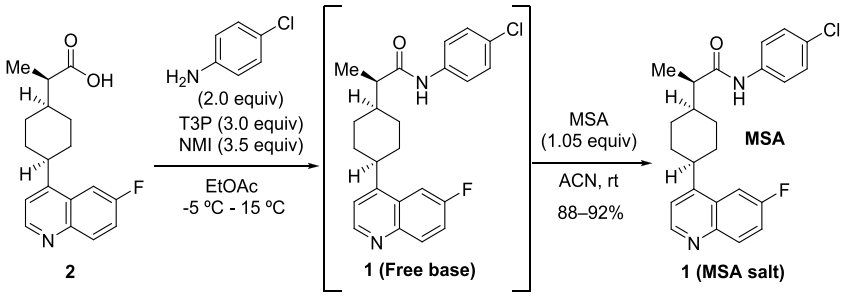
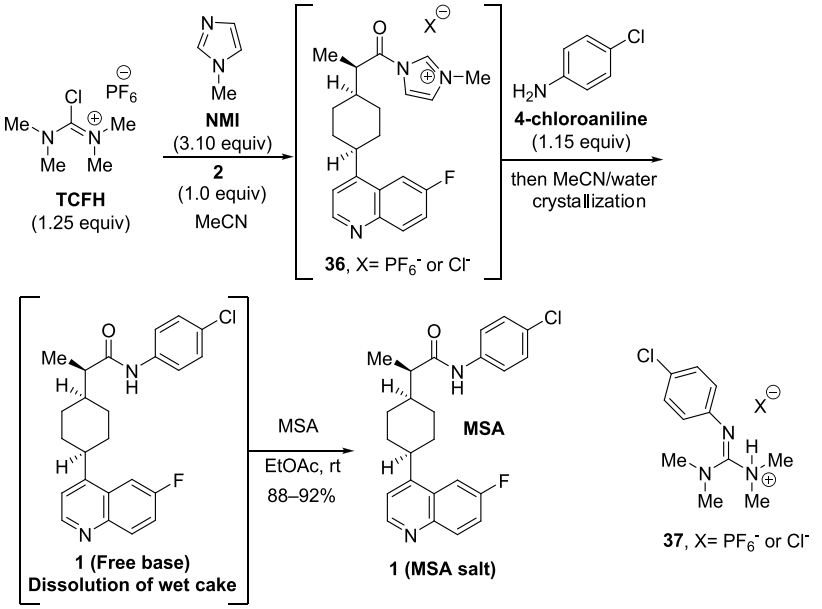
Scheme 11. Initial T3P Conditions To Produce 1




Scheme 12. TCFH Process To Synthesize API 1 and Impurity Adduct 37




level;[18] (2) operating the reaction in a continuous fashion to better control the rate of oxygen formation;[18] and (3) identifying alternative deprotection strategies that did not require the use of hydrogen peroxide.[19]

It was found that the oxygen off-gassing was addition-controlled when the lithium hydroxide is added at room temperature, and oxygen off-gassing quickly stops when lithium hydroxide addition is paused. By implementing a sufficient nitrogen sweep rate relative to lithium hydroxide addition rate and monitoring the oxygen level, the process could be safely scaled up in batch mode. Keeping the batch process allowed for easy incorporation into the existing equipment and minimized any delays to the production of API supplies. The finalized process was demonstrated on up to 215 kg scale and led to an 86−91% yield and >99.6 HPLC area percent purity.

**Coupling of 4-Chloroaniline and Isolation of the MSA Salt.** With the penultimate intermediate **2** available, we explored its coupling to 4-chloroaniline to provide the API **1**. We initially utilized propylphosphonic anhydride (T3P) as the coupling agent and *N*-methylimidazole (NMI) as the base, which successfully forged the amide bond. After workup, the resulting free base of **1** could then be converted to the methanesulfonic acid (MSA) salt, the form that was selected for initial clinical studies (Scheme 11). The optimized T3P process was used to generate up to 6.7 kg of **1** in a single batch and supported early clinical studies. Despite initial success with this process, the product purity was not consistent across additional batches. We were surprised to see that batches that had very low levels (<0.1 HPLC area percent) of 4-chloroaniline at the end of the reaction occasionally resulted in a product with high levels (0.8−1.0 HPLC area percent) in the isolated solids. It was determined that 4-chloroaniline/propylphosphonamide adducts (exact structures not elucidated) hydrolyzed under the aqueous workup conditions to release 4-chloroaniline back in the stream prior to MSA addition.

This led us to explore alternative coupling agents and conditions. Reaction screening identified tetramethylchloroformamidinium hexafluorophosphate (TCFH) in combination with NMI as competent in this coupling reaction with decreased cost relative to T3P.[21] To best accommodate the solubility of each species in this transformation, acetonitrile (MeCN) was chosen as the solvent. TCFH, NMI, and carboxylic acid **2** were charged in acetonitrile to generate acyl imidazolium **36.** Finally, 4-chloroaniline was added, which promotes the formation of **1** (Scheme 12). The excess 4-chloroaniline reacts further to generate adduct **37**, which is purged well during the crystallization.[21]

Although the desired MSA salt could be accessed in good quality and high yield directly from the crude reaction mixture by the addition of MSA, it was realized that a two-drop process offered some distinct advantages. By controlling chemical purity with the first drop and physical properties with the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second drop, the key aspects of the process were decoupled, making the development of the step simpler. In addition, the two-drop process actually offered an improved yield.[22] The free base monohydrate could be isolated via the addition of water to the crude reaction mixture.

Over the course of development of the free base crystallization, it was discovered that both oiling out of the product and phase separation were possible once water was introduced into this system. A phase map was generated to predict the state of the system as a function of temperature and solvent composition and to identify suitable conditions for the initial crystallization seeding (Figure 5, the section in green).

