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Convergent, Kilogram Scale Synthesis of an Akt Kinase Inhibitor

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Supporting Information

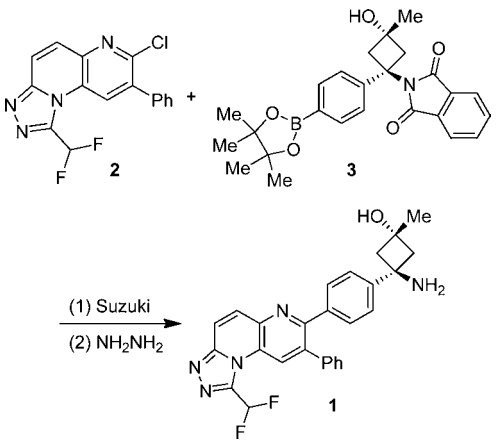
ABSTRACT: The development of a convergent, chromatography-free synthesis of an allosteric Akt kinase inhibitor is described. The route comprised 17 total steps and was used to produce kilogram quantities of the target molecule. A key early transformation, for which both batch and flow protocols were developed, was formylation of a dianion derived by deprotonation and subsequent lithium-halogen exchange from a 2-bromo-3-aminopyridine precursor. Improved reaction yield and practicality were achieved in the continuous processing mode. Further significant process developments included the safe execution of a high temperature and pressure hydrazine displacement, separation of substituted cyclobutane diastereomers by means of chemoselective ester hydrolysis, and a late-stage Suzuki fragment coupling under mild conditions.

INTRODUCTION

Cancer remains one of the leading causes of death in both developed and developing countries, with the annual worldwide death toll expected to exceed 11 million by 2030.[1,2] The emerging area of targeted cancer therapy entails finding target proteins uniquely mutated in cancer cells and identifying their upstream and downstream signaling pathways. The serine/threonine kinase Akt pathway plays a pivotal role, as it is involved in a number of apoptotic pathways and is abnormally upregulated in various types of cancers, including colon, breast, brain, lung, and prostate.[3,4] Inhibition of Akt for the treatment of cancer has been validated in both preclinical animal models and early phase human clinical trials.[2,5]

Compound **1** (Scheme 1) has been identified as a potent allosteric Akt inhibitor.[6] We were recently required to execute the first kilogram scale delivery of this active pharmaceutical ingredient (API). In this paper we report the development of a safe and scalable synthetic route that enabled the production of the required quantity of the target molecule.

Scheme 1. Previously Reported Suzuki Coupling Strategy



A synthesis of compound **1** on small scale has previously been reported, involving a late-stage Suzuki coupling between pyridyl chloride **2** and aryl boronate **3** (Scheme 1).[6] A similar disconnection was favored for the larger preparation as well, since it would allow for the convergent late-stage union of two fragments of roughly equal size and complexity. The preparation of *N*-phthalimido-protected boronate **3** required 10 steps, including multiple protecting group manipulations, and necessitated the use of genotoxic hydrazine in the final deprotection step to generate the API **1**. An alternative retrosynthesis of the corresponding *N*-Boc-protected boronate **6** was therefore proposed (Scheme 2), in which the primary amine moiety would be obtained through Curtius rearrangement, with a diastereoselective nucleophilic addition to ketone **7** serving to establish the relative stereochemistry around the cyclobutane ring. Control of the diastereoselectivity of the methyl addition was anticipated to be a potential challenge.

The aryl electrophile coupling partner (e.g., **2** or **4**) would arise from the sequential appendage of heterocyclic rings onto the functionalized pyridine core structure **5**, following the general strategy previously disclosed.[6] Key issues for scale up of the previously reported route included the use of microwave conditions for several steps run at high temperatures and pressures, and multiple chromatographic purifications.

