Organic Process Research & Development

Article

pubs.acs.org/OPRD

Process Development and Scale-Up of a Benzoxazepine-Containing Kinase Inhibitor

Sriram Naganathan,*[,†,§] Denise L. Andersen,[†,∥] Neil G. Andersen,[†,⊥] Stephen Lau,[†,#] Anders Lohse,[‡] and Mads Detlef Sørensen[‡]

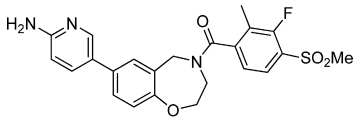
[†]Exelixis, Inc., 210 East Grand Avenue, South San Francisco, California 94080, United States

[‡]Niels Clauson-Kaas A/S, Rugmarken 28, Farum DK-3520, Denmark

ABSTRACT: The benzoxazepine core is present in several kinase inhibitors, including the mTOR inhibitor **1**. The process development for a scalable synthesis of 7-bromobenzoxazepine and the telescoped synthesis of **1** are reported. Compound **1** consists of three chemically rich, distinct fragments: the tetrahydrobenzo[*f*][1,4]oxazepine core, the aminopyridyl fragment, and the substituted (methylsulfonyl)benzoyl fragment. Routes were developed for the preparation of 3-fluoro-2-methyl-4-(methylsulfonyl)benzoic acid (**17**) and *tert*-butyl 7-bromo-2,3-dihydrobenzo[*f*][1,4]oxazepine-4(5*H*)-carboxylate (**2**). The processes for the two compounds were scaled up, and over 15 kg of each starting material was prepared in overall yields of 42% and 58%, respectively. A telescoped sequence beginning with compound **2** afforded 7.5 kg of the elaborated intermediate 5-(2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-2-amine dihydrochloride (**6**) in 63% yield. Subsequent coupling with benzoic acid **17** gave 7.6 kg of the target compound **1** in 84% yield. The preferred hydrochloride salt was eventually prepared. The overall yield for the synthesis of inhibitor **1** was 21% over eight isolated synthetic steps, and the final salt was obtained with 99.7% HPLC purity.

1. INTRODUCTION

Tyrosine kinases are important enzymes for signal transduction in cells. Therefore, they are often targets for the treatment of diseases that are caused by dysregulation of cellular processes, such as cancers. Mammalian target of rapamycin (mTOR) is a kinase in the phosphatidylinositol-3-kinase (PI3K) family of enzymes and is implicated in the regulation of cell growth and proliferation. Various inhibitors of mTOR have been explored as possible agents for treatment of various cancers,[1] including the benzoxazepine-containing candidate **1**.[2]



1

1.1. Discovery Synthesis of 1. The final product **1** consists of three distinct fragments, which are assembled in four steps (Scheme 1). First, bromobenzoxazepine **2** is converted to the corresponding boronic acid **3**. Palladium-mediated coupling with 5-bromo-2-aminopyridine (**4**) followed by the removal of the Boc group in aminopyridine **5** yields the penultimate diamine **6**. Final coupling with acid chloride **7** yields the active pharmaceutical ingredient (API) **1**.

While aminopyridine **4** is readily available from several commercial sources in large quantities, the other two starting materials, benzoxazepine **2** and acid chloride **7**, had to be synthesized. We report the process development and scale-up of each of these intermediates, ultimately leading to preparation of over 7 kg of drug substance **1** to enable clinical studies.

1.2. Discovery Synthesis of Bromobenzoxazepine 2. The initial synthesis of **2** was conducted beginning with 4-chromanone (**8**), as shown in Scheme 2,[3] and relied on a Schmidt rearrangement[4] to establish the benzoxazepine skeleton. Treatment of the chromanone raw material **8** with sodium azide afforded lactam **9**. Regioselective bromination could be achieved under standard conditions to yield lactam **10**. Reduction of the lactam to the amine was accomplished using complexed lithium aluminum hydride,[5] yielding benzoxazepine **11**. However, varying levels of debromination were observed during the reduction,[6] and the amount of debrominated product (**12**, Figure 1) was proportional to the reaction scale: on a 500 g scale, up to 40% yield of the byproduct **12** was obtained.

The step order was shown to be critical. When the bromination step followed the lactam reduction, the regioselectivity was severely compromised: the Schmidt rearrangement on the brominated chromanone gave the lactam in which the aryl group had migrated, affording the regiosiomeric lactam. Protection of the amine as the *tert*-butyl carbamate was achieved in a straightforward manner under the usual conditions[7] using aqueous base and Boc-anhydride to form **2**. While the brominated and debrominated products could be separated by careful chromatography, such separation was cumbersome and was not viable for the larger scales required to advance the clinical programs—the material needs of the proposed studies translated to requirements of approximately 12 kg of benzoxazepine **2**.

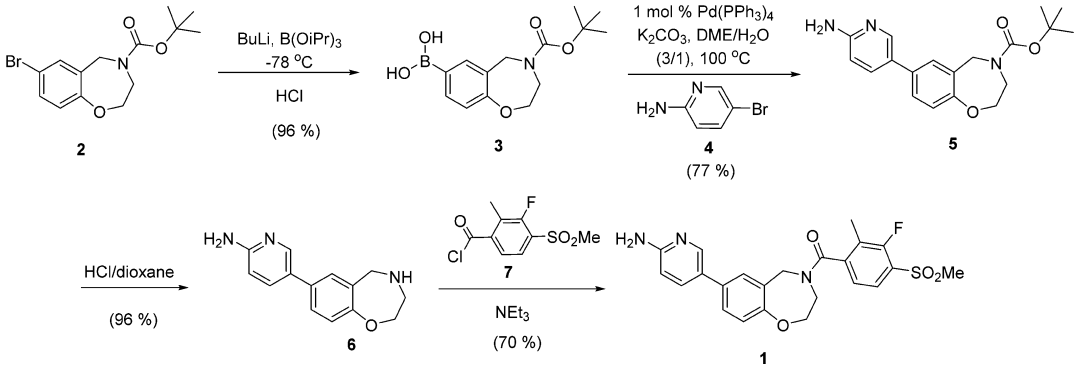
1.3. Discovery Synthesis of (Methylsulfonyl)benzoic Acid 17. The discovery synthesis of benzoic acid **17** was carried out in four steps from 2,3-difluorotoluene (**13**), which is

Special Issue: Sustainable Chemistry

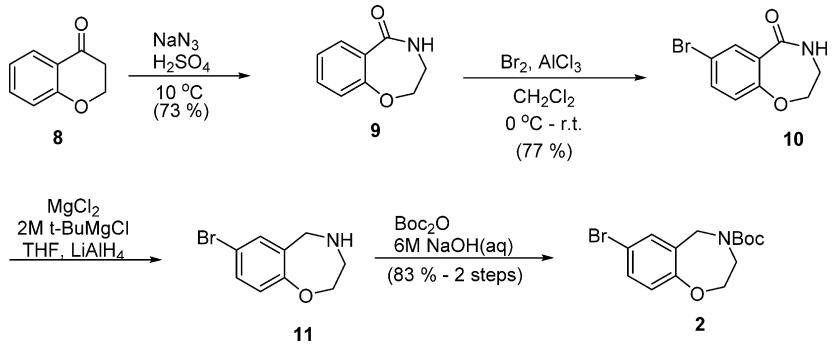
Received: February 3, 2015
Published: April 29, 2015

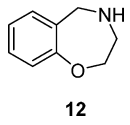
DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734

Scheme 1



Scheme 2





12

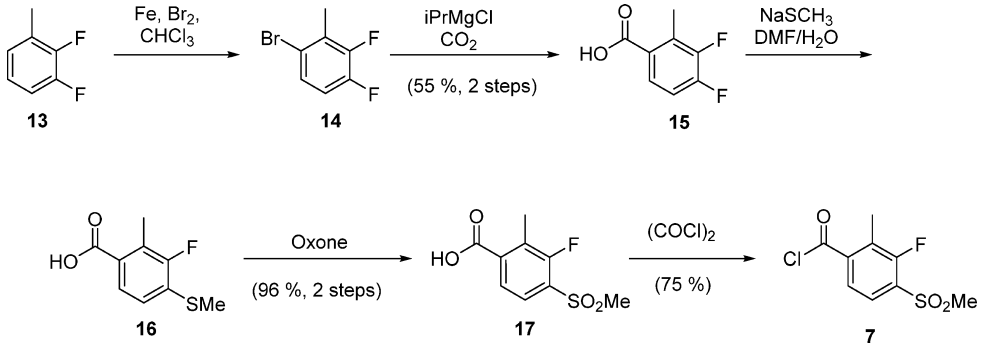
Figure 1. Structure of debrominated benzoxazepine.

readily available on a large scale (Scheme 3).[8] Bromination of **13** was conducted with elemental bromine mediated by iron powder to give 6-bromo-2,3-difluorotoluene (**14**). Metal–bromine exchange using isopropylmagnesium chloride[9] followed by trapping of the aryl Grignard reagent with dry ice gave benzoic acid **15**. Aromatic nucleophilic substitution with sodium methylthiolate furnished sulfide **16**, and a subsequent oxidation using Oxone[10] gave the desired sulfone **17**. While the overall route itself could be used for scale-up, there were several issues that precluded the direct scale-up of the initial synthesis.

The iron-powder-mediated bromination had an unpredictable induction period, which caused an exotherm that could not be readily controlled. Residual iron powder inside reaction vessels may lead to unforeseen complications in future reactions. Bromodifluorotoluene **14** was purified by vacuum distillation, which may limit the choice of contract manufacturers. Formation of the aryl Grignard reagent required low temperatures. However, there was another overriding factor that led us explore alternative reaction conditions: the excess alkyl Grignard reagent formed the corresponding alkyl carboxylic acid when treated with carbon dioxide (pentanoic acid if butylmagnesium chloride was used or isobutyric acid if isopropylmagnesium chloride was used). It was very difficult to remove these aliphatic carboxylic acids, and their effect on the downstream chemistry was unclear. Furthermore, it was difficult to monitor the reaction of the Grignard reagent with carbon dioxide.

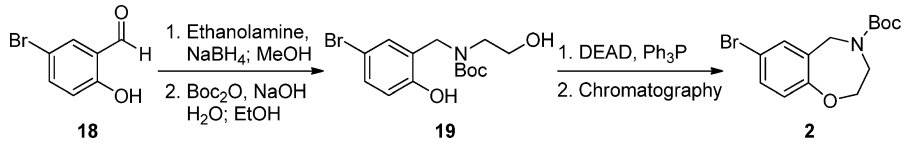
While the S_NAr reaction was high-yielding, repeated additions of aqueous sodium methylthiolate were necessary to obtain complete conversion to sulfide **16**. The oxidation using

Scheme 3

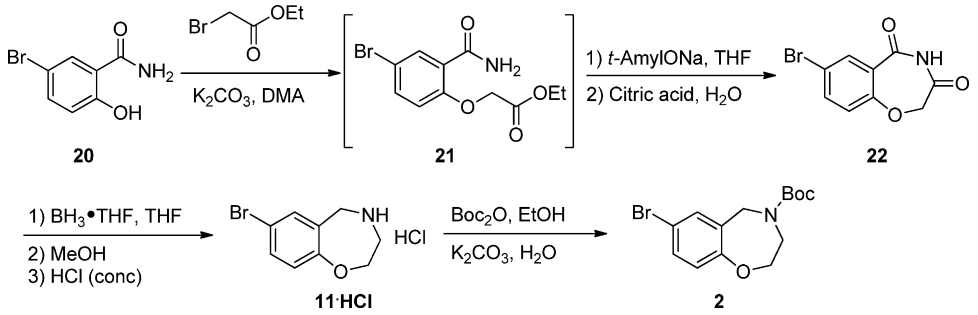


DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721–734

Scheme 4



Scheme 5



Oxone was not preferred because the reaction was extremely volume-intensive and therefore severely limited the throughput.