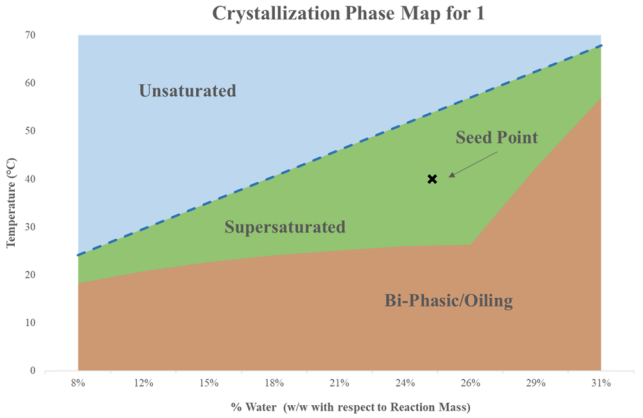



**Figure 5.** Phase map for crystallization of free base of **1**.

The seeding (1 wt % loading) was conducted at 25 wt % water with respect to reaction mass and 40 °C, which were easily controlled and avoided migration to the conditions that resulted in undesirable oiling out/phase separation (Figure 5, the section in red) and product dissolution (Figure 5, the section in blue). 4-Chloroaniline was highly soluble in the mother liquor of the free base crystallization and completely obviated any risk of it being present in the final MSA salt, thus offering an improvement to product quality over the initial process. The desired MSA salt was subsequently generated via the addition of MSA to a solution of the free base in ethyl acetate. The finalized process to **1** was demonstrated on up to 100 kg scale and led to a 92% yield and >99.9 HPLC area percent purity.

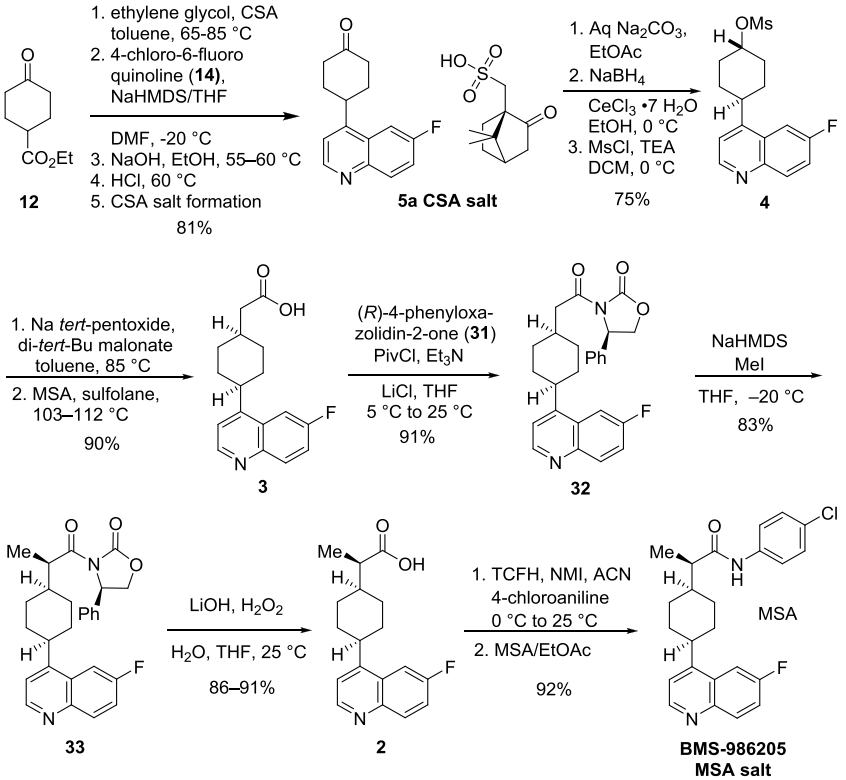
## CONCLUSIONS

In summary, we describe an efficient, 12-step and 7-isolation synthesis of BMS-986205 MSA salt (Scheme 13). All key intermediates were crystalline, and no special processing equipment was required, providing versatility in future manufacturing site selection. A new approach to the production of ketone **5** and mesylate **4** was implemented. The scale-up of the Evans auxiliary cleavage importantly identified oxygen off-gassing and implemented a mitigation strategy. The final process provides substantial improvements in overall yield (31 vs 8%) and process mass intensity (940 vs 1470 kg/kg) over the initial process to produce clinical supplies of BMS-986205 MSA salt. In addition, the revised process has been demonstrated on a multi-kilogram scale and is suitable for commercial manufacturing.

## EXPERIMENTAL SECTION

All reactions were performed under a nitrogen atmosphere. All reagents purchased from vendors were used as received unless otherwise indicated. Proton and carbon NMR were run on a Bruker AVANCE 400 at 400 MHz for proton and 100 MHz

**Scheme 13. Commercial Process to BMS-986205 MSA Salt**



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for carbon and a Bruker Avance III 600 NMR at 600 MHz for proton and 150 MHz for carbon.

