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Commercial Synthesis of a Pyrrolotriazine−Fluoroindole Intermediate to Brivanib Alaninate: Process Development Directed toward Impurity Control

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ABSTRACT: The development of a practical, commercial process for the preparation of 4-fluoro-2-methyl-indol-5-ol and its subsequent coupling with a pyrrolotriazine to form an advanced intermediate of the oncology therapy brivanib alaninate is described. A key aspect is the multikilogram-scale preparation of the fluoroindole intermediate from trifluoronitrobenzene and the subsequent coupling while achieving impurity minimalization. As brivanib alaninate is a high-dose drug, the synthesis of high-quality API with low levels of impurities is critical.

INTRODUCTION

Background and Goals of Process Development. Brivanib alaninate (**1**) is an investigational oncology therapy with the potential for applications against a wide variety of tumor types and stages of disease progression (Figure 1). The

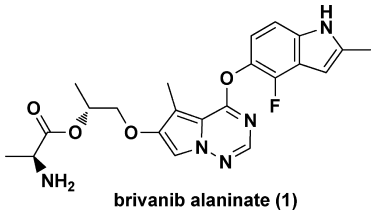

Figure 1. Structure of brivanib alaninate (**1**).

molecule is built upon the versatile medicinal properties of a pyrrolotriazine core which has been incorporated as well into several other Bristol-Myers Squibb drug candidates.[1] This *L*-alanine ester prodrug is an orally available, dual inhibitor of the vascular endothelial growth factor receptor-2 (VEGFR-2) and fibroblast growth factor receptor (FGFR) tyrosine kinases. Early studies indicated likely broad-spectrum antitumor activity for use in the treatment of hepatocellular carcinoma, colorectal cancer, and fibroblast growth factor-driven tumors by inhibition of angiogenesis.[2] Clinical and preclinical studies have shown the important role that the VEGF receptor family of transmembrane protein tyrosine kinases have on angiogenesis. A viable process to make multi-hundred kilogram batches was required to support clinical investigation of these properties and establish a commercially viable synthesis.

Our strategy for the process development of brivanib was focused on removing input-related impurities and avoiding/minimizing formation of new impurities during the preparation (Scheme 1). The emphasis on eliminating impurities was significant since brivanib alaninate is expected to be dosed at ∼800 mg/d, implying any associated impurities could be ingested at biologically impactful levels. As an aid to achieve high-purity intermediates, our early process development work included the identification of a 'quality gatekeeper' intermediate, a pivotal intermediate that could be prepared pure or easily purified prior to embarking on the final steps to the API.[3] If successful, the final steps leading to the API would not be burdened with input-related impurities, a key attribute for a successful process.

A manufacturing-scale process to make the proposed starting material pyrrolotriazine core **2** had been previously established from glycine ethyl ester, ethyl acetoacetate, dimethylformamide dimethyl acetal and formamide.[4] However, the ester moiety of **2** was not at the proper oxidation state for conversion to **1** and required carbon−carbon bond cleavage, a nontrivial transformation. As for most oxidative cleavages of this sort, the chemistry required is energetic and potentially hazardous. For instance, a runaway reaction resulted when an oxidative cleavage reaction of a derivative of **2** was heated to 60 °C. Accordingly, a continuous process was developed that overcame the safety concerns, permitting the metric-ton-scale manufacture of **3**. This molecule was established as the first regulatory starting material for brivanib alaninate.[5] The preparation of the second proposed regulatory starting material, fluoroindole **4**, existed, but additional process development was required for large-scale manufacture.

Our team initially engaged in an exploratory program of process scouting to understand the intrinsic parameters that impacted the rate, purity, and subsequent workup of the coupling of **3** and **4** to form the indole−pyrrolotriazine **5**. This work established that **5** was thermally stable, highly crystalline, and could be facilely purified in high yield on at least 100 g scale. A particularly attractive feature was the ability of recrystallization to significantly purge the majority of the precursors of **3** and **4** to undetectable levels while obtaining high recoveries of substrate. These qualities supported the selection of **5** as the aforementioned quality gatekeeper for the entire process. This permitted the chemical development program for API to proceed with the understanding that a

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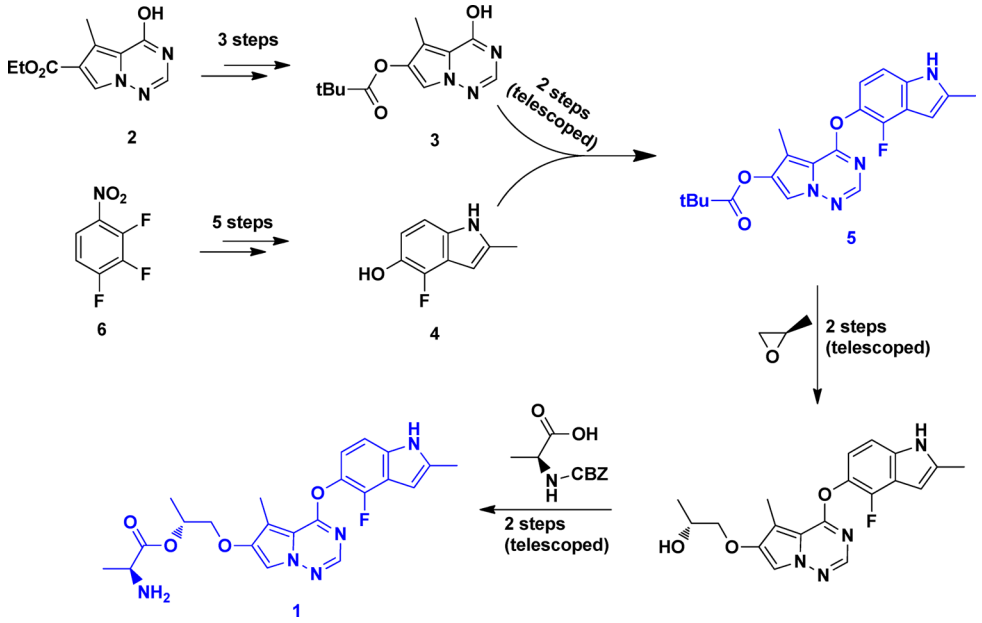
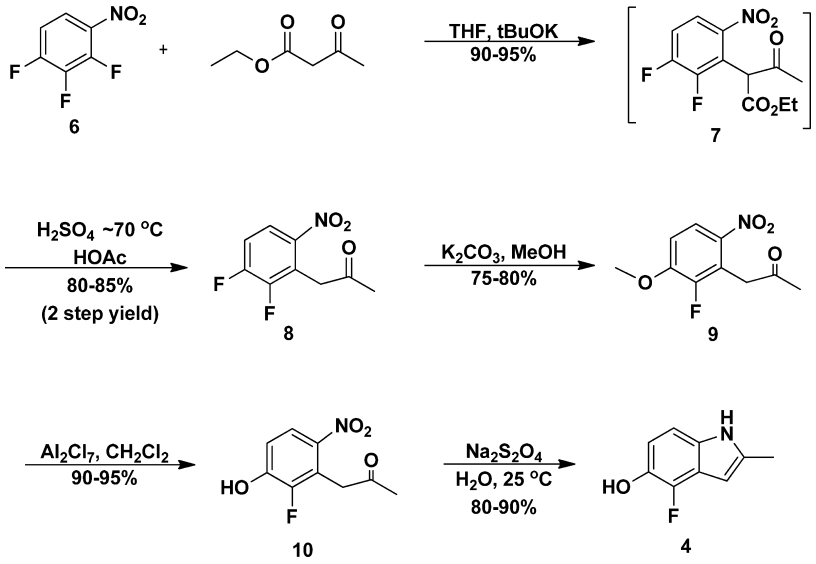
Scheme 1. Convergent synthesis of brivanib alaninate (1)



Scheme 2. Commercial synthesis of fluoroindole 4



process to produce highly pure **5** would be defined, a useful quality for the immediate precursor of a high-dose drug. Ultimately, **5** was condensed sequentially with (*R*)-propylene oxide (after PIV cleavage) and then a CBZ-protected synthon and was finally hydrogenated to reveal the drug substance.[6] Herein we describe the design and development of our optimized commercial process, producing the key intermediate **5** in single batches of up to ~300 kg in 93% yield of ≥99.95% purity.[7,10]

RESULTS AND DISCUSSION

Preparation of Fluoroindole 4. An attractive precursor to fluoroindole **4** is 2,3,4-trifluoronitrobenzene (**6**, Scheme 2), as it is inexpensive, available in bulk and properly functionalized to efficiently form the indole over five steps, concluding with a modified Reissert indole synthesis.[8] Following modification of an existing route,[1b] our process has produced metric tons of **4** from trifluoronitrobenzene while overcoming hazardous chemistry and the sensitivity of the product and precursors toward oxidation or basicity. On the basis of the successful development of this scalable route, **4** became our second regulatory starting material.

*Process Development of Arylpropanone **9**.* The reaction of trifluoronitrobenzene **6** with a mixture of potassium *tert*-butoxide and ethyl acetoacetate in THF led to ≥99.9% conversion to the α-ketoester **7**.[9] The reaction was reproducible, but variable purity of the product (75−95% purity) was correlated to the level of KOH in the base, which was remedied by setting a <5% specification for KOH. The workup was straightforward, but as the product **7** is an oil, it was more efficient to concentrate the worked-up product solution and telescope it into the following decarboxylation step. The presence of the nitro group required consideration for explosivity and exothermic events. As such, this and all the subsequent steps were evaluated by using a combination of

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DSC, calorimetry, ARC, and other safety-testing protocols to be assured of the safe operating ranges.[11]

The subsequent decarboxylation to the propanone **8** was conducted by heating a H_2SO_4/acetic acid solution of **7** to 70 °C, achieving a >99.7% conversion. Workup and concentration resulted in >100% as-is yields of a brown oil and 75−80% purity in batches up to 450 kg of **6**.[12] Once again this material was telescoped into the following step in order to reach a crystalline intermediate more amenable to purification and isolation.

The nascent hydroxy group was introduced by methoxide displacement of the fluorine at the 3-ring position to form anisole derivative **9**.[13] The reaction was conducted by refluxing **8** in methanol with 0.8 equiv of K_2CO_3 (≥99.5% conversion). None of the regioisomeric aryl-methyl ether was detected due to the strong directing influence of the nitro group. Screening the base charge determined that substoichiometric base was optimum in order to minimize deprotonation of the benzyl position, which would have deactivated the ring to further nucleophilic attack.[14] The anisole derivative **9** crystallized upon addition of water, and subsequent MTBE recrystallization along with charcoal treatment effectively removed any impurities carried along over the prior two telescoped chemical steps. The optimized process produced 75−80% yields (≥99.7% purity) in batches of **8** up to 600 kg.