1.4. Alternative Synthesis of Bromobenzoxazepine 2. A second approach for the synthesis of intermediate **2** was explored in which the benzoxazepine ring was formed by a Mitsunobu reaction (Scheme 4).[11] This strategy did not involve a lactam and thus avoided strong reducing conditions and the associated dehalogenation. Reductive amination of 5-bromosalicylaldehyde (**18**) with ethanolamine in methanol using sodium borohydride gave the amine, which was treated with aqueous base and Boc-anhydride to form diol **19**. Subjecting diol **19** to Mitsunobu conditions gave benzoxazepine **2**. While this approach was used to provide material on an interim basis in approximately 200 g batches, it was not sustainable for the longer term because of cost, safety concerns, and complexity of product isolation.

2. IMIDE-BASED SYNTHESIS OF BROMOBENZOXAZEPINE 2

The problem of debromination during the reduction of a lactam could be mitigated by using borane as the reducing agent.[12] However, an alternative strategy for the construction of the oxazepine ring was also required since there were several safety considerations associated with the Schmidt rearrangement step. We chose to form the seven-membered ring by forming an imide[3] and then reducing it to the amine using borane, thereby avoiding both problems encountered in the earlier synthesis (Scheme 5). The starting material, 5-bromosalicylamide (**20**), is readily available commercially on a large scale. Treatment of **20** with ethyl bromoacetate in dimethylacetamide using potassium carbonate as the base yielded ether **21**. Intermediate **21** was not isolated but was converted directly to the imide using the commercially available sodium *tert*-amylate solution in THF. Upon completion of the cyclization, the reaction mixture was treated with aqueous citric acid, and the precipitated product, benzoxazepine **22**, was collected by filtration. Imide **22** was reduced using borane·THF. A large excess of borane was required to effect the complete reduction of the amine, which resulted in a highly stable amine–borane complex. The excess borane was first quenched using methanol, and the amine–borane complex was broken by refluxing with concentrated hydrochloric acid. On smaller scales the reaction sequence worked efficiently. However, we encountered several problems during scale-up. First, the filtration of imide **22** on a large scale was extremely slow and took several days, as opposed to the expected few hours. Second, the yield of intermediate **22** was very low (23% instead of the expected 70–80%). An investigation of the various reaction streams revealed that the major product was acid–amide **23** (Figure 2), presumably formed by hydrolysis of the imide.[13]

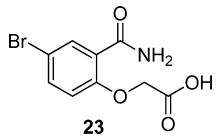


Figure 2. Structure of the hydrolysis byproduct during imide synthesis.

Since monitoring of the reaction progress revealed that the product was exclusively compound **22**, the most likely source of the hydrolysis was the quench. As the aqueous citric acid was added slowly to prevent excessive heat evolution during the quench, a sufficiently basic aqueous environment must have existed, leading to a substantial amount of hydrolysis[14] to form by product **23**.

2.1. Process Development of the Borane Reduction. A suspension of imide **22** in THF was treated with borane·THF complex for 24–36 h at 50 °C. Borane·THF was added slowly at the beginning to ensure that hydrogen evolved as a result of the reaction with the imide could be safely removed. Calorimetric evaluation showed that the heat evolution (Figure 3) and gas evolution (Figure 4) could be controlled by the rate of addition. The majority of the heat evolution was observed after the initial 10% of borane addition, while some heat evolution was observed until about one-third of the borane·THF had been added. Care was taken not to heat the reaction mixture in order to eliminate the risk of formation of diborane.[15]

When the imide had been completely consumed, methanol was added slowly over a period of 16–24 h to ensure that the liberated hydrogen was efficiently removed. Calorimetric evaluation (Figure 5) showed that the hydrogen evolution was mostly complete after the addition of the first 10% of the

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721–734

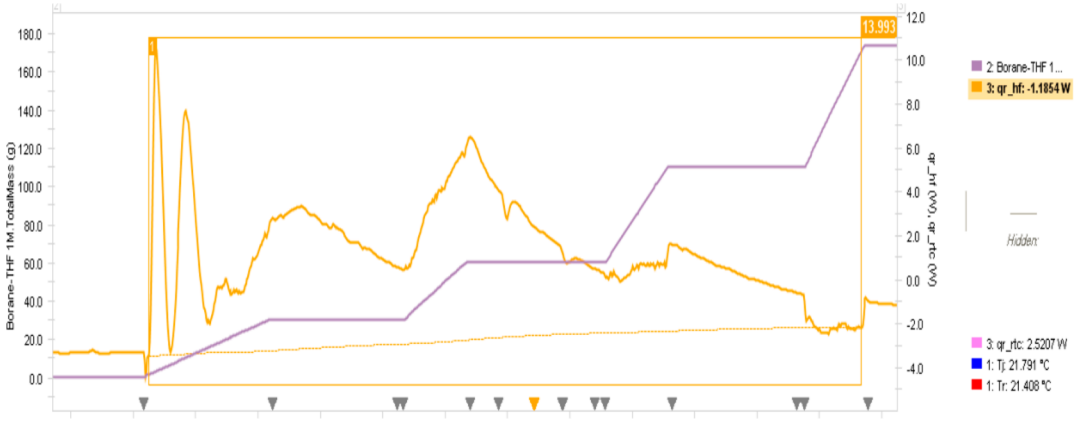


Figure 3. Heat evolution during addition of borane·THF to a THF suspension of imide **22**.

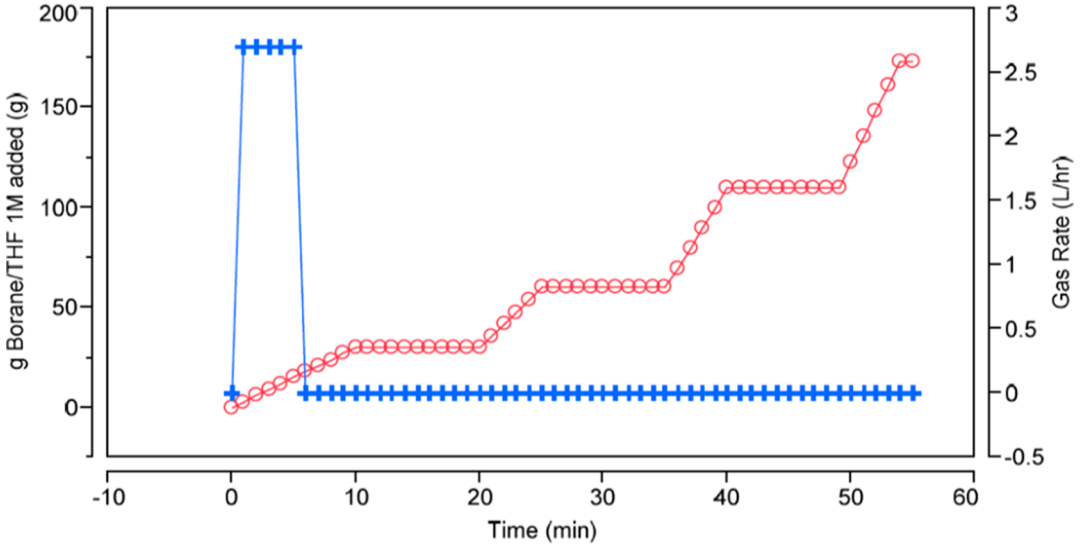


Figure 4. Hydrogen evolution during addition of borane·THF to a THF suspension of **22**.

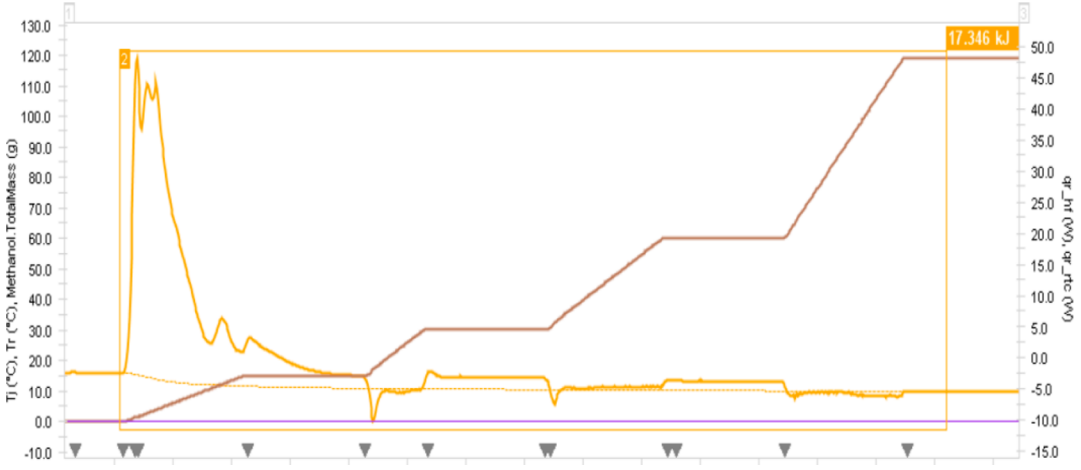


Figure 5. Heat evolution during addition of methanol to the borane reduction mixture.

charge of the methanol and was generally controlled by the rate of addition (Figure 6). Because of the limitation of the air-handling system's ability to safely sweep away the hydrogen gas liberated during the quench of the excess borane employed, the imide reduction was initially carried out in multiple batches of approximately 500 g each. The outputs from these batches were combined and carried forward. At the end of the quench, concentrated HCl was added, and the reaction mixture was heated at reflux to break down the amine−borane complex. The hydrochloride salt of the amine (**11**·**HCl**) was isolated by filtration.