RESULTS AND DISCUSSION

Synthesis of Triflate 4. Pyridyl aldehyde **5** was previously prepared on gram scale in 5 steps from picoline derivative **9**.[6] A

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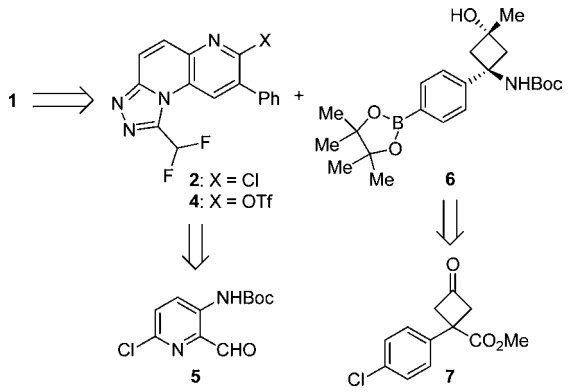
Scheme 2. Retrosynthesis of Target Compound 1 for Kilogram Scale Production

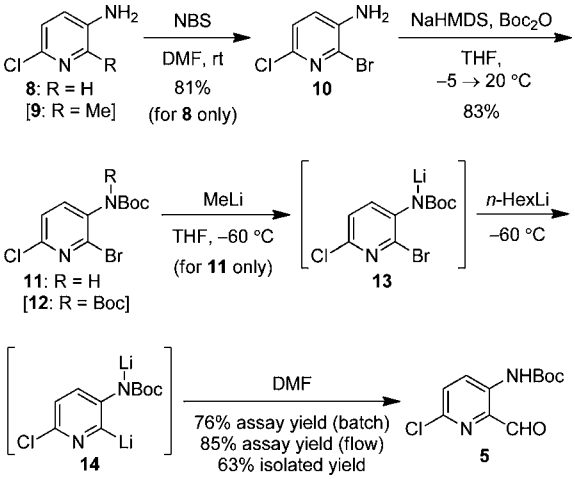


shorter synthesis was developed, as shown in Scheme 3, taking advantage of the potential for selective functionalization at the C-2 position of commercially available 3-amino-6-chloropyridine (**8**). Treatment of pyridine **8** with NBS in DMF resulted in highly regioselective monobromination[7,8] to give compound **10**, which was isolated in 81% yield by direct crystallization from the reaction mixture upon the addition of water.[9] Acetonitrile (MeCN) could also be used for this reaction; however, a higher yield of isolated product **10** was obtained using DMF.

Selective mono-Boc protection of aniline derivatives can be difficult due to low nucleophilicity of the sp^2-nitrogen. Protection of aniline **10** using Boc_2O/Et_3N/DMAP in MeCN was reported to proceed in 58% yield.[10] In our hands, the use of an established literature method (2 equiv of NaHMDS and then 1 equiv of Boc_2O in THF at room temperature)[11] resulted in improved yields but was plagued by incomplete conversion of aniline **10** and the formation of up to 11% bis-protected compound **12**. After operational improvements to this step, a reproducible protocol was developed that involved the addition of NaHMDS to a THF solution of aniline **10** and Boc_2O at −5 °C. This generated <1% bis-protected compound **12** on multikilogram scale, and bromide **11** was isolated in 83% yield and >99.5 wt % purity[12] by aqueous (aq) workup followed by crystallization from isopropanol (IPA)/water.

Conversion of bromide **11** to aldehyde **5** was initially very problematic. Experiments using ≥2 equiv of *n*-BuLi to generate

Scheme 3. Preparation of Pyridyl Aldehyde 5



the corresponding dianion (**14**) followed by quenching with DMF (or alternative electrophilic reagents) were found to be highly capricious even on gram scale.[13] After extensive experimentation, it was found that *N*-lithio monoanion **13** could be formed cleanly at low temperature by treating aniline **11** with 1 equiv of methyllithium (MeLi) in THF; addition of *n*-hexyllithium (*n*-HexLi)[14] then resulted in metal−halogen exchange to give dianion **14**, which could be quenched by DMF to give the desired aldehyde **5** in good assay yield (75−80%). One major impurity was generated (7−8%) that resulted from competitive debromination of starting material **11**; however, this was efficiently rejected during the product crystallization. Cryogenic temperatures were required (−45 °C or below) for the dianion formation; the yield began to drop significantly if the reaction was run at higher temperatures (e.g., 62% assay yield at −20 °C).

For the bulk production, this formylation step was first run in 2 × 5 kg batches in a 100 L vessel at −60 °C. During the second batch, the reaction solution turned into a thick gel at the dianion (**14**) stage, a phenomenon which had not been observed in gram scale experiments. The batch temperature had to be raised to −45 °C and the agitator manually manipulated until the mixture was sufficiently mobile to allow stirring to continue automatically. Fortuitously, these additional operations did not impact the reaction yield, as each 5 kg batch gave a 76% assay yield of aldehyde **5**. However, from a practical perspective, the gelling problem encountered with the longer hold times needed for temperature control in these kilogram scale runs presented a concern for further scale-up in fixed vessel equipment. This spurred a preliminary evaluation of the feasibility of performing the formylation under flow conditions, which have been applied to a number of other organolithium processes,[15,16] since the more efficient mixing and heat transfer in a continuous operation could result in shorter hold times.