*Synthesis of Nitroaryl Propanone **10**.* Demethylation of **9** was initially achieved with pyridine hydrochloride[1k] in a solvent-free medium by mixing the solids and heating to 160 °C. Following completion, the viscous reaction mixture was diluted with hydrochloric acid, followed by a tedious purification/isolation/recrystallization to produce 85−90% yields of >99.5% purity nitroaryl propanone **10**. Complications for this protocol included inputs that were unstable to the reaction conditions, handling black viscous oils, formation of poorly soluble tars, and interfaces that were difficult to detect during phase separations. The use of carbon treatment ameliorated some inconveniences, but a superior remedy was distinctly needed for further scale-up.

Ionic liquids[15] are usually used as solvents in that their atypical physical conditions permit reactivities and selectivities difficult to achieve in other ways. However, they can also be used as reagents. Demethylation of the anisole derivative **9** occurs in the chloroaluminate ionic liquid formed from the complexation of aluminum trichloride and trimethylammonium chloride in CH_2Cl_2.[15b] The resulting reagent, $[TMAH]Al_2Cl_7$, acts as a powerful Lewis acid, coordinating the ethereal oxygen and strongly activating the methyl group toward attack by chloride. Subsequent departure of chloromethane produced **10** as a result. The unusual Lewis acidity resulted in a reduction in the temperature necessary for demethylation from 160 °C in pyridine hydrochloride to 40 °C under the modified conditions.

At multikilogram scale, trimethylammonium chloride was added to a slurry of $AlCl_3$ in anhydrous CH_2Cl_2, followed by addition of a solution of **9**.[16] Holding this mixture at 40 °C led to ≥99.9% methyl cleavage. The chloromethane offgas was quenched by directing it through a methanolic solution of aqueous ammonia. The workup progressed by the addition to water to quench the chloroaluminate species and precipitate the product as a crystalline solid. High-purity nitroaryl propanone **10** was isolated by centrifugation. Yields from **9** were 85−95% at >99.4% assay in batches of up to 375 kg.

*Synthesis of Fluoroindole **4**.* The aryl nitroketone **10** may be reduced and cyclized to the fluoroindole **4** by a range of reducing reagents[17] via a Reissert indole cyclization.[8] The use of aqueous sodium dithionite or sodium hydrosulfite as reductants had the advantages of low cost, safety and mildness so as not to further impact the sensitive fluoroindole entity. A trace of HCl was added to all solutions of the process as the product **4** is not stable at pH 5−8. A further advantage of this reaction system was the rapid crystallization of the freshly formed **4** from the reaction medium, isolating the sensitive product from the remaining reactants.

The reaction proceeded once a methanolic solution of phenol **10** was added to an aqueous solution of sodium dithionite. The reaction had to be conducted expeditiously once the dithionite solution was prepared as it is not stable under acidic conditions. Upon reduction, the aniline immediately cyclized and crystallized from the solution. Following cooling and workup, this process resulted in 85−90% yields of fluoroindole.[18] While requiring administrative controls for immediate use of the dithionite solution, it is safe, scalable and high-yielding. The primary challenge now consisted of addressing the formation and removal of the remaining impurities, and defining conditions for storage and shipment. Improper isolation or storage conditions (failure to maintain an acidic pH or temperature >8 °C) would lead to decomposition and unacceptable material.

The formation of side products and decomposition products in this step was extensive at the onset of our investigations. The missing yield was primarily due to electrophilic aromatic substitution by SO_3 to produce the three arylsulfonate analogues of **4** (LC−MS analysis). While such polar impurities were easily washed away with water, the level of sulfonation varied widely (10−40%), impacting yields. Higher levels of impurities were correlated to the use of degraded sodium dithionite; thus, only freshly opened batches of recently manufactured sodium dithionite were used. The fluoroindole was also prone to form a variety of impurities such as dimers and higher oligomers (Figure 2). At pH 5−8, the indole

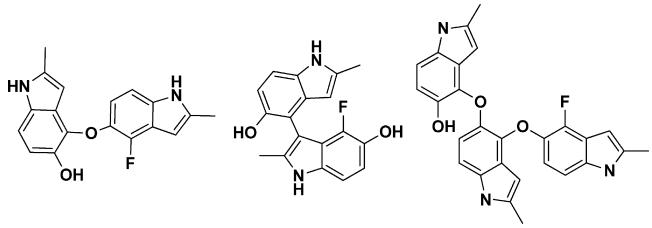

Figure 2. Oligomers of fluoroindole **4**.

polymerized via two distinct pathways. The fluorine could be displaced by the stabilized phenoxide oxygen to form a diarylether impurity, or the iminium tautomer would lead to a C−C-bonded coupling product. The aryl-ether impurity also further oligomerized to produce impurities up to heptamers[19] until the coformed HF increased the acidity of the mixture and rendered remaining **4** stable. As expected, these sources of impurities were easily suppressed by maintaining the pH below 4, leading to our protocol of adding dilute hydrochloric acid to the reaction mixture and all solutions subsequently used in the isolation to promote compound stability.

Furthermore, the crude fluoroindole typically contained 200−300 ppm of unreacted **10** due to the rapid crystallization of **4** from the reaction mixture, trapping other components. Modification of reaction conditions did not further reduce the

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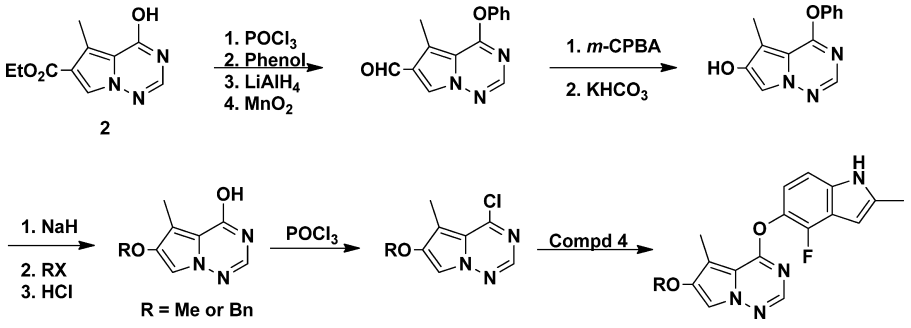
Scheme 3. Discovery Chemistry's preparation of coupled intermediate analogues to 5



levels of residual **10**. Thus, a recrystallization was mandated for the commercial procedure wherein it had been optional for the earlier protocols. Our recrystallization protocol was based on dissolution of **4** into cold acidic aqueous methanol followed by the addition of dilute aqueous HCl to initiate recrystallization. Filtration of the white crystals which resulted followed by cake washes with dilute HCl led to 65−75% recoveries of **4**. Preparation of the fluoroindole was piloted successfully up to 282 kg batches, producing 65−75% yields with >98.0% assay (>99.75 HPLC area).

*Fluoroindole **4** Stability and Storage Considerations.* The synthetic and purification problems had been solved, but fluoroindole **4** still required storage at <8 °C to avoid formation of dimeric impurities. This introduced inconvenience (temperature recorders added to shipments), expense (need for refrigerated warehouses) and risk (inadvertent warming leading to compromised product). Of note, our earliest fluoroindole preparations had not included a recrystallization operation and were thermally stable in comparison to these latter recrystallized batches. We hypothesized that the addition of the clarification step which required the filtration of the aqueous methanolic solution prior to recrystallization, removed a component that had imparted stability to non-recrystallized batches. Examination of material removed during the clarification revealed polar solids that largely consisted of inorganic sulfur salts. These insoluble salts were derived from sodium dithionite and most likely retained reducing potential, possibly protecting the non-recrystallized fluoroindole from oxidative decomposition pathways that in turn led to the impurities.

Clearly, some desirable stabilization attribute of fluoroindole **4** was being removed, but rather than return to a process with a critical variable we could not well control, we screened antioxidants and identified sodium metabisulfite as a useful component. If added to the cake washes, the process produced **4** with sulfur levels of 800−7000 ppm (IPC) which provided a measure of metabisulfite incorporation. The resulting **4** displayed acceptable stability upon accelerated stability testing. Of less desirability, this modification also produced sulfur-bridged dimer impurities (Figure 3) as high as 0.3% in otherwise acceptable batches of fluoroindole.

We developed methods to reduce the content of these new impurities to <0.05%, but even such levels led to daughter impurities three steps later which significantly reduced the hydrogenation rate to form API. In view of this development, the metabisulfite treatment was abandoned, the former recrystallization conditions were reestablished ,and cold storage for isolated product is now mandated.

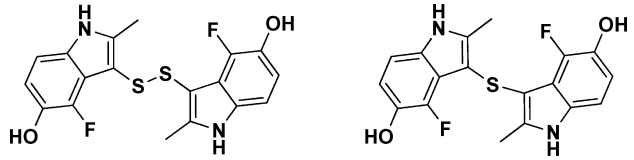


Figure 3. Sulfur-containing impurities resulting from sodium metabisulfite addition.

This process for fluoroindole **4**, the second regulatory starting material defined for brivanib alaninate, has been satisfactory over several campaigns. Batches of up to 144 kg of fluoroindole **4** have been made without issue, and over 1 MT of material has been prepared to date.

*Coupling Reaction Process Development for Preparing the Indole−Pyrrolotriazine **5**. Quality Gatekeeper **5** and Initial Considerations of the Process.* We initiated our process development of the coupling reaction sequence using chemistry developed by our Discovery colleagues (Scheme 3).[1] The pyrrolotriazine **2** was chlorinated with phosphorous oxychloride ($POCl_3$) to form the chlorotriazine without isolation after workup. Subsequent addition of phenol formed a diaryl ether as a protecting group. The ester was reduced to the aldehyde over two steps by reduction with lithium aluminum hydride (LAH) followed by reoxidation by manganese dioxide. Carbon−carbon bond oxidative cleavage proceeded subsequently by a Baeyer−Villiger reaction induced by *m*-chloroperbenzoic acid (*m*-CPBA) followed by formate cleavage.

The resulting hydroxyl group was protected as a methyl or benzyl ether followed by cleavage of the phenyl ether to reveal the triazine ring hydroxyl. Following another $POCl_3$ chlorination, addition of fluoroindole **4** furnished the coupled compound. This formed an analogue to indole−pyrrolotriazine **5** that could be further converted onto brivanib alaninate **1**. While this protocol fully satisfied Discovery Chemistry's need for synthetic flexibility to prepare analogues, the nine steps expended for the functionalization of only one group would be an issue for further scale-up. While the intermediates themselves might be viable components for a commercial process, it was clear a new process was required before multikilogram preparations could be considered.

*Pyrrolotriazine **3** Process Evolution (alternative routes).* A logical change would be incorporation of the indole portion first in place of the phenol protecting group, permitting elimination of a protection/deprotection cycle, and then addressing the C−C cleavage (Scheme 4).