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734

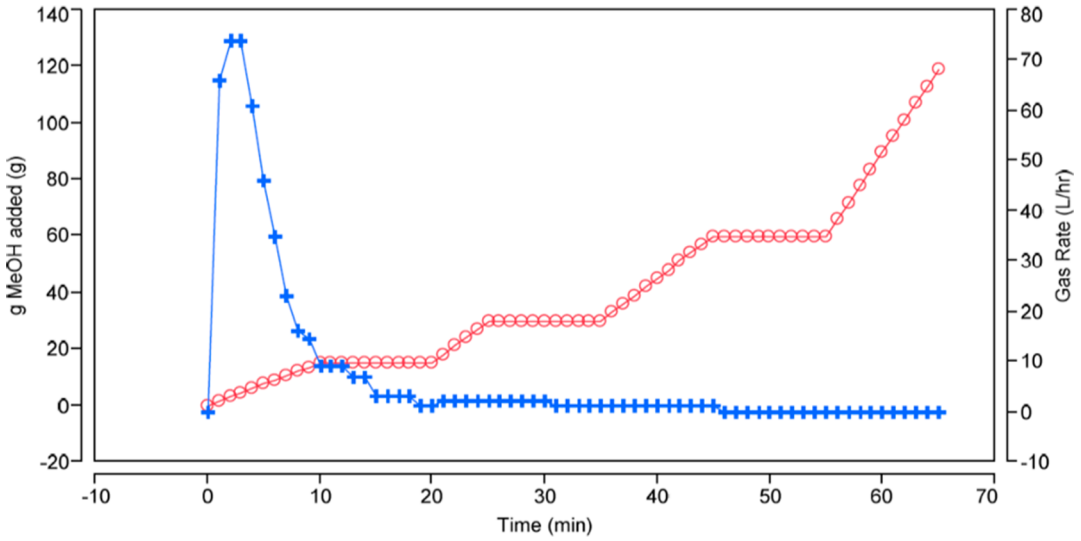
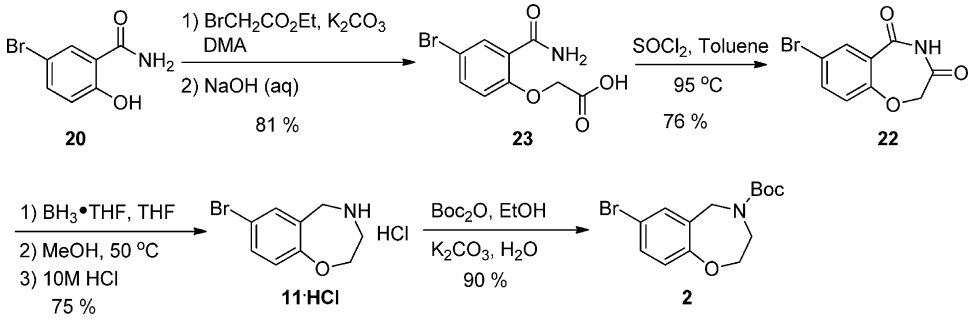
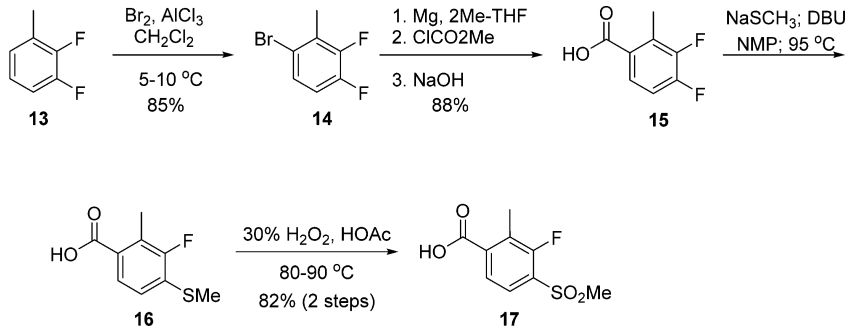


Figure 6. Hydrogen evolution during addition of methanol to the borane reduction mixture.

Scheme 6



Scheme 7



The Boc protection of the salt **11·HCl** was conducted in a straightforward manner using aqueous potassium carbonate and Boc-anhydride in ethanol. This procedure was utilized to prepare 2.9 kg of intermediate **2** in one batch and then to prepare the initial supplies for toxicological studies.

2.2. Scale-Up of the Imide Approach to Bromobenzoxazepine 2. A more robust and easily scaled synthetic approach was required for making larger quantities of compound **2** (Scheme 6). We investigated alternative ring-closure approaches in which imide **22** would not be exposed to aqueous base. We decided to take advantage of the facile alkaline hydrolysis to produce the acid and isolate it. Thus, the potassium carbonate-mediated coupling of salicylamide **20** and ethyl bromoacetate was followed by treatment with aqueous sodium hydroxide to complete the hydrolysis to give acid **23**.

The ring closure mediated by thionyl chloride[16] was modified such that the imide was prepared from salicylamide **20** in two steps. The isolated acid–amide **23** was treated with thionyl chloride in refluxing toluene to form imide **22** in good yield. The material could be isolated simply by cooling the reaction mixture and adding heptane. This two-step procedure was implemented on an approximately 4 kg scale, and a total of 20 kg of imide **22** was prepared.

The reduction was then scaled up at a contract manufacturing facility. Several changes were made to the small-scale procedure to render the process both safe and efficient, taking advantage of operational and engineering controls that are available at this facility. First, the borane treatment was conducted at a lower temperature (35 °C vs 50 °C), and longer reaction times were necessary. Second, a

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721–734

reverse quench was implemented as the produced hydrogen gas was swept directly to an incinerator using a nitrogen sweep. At the end of the quench, 31% aqueous hydrochloric acid was added (as opposed to concentrated hydrochloric acid, in order to avoid the fuming during handling) to break up the amine−borane complex at 50 °C. The precipitated hydrochloride salt was isolated by filtration, washed, and dried. The yield starting from 19.8 kg of imide was 75%.

Minor changes to the Boc-protection step were also made during scale-up. The reaction was seeded with the product prior to the addition of Boc-anhydride to facilitate the formation of larger particles, thereby easing filtration. The yield for this step was 90%, and 15 kg of intermediate **2** was prepared in this manner.

3. SCALED-UP SYNTHESIS OF BENZOIC ACID 17

Since the discovery route toward acid **17** was short and straightforward, the same synthetic approach was followed, but reagents and conditions more suited for large-scale preparation were employed (Scheme 7). Process development and scale-up were focused only on the preparation of acid **17** instead of acid chloride **7** because of poor regioselectivity for amidation and time constraints.

Bromination of arene **13** was conducted using elemental bromine but catalyzed by aluminum chloride.[17] While the bromination reaction could be conducted without solvent or using a variety of solvents, dichloromethane was employed as the solvent, and addition of bromine as a solution in dichloromethane at 5−10 °C was preferred, as it provided the cleanest product and most convenient means of isolation. When the bromination was conducted without solvent, a significant yield (nearly 10%) of a dibromo product was observed. When nonhalogenated solvents were utilized, layer cuts for aqueous washings during reaction workup were problematic, presumably because of the high density of bromoarene **14**. Also, the use of higher-boiling solvents interfered with the distillation of the product, bromoarene **14**. A small amount of a dibromo product was always formed but could be minimized by controlling the stoichiometry of bromine. Any remaining starting material **13** and dibromo products could be removed by distillation. The small amount of impurities present (up to 3%) did not affect the downstream chemistry.

A conventional Grignard reaction using elemental magnesium was chosen for the synthesis of acid **15**. The yield of the reaction with carbon dioxide was inconsistent, and it could not be determined when the addition was complete because there was no convenient way to monitor the progress of the reaction of the Grignard reagent with carbon dioxide. However, the product was easily purified using a pH swing, as the sodium salt of the acid was very water-soluble and the acid itself was very insoluble.

This property of the acid was exploited by first preparing the ester using methyl chloroformate as the electrophile and then saponifying the resulting ester and subsequently isolating the acid using acid−base extractions. While there was no substantial difference in the reactivity, 2-methyltetrahydrofuran (2-MeTHF) was preferred to THF itself, as the layer separations were considerably more facile and product losses were minimal. The Grignard reagent was added to a solution of methyl chloroformate at 0−8 °C. When the chloroformate was added to the Grignard reagent, significant quantities of the benzophenone and the biaryl were formed via addition of the Grignard reagent to the ester and oxidative coupling of the Grignard reagent, respectively. The ester hydrolysis was carried out with aqueous sodium hydroxide and methanol at 65 °C. When the ester hydrolysis was complete, the aqueous layer was acidified. The product was extracted into the organic layer, and inorganic salts were removed. The product was then extracted into the aqueous layer using dilute sodium hydroxide, and the aqueous layer was washed with heptane and acidified to precipitate the product. Several noteworthy aspects were observed in the acid−base extractions. When the initial reaction mixture was treated with dilute acid followed by ester hydrolysis and acidification (in order to save one operation), the product quality and yield were significantly lower. The final heptane wash of the basic aqueous layer was necessary to ensure that the acid **15** that precipitated upon acidification was not sticky, in order to facilitate filtration. The Grignard reaction was scaled up successfully multiple times, starting with 5−8 kg of bromide **14** per batch, to produce nearly 20 kg of the acid intermediate **15** in 75−89% yield.

Numerous inorganic and organic bases were screened in a variety of solvents for the S_NAr reaction of acid **15** with sodium methylthioate to give thioether **16**. The best conditions involved the use of 2.1 equiv of solid sodium methylthioate[18] and 2 equiv of DBU in *N*-methyl-2-pyrrolidone (NMP) at 95 °C. The product was isolated by initial dilution with water, cooling of the reaction mixture, and acidification. The choice of acid utilized turned out to be very important (vide infra). Since the oxidation reaction was run under aqueous conditions, it was not necessary to fully dry the filtered product, thioether **16**. An assay of the partially dried filter cake was obtained, and the stoichiometry of the reagents in the oxidation reaction was adjusted accordingly.

Oxidation of the sulfur in sulfide **16** to give sulfone **17** was accomplished using hydrogen peroxide in acetic acid, which was substantially more volume-efficient than the previous Oxone oxidation. The first oxidation to give the sulfoxide was found to be highly exothermic, while the second oxidation was observed to be endothermic and was aided by the exotherm of the first oxidation. External heat was necessary to complete the oxidation of the sulfoxide to the sulfone. In small-scale oxidations we observed significant heat evolution when hydrogen peroxide was added to a mixture of the starting material **16** and acetic acid with subsequent heating. If reactions under these conditions had been scaled up, there would have been a potential for an unsafe exothermic runaway. Calorimetric evaluation of the oxidation reaction revealed that when the mixture of sulfide **16** and acetic acid was first heated to 60−65 °C and then hydrogen peroxide was added slowly, the rate of the exotherm was proportional to the rate of addition of hydrogen peroxide and could be controlled by the rate of addition. The oxidation was scaled up using this procedure with 2.6 equiv of hydrogen peroxide. When HPLC analysis revealed that all of the starting material **16** and the intermediate sulfoxide were converted to sulfone **17**, the excess oxidant was quenched by the addition of DMSO. The precipitation of the product was completed by dilution with water, and sulfone **17** was isolated by filtration. The combined yield for the conversion of difluorobenzoic acid **15** to sulfone **17** was around 80%.