A solution of anion **13** in THF was preformed using MeLi below −40 °C and then fed into the flow reactor, the schematic for which is depicted in Figure 1 (see the Experimental Section for a detailed description). The reactor was constructed of 0.25-in. internal diameter stainless steel tubing and immersed in a dry ice/acetone bath to maintain a low temperature. Reagent streams were fed by peristaltic pumps with pressure gauges (PI) through polytetrafluoroethylene (PTFE) tubing. Within the flow reactor, the stream of anion **13** was mixed with *n*-BuLi (commercial 2.5 M solution in hexanes, used as is with no precooling) via a T-connector attached to the first static line mixer.[17] Upon exiting the mixer, the stream of the resulting dianion **14** was immediately combined with the solution of DMF/THF in a second T-connector/static mixer arrangement. In-process temperature was monitored using three stainless steel thermocouples (T1−3). The product stream was then fed through PTFE tubing into an aqueous quench solution (acetic acid/*tert*-butyl methyl ether/water) in a glass vessel for neutralization and workup. Pump flow rates and mixer residence times were optimized on laboratory scale to maximize conversion of bromide **11** to the desired aldehyde **5**. The residence times for the dianion formation and DMF alkylation steps could be reduced to 2 and 2.5 s, respectively, while still achieving complete conversion of the starting material and a reaction purity profile equal to or better than batch mode.

To demonstrate proof-of-principle for this process, a preparative scale run was perfomed using the setup shown at the bottom of Figure 1. The anion **13** derived from 1 kg of bromide **11** was processed through the flow reactor in 1 h, at a

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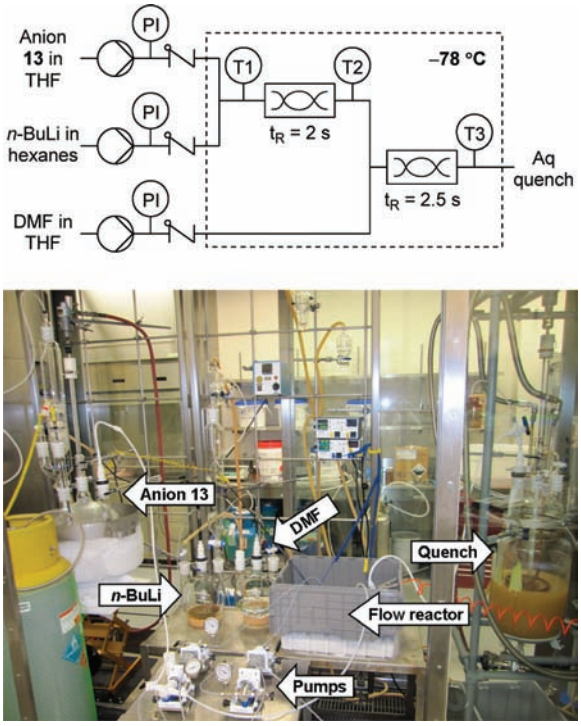


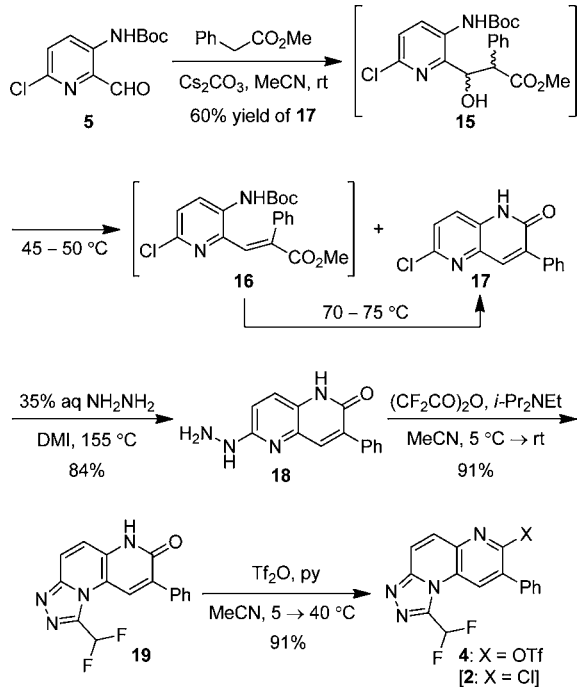
Figure 1. Flow setup: schematic (top) and kilogram-scale run (bottom).