**Preparation of 8-(6-Fluoroquinolin-4-yl)-1,4-dioxaspiro[4.5]decan-8-ol (8).** A reactor was charged with 4-bromo-6-fluoroquinoline (**6**, X = Br) (57.0 kg, 1.0 equiv) and 1,4-dioxaspiro[4.5]decan-8-one **7** (95.5 kg, 2.5 equiv) in MTBE (1055 kg). The mixture was cooled to −75 °C, and *n*-BuLi (181.3 kg, 2.5 equiv) was charged slowly while maintaining the temperature <−70 °C. The mixture was held for 4 h and then warmed to −10 °C. To the mixture was charged a 25 wt % aqueous $NH_4Cl$ solution (228 kg) while maintaining the temperature at <15 °C. To the mixture was charged a 7.5 wt % aqueous $NaHCO_3$ solution (308 kg). The biphasic mixture was stirred for 10−15 min, and then the aqueous was removed. The aqueous phase was back-extracted with MTBE (2 × 228 kg). The organic layers were combined and washed with a 15 wt % brine solution (342 kg). The organic layer was concentrated, and petroleum ether was charged (114 kg). The organic layer was concentrated, and petroleum ether was charged (171 kg). The mixture was heated to 60 °C for 2 h. The process stream was cooled to 25 °C, and the slurry was filtered. Reslurry in petroleum ether was repeated twice. The wet cake was dried at <40 °C for 12 h affording 41.7 kg of **8** in a 54.4% yield, 99.1 HPLC area percent. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.49 (dd, $J$ = 11.9, 2.5 Hz), 8.25 (d, $J$ = 4.5 Hz, 1H), 7.78 (dd, $J$ = 9.2, 5.9 Hz, 1H), 7.32−7.21 (m, 2H), 4.11 (br s, 1H), 3.88 (s, 4H), 2.22−2.13 (m, 4H), 2.02 (br d, $J$ = 11.1 Hz, 2H), 1.70 (br d, $J$ = 10.9 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 160.7, 158.2, 153.2, 148.7, 146.0, 132.1, 127.1, 119.1, 117.7, 111.1, 108.4, 72.8, 64.5, 64.2, 35.2, 30.4. High-resolution mass spectrometry (HRMS) [electrospray ionization (ESI)] calcd for $C_{17}H_{19}FNO_3$ ($[M + H]^+$), 304.1343; found, 304.1356.

**Preparation of 4-(6-Fluoroquinolin-4-yl)cyclohexan-1-one (5a).**[23] Original conditions to **5a** free base: a reactor was charged with 8-(6-fluoroquinolin-4-yl)-1,4-dioxaspiro[4.5]decan-8-ol **8** (84.0 kg, actual content adjusted for potency: 75.5 kg, 1.0 equiv) and pyridine (295.3 kg, 15.0 equiv). The mixture was agitated until all solids dissolved. The mixture was cooled to 5 °C, and then thionyl chloride (148.0 kg, 1244.0 mol, 5.0 equiv) was charged while maintaining the temperature between 5 and 15 °C. The reaction was held for 0.5 h, and then the mixture was charged to ice (650 kg) and water (500 kg) while maintaining the temperature <25 °C. The mixture was agitated for 15 min at which point dichloromethane (1080 kg) was charged. The biphasic mixture was stirred for 10−15 min, and then the aqueous layer was removed. The aqueous layer was back-extracted with dichloromethane (960 kg). The combined organic phases were washed with a 10 wt % aqueous acetic acid solution (3 × 527.9 kg) and then washed with water (528.5 kg). The organic layer was concentrated at 35−40 °C, and petroleum ether (100 kg) was charged. After holding for 1 h, the solution was concentrated to an oil. Petroleum ether (297 kg) was charged and agitated for 2 h. The upper clear liquid was transferred to another reactor and concentrated at 35−40 °C to afford a yellow/brown solid. To the solid was charged THF (80.0 kg). The mixture was concentrated. To the solid was charged THF (225.0 kg), affording a 301.0 kg solution (HPLC purity: 92.3%).

To a mixture of olefin **9** in THF (301.0 kg of solution containing 57.5 kg of **9**, 201.5 mol, 1.0 equiv) was charged 10% Pd/C (9.0 kg, ∼20% w/w to the starting material). The mixture was warmed to 30−35 °C and was stirred under an atmosphere of $H_2$ (0.15−0.20 MPa) for 40 h. An additional charge of 10% Pd/C (3.0 kg) was made, and the reaction was held under an atmosphere of $H_2$ (0.15−0.20 MPa) for 40 h until the reaction was complete (<5% of **9** remaining). The mixture was filtered through celite (5.0 kg). The celite cake was washed with ethanol (2 × 60 kg), and the filtrate was concentrated to afford the product in a 90.6 HPLC area percent and a 57.9 kg theoretical yield. The crude material was dissolved in ethanol (320 kg) and used directly in the next step.

A solution of **10** in ethanol (320 kg containing 57.9 kg of **10**, 1.0 equiv) was diluted with ethanol (216 kg), and then a 3 N aqueous solution of HCl (60 kg of concd HCl diluted with 187 kg of deionized water) was charged. The mixture was heated to 50−55 °C and held for 8 h until reaction completion was achieved (<6% of **10** remaining). The reaction mixture was concentrated at 50−55 °C, and the pH was adjusted to 8−9 with a 2 N aqueous NaOH solution (359 kg) while maintaining the temperature <25 °C. The resulting mixture was extracted with EtOAc (3 × 332 kg), and the combined extracts were washed with water (2 × 208 kg). The organic phase was concentrated at 40−50 °C, and EtOAc (75 kg) was charged. The mixture was concentrated, and EtOAc (42 kg) was charged to the resulting slurry. The mixture was heated to 55−60 °C and held until the solids dissolved. To the solution was charged petroleum ether, and the mixture was cooled down to 45−50 °C. The solution was seeded with **5a** (15 g), then was cooled to 30−35 °C, and petroleum ether (37 kg) was charged slowly. The mixture was further cooled to 15−20 °C and held for 6 h. The slurry was filtered, washed with petroleum ether (38 kg), and dried at 40−45 °C affording 34.8 kg of **5a** (free base) in a 58% corrected yield and a 91.8 HPLC area percent.