During process development and initial scale-up of the oxidation reaction, a new impurity was observed in the product, sulfone **17**, at a level of about 1% relative to the parent compound. This impurity was later-eluting in reversed-phase

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734

Scheme 8

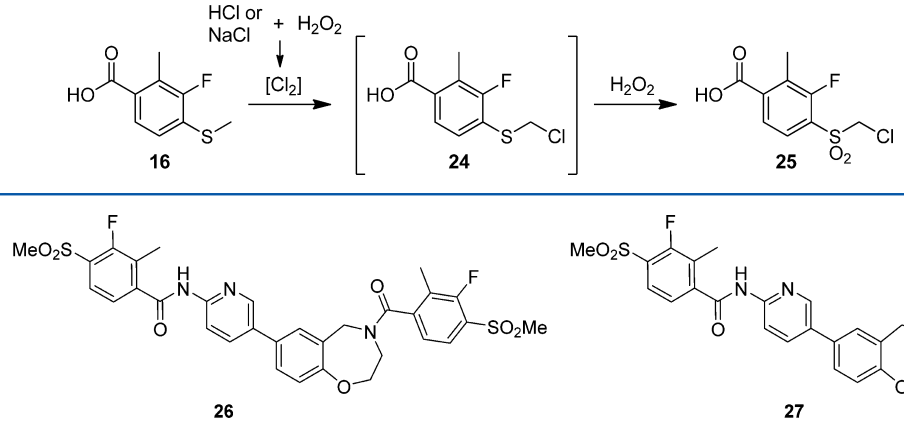
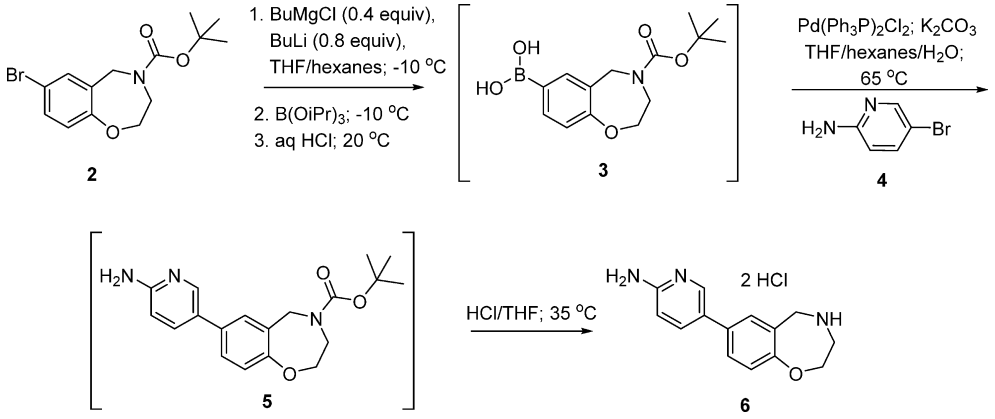


Figure 7. Major impurities formed during amidation.

Scheme 9



HPLC, and LC−MS analysis revealed the presence of one chlorine atom. Examination of its fragmentation pattern and comparison of this pattern to that obtained for sulfone **17** indicated the presence of a $-SO_2CH_2Cl$ fragment. The structure **25** was proposed for the impurity, and it could result according to the reaction pathway outlined in Scheme 8. Residual sodium chloride or hydrochloric acid from the use of hydrochloric acid to neutralize the aqueous base during the preparation of thioether **16** could be oxidized by hydrogen peroxide to afford elemental chlorine. Methyl sulfides readily undergo α-chlorination[19] under these conditions to form the corresponding chloromethyl sulfides (e.g., **24**), which can then be oxidized to the chloromethyl sulfones (e.g., **25**) by additional hydrogen peroxide. This hypothesis was confirmed by spiking experiments. A sample of sulfide **16**, which had been previously used to produce pure sulfone **17** without contamination by impurity **25**, was spiked with 0.1 equiv of hydrochloric acid. When this material was subjected to the typical oxidation conditions, compound **25** was the only major new product observed, at the expected level. Additional evidence for this hypothesis included the lack of a chlorine-containing impurity in the starting material, sulfide **16** (with a mass corresponding to that of compound **24**, a chloromethyl sulfide), and the absence of impurity **25** upon switching to concentrated sulfuric acid for the acidification following the S_NAr reaction. While other solutions were possible, such as additional aqueous washings to ensure removal of hydrochloric acid or sodium chloride and full drying of sulfide **16**, the switch to sulfuric acid was simpler because it preserved the option to move ahead with the wet cake.

4. TELESCOPED SYNTHESIS AND SCALE-UP OF API 1

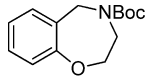
We chose to follow the same route employed during the discovery synthesis of compound **1**. However, several modifications were necessary to smoothly prepare large quantities of this material at a variety of contact manufacturers. The following were areas of emphasis we chose to explore: the cryogenic conditions required for the metal−halogen exchange to make the arylboronic acid (or arylboronate) limited the choice of manufacturers. The conditions for the Suzuki reaction were harsh and used an expensive catalyst. The choice of solvents for both the Suzuki reaction and the Boc deprotection were not preferable for large-scale production. Finally, using the acid chloride for coupling gave two major impurities, **26** and **27** (Figure 7), which were formed as a consequence of a lack of regioselectivity.

The synthesis would also be more efficient and productive if some steps of the sequence could be telescoped, minimizing losses due to isolation. The ideal opportunity for telescoping would be the initial three transformations. The Boc-deprotected diamine **6** would become the first isolated intermediate and provide a point of control before the final coupling. When we initiated the process development, it was not clear whether the free base or a salt would be selected for clinical development. Thus, we chose to design the process so

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734

that either could be the final isolated product. The telescoped sequence leading to diamine **6** is shown in Scheme 9.

Magnesiation using alkyl Grignard reagents in combination with alkyllithiums is a convenient and efficient alternative to the use of alkyllithiums alone to effect metal−halogen exchange of aryl bromides.[20] These metal−halogen exchange reactions can be conducted at significantly higher temperatures, typically −10 to +5 °C, as opposed to −50 °C and below for alkyllithiums alone. The resulting triaryl magnesiate adds readily to a trialkyl borate[21] to produce the required arylboronate, which can then be hydrolyzed to give the arylboronic acid. Metal−halogen exchange was effected by first adding *n*-butylmagnesium chloride to a solution of bromide **2** in THF at 0 °C, which was a stable mixture, followed by the addition of butyllithium to the mixture. Neither the addition of *n*-butylmagnesium chloride nor the addition of butyllithium was particularly exothermic. However, using dry THF was very important, and a moisture specification of <0.1% was established to ensure that that metalation reaction was complete. The progress of metalation was monitored using HPLC by observing the consumption of benzoxazepine **2** and the appearance of debrominated compound **28** (Figure 8) upon aqueous quenching. When



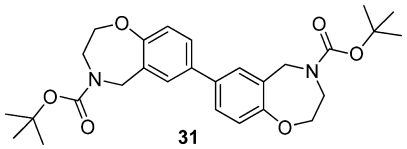
28

Figure 8. Debrominated product from aqueous quenching of the aryl magnesiate.

the metalation was determined to be complete, triisopropyl borate was added slowly while the temperature was maintained below −8 °C, and the mixture was stirred overnight at that temperature. If the reaction between the magnesiate and triisopropyl borate had not been allowed to proceed to completion, significant amounts of debrominated compound **28** would have resulted, thus diminishing the yield. Maintaining a low temperature maximizes the formation of the desired boronic ester intermediate **29**.

The hydrolysis of boronic ester **29** to the corresponding boronic acid **3** was accomplished using dilute hydrochloric acid (Scheme 10). While it was possible to conduct the Suzuki coupling with ester **29**, the coupling reaction was significantly faster with the boronic acid. The hydrolysis was rapid and clean, except for one major side product, which was tentatively identified as boroxine **30**.[22] The boronic acid and the boroxine remained in the organic layer while the salts were removed in the acidic aqueous layer. The **3**:**30** ratio was somewhat dependent on the temperature at which triisopropyl borate was added to the magnesiate. At higher temperatures, more boroxine **30** was produced: the range of the **3**:**30** ratio was from about 1.2:1 to 2:1. The combined yield of acid **3** and boroxine **30** was usually greater than 85 area % by HPLC. The Suzuki reaction was rapid with boronic acid **3** but much slower with boroxine **30**.

The organic layer was sparged with nitrogen to suppress the formation of biaryl **31** (Figure 9). Both the solution of boronic



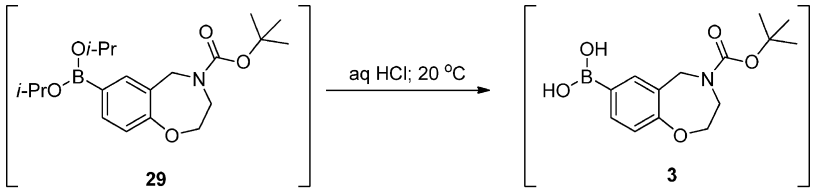
31

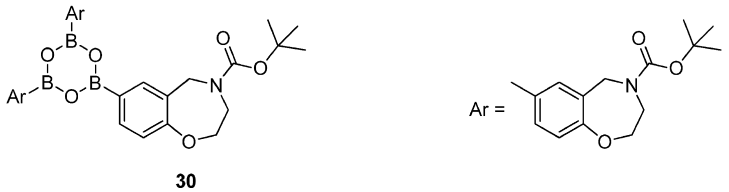
Figure 9. Structure of the biaryl byproduct formed during the Suzuki reaction.

acid **3** and the aqueous potassium carbonate solution were sparged with nitrogen, and all of the solids were added under a nitrogen atmosphere. Several catalyst−ligand combinations were investigated. High conversion to the product was observed under most conditions, and thus, the less-expensive, easily handled catalyst bis(triphenylphosphine)palladium dichloride was chosen. There was no observable difference when the catalyst was preformed or prepared in situ by adding triphenylphosphine and palladium dichloride to the reaction mixture. Upon completion of the coupling reaction, the basic aqueous layer was discarded, and the product was extracted into dilute aqueous hydrochloric acid.

The workup for the crude purification of the solution of intermediate **5** had to be carefully choreographed. While the rejection of major impurities was the primary objective, setting up the solution for removal of the Boc group was also equally important. We discovered that higher water content in the solution of compound **5** was detrimental (it slowed the deprotection considerably) and that reaction proceeded best in THF. Furthermore, not all of the impurities that were present at the end of the coupling reaction were apparent under standard analytical HPLC conditions.

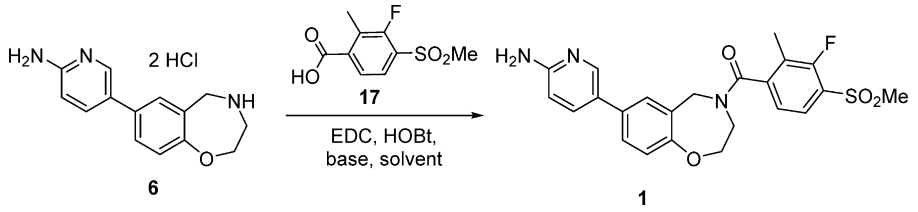
Scheme 10





DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734

Scheme 11



The solution of compound **5** in aqueous acid was treated with methyl *tert*-butyl ether (MTBE), causing unknown impurities to precipitate. Filtration through a pad of Celite removed this solid and helped simplify the following layer cuts. The organic layer was discarded, and isopropyl acetate was added to the aqueous layer. Basicification to pH >9 using 25% aqueous ammonium hydroxide allowed aminopyridine **5** to be extracted into the organic layer. Palladium scavenging was implemented at this point to ensure that the Pd content was at or below levels determined to be acceptable according to regulatory guidances.[23] A silica-based scavenger, SPM-32 from PhosphonicS, was chosen for this purpose.[24] During the scavenger treatment, another unknown impurity precipitated out, but it was removed during the filtration of the scavenger. We found that adding Celite to the reaction mixture, in addition to the pad used for filtration, was very helpful in decreasing the duration of the filtration. Following filtration, the filter pad was washed with additional isopropyl acetate, and the solvent was switched to THF by distillation of the isopropyl acetate under vacuum and addition of THF. The distillation was repeated, and THF was added to obtain an ∼10% (w/w) solution of aminopyridine **5** in THF.