Chlorination followed by addition of fluoroindole **5** produced the expected coupled compound **14** in good yield.[1i]

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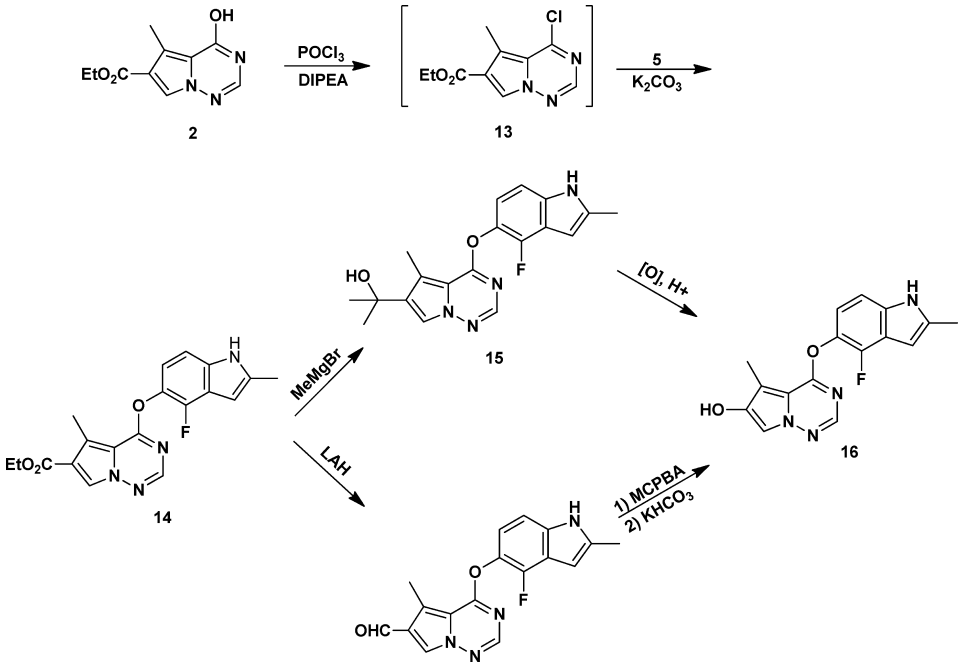
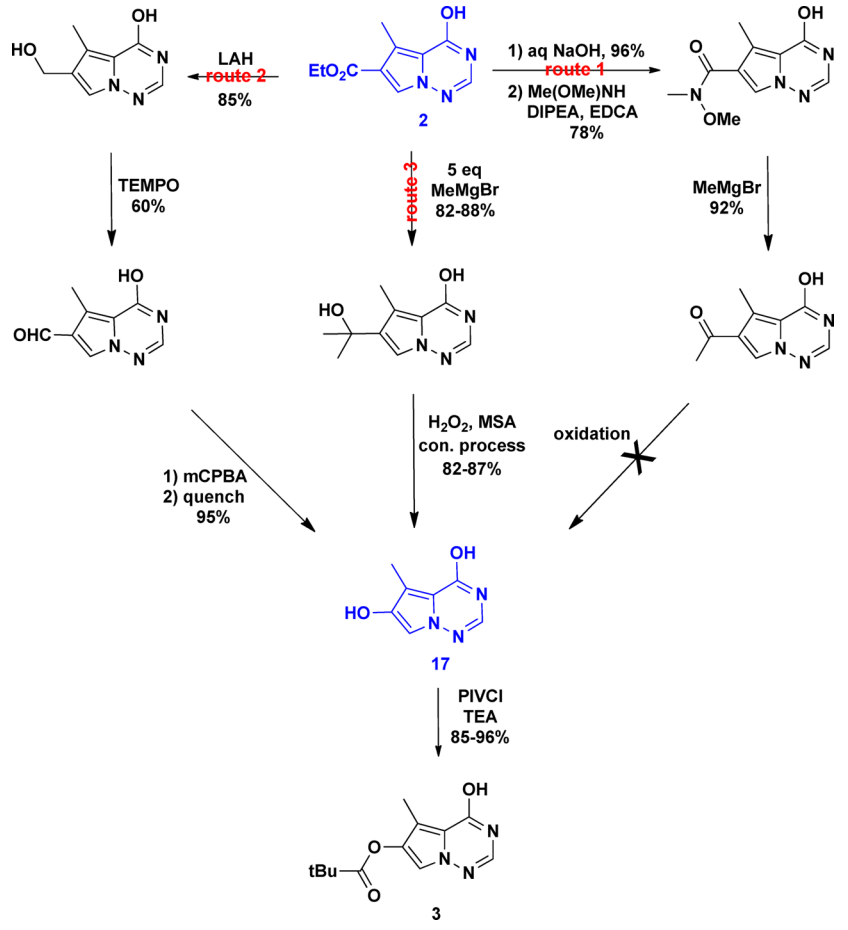
Scheme 4. Early routes to prepare des-PIV 5



Scheme 5. Conversion of pyrrolotriazine 2 to PIV-protected pyrrolotriazine 3



However, as indoles are prone to oxidation,[20] unacceptable impurity content occurred when the ester was subsequently oxidatively cleaved. In one approach, the ester was first exhaustively methylated to form the tertiary alcohol **15**. A subsequent acid-catalyzed oxidative cleavage formed the substituted pyrrolotriazine **16**.[5,21] Alternatively, LAH ester reduction and subsequent tetramethylpiperidine oxide (TEMPO)-catalyzed oxidation produced the benzylic aldehyde.

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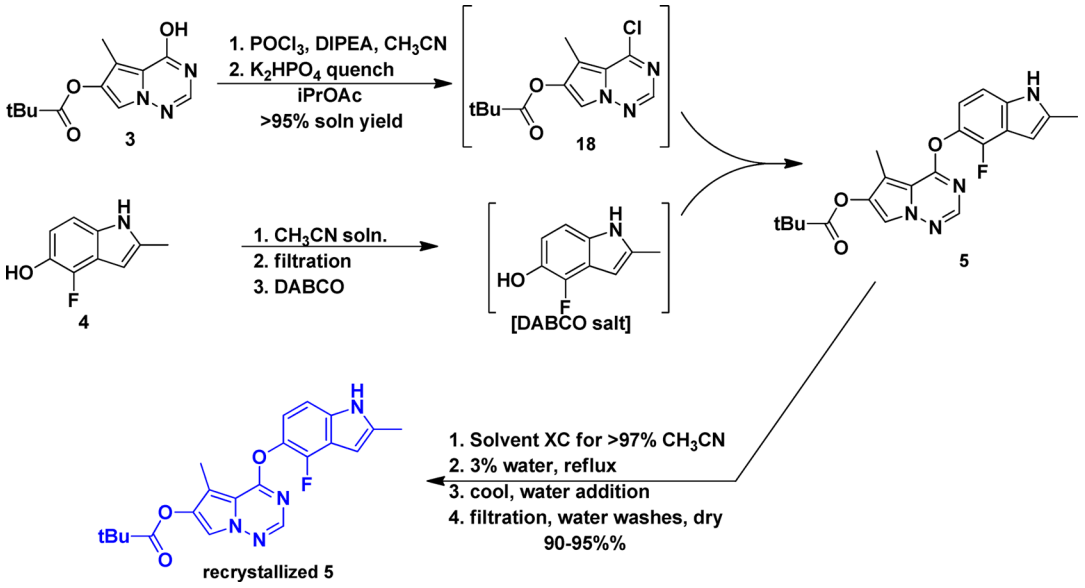
Scheme 6. Commercial preparation of coupled intermediate 5



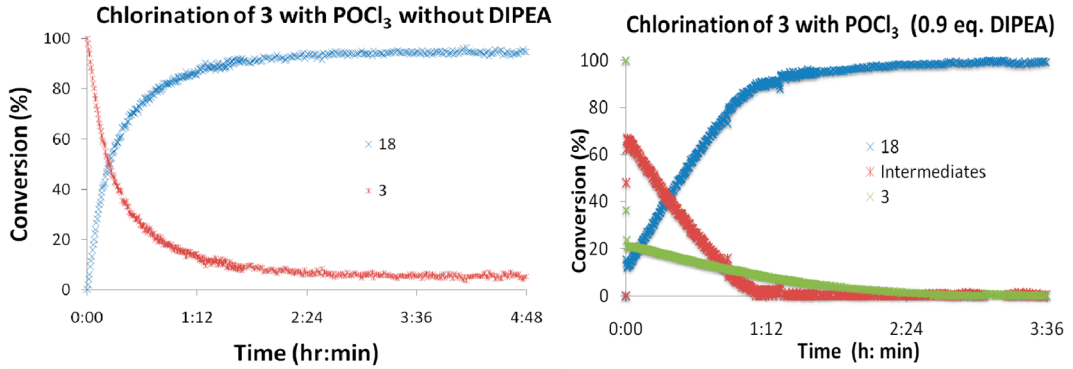


Figure 4. FTIR spectroscopy of DIPEA-catalyzed and DIPEA-free chlorinations.

A subsequent Baeyer–Villiger reaction cleaved the carbon–carbon bond via *m*-CPBA. Both reactions were low yielding and generated numerous impurities.

Clearly, the synthetic plan of shifting the oxidative cleavage to after the coupling was not viable in view of the indole's sensitive nature. The process team explored a wide variety of alternative routes to synthesize the pyrrolotriazine core in the correct oxidation state; however, none were superior to the existing chemistry. Instead, if the strategy was to keep the coupling step after the establishment of the pyrrole–oxygen bond, an additional benefit was that convergence would be established only a few steps from the API. It would fit in well with our overall strategy of impurity reduction as the product of a convergent synthesis should be easier to purify.[22]

The intrinsically hazardous oxidation chemistry would thus be addressed first at the pyrrolotriazine **3**, a superior substrate with regards to stability as compared to the indole–pyrrolotriazine **14** (Scheme 5). The ester was converted to the methyl ketone using the Weinreb amide (route 1),[23] but oxidation under Baeyer–Villiger conditions failed to further convert to **17**. If the aldehyde was formed instead using LAH reduction and TEMPO oxidation to the aldehyde (route 2), oxidation with mCPBA did form the diol **17** in 48% overall yield. This was considered for large-scale work, but route 3 led to success before this was developed.

A better solution for manipulation of energetic intermediates, particularly on multikilogram scale, is the use of flow chemistry.[24] A continuous oxidation by an acid-catalyzed benzylic hydroperoxide rearrangement was developed which did not require the prior protection of the triazine ring hydroxyl group (Scheme 5, route 3).[5,25] This proceeded by initial MeMgBr addition to form the tertiary alcohol, followed by a carefully defined continuous reaction with hydrogen peroxide and methanesulfonic acid. The stream was quenched and worked up to crude **17**. Rather than isolate this amorphous and hydrophilic diol, subsequent pivalate protection was specific for the pyrrole ring hydroxyl to form crystalline pyrrolotriazine **3**. The PIV protection would have been required in any event as chlorination with $POCl_3$ on **17** is not regiospecific. This process from the ester **2** to PIV-protected **3** has been successfully used by vendors to make several metric tons of pyrrolotriazine **3**. While not a robust process since the continuous oxidation conditions are narrowly defined, it is now a safe and reproducible process to permit commercial preparation of a key starting material.