**Revised Conditions with Isolation as 5a CSA Salt.** A reactor was charged with ethyl 4-oxocyclohexane-1-carboxylate **12** (129 kg, 1.4 equiv), toluene (1122 kg), ethylene glycol (93 kg, 2.1 equiv), and (1*R*)-(−)-10-camphorsulfonic acid (CSA) (1.6 kg, 0.010 equiv). The mixture was heated to reflux (60 °C) under vacuum under the Dean−Stark conditions. The mixture was held for 4 h and then cooled to 25 °C. The crude reaction stream was washed with a 5% aqueous solution of $NaHCO_3$ (2 × 325 kg). The organic layer was washed with water (309 kg), and the organic layer was concentrated to 650 L. The mixture was charged to a solution of 4-chloro-6-fluoroquinoline **14** (129 kg, 1.0 equiv) and DMF (611 kg). The solution was agitated until homogeneous and cooled to −20 °C. To this solution was charged a 40 wt % NaHMDS solution in THF (719 kg) while maintaining the temperature <−20 °C followed by THF (92 kg). The reaction was held for 3 h at <−20 °C. The mixture was quenched with a 12 wt % aqueous $NH_4Cl$ solution (1417 kg) while maintaining the temperature less than 20 °C. The mixture was agitated, the phases were allowed to split, and the lower aqueous layer was discarded. The mixture was washed with a 12 wt % aqueous NaCl solution (3 × 662 kg). The batch was concentrated to 650 L. Ethanol (650 L) was charged, and the batch was distilled at ≤50 °C to a volume of 650 L a total of three times. The mixture was diluted with ethanol (424 kg), and a solution of potassium hydroxide (200 kg, 5.0 equiv) and water (258 kg) was charged. The mixture was heated to 55−60 °C for 10−24 h. The batch was then cooled to 20 °C. A mixture of water (338 kg) and 37 wt % aqueous solution of HCl (519 kg, 7.0


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equiv) was heated to 60−65 °C. The process stream of **16**/EtOH was charged to the hot aqueous HCl, which results in off-gassing. The reaction was held at 60−65 °C for 3 h during which time further off-gassing was observed. The reaction mixture was cooled to 35 °C, and 10 N potassium hydroxide (256 kg) was charged over 2 h maintaining the temperature <45 °C. To the mixture was charged EtOAc (1735 kg). The mixture was cooled to 25 °C, the phases were allowed to split, and the lower aqueous layer was discarded. The organic layer was washed with a 12% aqueous solution of sodium chloride (4 × 485 kg). The organic layer was concentrated under vacuum at <60 °C to 520 L. EtOAc (645 L) was charged, and the batch was distilled at ≤60 °C to a volume of 520 L a total of four times. The organic stream was diluted with EtOAc (360 kg). Solids were removed by polish filtration, and the filter was washed with ethyl acetate (205 kg).

(1*R*)-(−)-10-Camphorsulfonic acid (147 kg, 1.0 equiv) and EtOAc (2057 kg) were charged to a separate reactor and heated to 60 °C. **5a** free base/EtOAc stream of 45% was charged to the (1*R*)-(−)-10-camphorsulfonic acid/EtOAc. Seeds of **5a** CSA salt (0.6 kg, 0.005 equiv) were charged, and the slurry was held at 60 °C for 1 h. The remaining 55% of the **5a** free base/EtOAc stream was charged over 4 h. The slurry was held 60 °C for 1 h, cooled to 20 °C over 2 h, and held for 8 h. The solids were filtered and washed with EtOAc (2 × 617 kg). The solids were dried under vacuum at <50 °C affording 340.2 kg of **5a** CSA salt in an 84.8% yield and 98.0 HPLC area percent as an off-white solid. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.21 (d, $J$ = 5.6 Hz, 1H), 8.56 (dd, $J$ = 10.5, 2.7 Hz, 1H), 8.36 (dd, $J$ = 9.3, 5.3 Hz, 1H), 8.09−7.98 (m, 2H), 6.68−6.58 (m, 4H), 4.17 (m, 1H), 2.96 (d, $J$ = 14.7 Hz, 1H), 2.84 (m, 2H), 2.72−2.55 (m, 1H), 2.50−2.46 (m, 1H), 2.42−2.33 (m, 2H), 2.29−2.05 (m, 5H), 2.02−1.79 (m, 3H), 1.38−1.25 (m, 2H), 1.05 (s, 3H), 0.75 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 216.0, 209.4, 162.5, 161.8, 161.8, 160.0, 145.1, 136.0, 128.3, 128.2, 125.9, 125.8, 123.8, 123.5, 119.6, 109.3, 109.1, 58.1, 47.1, 46.9, 42.2, 42.1, 40.3, 36.8, 31.8, 26.3, 24.1, 19.9, 19.5. HRMS (ESI) calcd for free base $C_{15}H_{15}FNO$ ([M + H]$^+$), 244.1132; found, 244.1142.

**Preparation of (1r,4r)-4-(6-Fluoroquinolin-4-yl)-cyclohexan-1-ol (11).** *Original Procedure Using Free Base of **5a**.* A reactor was charged with **5a** (85.0 kg, actual content: 73.5 kg, 1.0 equiv) and EtOH (520.0 kg). The solution was agitated at 25 °C until the solids dissolved, and cerium(III) chloride heptahydrate (39.4 kg, 0.35 equiv) was charged. The mixture was held for 1 h until all solids dissolved, cooled to 5 °C, and $NaBH_4$ (17.0 kg, 1.5 equiv) was added portion-wise over 5 h maintaining the temperature <10 °C. The mixture was held for 12 h, and a premixed solution of acetic acid (20.0 kg, 1.0 equiv) in water (260 kg) was added while maintaining the temperature between 5 and 10 °C. The mixture was warmed to 20−25 °C and extracted with DCM (1000 kg). The aqueous layer was back-extracted with DCM (2 × 550 kg). The combined organic phases were washed with a 9 wt % aqueous NaCl solution (2 × 550 kg). The organic phase was passed through celite (15.0 kg) and concentrated. The process stream was diluted with MTBE (250 kg) and then reconcentrated twice. The resulting solids were diluted once again with MTBE (215 kg), and the slurry was heated to 40−45 °C for 4 h, cooled to 20 °C for 4 h, and filtered. The wet cake was washed with MTBE (80 kg) and dried at <40 °C to afford 59.2 kg of **11** as a yellow solid in a 68.1% corrected yield and 91.3 HPLC area percent. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.89−8.60 (m, 1H), 8.12−7.81 (m, 2H), 7.67−7.54 (m, 1H), 7.49−7.24 (m, 1H), 4.67 (s, 1H), 3.49 (s, 1H), 3.21 (s, 1H), 1.93 (s, 2H), 1.80 (s, 2H), 1.50 (s, 4H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 160.59 (d, $J$ = 244.7 Hz), 152.73 (d, $J$ = 5.2 Hz), 150.42, 145.76, 133.26 (d, $J$ = 9.4 Hz), 127.98 (d, $J$ = 9.4 Hz), 119.64 (d, $J$ = 25.8 Hz), 118.90, 107.84 (d, $J$ = 22.7 Hz), 69.43, 37.71, 36.08, 31.82. HRMS (ESI) calcd for $C_{15}H_{17}FNO$ [M + H]$^+$: 246.1289, found: 246.1694.