It was possible to conduct the extraction and Pd-scavenging operation in THF by adding THF instead of isopropyl acetate prior to basicification. However, there were several reasons for adopting the two-solvent approach. First, the impurity that was removed during the Pd-scavenging step was carried through to the next step when THF was used. Second, the water content in the THF solution of aminopyridine **5** was very high, and repeated washing with brine was required in order to reduce the moisture to an acceptable level to allow for smooth deprotection. Unfortunately, the Boc deprotection reaction did not proceed well in isopropyl acetate.

The Boc deprotection of aminopyridine intermediate **5** in THF solution was accomplished by initial heating to ∼35 °C followed by treatment with concentrated hydrochloric acid. While the deprotection was ∼99% complete in the first 8 h, heating was usually continued overnight to ensure complete deprotection. At the end of the reaction, the mixture was cooled to room temperature, and the precipitated product was filtered, washed, and dried. The dihydrochloride salt was extremely well behaved, nonhygroscopic, and easily filtered and handled. Typical yields for the preparation of compound **6** using the telescoped sequence ranged from 55 to 64%. On the largest scale, the yield of dihydrochloride **6** was 63% starting with 12.3 kg of bromobenzoxazepine **2**.

Initial abbreviated polymorph screening of drug substance **1** revealed that there was only one major physical form, which could be consistently prepared from a variety of solvents. A series of coupling conditions, reagents, and solvents were investigated (Scheme 11), and the *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC)/1-hydroxybenzotriazole (HOBt) coupling system was chosen because these reagents are inexpensive and easily handled. Unfortunately, none of the class-3 solvents[25] were suitable for the coupling reaction: while very high conversion could be achieved for the coupling reaction itself in most of the solvent systems tested, the properties of the product were such that there were insurmountable problems encountered during workup and isolation.

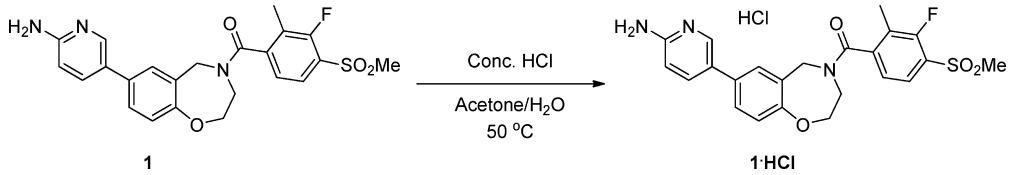
For initial toxicological studies, acetonitrile/water was chosen as the solvent system with *N*-methylmorpholine (NMM) as the base. Under these conditions, the regioselectivity of the coupling was very high and the levels of diacylated byproduct **26** were very low. A slight molar excess of the acid (1.2 equiv) was activated with EDC in a separate reactor and then added to a solution of amine **6** in acetonitrile/water that had been neutralized with NMM. The coupling reaction was complete, according to HPLC analysis, in ca. 90 min at room temperature. The reaction mixture was washed three times with 6 M potassium carbonate. Distillative crystallization was employed to aid in product isolation: acetonitrile was distilled at atmospheric pressure and continually replaced with MTBE until the HPLC analysis revealed that the concentration of product **1** in the supernatant solution was <5 mg/mL. Achieving this concentration ensured that the product crystallized in high yield and with high purity. At this stage, additional MTBE was added to complete the crystallization, and the mixture was cooled to room temperature. The product was filtered, washed with MTBE, and then dried under vacuum. The yield using 0.5−1 kg of **6** was 60−65%, with the predominant loss of product occurring during the aqueous carbonate washings. The losses were also more pronounced on larger scales. The purity by LC area percentage (LCAP) was between 98.6 and 99.5%.

While this process was adequate for preparation of initial supplies for toxicological studies, there were several issues that had to be addressed before embarking on production of drug substance **1** under cGMP for clinical studies. The loss to washings had to be minimized, and it was also necessary to identify a convenient point to institute a polish filtration.

The choice of solvent for the coupling reaction was revisited for the scale-up, and attention was directed toward a combination of DMF and dichloromethane, which had also shown considerable potential. The main advantage of this solvent system was that the product was very soluble, allowing for smooth aqueous workup, although slightly higher levels of impurity **26** were formed. The amount of compound **26** could easily be controlled by manipulating the stoichiometry of diamine **6** and acid **17** as well as that of EDC and HOBt. An excess of diamine **6** was ultimately employed because it limited the formation of diamide **26** and its availability was no longer limited. The base was switched to 3 M aqueous sodium hydroxide, which also helped remove the excess benzoic acid **17**. A polish filtration could be also readily incorporated during

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734

Scheme 12



a recrystallization, which provided an upgrade in the overall purity with minimal product loss.

Thus, the final process involved the activation of acid **17** in 3:1 dichloromethane/DMF using EDC and HOBt. In a separate vessel, dihydrochloride **6** was suspended in the same solvent system, neutralized with 2 equiv of 3 M aqueous NaOH, and treated with the activated acid at 15 °C. After overnight reaction, the organic layer was washed twice with aqueous monobasic potassium phosphate solution. A small quantity of DMF was added to ensure that the product stayed in solution, and the organic layer was washed once with 1 M aqueous NaOH. The product was precipitated from aqueous DMF using distillative crystallization by distilling out dichloromethane and replacing it with water. The product was then isolated by filtration, washed with water, and partially dried. The wet cake was dissolved in refluxing THF/water and polish-filtered while hot. The solution was concentrated to about half its volume by vacuum distillation and cooled to 10 °C. Seeds were then added, and the product was crystallized by addition of MTBE and isolated by filtration. The yield using 6.6 kg of diamine **6** was 84%, producing 7.6 kg of compound **1** with 98.8% LCAP purity. The purity profile of the material produced on the larger scale under cGMP was comparable to those of batches produced on the 0.5−1 kg scale, and no new impurities were observed.

The HCl salt of compound **1** was selected for clinical studies involving oral administration. Abbreviated salt and form screening showed that a stable and consistent form of **1·HCl** was obtained from acetone and acetone/water. When a suspension of the free base in acetone and concentrated HCl were combined, the monohydrochloride salt was formed in good yield (Scheme 12). However, there was an intermediate stage where the mixture turned sticky and stirring was severely compromised.

While screening the conditions to optimize the salt formation, we also investigated the possibility of directly converting the wet cake of the free base into the desired salt. Systematic screening of the amount of water present in the reaction from 0 to 1.5 equiv (w/w) revealed that 0.5 equiv (w/w) of water was optimal in the salt formation. The physical properties of the salt formation at lower water contents were undesirable, while at higher water contents there were considerably higher losses of product to the filtrate. When 1.5 equiv (w/w) of water was used, the isolated yield was only 71%, compared with 92−95% using 0.5 equiv (w/w) or less. When concentrated HCl was added to a heated suspension of free base **1** in acetone/water, a brief solution resulted, followed by product crystallization. Unfortunately, the duration of the solution was variable and too short to enable a polish filtration at this stage. Therefore, it was decided to utilize filtered acetone, water, and concentrated HCl for the salt formation and to conduct the polish filtration during the isolation of the free base. The crystallization was completed at 20 °C, and the product was isolated by filtration, washed with acetone, and dried under vacuum at 50 °C. Finally, 7.8 kg (95% yield) of **1·HCl** was produced with 99.7% LCAP purity. The final levels of residual DMF and DCM were below 100 ppm, which are well below the specified limits of 880 and 600 ppm, respectively. The final level of residual Pd was below 0.2 ppm, which is also well below the specified limit of 20 ppm.

5. CONCLUSIONS

We have developed a scalable and efficient process for the synthesis of 7-bromobenzoxazepine, an important scaffold present in several kinase inhibitors. By means of this process, over 15 kg of this intermediate was prepared. Concurrently, a process for the large-scale preparation of a highly substituted benzoic acid has also been developed. Finally, we have also demonstrated a telescoped multikilogram-scale synthesis of a clinical candidate that incorporates this benzoxazepine core. Several batches of the drug substance **1** have been prepared to support the development programs.

6. EXPERIMENTAL SECTION

General Information. All of the reagents and solvents employed in the synthesis were purchased commercially and used without further purification. Reactions requiring an inert atmosphere were conducted under dry nitrogen. NMR spectra were recorded on a Varian Mercury Plus 400 MHz instrument. Peaks are reported as observed, without accounting for splitting due to carbon−fluorine coupling. For ^{1}H NMR spectra, chemical shifts are reported in parts per million (ppm) relative to an internal standard of tetramethylsilane; for ^{13}C NMR spectra, chemical shifts are referenced to the corresponding deuterated solvent peak. Positive ion FAB high-resolution mass spectrometry was conducted by Analytical Instrument Group, Inc. (Raleigh, NC). HPLC analyses were conducted on an Agilent 1200 series or Waters Empower System instrument equipped with photodiode array detectors using Waters SunFire 3.5 μm C18 columns (4.6 mm × 100 mm) and mobile-phase gradients consisting of 0.05% phosphoric acid in water and 0.05% phosphoric acid in acetonitrile.

The procedures outlined in this section are those employed for the reactions run at the largest scale. Analytical characterizations were obtained on materials that were representative or purified for that purpose.

2-(4-Bromo-2-carbamoylphenoxy)acetic Acid (23). A 100 L jacketed reactor was charged with 5-bromosalicylamide (4 kg, 18.5 mol) in dimethylacetamide (DMA) (18.5 L) followed by potassium carbonate (20.3 mol) and ethyl bromoacetate (3.24 kg, 19.4 mol). The mixture was heated to 50 °C, and when HPLC revealed that <5% of the bromosalicylamide remained (ca. 3 h), the reaction mixture was cooled to room temperature. Then 7.5 L of 20% aqueous NaOH was added, and the mixture was heated at 50 °C until no more ester remained (ca. 2 h). The reaction mixture was cooled to room temperature, and the pH was adjusted to <2 using 6 M aqueous HCl. The precipitated product was

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734

collected by filtration, washed with water, and dried in a vacuum oven to yield 4.1 kg of compound **23** as a white solid (81%).