Chlorination of Pyrrolotriazenol 3. There is good general precedent for triazine **3** chlorination with $POCl_3$ to chloroimidate **18**, followed by addition of the fluoroindole **4** to form the indole–pyrrolotriazine **5**. (Scheme 6)[1m,26,27] We determined that chlorination proceeded in almost all nonprotic

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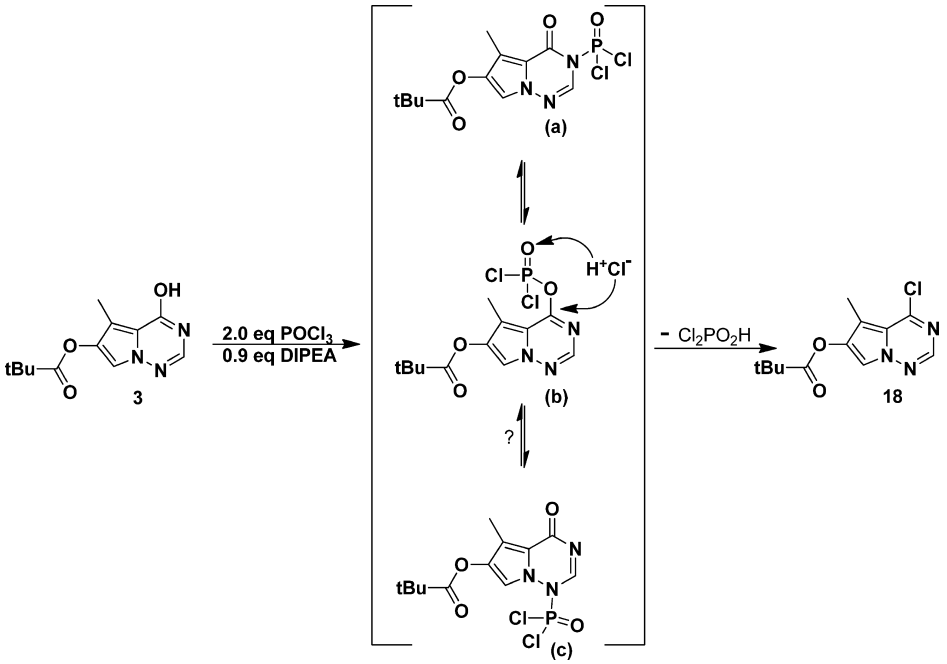
Scheme 7. Hypothesized chlorination mechanism to form chloroimidate 18



solvents examined,[28] and that, while a base was not necessary, the rate and purity was improved by the presence of amine bases.[29] Our optimized final process consisted of charging 2.0 equiv $POCl_3$ to a slurry of **3** in acetonitrile followed by a charge of 0.9 equiv DIPEA at <40 °C, leading to a clean >99.5% chlorination conversion after 5−9 h of reflux. The reaction was quenched into aqueous dipotassium phosphate (K_2HPO_4). Isopropyl acetate was included to allow a phase separation from the aqueous quench layer. A wash with aq K_2HPO_4 adjusted the pH to 8−9. Product solutions treated in this manner possessed 10 days of stability against chloroimidate hydrolysis back to **3**. The solution of **18** obtained from the workup consisted of a water-saturated solution of isopropyl acetate and acetonitrile, acceptable for the subsequent coupling reaction. However, further examination of the chlorination mechanism revealed significantly more complexity to be understood before a robust process would be attained.

Optimization of Chlorination Kinetics and Reaction Parameters. While there are numerous instances of similar chlorinations,[1m,27] the mechanistic understanding of rate and formation of impurities often differ significantly between examples and prevent drawing broader conclusions.[30] Using FTIR spectroscopy, different kinetics to form **18** became apparent, depending on whether DIPEA was present. When $POCl_3$ was added to a solution of triazine **3** and DIPEA, an intermediate's signal immediately appeared and slowly decayed in intensity as that of chloroimidate **18** grew steadily; whereas without DIPEA, the rates of **18**'s formation and **3**'s disappearance were nearly equal (Figure 4) without detection of an intermediate. HPLC analysis of the DIPEA-containing reaction revealed three transient intermediates (tentatively identified as isomers a, b, and c; Scheme 7) of equivalent mass attributed to the three possible regioisomeric chlorinated phosphate intermediates, on the basis of mass spectroscopy and phosphorous/proton NMR spectroscopy.[37,38] Unlike a similar substrate,[30] apparently the possible oligomeric intermediates occasionally seen for other substrates consisting of a single $POCl_3$ bridging two or more triazine cores are not significant, as once the first chloride has reacted, the remaining chlorides are kinetically less reactive.[31]

These observations can best be explained by DIPEA catalyzing the first step to form interconverting chlorinated phosphate intermediates followed by a slow step of chloride (from HCl) displacement of the dichlorophosphonate moiety to form chloroimidate **18**. In comparison, the rate-determining step for the reaction without base was the initial formation of the chlorinated phosphate intermediate which then would subsequently rapidly rearrange to chloroimidate **18**. The transient dichlorophosphonates would not be detected by FTIR.

While the initial chlorination rates were comparable, the absence of DIPEA also produced a reaction mixture containing numerous side products, resulting in a less pure and lower-yielding product solution. These studies provided clear support that the inclusion of DIPEA was advantageous, but the optimum charge remained to be determined.

The reaction space parameters for DIPEA were determined via a study comparing equivalents of DIPEA versus reaction completion and quality for 2.0 equiv of $POCl_3$. This established that 0.85−0.95 equiv of DIPEA versus triazine **3** produced the fastest chlorination completion and highest purity of **18**. When more than 1.1 equiv of DIPEA was introduced, the chlorinated phosphate intermediates only slowly converted to **18**. However, if water was subsequently added, the chlorination rate increased.

As stated, if no DIPEA is charged, the initial conversion to the phosphonate ester is slow and rate determining. However, once the chlorinated phosphate intermediates do form, the abundance of HCl present due to the absence of base rapidly converts the dichlorophosphonate onto chloroimidate, and no intermediate is observed in an overall slow reaction. If 1.0 equiv or more of DIPEA is present, the first step to chlorinated intermediates remains rapid. However, the base effectively complexes all the HCl formed in the first step, and the further conversion to the chloroimidate **18** becomes rate determining due to the low concentration of free acid. In this case, the

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phosphonate ester intermediate(s) are detected as long-lived intermediate(s), but if water is then subsequently added, hydrolysis of excess $POCl_3$ forms more HCl to drive the second step. When the optimized level of base (0.9 equiv) is present, the substochiometric base charge leaves sufficient HCl free[32] for the nucleophilic chloride displacement of the dichlorophosphate. The second step for formation of **18** is still rate determining, but the overall reaction is faster.

Optimization of $POCl_3$ Charge. Stress testing indicated that as little as 0.7 equiv of $POCl_3$ would lead to high conversions of chloroimidate, but as the rate is correlated to the $POCl_3$ charge, reaction completion would have been unreasonably long. In addition, it was important to avoid undercharging $POCl_3$ below 1.8 equiv as a dimeric impurity, **19A** (Figure 5), began to form as a side product.[30,33] Up to 4 equiv of $POCl_3$ was used in the early phases of development. While those chlorinations proceeded rapidly, our selection of reactor sets was limited due to the relatively large volume of aqueous K_2HPO_4 required during the quench to maintain a homogeneous phase cut. The charge was optimized at 2.0 equiv which minimized impurities, produced an acceptable rate and allowed a reasonable quench volume.

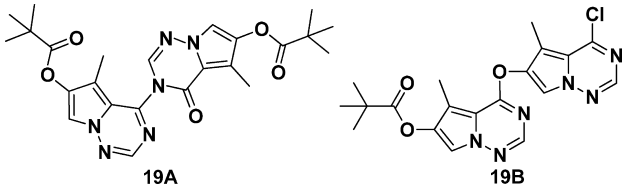


Figure 5. Self-condensation side products from chlorination.

Chlorination Workup and Reaction Modifications. The subsequent workup for the chlorination required balancing the hydrolysis of the remaining reagent against the propensity of chloroimidate **18** to hydrolyze.[34] Stress tests had established that the hydrolysis rate of **18** would increase at pH ≤3 or ≥10. The hydrolysis of **18** increased the titer of the side product HCl, which would autocatalyze further hydrolysis. Cold aqueous K_2HPO_4 proved to be an advantageous quench solution, as in case of an accidental overcharge, it would not result in an overly caustic quench mixture. Three equivalents of 12 wt % K_2HPO_4 solution hydrolyzed the remaining phosphoryl chloride quickly to produce a pH 4 mixture, and a follow-up base wash brought up the pH to 7.5–8.5. Using two separate K_2HPO_4 treatments rather than one ameliorated the otherwise inconveniently high maximum volume (V_{max}). Using a base with more capacity to neutralize acid, i.e. K_3PO_4, that required less water to dissolve per base equivalent, was not advantageous in that a new self-condensation impurity (**19B**) formed.[35]

Understanding of the mechanism and kinetics of the chlorination of **3** in acetonitrile has allowed the development of a reaction, workup and storage protocol that met our needs for a commercial preparation. This procedure has been reproducible on large scale—our last campaign produced 10 batches totaling ~1 MT of **18** in solution of 99.5–99.6% HPLC area %.

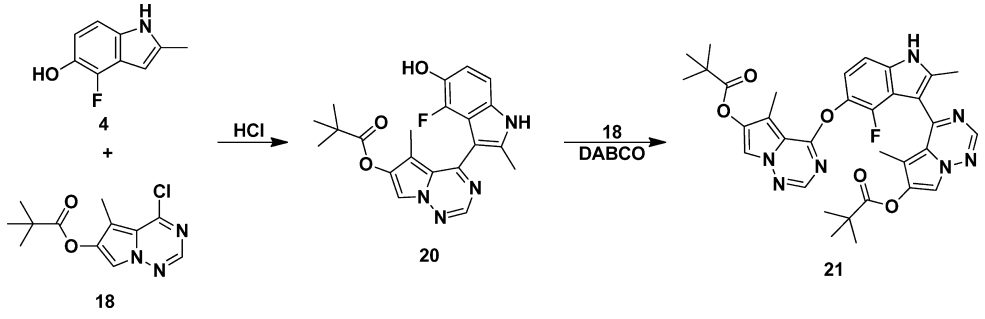
*Coupling with Fluoroindole To Synthesize Indole–Pyrrolotriazine **5**. Coupling Process Using Acetonitrile and Ethyl Acetate As Solvents.* In comparison to the precise conditions needed for optimal chlorination, the coupling reaction of chloroimidate with fluoroindole will proceed well under a wide variety of reaction conditions. We substituted DABCO for NaH, which was not safe[36] and unnecessarily strong (pK_a = ~35).[37] The base was charged to a mixture of the fluoroindole **4** and the chloroimidate **18** and heated to 50 °C to complete the coupling. Dilution of the acetonitrile reaction mixture with water to isolate the crystalline product produced 90–91% yields and 99.4–99.7% purity.

This coupling procedure remained uneventful for hundreds of chlorinations until one reaction unexpectedly produced 8 mol % of a new impurity: the overcondensation product **21**. Subsequent investigation established that this impurity had formed because of an unknown acidic impurity present in the coupling vessel which catalyzed the formation of **20** (Scheme 8). Upon addition of DABCO, **20** then further reacted to form the trimeric **21**.