**Preparation of (1r,4r)-4-(6-Fluoroquinolin-4-yl)-cyclohexyl Methanesulfonate (4).** *Original Procedure Starting from Isolated **11**.* A reactor was charged with (1r,4r)-4-(6-fluoroquinolin-4-yl)cyclohexan-1-ol **11** (59.0 kg, actual content adjusted for potency 52.0 kg, 1.0 equiv), acetonitrile (82.0 kg), and pyridine (30.0 kg, 379.3 mol, 1.8 equiv). Methanesulfonyl chloride (34.0 kg,1.4 equiv) was charged over 4 h maintaining the temperature less than 10 °C. The mixture was warmed to 20−25 °C and held for 19 h until the reaction reached completion. The mixture was quenched with a 20 wt % aqueous $NH_4Cl$ solution (520 kg), and dichloromethane (420 kg) was charged. The mixture was agitated, the phases were allowed to split, and the upper aqueous layer was transferred to a separate reactor. The aqueous solution was back-extracted with dichloromethane (2 × 280 kg). The combined organic phases were then washed with a citric acid/water/NaOH mixture (75:750:14.5) (3 × 260 kg). The resulting organic phase was washed with an aqueous $NaHCO_3$ solution (13.0 kg of $NaHCO_3$ in 250 kg of water) and then dried with $Na_2SO_4$ (50.0 kg). The mixture was filtered through a layer of silica gel (30 kg). The cake was washed with dichloromethane (2 × 140 kg), and the filtrate was concentrated. The concentrate was dissolved in dichloromethane (280 kg) at 30−35 °C, hexane (80 kg) was charged, and the mixture was stirred for 2 h. To the mixture was charged hexane (320 kg), and the slurry was held for 6 h at 15−20 °C. The slurry was filtered, and the cake was washed with a mixture of DCM (40.0 kg) and hexane (70.0 kg). The cake was dried at <45 °C to afford 56.5 kg of **4** in a 79.6% yield and 97.6 HPLC area percent as a yellowish solid.

*Telescoped Procedure from the CSA Salt of **5a**.* A reactor was charged with 4-(6-fluoroquinolin-4-yl)cyclohexan-1-one ((1*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-methanesulfonate **5a** (243.6 kg, 1.0 equiv), ethyl acetate (1747 kg), and an 8.3 wt % aqueous solution of sodium carbonate (1324 kg). The mixture was agitated for 30 min until homogeneous. Agitation was stopped, the phases were allowed to split, and the lower aqueous layer was discarded. The organic stream was washed with 15 wt % aqueous NaCl (1336 kg). The stream was concentrated to 980 L. Ethanol (980 L) was charged, and the batch was distilled at ≤50 °C to a volume of 980 L a total of two times.

A separate reactor was charged with cerium(III) trichloride heptahydrate (38.2 kg, 0.20 equiv) and ethanol (771 kg). The mixture was held at 25 °C for 1 h until it was homogeneous, cooled to 5 °C, and then transferred to the solution of **5a**/ethanol. The process stream was cooled to −10 °C. Sodium borohydride (19.4 kg) was charged in four portions, ensuring that the batch temperature did not exceed 0 °C. The mixture was held at −10 to 0 °C for 1 h. The reaction was quenched with 10 wt % aqueous citric acid (1508 kg) while maintaining the temperature <20 °C. The temperature was adjusted to 20 °C, and the mixture was agitated for 4 h. The pH was adjusted between 4 and 6 by charging a 7.9 wt % aqueous sodium bicarbonate solution (1156 kg). Dichloromethane (1617 kg)


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was charged. The mixture was agitated for 30 min, the phases were allowed to split, and the upper aqueous layer was transferred to a separate reactor. The aqueous layer was back-extracted with dichloromethane (1617 kg). The organic layers were combined, and 10 wt % aqueous citric acid (1508 kg) followed by a 7.9 wt % aqueous sodium bicarbonate solution (1156 kg) was charged. The mixture was agitated, the phases were allowed to split, and the upper aqueous layer was discarded. The organic layer was washed with 4.9 wt % aqueous sodium bicarbonate (1276 kg) and further washed with 10 wt % aqueous NaCl (1348 kg).

The batch was concentrated to 980 L. Dichloromethane (1460 L) was charged, and the batch was distilled at <40 °C to a volume of 980 L a total of five times. The reaction mixture was cooled to 20 °C, and triethylamine (88.4 kg, 1.7 equiv) was charged. The mixture was cooled to −5 °C, and methanesulfonyl chloride (70.5 kg, 1.2 equiv) was charged maintaining the temperature at <0 °C. The batch was held at −10 to 0 °C for 1 h. The reaction was quenched with 12 wt % aqueous ammonium chloride (887 kg) maintaining the temperature <20 °C, and the mixture was warmed to 20 °C. Dichloromethane (1293 kg) was charged. The mixture was agitated, the phases were allowed to split, and the upper aqueous layer was discarded. The organic stream was washed with water (850 kg). The stream was concentrated down to 730 L. THF (1458 L) was charged, and the batch was distilled down to 730 L a total of three times.