7-Bromobenzo[*f*][1,4]oxazepine-3,5(2*H*,4*H*)-dione (22). A suspension of **23** (4.1 kg, 15 mol) in toluene (25 L) was heated to 90 ± 5 °C, and thionyl chloride (7.12 kg, 52 mol) was added over ca. 15 min. The reaction mixture was heated at that temperature until no more starting material remained as determined by HPLC analysis (ca. 4 h). The reaction mixture was cooled to 10 °C, and heptane (8.2 L) was added to precipitate the product. The slurry was aged at that temperature for 1 h, and the product was collected by filtration, washed with heptane (8.2 L), and dried in a vacuum oven to yield 2.9 kg of **22** as a white solid (76%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.54 (s, 1H), 8.07 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 8, 2.4 Hz, 1H), 7.17 (d, J = 8 Hz, 1H), 4.81 (s, 2H).

7-Bromo-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine Hydrochloride (11·HCl). A 1000 L Hastelloy C vessel connected to an incinerator for H_2-containing off-gas was charged with **22** (19.8 kg, 77.33 mol). After a nitrogen purge, THF (86.4 kg) was added, followed by borane·THF complex (BH_3·THF) (288.4 kg, 328 mol) over ca. 1.5 h from a cylinder maintaining an inner temperature of 30−32 °C (***Caution! Evolution of hydrogen gas and exotherm***). The reaction mixture was stirred for 4 h at 35 °C, after which an additional portion of BH_3·THF (144.2 kg, 164 mol) was added (***Caution! Evolution of hydrogen gas and exotherm***) and the mixture was stirred for 120 h.

A 2500 L glass-lined quench vessel was charged with MeOH (123.6 kg), and at 45 °C the reaction mixture from above was added at a rate of 200 kg/h (***Caution! Evolution of hydrogen gas and exotherm***). The quench vessel was purged for 1 h with nitrogen to flush liberated hydrogen to the incinerator. Aqueous 31% HCl (14.2 kg) was added in portions over 20 min, and the reaction mixture was stirred for 3 h under nitrogen at 50 °C, cooled to 20 °C over 3 h, and stirred for 8 h. The precipitated product was filtered, washed with EtOH (33 kg), and blow-dried overnight to yield 16.5 kg of **11·HCl** (75% yield, 81% potency).

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.77 (br s, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.52 (dd, J = 8, 2.4 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 4.30 (s, 2H), 4.21 (m, 2H), 3.45 (m, 2H).

***tert*-Butyl 7-Bromo-2,3-dihydrobenzo[*f*][1,4]-oxazepine-4(5*H*)-carboxylate (2).** In a glass-lined 400 L reactor, **11·HCl** (16.5 kg, 62.4 mol) was dissolved in EtOH (24.5 kg) at 20 °C. Aqueous K_2CO_3 (16 wt %; 61.8 kg, 71.5 mol) was added, and the mixture was seeded with 25 g seed crystals of **2**. Solid di-*tert*-butyl dicarbonate (14.9 kg, 68.3 mol) was added in portions, maintaining a reaction temperature of <30 °C. The mixture was stirred overnight and filtered. The product on the filter was washed with 29 kg of a 3:1 mixture of water and EtOH followed by 30 kg of water and then dried under a stream of nitrogen to afford compound **2** as a white solid (15.0 kg, 90%).

6-Bromo-2,3-difluorotoluene (14). A 50 L jacketed reactor was charged with 2,3-difluorotoluene (**13**) (4.8 kg, 37.5 mol) and dichloromethane (15 L) and cooled to below 10 °C. Solid aluminum chloride (50 g, 0.375 mol) was added in one portion. A solution of bromine (6 kg, 37.5 mol) in dichloromethane (5 L) was added over a period of 3 h while the temperature was maintained below 10 °C. When HPLC analysis showed that <5% of **13** remained (1 h at 10 °C), water (15 L) was added slowly while the temperature was maintained below 25 °C. The organic layer was washed once with 1 M aqueous HCl (5 L) and 5% aqueous $NaHSO_3$ solution (5 L), dried over anhydrous $MgSO_4$, and concentrated by atmospheric-pressure distillation. When the internal temperature reached 50 °C, the product was purified by vacuum distillation in two portions from a 5 L round-bottom flask. The fraction boiling between 78 and 83 °C at 20−30 Torr was collected, yielding two batches of bromide **14** as a colorless liquid (3.13 and 3.46 kg; combined yield 6.59 kg, 85%).

HPLC: 96.7% and 97.2% LCAP, respectively; 2.7% and 2.5% "regioisomer"; 0.5% and 0.3% dibromo product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 1H), 6.91 (dq, 1H), 2.35 (d, 3H).

3,4-Difluoro-2-methylbenzoic Acid (15). A 50 L jacketed reactor was flushed with nitrogen and charged with magnesium turnings (852 g, 35 mol) followed by a few crystals of iodine (0.2 g) and 2-methyltetrahydrofuran (2-MeTHF) (20 L). The temperature of the reactor jacket was set at 45 °C. A solution of **14** (6.52 kg, 31.5 mol) in 2-MeTHF (7 L) was prepared, and approximately 0.5−1 L of the bromide solution was added when the internal temperature reached 35 °C. When the formation of the Grignard reagent had initiated (at around 40 °C internal temperature), the remainder of the solution of **14** was added at such a rate that the internal temperature was maintained between 75 and 80 °C (the jacket temperature was set at 45−50 °C); the addition took ca. 2 h. The brownish solution was heated at 75−80 °C for an additional 1 h. HPLC analysis revealed that <1% of the bromide remained. The Grignard solution was cooled to below 25 °C.

A 100 L jacketed reactor was flushed with nitrogen, charged with methyl chloroformate (4 kg, 42.3 mol) and 2-MeTHF (7 L), and cooled to below 5 °C. The Grignard reagent solution was added slowly over ca. 5 h while the internal temperature was maintained below 8 °C (the jacket temperature was set at −15 °C). At the end of the addition, the reaction mixture was warmed to 20 °C and stirred at that temperature for about 1 h. HPLC showed that <2% of **14** remained and mostly the ester was present. A cold solution of sodium hydroxide (8 L of 50% aqueous solution) in water (20 L) and methanol (3 L) was added over 30 min. The resulting suspension was heated at 60−65 °C for 8 h. The reaction mixture was analyzed by HPLC to ensure complete conversion of the ester to the carboxylic acid. The suspension was then cooled to below 25 °C, and concentrated HCl (13 L) was added over about 1 h while the temperature was maintained below 25 °C to obtain a pH of <2 in the aqueous layer.

The aqueous layer was removed, and water (20 L) was added to the organic layer, followed by 50% aqueous NaOH solution (2 L) to obtain a pH of >10 in the aqueous layer. When the target pH was achieved, heptane (10 L) was added, and the aqueous layer was washed twice more with heptane (10 L each). The aqueous layer was then cooled to below 20 °C, and concentrated HCl (3 L) was added to obtain a pH of <2. The precipitated product was collected by filtration, washed with water (2 × 10 L) and heptane (5 L), and dried under vacuum at 40 °C to obtain 4.82 kg of **15** as a colorless solid (88%).

HPLC assay: 98.1 wt %. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.3 (s, 1H), 7.71 (m, 1H), 7.35 (q, 1H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.7, 153.6, 153.5, 151.1, 150.9, 150.3, 150.1, 147.8, 147.7, 129.8, 129.7, 128.7, 128.6, 127.7, 127.6, 115.0, 114.9, 12.6, 12.5. IR: 1681, 1455, 1276, 1012, 771 cm^{-1}. MS (EI) for $C_8H_6F_2O_2$: found 171 ([M −

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734

$H]^-$). FAB-MS for $C_8H_6F_2O_2$: found 173.04135 ($[M + H]^+$), calcd 173.04136.

3-Fluoro-2-methyl-4-(methylthio)benzoic Acid (16). An inert 100 L jacketed reactor was charged with 3,4-difluoro-2-methylbenzoic acid (**15**) (3.88 kg, 22.5 mol) followed by NMP (11.6 L, 3 volumes) and DBU (6.9 L, 46.2 mol, 2.05 equiv). The resulting mixture was heated to ca. 50 °C, and NaSMe (3.3 kg, 47 mol, 2.1 equiv) was added in one portion to give a thick slurry. The mixture was heated to approximately 95−100 °C and held at that temperature for 2 h. The mixture became homogeneous at around 60 °C. Additional NaSMe was added in two portions (1.4 kg each) to achieve consumption of the starting material. When HPLC analysis showed that <5% of **15** remained, the solution was treated with water (40 L, 10 volumes) over ca. 45 min and cooled to below 25 °C. The reaction mixture was acidified to a pH of <2 with concentrated sulfuric acid (4.25 L) over ca. 2 h while the temperature was maintained below 25 °C. The resulting thick slurry was aged for ca. 1 h, and the product was collected by filtration and washed with water (2 × 25 L). The filter cake was partially dried under vacuum in the filter at 50 °C to yield compound **16** as an off-white solid (8.1 kg, 51.7 wt %; the purity was established by HPLC analysis against an external standard, and the material was used as such in the next step). A sample for analytical characterization could be obtained by further drying and slurrying in methanol at 50 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ 13.01 (br s, 1H), 7.69 (d, 1H), 7.22 (t, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.3, 168.2, 158.4, 156.0, 131.6, 131.4, 128.7, 128.6, 127.3, 127.2, 126.2, 126.0, 123.2, 123.1, 13.8, 12.4, 12.3. IR: 1672, 11412, 1278, 1220, 1178, 923, 755, 766 cm^{-1}. MS (EI) for $C_9H_9FO_2S$: found 199.1 ($[M - H]^-$). FAB-MS for $C_9H_9FO_2S$: found 200.03065 (M^+), calcd 200.03066.

3-Fluoro-2-methyl-4-(methylsulfonyl)benzoic Acid (17). An inert 100 L jacketed reactor was charged with compound **16** (8.1 kg, 20.5 mol, 4.1 kg corrected for assay) and glacial acetic acid (20 L, 5 volumes). The resulting slurry was heated to 60−65 °C under a nitrogen atmosphere, and 30 wt % H_2O_2 solution (5.4 L, 52.9 mol, 2.6 equiv) was added at such a rate that the temperature remained at 80 ± 5 °C; the addition required 3−4 h. After 1 h at ca. 95 °C, HPLC analysis showed that <1% of the intermediate sulfoxide remained. Excess peroxide was neutralized by the addition of DMSO (1.45 L, 20.5 mol, 1.0 equiv) and heating for 1 h at 95 °C, until a starch/iodide test for peroxides was negative. The solution was treated with water (55 L, 12 volumes) over ca. 90 min to furnish a thick white slurry. The mixture was cooled to 25 °C, aged for ca. 2 h, and filtered. The filter cake was washed twice with water (18 L each) and dried under suction for 2 h. The product was further dried at 50 °C under vacuum to give 4.29 kg of **17** (82% yield for two steps).

HPLC analysis of the isolated solid: 100% LCAP at λ = 230 nm and 102 wt %. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.74 (br s, 1H), 7.82−7.76 (m, 2H), 3.37 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.7, 167.7, 159.1, 156.6, 139.3, 139.3, 131.0, 130.9, 128.2, 128.0, 126.8, 126.4, 126.3, 44.1, 44.1, 12.3, 12.2. IR: 1706, 1681, 1568, 1421, 1406, 1383, 1328, 1303, 1264, 1218, 1189, 1150, 1133, 1045, 976, 967, 925, 848.787. 767, 758 cm^{-1}. MS (EI) for $C_9H_9FO_4S$: found 231 ($[M - H]^-$). FAB-MS for $C_9H_9FO_4S$: found 233.02827 ($[M + H]^+$), calcd 233.02827.