As little as 5 mol % of strong acids catalyzed the formation of **20**. This sensitivity to acid was worrisome on large scale. The possibility of forming **21** was eliminated by a simple change in the process charge order. Instead of adding DABCO last, the coupling vessel was now initially charged with fluoroindole **4** and DABCO in acetonitrile to form a slurry of the DABCO salt of **4**. Only then was the chloroimidate **18** solution charged. If any acid was present, the DABCO would neutralize it before **4** was present. This reversal in charge order had no other effect on the chemistry and has provided a simple remedy against these impurities.

Along with the change in charging order, both fluoroindole **4** and DABCO were now charged in 10% excess. This would hasten reaction completion with chloroimidate **18** and minimize the presence of any **18** remaining in the mature reaction mixture. The remaining fluoroindole **4** and DABCO had high water solubility and were removed by the subsequent water washes, whereas **18** was a problematic impurity. The initial DABCO/fluoroindole mixture underwent a slurry to slurry transition to one of indole–pyrrolotriazine **5** and

Scheme 8. Formation of acid-catalyzed abnormal coupling impurity



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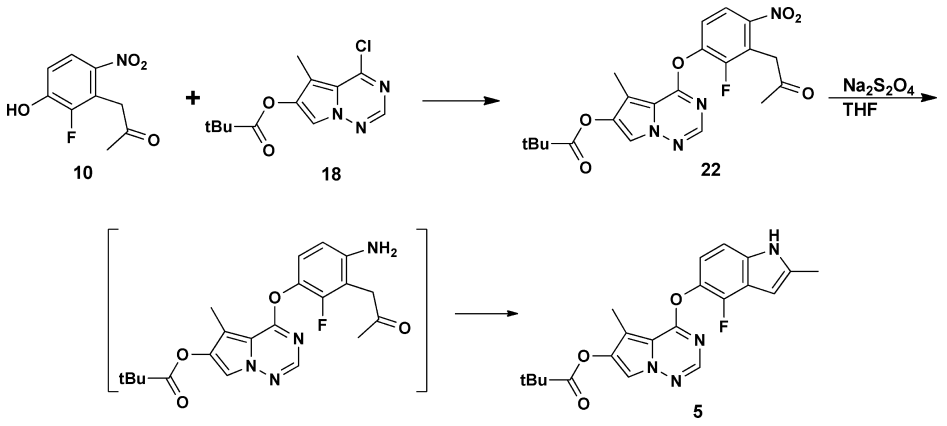
Scheme 9. Formation of the 22 in the coupling process and conversion to 5



DABCO−HCl over 1−2 h (<0.5% **18**). The slurry was diluted with water and the product collected by filtration. Overall the process has produced 3 MT of **5** over 19 batches in 93−97% yields of >99.8% purity. Only three batches required further aqueous acetone recrystallization as they were above the 0.10% specification for individual impurities.

Final Workup Modifications To Achieve a Quality Gate Intermediate. As our process entered phase III, the yields were excellent, the hazards were controlled, and thus, the focus remained on optimizing quality with control of impurities to appropriately low limits. The chloroimidate **18** and its precursor pyrrolotriazine **3** were the predominant impurities. Although the chloroimidate was minimized by extending the coupling reaction, 0.1−0.3% of **18** would routinely became entrapped within the particles of the heterogeneous mixture and was effectively isolated from further coupling. This could be demonstrated by separate analysis of the supernatant and the solids after 3 h; 90% of the remaining chloroimidate **18** resided in the solids, and the levels did not decrease during further hold times or any other modifications of the process.

Another persistent impurity concern arose from a fluoroindole precursor. Residual nitroketone **10** would produce the corresponding **22** once it coupled with chloroimidate **18** (Scheme 9). The coupled nitroketone **22** would not purge from **5**, but there was an alternative means to eliminate it. If sodium dithionite and THF were charged into the mature coupling mixture, all solids would dissolve at reflux.

As expected, **22** was reduced and converted immediately into the desired product **5**, a satisfactory means to eliminate an impurity. While subsequent cooling led to recrystallization of product containing no detectable levels of **22**, we felt this change was too radical at this stage and sought an alternative resolution that did not require new reagents and solvents.

Instead, we reconsidered the isolation of the indole−pyrrolotriazine **5** for rejecting these impurities. The current workup (crystallization of **5** from the slurry of fluoroindole + DABCO in CH_3CN/iPrOAc followed by filtration/washes) had worked reproducibly to date. Nevertheless, slurry to slurry transformations can present challenges upon scale-up due to mass transfer effects which may be dependent on equipment and operating parameters. We noted the ability of a recrystallization to remove the nitroketone impurity **22**, and began to explore means to introduce a direct classical recrystallization of **5**. This should negate the propensity of the previously uncontrolled crystallization to trap chloroimidate, **18**, and possibly also remove other impurities to deliver a nearly pure compound that would fulfill our goal of a quality gate intermediate.

However, all recrystallization systems examined did a poor job of rejecting **18**. We previously had noted the sensitivity of **18** toward hydrolysis back into pyrrolotriazine **3** and considered if this propensity could be exploited. While the conversion of one impurity for another seems a poor exchange, the following step was intolerant of **18**, as it would form a persistent daughter impurity. But the subsequent reaction could tolerate up to 5% of the pyrrolotriazine **3**, which formed an impurity which was easily purged. Clearly, **3** was preferred.

Once the reaction mixture's solvents were distilled to reduce the isopropyl acetate component to <3% to avoid the appearance of a second phase during the later water addition, screening various levels of water indicated that only the range of 2−6% water would produce a solution of the reaction mixture at reflux. Presumably a level of <2% water did not completely dissolve all of the salts while >6% water levels similarly did not completely dissolve the organic components. Within this range, the now solubilized chlorimidate impurity completely hydrolyzed back to triazine **3** over 30−90 min at reflux as it is exposed to water once the particles dissolve. The 90 min reflux limit was important as exceeding this period led to detectable levels of cleavage of the PIV group. Upon cooling and seeding at 70 °C, a seed bed was established and subsequent cooling at 10 °C/h led to controlled recrystallization. We were pleased to note that all 8 impurities that required monitoring were now below the required levels. Recrystallization from aqueous acetone is no longer required but if incorporated, all nonsolvent impurities fall below detection limits. In summary, the simple incorporation of a controlled amount of water followed by a recrystallization under carefully defined conditions completely hydrolyzed all remaining chloroimidate **18** and rejected the remaining impurities with no impact to the yield.

This new process has been run at up to 284 kg product scale to produce **5** with reproducibly low impurity levels and >99.95% purity. Three vendor campaigns have been completed with yields averaging 93% without any complications while producing over 1.6 MT of compound. On scale, all batches were recrystallized as a precaution however the nonrecrystallized material met all the specifications. This revised process will be used for manufacture of **5** and establishes this intermediate as a quality gatekeeper for the brivanib commercial process. The further transformation of **5** into API is described in ref 6.

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CONCLUSIONS

A number of process challenges to the preparation of the key intermediate to brivanib alaninate were overcome over a series of campaigns. Each campaign established a basis for further process development that ultimately led to 93% yield and >99.95% purity of indole−pyrrolotriazine **5.** These attributes enabled the establishment of a gatekeeper intermediate for the process to API. Key for these accomplishments was an understanding of the stability of the fluoroindole **4** that enabled the development of chemistry to prepare this regulatory starting material, delineating the mechanism of the $POCl_3$ chlorination chemistry that led to a reproducible chlorination to chloroimidate **18**, and finally the development of a preparation/purification of the indole−pyrrolotriazine **5** that targeted the efficient destruction of remaining chloroimidate **18**.

EXPERIMENTAL SECTION

General. In process methods for **7** and **8** (Steps 1 and 2 for preparation of **4**). **Diluent:** Acetonitrile. **Mobile phase A:** 90% Water, 10% MeCN, 0.05% TFA. **Mobile phase B:** 90% MeCN, 10% water, 0.05% TFA. **Column:** Waters SymmetryShield RP8 150 mm × 4.6 mm, 3.5 μm. **Column Temperature:** 25 °C. **Detector Wavelength:** 237 nm. **Injection Volume:** 10 μL. **Flow Rate:** 1.0 mL/min. **Program**: 0 min 30% B, 30 min 90% B. **Typical Retention Times: 6** (RT 10.71 min, RRT 1.00 R). **7** (RT 17.27 min, RRT 1.61). **8** (RT 8.88 min, RRT 0.83).

In process methods for conversion of **8** to **9** (Step 3 for preparation of **4**). **Diluent:** Acetonitrile. **Mobile phase A:** 80% Water, 20% methanol, 0.05% TFA. **Mobile phase B:** 80% Acetonitrile, 20% methanol, 0.05% TFA. **Column:** Zorbax SB-Aq, 150 mm × 4.6 mm, 3.5 μm. **Column Temperature:** 25 °C. **Detector Wavelength:** 220 nm. **Injection Volume:** 10 μL. **Flow Rate:** 1.2 mL/min. **Program:** 0 min 0% B, 25 min 25% B, 40 min 85% B. **Typical Retention Times: 8** (RT 17.8 min, RRT 0.83). **9** (RT 21.4 min, RRT 1.00).

In process method for conversion of **9** to **10** to **4** (Steps 4 and 5 for preparation of **4**) and purity method for **4**. **Diluent:** Acetonitrile/methanol/TFA 800/200/0.5. **Mobile phase A:** 80% Water, 20% methanol, 0.05% TFA. **Mobile phase B:** 80% Acetonitrile, 20% methanol, 0.05% TFA. **Column:** Zorbax SB-Aq, 150 mm × 4.6 mm, 3.5 μm. **Column Temperature:** 25 °C. **Detector Wavelength:** 237 nm. **Injection Volume:** 10 μL. **Flow Rate:** 1.2 mL/min. **Program**: 0 min 0% B, 25 min 25% B, 40 min 85% B. **Typical Retention Times: 9** (RT 20.9 min, RRT 1.71). **10** (RT 14.1 min, RRT 1.15). **4** (RT 12.2 min, RRT 1.00).

In process method for conversion of **3** to **18** to **5**. **Diluent:** Acetonitrile. **Mobile phase A:** 0.05% TFA in water. **Mobile phase B:** 0.05% TFA in acetonitrile. **Column:** Synergi Hydro-RP 150 mm × 4.6 mm, 4 μm. **Column Temperature:** 25 °C. **Detector Wavelength:** 237 nm. **Injection Volume:** 10 μL. **Flow Rate:** 2 mL/min. **Program**: 0 min 10% B, 2 min 10% B, 15 min 100% B, 18 min 100% B . **Typical Retention Times: 3** (RT 8.1 min). **18** (RT 12.1 min). **5** (RT 12.9 min), **4** (RT 5.8 min).

In process method for isopropyl acetate determination. **Column:** Stabilwax-DB, length 30 m, ID 0.32 mm, film 1.00 μm. **Injector Temperature:** 30 °C. **Detector Temperature:** 250 C. **Injection Volume:** 10 μL. **Flow Rate:** 1.5 mL/min helium, split flow 50 mL/min. Detector: FID, hydrogen 40 mL/min, air 400 mL/min, make up 25 mL/min. **Program**: 2 min at 40 °C, then 5 °C/min to 70 °C, then 20 °C/min to 220 °C. **Typical Retention Times: isopropyl acetate** (RT 7.9 min). **acetonitrile** (RT 10.5 min).