The mixture was polish-filtered, washed with THF (434 kg), and distilled under vacuum at <45 °C to a volume of 850 L. The batch was cooled to 20 °C, and 0.1 kg of seeds were charged. *n*-Heptane (835 kg) was charged over 3 h. The slurry was held at 20 °C for 3 h and filtered. The cake was washed with a premixed solution of THF (145 kg) and *n*-heptane (223 kg) followed by a wash with *n*-heptane (334 kg). The cake was dried under vacuum at <50 °C to obtain 124.4 kg in a 75.1% yield, 99.0 AP as an off-white solid.

$^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.80 (d, $J$ = 4.5 Hz, 1H), 8.08 (t, $J$ = 7.7 Hz, 1H), 8.02 (d, $J$ = 10.4 Hz, 1H), 7.65 (m, 1H), 7.40 (d, $J$ = 4.7 Hz, 1H), 4.77−4.68 (m, 1H), 3.40−3.30 (m, 1H), 2.19 (m, 2H), 1.95−1.81 (m, 4H), 1.76−1.64 (m, 2H). $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 160.8, 159.1, 151.1, 149.8, 145.1, 132.6, 127.2, 119.1, 118.9, 118.2, 107.3, 107.1, 80.6, 37.8, 36.0, 32.2, 30.5. HRMS (ESI) calcd for $C_{16}H_{19}FNO_3S$ $[M + H]^+$: 324.1064; found, 324.1077.

**Preparation of 2-((1s,4s)-4-(6-Fluoroquinolin-4-yl)-cyclohexyl)acetic Acid (3).** A reactor was charged with toluene (1035 kg) and sodium *tert*-pentoxide (115.2 kg, 1.70 equiv). The mixture was heated to 35 °C, and di-*tert*-butyl malonate (232.9 kg, 1.75 equiv) was charged maintaining the temperature at 35 °C. The mixture was stirred for 1 h, and (1r,4r)-4-(6-fluoroquinolin-4-yl)cyclohexyl methanesulfonate **4** (199.0 kg, 1.0 equiv) and toluene (515 kg) were charged. The mixture was heated to 85 °C and held for 12 h.

The mixture was cooled to 55 °C, and water (40 kg) and sulfolane (1255 kg) were charged, followed by methanesulfonic acid (532.2 kg, 9.0 equiv). The mixture was warmed to 60 °C and held for 1 h. The mixture was then heated to 105 °C and held for 14 h. The mixture was cooled to 60 °C, and water (792 kg) was charged. After cooling to 25 °C, aqueous potassium hydroxide (442 kg of KOH and 535 kg of water) was charged. The mixture was held at 25 °C for 1 h until all solids dissolved; the agitation was halted, the phases were allowed to split, and the lower aqueous phase was transferred to a separate reactor. The pH was adjusted to 5.5 using an aqueous acetic acid solution prepared from 88.7 kg of acetic acid and 1287 kg of water. The mixture was held for 2 h and filtered. The wet cake was washed with water (2 × 990 kg) and toluene (2 × 862 kg). After drying under vacuum at <50 °C, 156.9 kg of **3** was obtained in an 88.7% yield, 99.5 HPLC area percent as an off-white solid.

$^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 12.07 (br s, 1H), 8.79 (d, $J$ = 4.3 Hz, 1H), 8.07 (dd, $J$ = 9.1, 5.9 Hz, 1H), 7.92 (dd, $J$ = 10.8, 2.4 Hz, 1H), 7.63 (td, $J$ = 8.6, 2.5 Hz, 1H), 7.48 (d, $J$ = 4.5 Hz, 1H), 3.43−3.25 (m, 1H), 2.42 (d, $J$ = 7.7 Hz, 2H), 2.34−2.19 (m, 1H), 1.89−1.76 (m, 2H), 1.72−1.60 (m, 6H). $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 174.2, 160.7, 159.1, 152.3, 149.8, 145.1, 132.7, 127.2, 118.6, 107.2, 37.5, 36.2, 29.5, 29.1, 27.4. HRMS (ESI) calcd for $C_{17}H_{19}FNO_2$ $[M + H]^+$: 288.1394; found, 288.1406.

**Preparation of (*R*)-3-(2-((1s,4s)-4-(6-Fluoroquinolin-4-yl)cyclohexyl)acetyl)-4-phenyloxazolidin-2-one (32).** A reactor was charged with THF (1138 kg) and 2-((1s,4s)-4-(6-fluoroquinolin-4-yl)cyclohexyl)acetic acid **3** (105.1 kg, 1.0 equiv). The mixture was cooled to −5 to 5 °C. Pivaloyl chloride (64.0 kg, 1.45 equiv) was charged. Triethylamine (101.1 kg, 2.70 equiv) was charged, maintaining the temperature at −5 to 5 °C, and then the mixture was aged for 1 h. (*R*)-(−)-4-Phenyl-2-oxazolidinone **31** (68.1 kg, 1.15 equiv) and lithium chloride (20.2 kg, 1.30 equiv) were charged, and then the reactor wall was rinsed with THF (15.8 kg). The mixture was warmed to 25 °C and held for 8 h.

Water (1050.6 kg) and isopropyl acetate (825.8 kg) were added into the mixture. After mixing for 1 h, the phases were allowed to separate, and the bottom aqueous layer was discarded. The organic stream was then washed with 10 wt % aqueous NaCl (1050 kg). The organic stream was concentrated down to 500 L. Isopropyl acetate (466.3 kg) was added, and the organic stream was concentrated down to 500 L. Isopropyl acetate (1850.5 kg) was added into the mixture at 45−55 °C and stirred for 1 h. The organic stream was filtered to remove inorganics, and the filter was rinsed with isopropyl acetate (187.0 kg). The combined stream was concentrated under reduced pressure until 700 L was left.

The organic stream was heated to 70−75 °C until the solid completely dissolved. The mixture was cooled to 45 °C, and then seeds (0.2 kg) were added into the mixture. The mixture was stirred for 1 h. *n*-Heptane (1178.5 kg) was added into the mixture over 3 h and then aged at 45 °C for 1 h. The mixture was cooled to 10 °C over 4 h and allowed to age for 6 h. The slurry was filtered with a centrifuge. The solid was rinsed with a premixed solution of isopropyl acetate (45.2 kg) and *n*-heptane (321.5 kg). The solids were then rinsed with *n*-heptane (2 × 358.2 kg). The cake was dried under vacuum at <50 °C to obtain 139.6 kg **32** in an 88.2% yield, 99.95 HPLC area percent as a white solid.