***tert*-Butyl 7-Dihydroxyboryl-2,3-dihydro-5*H*-benzo[*f*]-[1,4]-oxazepine-4(5*H*)-carboxylate (3).** An inert 250 L reactor was charged with THF (54 kg) and *N*-Boc-7-bromobenzoxazepine (**2**) (12.33 kg, 37.6 mol) under an inert atmosphere and cooled to −10 to −5 °C. A solution of 20% *n*BuMgCl in THF (8.77 kg, 15.0 mol) was added over 30 min while the temperature was maintained below −2 °C. A solution of 23% *n*-BuLi in hexane (8.38 kg, 30.1 mol) was added over 60 min, while the temperature was maintained below −2 °C. The mixture was stirred for 15 min, and HPLC analysis showed that <5% of **2** remained. The mixture was cooled to −15 to −10 °C, and triisopropyl borate (9.20 kg, 48.9 mol) was added over 30 min while the temperature was maintained below −8 °C. The mixture was stirred at −10 to −8 °C for 12−24 h until HPLC analysis showed that <5% **28** was present. A solution of 2 M HCl (31 kg) was added over 30 min while the temperature was maintained below 20 °C. The mixture was stirred for 15−30 min at ca. 20 °C and then allowed to separate, and the aqueous layer was removed. The THF layer was used as such for the next step. A sample of **3** for analytical characterization was prepared by precipitation using hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07−7.03 (m, 3H), 4.87−4.44 (m, 2H), 4.17−4.06 (m, 2H), 3.86−3.80 (m, 2H), 1.45−1.41 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 155.3, 137.7, 136.9, 131.6, 125.3, 121.4, 80.5, 73.1, 50.7, 49.9, 28.6 (major isomer). IR: 1697, 1603, 1572, 1456, 1409, 1364, 1333, 1304, 1281, 1267, 1240, 1171, 1134, 1111, 1071, 1025, 982, 868 cm^{-1}. FAB-MS for $C_{14}H_{20}BNO_5$: found 293.14334 (M^+), calcd 293.14335.

***tert*-Butyl 7-(6-Aminopyridin-3-yl)-2,3-dihydrobenzo-[*f*][1,4]oxazepine-4(5*H*)-carboxylate (5).** The THF solution of **3** from the previous step was subjected to a subsurface nitrogen sparge for at least 1 h. Potassium carbonate (10.4 kg, 75.3 mol) was dissolved in water (12.3 kg), subjected to a subsurface nitrogen sparge for at least 1 h, and then added to the sparged THF solution of the boronic acid. Solid 2-amino-5-bromopyridine (**4**) (6.51 kg, 37.6 mol) and bis-(triphenylphosphine)palladium(II) dichloride (238 g, 3.4 mol) were added under nitrogen. The mixture was heated to reflux and stirred 12−24 h until HPLC analysis confirmed >97% conversion.

The mixture was cooled to 25−30 °C, and the aqueous phase was removed. A solution of 1 M HCl (95 kg) was added over 15 min while the temperature was maintained below 30 °C, to reach a pH of <2.0. MTBE (23 kg) was added, and the mixture was stirred for 45 min at 20−25 °C. Celite (3 kg) was added, and the mixture was filtered over a Celite pad (6 kg) wetted with MTBE (20 kg). The reactor was rinsed with 1 M HCl (11 kg), and the rinse was used to wash the Celite pad. The combined filtrate was collected in a clean 250 L reactor, and the lower aqueous phase containing the product was separated and washed with MTBE (23 kg).

Isopropyl acetate (54 kg) was added to the aqueous phase, and the mixture was cooled to 10−15 °C. A 25% aqueous ammonium hydroxide solution (8.2 kg) was added over 15 min while the temperature was maintained below 15 °C, to reach a pH of >9. The mixture was stirred for 15 min at 18−20 °C, and the lower aqueous phase was removed. 3-Mercaptopropyl ethyl sulfide silica (336 g) was added, and the mixture was stirred for 12−24 h at 20−25 °C. Celite (3 kg) was added, and the mixture was filtered through a pad of Celite (6 kg) wetted with isopropyl acetate (13 kg). The filter pad was washed with isopropyl acetate (2 × 10 kg), and the volume of the filtrate was reduced by distillation under vacuum until ∼16 L of residue remained. THF (100 kg) was added, and the distillation under

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734

vacuum was continued until ~18 L of residue remained. THF (130 kg) was added, and the solution was used as such for the next step. A sample of **5** for analytical characterization was prepared following trituration of the crude reaction mixture with hexanes.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29−8.28 (m, 1H), 7.63−7.08 (m, 4H), 6.58−6.56 (m, 1H), 4.63 (br s, 2H), 4.54−4.46 (d, 2H), 4.07 (t, J = 4.4 Hz, 2H), 3.82 (t, J = 4.2 Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 157.8, 155.1, 146.3, 136.5, 133.9, 132.7, 127.6, 126.8, 126.7, 122.1, 108.8, 80.4, 73.2, 50.8, 50.0, 28.7. IR (film): 1674, 1636, 1605, 1486, 1459, 1416, 1386, 1365, 1301, 1282, 1269, 1239, 1219, 1167, 1136, 1110, 1072, 1049, 1026, 1013, 978, 944, 883, 818 cm^{-1}. MS (EI) for $C_{19}H_{23}N_3O_3$: found 342 ([M + H]$^+$). FAB-MS for $C_{19}H_{23}N_3O_3$: found 342.18161 ([M + H]$^+$), calcd 342.18162.

5-(2,3,4,5-Tetrahydrobenzo[*f*][1,4]oxazepin-7-yl)-pyridine-2-amine (6). To the THF solution of **5** from the previous step was added a solution of 37% HCl (18.5 kg, 188 mol, 5.0 equiv) over 30 min while the temperature was maintained below 35 °C. The mixture was stirred at 34−36 °C for 12−24 h until HPLC analysis confirmed >98% conversion to the product. The resulting suspension was cooled to 24−26 °C and stirred for 1 h. The product was isolated by filtration, washed with THF (40 kg), and dried under vacuum at 47−50 °C to yield 7.48 kg of **6** (63.3% from **2**) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28−8.27 (m, 1H), 7.63−7.60 (m, 1H), 7.31−7.29 (m, 1H), 7.27 (s, 1H), 7.10−7.07 (m, 1H), 6.57−6.55 (m, 1H), 4.47 (br s, 2H), 4.07 (dd, J = 4.4, 3.2 Hz, 2H), 4.02 (s, 2H), 3.25 (dd, J = 4.4, 3.2 Hz, 2H), 1.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 157.4, 146.2, 136.4, 135.5, 133.6, 127.2, 126.9, 126.1, 121.6, 108.5, 75.4, 53.4, 52.4. IR (film): 1660, 1603, 1487, 1443, 1387, 1320, 1284, 1222, 1171, 1128, 1098, 1055, 1011, 985, 925, 905, 893, 848, 817 cm^{-1}. MS (EI) for $C_{14}H_{15}N_3O$: found 242 ([M + H]$^+$). FAB-MS for $C_{14}H_{15}N_3O$: found 242.12925 ([M + H]$^+$), calcd 242.12926.

[7-(6-Aminopyridin-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl][3-fluoro-2-methyl-4-(methylsulfonyl)-phenyl]methanone (1). An inert 250 L glass-lined reactor was charged with dichloromethane (105 kg), DMF (19 kg), HOBt hydrate (3.06 kg,20 mol) and 3-fluoro-2-methyl-4-(methylsulfonyl)benzoic acid (**17**) (4.64 kg, 20 mol). The mixture was cooled to 15 °C and EDC·HCl (3.83 kg, 20 mol) was added. The resulting mixture was stirred for 1 h.

Another inert 250 L glass-lined reactor was charged with dichloromethane (105 kg), DMF (19 kg), 5-(2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-7-yl)pyridin-2-amine bis-(hydrochloride) (**6·HCl**) (6.60 kg, 21 mol), and 3 M NaOH solution (14.2 kg, 42 mol). The mixture was cooled to 15 °C, and the activated benzoic acid from the first reactor was added over 45 min. The resulting mixture was stirred for 18 h.

Stirring was stopped and the phases were allowed to separate. The aqueous layer was discarded, and the lower organic layer was washed with 1 M monobasic sodium phosphate solution (2 × 50 kg). DMF (19 kg) was added, and the organic phase was washed with 1 M NaOH (50 kg). Dichloromethane (80−90 L) was removed by distillation, and water (53 kg) was added. The distillation was continued to remove another 30−50 L of dichloromethane, resulting in a suspension, which was cooled to 15−20 °C, filtered, and washed with water (25 kg).

The wet cake was returned to the reactor, and THF (128 kg) and water (11.4 kg) were added. The mixture was heated to reflux, and the solution was polish-filtered while hot. The filtrate was collected in a clean reactor, and approximately 80−90 L of was distilled off at approximately 360 mbar. The mixture was cooled to 8−12 °C, and seeds of **1** (0.5 wt %) and MTBE (74 kg) were added. The resulting mixture was stirred for 19 h, after which the product was isolated by filtration, washed with MTBE (24 kg), and dried under vacuum at 50 °C to yield **1** as a white solid (7.61 kg, 84%, 98.8% purity by AN-HPLC). Compound **1** was observed as a mixture of two rotational isomers in the ^{1}H and ^{13}C NMR spectra.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24−8.03 (dd, 1H), 7.79−7.71 (m, 1H), 7.71−7.69 (dd, 0.5H), 7.57−7.57 (d, 0.5H), 7.44−7.40 (m, 1.5H), 7.29−7.19 (dd, 1H), 7.05−7.01 (dd, 1H), 6.64−6.63 (d, 0.5H), 6.54−6.45 (dd, 1H), 6.06 (s, 2H), 4.93−4.31 (m, 2H), 4.31−3.54 (m, 4H), 3.37−3.36 (d, 3H), 2.12−1.77 (d, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 167.2, 166.6, 166.6, 158.9, 158.9, 158.4, 158.4, 157.4, 157.2, 155.9. 155.8, 145.4, 145.1, 145.1, 144.0, 143.9, 135.0, 134.7, 132.9, 132.8, 129.4, 129.2, 128.2, 128.2, 128.1, 128.0, 127.0, 126.9, 126.8, 125.9, 125.6, 125.4, 123.6, 123.5, 123.3, 123.1, 122.8, 122.0, 122.0, 121.9, 121.9, 121.2, 120.7, 107.8, 107.8, 70.9, 70.8, 51.1, 51.1, 47.4, 46.5, 43.5, 43.5, 43.5, 43.4, 11.0, 10.9, 10.7, 10.6. IR (KBr pellet): 1623, 1487, 1457, 1423, 1385, 1314, 1269, 1226, 1193, 1144, 1133, 1054, 1031, 962, 821, 768 cm^{-1}. MS (EI) $C_{23}H_{22}FN_3O_4S$: found 456.2 ([M + H]$^+$). High-resolution MS (FAB-MS using glycerol as a matrix) for $C_{23}H_{22}FN_3O_4S$: found 456.13943 ([M + H]$^+$), calcd 456.13878.