CAUTION: nitroaromatics are potentially explosive; do not run these processes without completing appropriate safety studies and precautions.

*Ethyl 2-(2,3-Difluoro-6-nitrophenyl)-3-oxobutanoate (**7**).* Ethyl acetoacetate (739 kg, 5679 mol) was added over 7 h 45 min at 10 °C to a solution of potassium *tert*-butoxide (637 kg, 5677 mol) in anhyd THF (1625 kg) cooled to 10 °C. The transfer line was rinsed with THF (80 kg) and 1,2,3-trifluoro-4-nitrobenzene (**6**, 447 kg, 2524 mol) was added over 2 h 10 min at 10−20 °C and the transfer line rinsed again with THF (80 kg). The solution was heated to 22 °C over 20 min and stirred at this temperature for 2.5 h. After reaction completion was determined by HPLC (no **6** detected), the pH was adjusted to 7.8 with 5% aq HCl (2050 L) maintaining <30 °C. The bulk was extracted with ethyl acetate (1370 kg) at 22 °C stirring for 20 min. The phases were allowed to settle for 5 h and separated. The organic layer was concentrated until no additional distillate collected under vacuum (P = 700−70 mbar) at 52−58 °C. This is used as is in the next step. An analytical sample was purified by chromatography of the concentrated oil on silica gel using heptanes/EtOAc 100/0 to 90/10 and isolating the purest fractions to produce a viscous yellow oil of 96% HPLC purity: ^{1}HNMR (CD_3CN, 399.78 MHz) 1.08 (t, 3H, J = 6 Hz), 1.86 (s, 3H), 4.00−4.25 (m, 2H), 7.45−7.55 (m, 1H), 7.92−7.98 (m, 1H), 13.13 (s, 1H). ^{13}CNMR (CD_3CN, 100.53 MHz) 14.49, 20.24, 62.60, 122.77, 146.98, 148.35, 150.81, 153.29, 155.85, 156.00, 171.81, 176.75.

*1-(2,3-Difluoro-6-nitrophenyl)propan-2-one (**8**).* The oil from the previous step was diluted with glacial HOAc (880 kg) over 5 min and warmed to 70 °C, and 95−97% H_2SO_4 (1535 kg) was added at <70 °C over 35 min. The mixture was heated to 70 °C over 3 h 25 min and stirred at this temperature for 3 h. After reaction completion was determined by HPLC (0.5% **7** remaining), it was cooled to −5 °C over 7 h 35 min, and water (3793 kg) was added at <25 °C over 2 h 40 min. The mixture was stirred at 22 °C for 40 min and allowed to settle for 15 min. The layers were separated, and the upper aqueous phase was extracted with ethyl acetate (1873 kg). The combined organic phases were washed at 22 °C with water (235 kg), ethyl acetate was added (806 kg), the organic phase was washed with 6% $NaHCO_3$ solution (3367 kg), stirred for 15 min, and settled for 30 min. After phase separation, it was washed with a 5% brine (2860 kg) wash by stirring for 10 min and settling for 90 min. The organic solution was distilled until no further distillate collects under vacuum (P = 420−55 mbar/34−60 °C) over 9 h 10 min at a jacket temperature of ≤60 °C. The crude product was isolated as a brown oil (654 kg, 77.6% HPLC purity). This was used as is in the next step. ^{1}HNMR (DMSO-d_6, 399.78 MHz) 2.29 (s, 3H), 4.25 (d, 2H, J = 1.5 Hz), 7.68 (q of d, 1H, J = 1.5, 9 Hz), 8.05 (q of d, 1H, J = 2, 5 Hz).

*1-(2-Fluoro-3-methoxy-6-nitrophenyl)propan-2-one (**9**).* Potassium carbonate (286 kg, 2069 mol) was added in portions at 9−25 °C to a solution of **8** (654 kg, 3040 mol) in methanol (1706 kg). The reaction mixture was heated to reflux over 110 min and stirred for 17 h. After reaction completion determination by HPLC (0.4% **9**), ∼1/3 of the solvent (800 L) was distilled off at 68−70 °C over 7 h 45 min. The solution was diluted with water, (644 kg) while allowing the internal temperature to decrease to 39 °C. The solution was seeded to induce crystallization. The suspension was stirred for 30 min,

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then cooled to 3 °C, and stirred at this temperature for 90 min. The product was collected by centrifuge over 11 h 45 min, and the cake was washed with water (372 kg) in two portions. The wet powder (394 kg) was dried under vacuum at 48−55 °C for 21 h 30 min to yield 375.0 kg (92.8% purity). This was dissolved in MTBE (1859 kg) by heating to reflux over 4 h 35 min. Charcoal (15 kg) in MTBE (84 kg) was added and stirred for 40 min at reflux. The slurry was filtered at 56 °C over 2 h 45 min and the line rinsed with hot MTBE (140 kg). Approximately 2230 L solvent was removed by distillation at 56 °C over 2 h 40 min, cooled to 45 °C, seeded, and held for 30 min. It was finally cooled to 0 °C over 3 h and held for additional 2 h. The product was collected by centrifuge over 12 h and the wet cake washed three times with cold *tert*-butyl methyl ether (total 208 kg). The wet powder was dried under vacuum at 48−55 °C for 9 h to yield 271 kg of crystals (99.9% assay; overall uncorrected yield from **6** = 47.3%). ^{1}HNMR (DMSO-d_6, 399.78 MHz) 2.27(s, 3H), 3.96(s, 3H), 4.18(d, 2H, J = 4 Hz), 7.20−7.35(m, 1H), 7.95−8.05(m, 1H). ^{13}CNMR (DMSO-d_6, 100.53 MHz) 29.60, 56.69, 111.41, 120.17, 122.18, 140.72, 148.04, 150.48, 151.81, 202.95.

*1-(2-Fluoro-3-hydroxy-6-nitrophenyl)propan-2-one (**10**).* Trimethylammonium chloride (466 kg, mol) was added in portions at ≤25 °C to a previously prepared slurry of aluminum trichloride (1301 kg, mol) in dry CH_2Cl_2 (1336 kg) over 150 min. To trap offgasses, the reaction vessel was connected to an empty vessel, then a scrubber was filled with methanol/25% aq ammonia/water (1:31.7:1.35 v/v/v) and finally a vessel filled with dilute sulfuric acid to trap basic vapors. The mixture was stirred for 1 h at 22 °C. A 32−38 °C solution of **9** (336 kg, mol) in dry CH_2Cl_2 (445 kg) was added at 22−33 °C over 35 min, maintaining 3 bar pressure to account for CH_3Cl offgas pressure, followed by a line rinse with CH_2Cl_2 (87 kg). (**CAUTION**: CH_3Cl is a hazardous gas!). The mixture was heated to 42 °C over 65 min and stirred at this temperature for a total of 5 h 5 min, taking care to maintain $P_{(vessel)}$ at 3 bar pressure throughout the stirring. HPLC analysis indicated no starting material, and the mixture was degassed with nitrogen through the scrubber, cooled to 22 °C over 40 min, and poured into 2 °C water (3360 kg) at 2−22 °C over 7 h 20 min. The line was rinsed with CH_2Cl_2 (87 kg), the mixture was cooled to 0 °C over 80 min and stirred at this temperature for 1 h, and collected by centrifuge over 20 h 25 min. The wet cake was washed with water (168 kg). Wet crude **10** was then added to 22 °C water (1680 kg), the slurry was stirred at 22 °C for 1 h and collected by centrifuge over 10 h 50 min. The wet cake was washed with water (672 kg), and the cake was checked for the presence of residual chloride. Additional water washes were added if necessary. The wet product was dried under vacuum at 50 °C for 13 h 20 min to yield 282 kg of solids (89.4% yield, 99.4% HPLC assay). ^{1}HNMR (DMSO-d_6, 399.78 MHz) 2.26 (s, 3H), 4.16 (s, 2H), 7.04 (dd, 1H, *J* = 12,8 Hz), 7.90 (d, 1H, *J* = 8 Hz), 11.35−11.50 (m, 1H). ^{13}CNMR (DMSO-d_6, 100.53 MHz) 29.72, 115.34, 120.93, 122.49, 139.51, 150.18, 150.89, 151.01, 203.15.

*4-Fluoro-2-methyl-1H-indol-5-ol (**4**).* Compound **10** (270 kg, mol) was dissolved in methanol (535 kg) at 27 °C and cooled to 22 °C. A freshly prepared solution of sodium hydrosulfite (1216 kg, mol, 83% assay) in water (4050 kg) was prepared in a separate vessel and at 24 °C (**CAUTION**: sodium dithionite has reports of exothermic decomposition when moist; an aqueous solution was stable up to 170 °C). The methanolic solution of **10** was added to the aqueous dithionite over 60 min, maintaining 20−25 °C. The line was rinsed with methanol (37 kg). The product began to crystallize during the addition of **10**. The mixture was stirred at 20−25 °C for 4 h, and reaction completion was determined at <0.5% (none detected) by HPLC. The reaction mixture was cooled to 0 °C over 195 min, stirred at this temperature for 5 h, and collected by centrifuge over 14 h. The wet cake was rinsed with a solution of 33% aq HCl (13 kg) and water (1070 kg) to yield 220 kg of wet **4**, and then dried under vacuum at 44−45 °C for 16 h to yield 164 kg. This was dissolved at 22 °C in a solution of methanol (411 kg), 33% aq HCl (6 kg) and water (31 kg) by stirring for 150 min. Cellulose-base filtration aid (7 kg) was added and the mixture stirred for 30 min. The filtration aid was filtered off through a pad of additional filter aid over 7.5 h, and the line was rinsed with degassed methanol (33 kg). A solution of 33% aq HCl (8 kg) and water (813 kg) was added to the filtrate over 45 min to precipitate the product. The slurry was cooled to 0 °C over 70 min, stirred for 5 h, and collected by centrifuge. The line and the cake were rinsed with a solution of 33% aq HCl (9 kg) and water (650 kg), and the wet powder was dried under vacuum at 45 °C for 15 h to yield 144.3 kg (69%, 99.8% assay, >99.95 HPLC area %, no detected GTIs, total volatiles 0.1%, KF 0.3%). ^{1}HNMR (DMSO-d_6, 600 MHz) 2.34 (s, 3H), 6.06 (s, 1H), 6.66 (t, 1H, *J* = 8.6 Hz), 6.88 (d, 1H, *J* = 8.6 Hz), 8.74 (s, 1H), 10.85 (s, 1H). ^{13}CNMR ($CDCl_3$, 125.8 MHz) 13.3, 94.2, 106.0, 111.9, 118.4, 132.3, 135.8, 136.3, 142.6.