$^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.80 (d, $J$ = 4.5 Hz, 1H), 8.08 (dd, $J$ = 9.2, 5.8 Hz, 1H), 7.92 (dd, $J$ = 10.9, 2.6 Hz, 1H), 7.63 (td, $J$ = 8.7, 2.6 Hz, 1H), 7.43 (d, $J$ = 4.5 Hz, 1H), 7.39−7.35 (m, 2H), 7.34−7.27 (m, 3H), 5.50 (dd, $J$ = 8.7, 3.8 Hz, 1H), 4.75 (t, $J$ = 8.7 Hz, 1H), 4.16 (dd, $J$ = 8.7, 3.8 Hz, 1H), 3.34−3.25 (m, 1H), 3.17 (dd, $J$ = 15.6, 6.8 Hz, 1H), 3.02 (dd, $J$ = 15.7, 8.0 Hz, 1H), 2.35 (br s, 1H), 1.83−1.75 (m, 2H), 1.73−1.56 (m, 6H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 171.6, 160.7, 159.1, 153.7, 152.2, 152.1, 149.8, 145.1, 140.0, 132.6, 132.6, 128.7, 127.9, 127.1, 127.1, 125.7, 119.0, 118.8, 118.4, 107.1, 107.0, 69.9, 57.0, 37.4, 36.5, 29.6, 29.0, 28.7, 27.4.


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HRMS (ESI) calcd for $C_{26}H_{26}FN_2O_3$ $[M + H]^+$: 433.1922, found 433.1936.

**Preparation of (*R*)-3-((*R*)-2-((1s,4s)-4-(6-Fluoroquinolin-4-yl)cyclohexyl)propanoyl)-4-phenyloxazolidin-2-one (33).** A reactor was charged with (*R*)-3-(2-((1s,4s)-4-(6-fluoroquinolin-4-yl)cyclohexyl)acetyl)-4-phenyloxazolidin-2-one **32** (95.0 kg, 1.0 equiv) and THF (838.1 kg). The mixture was heated to 45 °C, and then THF (85 kg) was charged. The organic stream was transferred through a filter to another reactor, and the filter was rinsed with THF (41.1 kg). The mixture was cooled to −20 °C, and then THF (21 kg) and methyl iodide (50.1 kg, 1.60 equiv) were charged. Sodium bis(trimethylsilyl) amide (NaHMDS) (1 M) in THF (252.3 kg, 1.25 equiv) was charged while maintaining the temperature at −20 °C. The reactor was rinsed with THF (25.8 kg), and then the organic stream was held at −20 °C for 3 h. The reaction was quenched by the addition of a 4.6 wt % aqueous acetic acid solution (357 kg) while maintaining the temperature at less than −10 °C. The organic stream was warmed to 25 °C, and 12.5 wt % aqueous NaCl (519 kg) was charged. After mixing for 30 min, the phases were allowed to separate, and the bottom aqueous layer was discarded. The organic layer was concentrated to 500 L. Acetonitrile (2 × 741 kg) was charged, and the resulting mixture was twice distilled down to 500 L. Acetonitrile (378 kg) was charged, and the solution was warmed to 60 °C and held at that temperature for 30 min. Water (252 kg) was charged over 2.5 h, and the temperature was cooled to 52 °C. Seeds (1.0 kg) were charged, the slurry was held for 2 h, and water (604 kg) was charged over 3 h while maintaining the temperature at 52 °C. The slurry was cooled to 20 °C over 2.5 h and held for 4 h. The slurry was filtered and then washed twice (2 × 424 kg) with a premixed solution of acetonitrile (378 kg) and water (475 kg), followed by washing with water (237 kg) and *n*-heptane (162 kg). The cake was dried at 55 °C to afford 80.9 kg of **33** in an 83% yield, 99.94 HPLC area percent as an off-white solid.

$^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 8.85 (d, $J$ = 4.5 Hz, 1H), 8.10 (dd, $J$ = 9.2, 5.8 Hz, 1H), 7.97 (dd, $J$ = 10.9, 2.6 Hz, 1H), 7.66 (dd, $J$ = 8.7, 2.6 Hz, 1H), 7.41−7.40 (m, 3H), 7.32−7.30 (m, 3H), 5.53 (dd, $J$ = 8.7, 3.8 Hz, 1H), 4.76 (t, $J$ = 8.7 Hz, 1H), 4.29 (m, 1H), 4.15 (dd, $J$ = 8.6, 4.2 Hz, 1H), 3.42−3.38 (m, 1H), 2.05−2.01 (dd, 1H), 1.83−1.58 (m, 1H), 1.05 (d, $J$ = 8.7 Hz, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 175.9, 160.7, 159.1, 153.6, 152.3, 152.3, 149.8, 145.2, 139.9, 132.7, 132.6, 128.8, 127.9, 127.2, 127.1, 125.5, 119.0, 118.9, 118.3, 107.2, 107.0, 68.8, 57.0, 37.1, 36.0, 34.7, 28.4, 27.9, 27.5, 26.1, 15.8; HRMS (ESI) calcd for $C_{27}H_{28}FN_2O_3$ $[M + H]^+$: 447.2079, found 447.2091.