[7-(6-Aminopyridin-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl][3-fluoro-2-methyl-4-(methylsulfonyl)-phenyl]methanone Hydrochloride (1·HCl). A clean inert 250 L glass-lined steel reactor was charged with acetone (44 kg), purified water (3.65 kg) and free base **1** (7.30 kg, 16.0 mol). The mixture was heated to 50 °C, and 37% HCl (3.16 kg, 32 mol) was added. The mixture was stirred for 10 min, cooled to 15−20 °C, and stirred for 1 h. The product was isolated by filtration, washed with acetone (33 kg), and dried under vacuum at 50 °C to yield **1·HCl** as a white solid (7.81 kg, 95%, 99.7% purity by AN-HPLC).

Analyses: OVI: DMF < 100 ppm, DMC < 100 ppm, acetone = 3081 ppm, MTBE < 100 ppm, iPAc < 100 ppm, THF < 100 ppm. Heavy metals: Pd ≤ 0.2 ppm, others < 20 ppm (USP ⟨231⟩). ^{1}H NMR (400 MHz, DMSO-d_6), equimolar amounts of two rotamers: δ 8.20−8.40 (br s, 2H), 8.33 (s, 0.5H), 8.31 (d, J = 2.8 Hz, 0.5H), 8.15 (d, J = 2.0 Hz, 0.5H), 7.96 (dd, J = 9.7, 2.0 Hz, 0.5H), 7.70−7.78 (m, 1.5H), 7.55−7.57 (m, 0.5H), 7.51−7.55 (m, 0.5H), 7.28 (d, J = 8.6 Hz, 0.5H), 7.17 (d, J = 3.1 Hz, 0.5H), 7.15 (d, J = 5.1 Hz, 0.5H), 7.05−7.11 (m, 1.5H), 6.83 (d, J = 2.7 Hz, 0.5H), 4.86−4.99 (m, 1H), 4.29−4.56 (m, 1H), 4.10−4.27 (m, 2H), 3.93−4.04 (m, 0.5H), 3.45−3.65 (m, 1.5H), 3.37 (s, 1.5 H), 3.35 (s, 1.5H), 2.12 (d, J = 2.0 Hz, 1.5H), 1.76 (d, J = 2.0 Hz, 1.5H). ^{13}C NMR (100 MHz, DMSO-d_6), equimolar amounts of two rotamers: δ 168.1, 167.5, 159.4, 159.2, 159.1, 156.6, 153.9, 153.8, 144.6, 142.9, 142.3, 133.0, 132.7, 130.0, 129.9, 129.7, 129.5, 129.1, 129.0, 128.9, 128.8, 128.5, 127.7, 127.6, 127.5, 127.1, 126.9, 124.4, 124.3, 124.1, 122.7, 122.1, 121.6, 114.4, 71.2, 51.7, 51.3, 47.9, 46.9, 44.3, 44.2, 11.7, 11.4.

AUTHOR INFORMATION

Corresponding Author

*E-mail: sriram.naganathan@dermira.com.

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734

Present Addresses

[§]S.N.: Dermira, Inc., 275 Middlefield Road, Suite 150, Menlo Park, CA 94025.

[∥]D.A.: Threshold Pharmaceuticals, 170 Harbor Way, Suite 300, South San Francisco, CA 94080.

[⊥]N.G.A.: Astex Pharmaceuticals, Inc., 4140 Dublin Boulevard, Suite 200, Dublin, CA 94568.

[#]S.L.: Gilead Sciences, 333 Lakeside Drive, Foster City, CA 94404.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Otute Akiti and Sean Cusack for evaluating the safety risks associated with the borane reduction and oxidation steps. We thank Nathan Guz, Matthew Pfeiffer, and Norma Tom for their assistance with the borane reduction; James Robinson, Tri Tran, and Sharique Zuberi for their assistance with the imide synthesis; James Tam, Jim Zhan, and Shigang Zhang for help with analytical development and support; Rahul Manek and Shital Rane for their contributions to salt and form screening and obtaining solid-state data; Bill Atkins (BASF Corporation, Evans City, PA) for helpful suggestions and guidance regarding safe handling of borane·THF; and Jens Wittenberg and Martin Völkert (BASF Corporation, Ludwigshafen, Germany) for their efforts in the scale-up of the borane reduction. We also thank Jo Ann Wilson and Norma Tom for their help in reviewing the manuscript.

■ REFERENCES

(1) Fruman, D. A.; Rommel, C. *Nat. Rev. Drug Discovery* **2014**, *13*, 140 and references therein. Nuss, J. M.; Tsuhako, A. L.; Anand, N. K. *Annu. Rep. Med. Chem.* **2009**, *44*, 339 and references therein.

(2) Anand, N.; et al. Benzoxazepines as Inhibitors of PI3K/mTOR and Methods of their Use and Manufacture. U.S. Patent 8,648,066, Feb 11, 2014. Aay, N.; et al. Benzoxazepines as Inhibitors of PI3K/mTOR and Methods of their Use and Manufacture. U.S. Patent 8,637,499, Jan 28, 2014.

(3) Kamei, K.; Maeda, N.; Nomura, K.; Shibata, M.; Katsuragi-Ogino, R.; Koyoma, M.; Nakajima, M.; Inoue, T.; Ohno, T.; Tatsuoka, T. *Bioorg. Med. Chem.* **2006**, *14*, 1978. Chupak, L. S.; et al. Preparation of N-Substituted Bicyclic Oxazolidinones as Antibacterial Agents. WO 2004069244 A1, Aug 19, 2004.

(4) Schmidt, K. F. *Ber. Dtsch. Chem. Ges.* **1924**, *57B*, 704. Wolff, H. *Org. React.* **1946**, *3*, 307.

(5) Ashby, E. C.; Schwartz, R. D. *Inorg. Chem.* **1972**, *11*, 919. Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 1557.

(6) Kwiecień, H.; Baumann, E. *Pol. J. Chem.* **2000**, *74*, 141.

(7) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1999; pp 518−525, 736−739.

(8) Takeuchi, C. S.; Kim, B. G.; Blazey, C. M.; Ma, S.; Johnson, H. W. B.; Anand, N. K.; Arcalas, A.; Baik, T. G.; Buhr, C. A.; Cannoy, J.; Epshteyn, S.; Joshi, A.; Lara, K.; Lee, M. S.; Wang, L.; Leahy, J. W.; Nuss, J. M.; Aay, N.; Aoyama, R.; Foster, P.; Lee, J.; Lehoux, I.; Munagala, N.; Plonowski, A.; Rajan, S.; Wollfrey, J.; Yamaguchi, K.; Lamb, P.; Miller, N. *J. Med. Chem.* **2013**, *56*, 2218. Anand, N.; et al. Benzoxazepine Derivatives as mTOR Kinase Inhibitors and Their Preparation and Use for the Treatment of Cancer. WO 2010118208, Oct 14, 2010. Schmitt, M.; et al. Preparation of 3-Cyclopropyl-4-(3-amino-2-methylbenzoyl)pyrazole Derivatives as Herbicides. WO 2006061074, June 15, 2006.

(9) For example, see: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(10) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(11) Mitsunobu, O. *Synthesis* **1981**, 1. Hughes, D. L. *Org. React.* **1992**, *42*, 335. For a recent review, see: But, T. Y. S.; Toy, P. H. *Chem.—Asian J.* **2007**, *2*, 1340.

(12) Lane, C. F. *Chem. Rev.* **1976**, *76*, 773. Brown, H. C.; Krishnamurthy, S. *Aldrichimica Acta* **1979**, *12*, 3. Ho, T.-L.; Fieser, M.; Smith, J.; Fieser, L. Borane-Tetrahydrofuran. In *Fieser and Fieser's Reagents for Organic Synthesis*; Wiley: New York, 2006. Young, S. D.; Wiggins, M. J.; Huff, J. R. *J. Org. Chem.* **1988**, *53*, 1114.

(13) Structural assignment of the regiochemistry of the acid−amide is tentative and based on preliminary spectral analyses (MS and ^{1}H NMR). It is possible that the acid and amide groups are opposite of what is shown. No attempt was made to rigorously assign the regiochemistry.

(14) Edward, J. T.; Terry, K. A. *J. Chem. Soc.* **1957**, 3527.

(15) Atkins, W. J.; Burkhardt, E. R.; Matos, K. *Org. Process Res. Dev.* **2006**, *10*, 1292. Atkins, W. J. *Borane-THF BASF Safety and Handling Presentation*; BASF Corporation: Evans City, PA, 2009.

(16) Luk'yanov, B. S.; Maksimenko, A. A.; Borodkin, G. S.; Maksimenko, A. A. *Chem. Heterocycl. Compd.* **2003**, *39*, 1539.

(17) De la Mare, P. B. D. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, U.K., 1976.

(18) While both solid NaSMe and NaSMe in aqueous solution are commercially available, use of the aqueous solution is very inefficient, and it is very difficult to completely consume **15**.

(19) Douglass, I. B.; Martin, F. T. *J. Org. Chem.* **1950**, *15*, 795. Douglass, I. B. *J. Am. Chem. Soc.* **1952**, *74*, 5770. Senning, A.; Lawesson, S.-O. *Acta Chem. Scand.* **1962**, *16*, 117.

(20) Lau, S. Y. W.; Hughes, G.; O'Shea, P. D.; Davies, I. W. *Org. Lett.* **2007**, *9*, 2239 and references therein.

(21) Ito, S.; Kubo, T.; Morita, N.; Matsui, Y.; Watanabe, T.; Ohta, A.; Fujimori, K.; Murafuji, T.; Sugihara, Y.; Tajiri, A. *Tetrahedron Lett.* **2004**, *45*, 2891.

(22) Brown, H. C. *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972. While the structure of boroxine **30** was not rigorously established, support for the structural assignment was obtained by subjecting a sample of boronic acid **3** to dehydrating conditions. HPLC analysis revealed that **3** was cleanly converted to **30**.

(23) Guideline on the specification limits for residues of metals catalysts or metal reagents, EMEA/CHMP/SWP/4446/2000. *ICH Q3D Guideline for Elemental Impurities* (ICH, Dec 16, 2014).

(24) Galaffu, N.; Man, S. P.; Wilkes, R. D.; Wilson, J. R. H. *Org. Process Res. Dev.* **2007**, *11*, 406. It was not immediately apparent at the time of this work that a Pd-scavenging operation was compulsory, and the process as designed may have been able to reduce the Pd content to acceptable levels. However, because of constraints of time and project need, a scavenging operation was introduced in order to be certain.

(25) *ICH Q3C (R5) Impurities: Guideline for Residual Solvents* (ICH, Feb 4, 2011).

DOI: 10.1021/acs.oprd.5b00037
Org. Process Res. Dev. 2015, 19, 721−734