*4-Chloro-5-methylpyrrolo[1,2-f][1,2,4]triazin-6-yl pivalate (**18**).* A slurry of pyrrolotriazine **3** (89.0 kg, 357 mols) in dry acetonitrile (156 kg, <0.05% water) was treated with phosphorous oxychloride (66 L, 706 mols) over 8 min at 23−24 °C followed by an acetonitrile (45 kg) rinse. Diisopropylethylamine (56 L, 321 mol) was added over 20 min at 22−29 °C followed by an acetonitrile (45 kg) rinse, and the mixture was heated to reflux at 85 °C over 57 min. After 11.5 h, the reaction was sampled, indicating reaction completion (0.18 HPLC area % **3**). The solution was cooled to 30−35 °C and stored in drums until a similar chlorination was completed. The reaction mass was transferred into a quench solution of 12.4 wt % aqueous K_2HPO_4 solution (2894 kg), isopropyl acetate (743 kg) and acetonitrile (35 kg) over 20 min at 2−10 °C followed by an acetonitrile rinse (39 kg). The quenched solution was stirred for 1 h at 15−17 °C, allowed to settle for 1 h and separated. The organic phase was washed with 15 wt % aqueous K_2HPO_4 solution (398 kg) for 1 h followed by 1 h of settling before separation to produce a final pH of 8.90 (water layer). The organic layer yielded 985 kg of solution of 99.5 HPLC A% **18**. In addition, 79 kg of acetonitrile rinse containing more **18** was also collected for the next step. A second identical chlorination and quench was undertaken that eventually yielded 960 kg of solution and was combined with the first solution for the subsequent coupling step. A purified sample was prepared by concentration of the product solution to solids, dissolution into 1:1 EtOAc/heptanes, filtration through a plug of silica gel, concentration, and dissolution into hot heptanes. Recrystallization was initiated by cooling and seeding. Following cooling to 5 °C, filtration and pumping, a light-yellow powder was obtained: DSC mp = 82.4 °C; Anal. Calcd For $C_{12}H_{14}N_3O_2Cl$: C, 53.83; H, 5.27; N, 15.69; Cl, 13.24. Found: C, 53.91; H, 5.20; N, 15.75; Cl, 13.26. ^{1}HNMR (DMSO-d_6, 399.78 MHz) 1.35 (s, 9H), 2.38 (s, 3H), 8.28 (s, 1H), 8.36 (s, 1H). ^{13}CNMR (DMSO-d_6, 100.53 MHz) 9.22, 27.34, 39.41, 107.04, 113.49, 116.61, 139.98, 175.75.

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*4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo-[1,2-f][1,2,4]triazin-6-yl pivalate (**5**).* For the purposes of stoichiometry, a quantitative yield is assumed for the previous step. The indole **4** (130.0 kg, 787 mol) was dissolved into acetonitrile (222 kg), stirred 4 h to dissolve, and passed through a 1 μm filter over 1 h. Additional acetonitrile (30 kg) was used to wash over the remaining amounts. 1,4-Diazabicyclo[2.2.2]octane (88.0 kg, 785 mols) was charged to the solution via a rotary feeder over 35 min at 20−29 °C. After 70 min of stirring at 26−27 °C, the solution of **18** prepared above was charged over 50 min through an inline filter at 26−28 °C and washed in with the acetonitrile wash that was collected in the subsequent step. The mixture was stirred for 3 h, at which point HPLC indicated reaction completion (0.31 HPLC area % **18**). The mixture was concentrated by distillation at 200 mbar at 37−39 °C for 3.5 h until 1290 kg remained in the reactor (reactor is on a weight cell), acetonitrile (1216 kg) was charged and an equal weight distilled off, and finally acetonitrile (1222 kg) was charged and 1220 kg distilled off. The isopropyl acetate content by GC was measured as 2.4 vol % (call point ≤3%) and KFT as 0.13%. More acetonitrile (278 kg) was added to bring the volume to the desired concentration. Water (30 kg) was added and the KFT measured as 2.0% (desired range 2−3%). The slurry was heated to reflux (80−81 °C) over 43 min to dissolve the solids and was held 1 h. The solution was cooled to 67 °C over 15 min, forming a thin suspension, and seed crystals (1.4 kg) in acetonitrile suspension were added. The seed bed was established over 75 min, and then the slurry was cooled to 24 °C over 3 h 10 min. Water (1780 kg) was added over 150 min at 23−24 °C and held 1 h. The solids were collected by filtration on a pressure filter over 165 min. A displacement wash of 297 kg water was done followed by four washes of 667 kg water each. The cake was dried under vacuum for 3 h to produce 324 kg of wet (LOD 15.4%) crystals. This was recrystallized from acetone (1464 kg) by heating over 40 min to 55 °C, holding 35 min, and cooling to 38 °C over 12 min, holding 25 min, at which point 1.5 kg of seed crystals were added. The slurry was stirred 65 min and cooled to 23−25 °C over 160 min. It was held 152 min, and water (1145 kg) was added over 155 min at 20−24 °C. The slurry was held 130 min, and the crystals were collected by centrifuge over 25 h and washed with water (1176 kg) to produce 298 kg wet crystals. This was dried at 18−63 °C over 7 h 30 min to produce 264 kg white powder, (93% yield, 0.05% KFT) after sieving through a 1.2 mm mesh (≥99.95% HPLC A%, assay ≥99.9%, 0.11% volatiles. No detectable GTIs.) ^{1}HNMR (DMSO-d_6, 399.78 MHz) 1.40 (s, 9H), 2.43 (s, 3H), 2.48 (s, 3H), 6.32 (s, 1H), 6.96 (dd, 1H, J = 8.3, 8.6 Hz), 7.06 (d, 1H, J = 8.8 Hz), 7.84 (s, 1H), 7.90 (s, 1H), 8.07 (br s, 1H). ^{13}CNMR (DMSO-d_6, 100.53 MHz) 8.88, 13.78, 27.35, 39.46, 97.26, 105.65, 106.18 (d, J = 4.0 Hz), 110.16, 111.33, 116.07, 119.03 (d, J = 19.1 Hz), 130.73 (d, J = 11.1 Hz), 136.45 (d, J = 11.1 Hz), 136.64, 138.41, 145.76, 146.46 (d, J = 249.3 Hz), 162.46, 175.91.

*Optional Recrystallization for 4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[1,2-f][1,2,4]triazin-6-yl pivalate (**5**).* Crude **5** (46.8 kg, 99.5 HPLC area %) was dissolved into acetone (267 L) and heated to 54 °C over 40 min and held for 30 min. This was clarified by passage through a 5 μm in-line filter to a second reactor over 20 min. A further 14 L of acetone was used to rinse the reactor. The mixture was heated to 54 °C to redissolve solids and cooled to 19 °C. Water (187 L) was added over 66 min, and the slurry was cooled to 5 °C over 56 min. After a 16.5 h hold, the solids were collected by filtration and washed with water (94 L). The solids were dried at 60 °C over 35 h (KF = 0.04%) to produce 45.0 kg of cream-colored solids (96.2% recovery, 99.89 HPLC area %, 99.8 wt %).

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Bhide, R. S.; Cai, Z.-W.; Zhang, Y.-Z.; Qian, L.; Wei, D.; Barbosa, S.; Lombardo, L. J.; Borzilleri, R. M.; Zheng, X.; Wu, L. I.; Barrish, J. C.; Kim, S.-H.; Leavitt, K.; Mathur, A.; Leith, L.; Chao, S.; Qautlet, B.; Mortillo, S.; Jeyaseelan, R., Sr.; Kukral, D.; Hunt, J. T.; Kamath, A.; Fura, A.; Vyas, V.; Marathe, P.; D'Arienzo, C.; Derbin, G.; Fargnoli, J. *J. Med. Chem.* **2006**, *49*, 2143−2146. (b) Bhide, R. S.; Fan, J.; Parlanti, L.; Barbosa, S.; Qian, L.; Cai, Z.; Gibson, F. S. PCT Int. Appl. 2004, WO/2004/009542; CAN 140:146018. (c) Hunt, J. T.; Mitt, T.; Borzilleri, R.; Gullo-Brown, J.; Fargnoli, J.; Fink, B.; Han, W. C.; Mortillo, S.; Vite, G.; Wautlet, B.; Wong, T.; Yu, C.; Zheng, P.; Bhide, R. S. *J. Med. Chem.* **2004**, *47*, 4054−4059. (d) Borzilleri, R. M.; Bhide, R. S.; et al. *Bioorg. Med. Chem. Lett.* **2005**, 1429−1433. (e) Cai, Z. W.; Zhang, Y.; Qian, L.; Barbosa, S.; Wei, D.; Borzilleri, R. M.; Zheng, X.; Wu, L.; Fan, J.; Shi, Z.; Wautlet, B. S.; Mortillo, S.; Jeyaseelan, R.; Kukral, D. W.; Kamath, A.; Marathe, P.; D'Arienzo, C.; Derbin, G.; Barrish, J. C.; Hunt, J. T.; Lombardo, L. J.; Fargnoli, J.; Bhide, R. S. *J. Med. Chem.* **2008**, *51*, 1976−1980. (f) Borzilleri, R. M.; Zheng, X.; Qian, L.; Ellis, C.; Cai, Z.-w.; Wautlet, B. S.; Mortillo, S.; Jeyaseelan, R.; Kukral, D. W.; Fura, A.; Kamath, A.; Vyas, V.; Tokarski, J. S; Barrish, J. C.; Hunt, J. T.; Lombardo, L. J.; Fargnoli, J.; Bhide, R. S. *J. Med. Chem.* **2005**, *48*, 3991−4008. (g) Padilla, I.; Siu, L. L. *Expert Opin. Investig. Drugs* **2011**, *20*, 577−586. (h) Ayers, M.; Fargnoli, J.; Lewin, A.; Wu, Q.; Platero, J. S. *Cancer Res.* **2007**, *67*, 6899−6906. (i) Bhide, R.; Cai, Z. W.; Qian, L.; Barbosa, S. PCT WO/2004/009784, 2004; CAN 140:124558. (j) Qian, C.; Cai, X.; Zhai, H. U.S. Patent Appl. 2009/0076044, March 19, 2009. (k) Bhide, R. S.; Cai, Z. W.; Qian, L.; Barbosa, S.; Lombardo, L.; Robl, J. U.S. Patent 7,820,814 B2, October 26, 2010. (l) Hennequin, L. F. A. Patent WO/2002/12226 A1, Feb 14, 2002. (m) Zheng, B.; Conlon, D. A.; Corbett, R. M.; Chau, M.; Hsieh, D.-M.; Yeboah, A.; Hsieh, D.; Müslehiddinoğlu, J.; Gallagher, W. P.; Simon, J. N.; Burt, J. *Org. Process Res. Dev.* **2012**, *16*, 1846−1853.

(2) (a) Saharinen, P.; Eklund, L.; Pulkki, K.; Bono, P.; Alitalo, K. *Trends Mol. Med.* **2011**, *17*, 347−362. (b) Ivy, S. P.; Wick, J. Y.; Kaufman, B. M. *Nat. Rev., Clin. Oncol.* **2009**, *6*, 569−579. (c) Kiselyov, A.; Balakin, K. V.; Tkachenko, S. E. *Expert Opin. Investig. Drugs* **2007**, *16*, 83−107.