**Preparation of (*R*)-2-((1s,4s)-4-(6-Fluoroquinolin-4-yl)cyclohexyl)propanoic Acid (2).** A reactor was charged with THF (640 kg) and (*R*)-3-((*R*)-2-((1s,4s)-4-(6-fluoroquinolin-4-yl)cyclohexyl)propanoyl)-4-phenyloxazolidin-2-one **33** (144 kg, 1.0 equiv) followed by THF (320 kg). The reactor was charged with a 35 wt % aqueous solution of hydrogen peroxide (144 kg, 4.6 equiv) followed by water (14 kg). The mixture was heated to 25 °C, and a nitrogen sweep was established to control oxygen off-gassing during the LiOH solution charge. A solution of LiOH anhydrous (12.4 kg, 1.6 equiv) in water (144 kg) was charged over 6 h in two portions of 3 h each while maintaining the temperature at 25 °C and the oxygen content at <2.5% in the reactor headspace. After the first portion of the LiOH solution, THF was charged (128 kg). After the second LiOH solution portion, the reactor was charged with water (14 kg) and THF (128 kg). The reaction was held for 3 h.

The mixture was cooled to 10 °C, and a 30 wt % aqueous solution of sodium bisulfite (601 kg) was charged slowly while maintaining the temperature at <35 °C. After mixing for 30 min, the phases were allowed to separate, and the bottom aqueous layer was discarded. The mixture was charged with *N*,*N*-dimethylacetamide (DMAc) (541 kg). The mixture was stirred for 1 h at 25 °C and then polish-filtered into a separate distillation vessel. After rinsing through the polish filter with THF (128 kg) and transferring into the distillation vessel, the batch was vacuum-distilled at 130 mbar until a temperature of 70 °C was obtained. The reactor was charged with DMAc (68 kg) at 70 °C, and then water (389 kg) was added over 30 min. The batch was held at 70 °C for 1.5 h, and then additional water (158 kg) was added over 2 h. The batch was held at 70 °C for 1.5 h. The mixture was cooled to 20 °C over 6 h and held for at least 8 h. The slurry was filtered and washed with a premixed solution of DMAc (203 kg) and water (216 kg). The solids were further washed with a premixed solution of acetonitrile (171 kg) and water (648 kg). The solids were dried at 50 °C under vacuum to afford 86.5 kg of **2** in an 89% yield, 99.7 HPLC area percent as a white solid. $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 12.09 (s, 1H), 8.80 (d, $J$ = 4.5 Hz, 1H), 8.06 (dd, $J$ = 9.2, 5.8 Hz, 1H), 7.91 (dd, $J$ = 10.9, 2.8 Hz, 1H), 7.61 (ddd, $J$ = 9.1, 8.2, 2.8 Hz, 1H), 7.45 (d, $J$ = 4.5 Hz, 1H), 3.41−3.27 (m, 1H), 2.72−2.63 (m, 1H), 1.86−1.61 (m, 9H), 1.08 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 177.7, 159.9, 152.2, 149.8, 145.1, 132.6, 127.2, 118.9, 118.7, 107.1, 39.1, 37.2, 35.7, 28.7, 27.8, 27.2, 26.2, 15.6; HRMS (ESI) calcd for $C_{18}H_{21}FNO_2$ $[M + H]^+$: 302.1551, found 302.1563.

**Preparation of (*R*)-*N*-(4-Chlorophenyl)-2-((1s,4s)-4-(6-fluoroquinolin-4-yl)cyclohexyl)propanamide Methanesulfonate (1 MSA Salt).** A reactor was charged with *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate (TCFH) (95 kg, 1.25 equiv) and acetonitrile (237 kg). *N*-Methylimidazole (69 kg, 3.10 equiv) was added followed by acetonitrile (32 kg). (*R*)-2-((1s,4s)-4-(6-Fluoroquinolin-4-yl)cyclohexyl)propanoic acid **2** (82.0 kg, 1.0 equiv) was added followed by acetonitrile (63 kg). The mixture was held for 0.5 h, and then a solution of 4-chloroaniline (40 kg, 1.15 equiv) dissolved in acetonitrile (96 kg) was charged followed by acetonitrile (63 kg). The mixture was maintained at 20 °C for 3 h, and then acetonitrile (128 kg) was added. The solution was then heated to 60 °C, and water (303 kg) was charged. The solution was cooled to 40 °C, seeds (0.8 kg) were charged, and the resulting slurry was maintained for 1 h. The slurry was cooled to 20 °C over 3 h. Water (820 kg) was charged over 1.5 h, and the slurry was aged for 1 h. The slurry was filtered, and the cake was washed three times (3 × 455 kg) with a premixed solution of water (325 kg) and acetonitrile (130 kg). The cake was dried at 50 °C, and the dried cake was dissolved with ethyl acetate (1055 kg). The organic stream was charged with seeds (1.7 kg). A solution of methanesulfonic acid (28 kg) in ethyl acetate (453 kg) was charged over 2 h, and the slurry was aged for 1 h. The slurry was then filtered and washed with ethyl acetate (3 × 320 kg). The cake was dried under vacuum at 50 °C to yield 124.8 kg of **1** MSA salt in a 90% yield, 99.94 HPLC area percent as a white solid.

$^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 10.19 (s, 1H), 9.24 (d, $J$ = 5.7 Hz, 1H), 8.40 (dd, $J$ = 10.3, 2.6 Hz, 1H), 8.33 (dd, $J$ =



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9.4, 5.3 Hz, 1H), 8.09 (d, $J$ = 5.7 Hz, 1H), 8.04 (t, $J$ = 8.6 Hz, 1H), 7.71−7.64 (m, 2H), 7.37−7.30 (m, 2H), 3.64 (ddt, $J$ = 10.8, 7.3, 3.8 Hz, 1H), 2.98−2.89 (m, 1H), 2.43 (s, 3H), 2.05−1.60 (m, 9H), 1.14 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$) $\delta$ 175.0, 162.7, 161.1, 145.4, 138.2, 136.8, 128.6, 128.1, 126.7, 126.4, 123.3, 120.8, 119.8, 109.0, 39.8, 39.7, 38.6, 35.5, 28.3, 27.6, 27.2, 26.1, 16.2 HRMS (ESI) calcd for $C_{24}H_{25}ClFN_2O$ $[M + H]^+$: 410.1634; found, 410.1625.

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### Notes

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