(3) Srivastava, S. Quality by Design in Drug Substance Development: Opportunity or Challenge for Commercialization? Sino Food and Drug Association Meeting, Beijing, China, June 17, 2010.

(4) Shi, Z.; Kiau, S.; Lobben, P.; Hynes, J.; Wu, H.; Parlanti, L.; Discordia, R. P.; Doubleday, W.; Leftheris, K.; Dyckman, A. J.;

Wrobleski, S. T.; Dambalas, K.; Tummala, S.; Leung, S. S. W.; Lo, E. T. *Org. Process Res. Dev.* **2012**, *10*, 1618−1625.
(5) LaPorte, T. L.; Spangler, L.; Hamedi, M.; Lobben, P.; Chan,S. H.; Muslehiddinoglu, J.; and Wang, S. Y. *Org. Process Res. Dev.*, to be submitted.
(6) A paper to be submitted to *Org. Process Res. Dev.* describes the process development from **5** to the active pharmaceutical ingredient (API) or brivanib alaninate.
(7) Crispino, G. A.; Hamedi, M.; LaPorte, T. L.; Thornton, J. E.; Pesti, J. A.; Xu, Z.; Lobben, P. C.; Leahy, D. K.; Müslehiddinoğlu, J.; Lai, C.; Spangler, L. A.: Discordia, R. P.; Gibson, F. S. Process for the Preparation of [(1*R*),2*S*]-2-Aminopropionic acid 2-[4-(4-fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy]-1-methylethyl ester. U.S. Patent 7,671,199, Mar 2, 2010.
(8) (a) Reissert, A. *Ber.* **1897**, *30*, 1030. (b) Baeyer, J. *Ber.* **1880**, *13*, 187. (c) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; pp 176−183.
(9) Alternative bases to *t*-BuOK and alternative solvents have been demonstrated: (a) Parikh, V. D.; Fray, A. H.; Kleinman, E. F. *Synthesis* **1988**, 1567−1569. (b) Arnott, E. A.; Crosby, J.; Evans, M. C.; Ford, J. G.; Jones, M. F.; Leslie, K. W.; McFarlane, I. M.; Sependa, G. J. Patent WO/2008/053221 A2; May 8, 2008. The benzyl position acidity of **7** competes with deprotonation of the ethyl acetoacetate by *t*-BuOK. Two equivalents of ethyl acetoacetate anion were necessary since one would be quenched by the product. The side product formed by nucleophilic displacement of the fluoride by *tert*-butoxide on the starting material was minimized by maintaining ≤25 °C during the addition of ethyl acetoacetate.
(10) All purities are HPLC area % unless otherwise specified.
(11) DSC/calorimetry detected the following exothermic events: 6 kJ/kg at 54 °C; 85 kJ/kg at 124 °C, and 74 kJ/kg at 221 °C. The various stages of the workup revealed no concerns below 171 °C. Note that these measurements were specific to our starting materials, facilities and protocols. Repeating any of this chemistry requires independent safety examination for prudent chemical practices.
(12) Following H_2SO_4 addition, exothermic events are detected at 8 kJ/kg at 66 °C, 256 kJ/kg at115 °C, 282 kJ/kg at 295 °C, and after 3 h of reaction: 279 kJ/kg at 103 °C and 305 kJ/kg at 295 °C, indicating a reaction temperature of 70 °C permitted a safe operation. The concentrated oil was stable and displayed a DSC exotherm of 1193 kJ/kg at 210 °C.
(13) Arnott, E. A.; Crosby, J.; Evans, M.C..; Ford, J. G.; Jones, M. F.; Leslie, K. W.; Mcfarlane, I. M.; Sependa, G. J. PCT Int. Appl. (2008), WO/2008/053221 A2 20080508. CAN 148:517536.
(14) Safety examination of the reaction solution established exotherms of 12 kJ/kg at 108 °C and 250 kJ/kg at 180 °C and no other points of concern for the rest of the reaction, workup, recrystallization and drying.
(15) (a) Boovanahalli, S. K.; Kim, D. W.; Chi, D. Y. *J. Org. Chem.* **2004**, *69*, 3340−3344. (b) Kemperman, G. J.; Roeters, T. A.; Hilberink, P. W. *Eur. J. Org. Chem.* **2003**, *9*, 1681−1686. (c) Parvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615−2665.
(16) DSC and safety testing identified exotherms of 208 kJ/kg at 90 °C and 77 kJ/kg at 275 °C, indicating little danger if CH_2Cl_2 was the solvent and no other points of concern for the rest of the reaction, workup, recrystallization and drying. While $AlCl_3$ alone will cleave aromatic methyl ethers, it requires forcing conditions: Gutman, A.; Nisnevich, G.; Yudovitch, L. U.S. Patent 7,312,345 B2, December 25, 2007.
(17) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875−2911. (b) Hegedus, L. S. *Angew. Chem.* **1988**, *100*, 1147−61. (c) Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1−8.
(18) Safety testing indicated exothermic events of 81 kJ/kg at 164 °C and 16 kJ/kg at 264 °C and no significant events for all other stages of the workup, recrystallization and drying.
(19) MS would detect components up to MW = 1035.
(20) 2-Methylindoles are known to undergo ring oxidations for many oxidants: (a) Julian, P. L.; Mueyer, E. W.; Printy, H. C. In *The Chemistry of Indoles*; Elderfield, R. C., Ed.; Heterocyclic Compounds, Vol. 3, p 77; New York: John Wiley & Sons Inc., 1952. (b) Bird, C. W.; Cheeseman, G. W. H. Structure of Five-membered Rings with One Heteroatom. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 246−254.
(21) Hamann, H. J.; Liebscher, J. *J. Org. Chem.* **2000**, *65*, 1873−1876.
(22) Convergent reactions typically produce impurities that differ significantly from the desired product and should be amenable to more efficient purification. Zhang, T. Y. *Chem. Rev.* **2006**, *106*, 2583−2595.
(23) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.
(24) Pesti, J., Ed. *Org. Process Res. Dev.* **2012**, *16*, 840 and manuscripts following in the same issue: pp 844−1150.
(25) (a) *Tetrahedron Lett.* **1987** *28*, 1027−1030. (b) *Tetrahedron Lett.* **1993** *34*, 7667−7668.
(26) A large variety of other chlorinating agents will also form **18**, at least in low yield, such as thionyl chloride, oxalyl chloride, phosphorous trichloride, and phosphorus pentachloride. Similarly, phosphorous oxybromide permitted impure preparations of the analogous bromide. Methanesulfonyl chloride and DIPEA in dichloromethane formed the *N*-mesylate, unreactive when further treated with **4** and DABCO.
(27) (a) Ford, J. G.; Pointon, S. M.; Powell, L.; Siedlecki, P. S. *Org. Process Res. Dev.* **2010**, *14*, 1078−1087. (b) Ford, J. G.; O'Kearney-McMullan; Pointon, S. M.; Powell, L.; Siedlecki, P. S.; Purdie, M.; Withnall, J.; Wood, P. O. F. *Org. Process Res. Dev.* **2010**, *14*, 1088−1093. (c) Broxer, S.; Fitzgerald, M. A.; Sfouggatakis, C.; Defreese, J. L.; Barlow, E.; Power, G. L.; Peddicord, M.; Su, B-N; Tai-Yuen, Y.; Pathirana, C.; Sherbine, J. P. *Org. Process Res. Dev.* **2011**, *15*, 343−352. (d) Sun, Z.; Wang, H.; Wen, K.; Li, Y.; Fan, E. *J. Org. Chem.* **2011**, *76*, 4149−4153. (e) See refs 1m and 33 (f) Thiel, O. R.; Achmatowicz, M.; Bernard, C.; Wheeler, P.; Savarin, C.; Correll, T. L.; Kasparian, A.; Allgeier, A.; Bartberger, M. D.; Tan, H.; Larsen, R. D. *Org. Process Res. Dev.* **2009**, *13*, 230−241.
(28) Crispino, G.; Barbosa, S.; Fan, J.; Cai, Z. W. U.S. Patent Appl. 2005/0288289 A1, December 29, 2005. Solvents that permitted chlorination with $POCl_3$ included toluene, acetonitrile, dimethyl carbonate, MTBE, ethyl acetate, isopropyl acetate, *n*-butyl acetate as well as neat $POCl_3$ itself.
(29) Other productive bases were quinoline, quinoxaline, triethylamine, and most secondary and tertiary amines that were tested.
(30) For an excellent investigation of the chlorination kinetics and mechanism for 4-quinazolones and the appearance of a similar dimer see: Arnott, E. A.; Chan, L. C.; Cox, B. G.; Meyrick, B.; Phillips, A.. *J. Org. Chem.* **2011**, 1653−1661.
(31) Archmatowicz, M. M.; Thiel, O. R.; Colyer, J. T.; Hu, J.; Elipa, M. V. S.; Tomaskevitch, J.; Tedrwo, J. S.; Larsen, R. D. *Org. Process Res. Dev.* **2010**, *14*, 1490−1500.
(32) The ring nitrogens of the pyrrolotriazine are not sufficiently basic to complex HCl.
(33) The structure of this impurity was established by ^{1}HNMR and single crystal X-ray spectroscopy. It became the primary product by treating triazine **3** with 0.3 equiv of $POCl_3$ and 1.2 equiv of DIPEA. Similar dimers have been detected by others when reaction conditions are not optimal: Anderson, N. G.; Ary, T. D.; Berg, J. L.; Bernot, P. J.; Chan, Y. Y.; Chen, C.-K; Davies, M. L.; DiMarco, J. D.; Dennis, R. D.; Deshpande, R. P.; Do, H. D.; Droghini, R.; Early, W. A.; Gougoutas, J. Z.; Grosso, J. A.; Harris, J. C.; Haas, O. W.; Jass, P. A.; Kim, D. H.; Kodersha, G. A.; Kotnis, A. S.; LaJeunesse, J.; Lust, D. A.; Madding, G. D.; Modi, S. P.; Moniot, J. L.; Nguyen, A.; Palaniswamy, V.; Phillipson, D. W.; Simpson, J. H.; Thoraval, D.; Thurston, D. A.; Tse, K.; Polomski, R. E.; Wedding, D. L.; Winter, W. J. *Org. Process Res. Dev.* **1997**, *1*, 300−310 See also ref 2f..
(34) Archmatowicz et al. has published an excellent analysis and understanding of the quench of $POCl_3$ in a similar reaction but states that each reaction is unique and recommends full hazard analysis before scale-up; see ref 31.

(35) This structure based on LC−MS data. The analogous impurity is also known to form when a quinazolinone was chlorinated by $POCl_3$. See refs 27 (a) and (b).
(36) *Handbook of Reactive Chemical Hazards*, 3rd ed.; Breherick, L. Ed.; Butterworths: London, 1975, pp1132−1134.
(37) Buncel, E.; Menon, B. *J. Am. Chem. Soc.* **1977**, *99*, 4457−4461.
(38) The assignment for regioisomer (c) is tentative.