flow rate of 114 mL/min. Efficient cooling of the system in the rudimentary cold bath was maintained even at this high flow rate (the temperatures recorded at steady-state were −70, −65, and −55 °C at T1, T2, and T3, respectively). The solution assay yield of aldehyde **5** at the end of the run (85%) was higher than on the 5 kg scale in batch mode (76%), and the level of debrominated side-product was lower (4% vs 7−8%). Furthermore, even with a slightly higher concentration of dianion **14** in flow mode (in 7 volumes of solvent compared to 10 in batch mode), no gelling or plugging of the reactor was observed.

After workup, the organic layer from the 1 kg flow run was combined with both 5 kg batches, and aldehyde **5** crystallized as one lot by solvent-switch into IPA followed by addition of water. A total of 6 kg of aldehyde **5** was isolated for a combined isolated yield of 63%. A relatively high loss of product (13%) to crystallization liquors was accepted for this delivery, since the addition of too much water antisolvent resulted in oiling out of the product.

The reported conditions for the conversion of aldehyde **5** to naphthyridone **17** used phenylacetyl chloride and DBU in THF at 100 °C.[6] An alternative procedure was developed that proceeded under milder conditions using methyl phenylacetate and Cs_2CO_3 in MeCN. The reaction temperature was ramped successively from room temperature (rt) to 45−50 °C to 70−75 °C to funnel the proposed intermediates **15** and **16** along the mechanistic pathway illustrated in Scheme 4.[18] Cyclized product **17** crystallized directly from the reaction mixture at the end of the reaction, with excellent rejection of impurities.[19] Water was then added to dissolve inorganic salts, and the product was collected by filtration. The isolated yield (92 wt %, 60% corrected yield) was moderate; however, the conditions were reproducible and the constraints of the project timeline precluded further optimization of this step.

Scheme 4. Conversion of Aldehyde 5 to Triflate 4



The displacement reaction to convert chloride **17** to hydrazine **18** had used 7 equiv of hydrazine hydrate in pyridine under microwave irradiation at 160 °C.[6] Our own screening efforts confirmed that very forcing conditions were indeed required to effect this transformation. The most practical procedure that could be developed, within the time frame of meeting the target API delivery date, involved reacting chloride **17** in 4−5 volumes of 1,3-dimethyl-2-imidazolidinone (DMI) with 18 equiv of hydrazine (35% aq solution) at 155 °C in an autoclave.

Such conditions involving the use of aqueous hydrazine at high temperature clearly mandated rigorous safety evaluation before being run on scale. A differential scanning calorimetry (DSC) analysis of a sample of the reaction mixture prior to heat up showed only a minor exotherm of 7.5 cal/g of reaction mixture initiating at 221 °C. Further testing was performed using a closed system rapid screening device (RSD). In one experiment a reaction mixture sample was heated to 166 °C and aged for 14 h, with no unexpected exothermic activity being observed (Figure 2a). However, noncondensable gas was generated, with the maximum gas generation rate (1.92 psi/min) occurring at the start of the age, reaching a maximum pressure of 382 psi after ∼4 h, and then decreasing to 282 psi over the remaining ∼11.5 h. Assuming hydrazine was the source of generated gas, 0.21 mol of gas was generated per mol of hydrazine. In the second experiment, a sample was heated from 22 to 255 °C (100 °C above the proposed reaction temperature) at 3 C°/min (Figure 2b). Again, no unexpected thermal activity was observed, but there was noncondensable gas generation. The pressure of 652 psi was observed after cool-down to 155 °C, equating to 0.48 mol of gas generated per mole of hydrazine.[20] Extrapolating these results to the proposed production scale resulted in a predicted maximum gas generation rate of 6.7 L/min and a maximum pressure for a closed system (with no venting) of 1454 psig at 166 °C and of 2923 psig at 155 °C after first heating to 255 °C. These values were well within the operating range of the equipment train to

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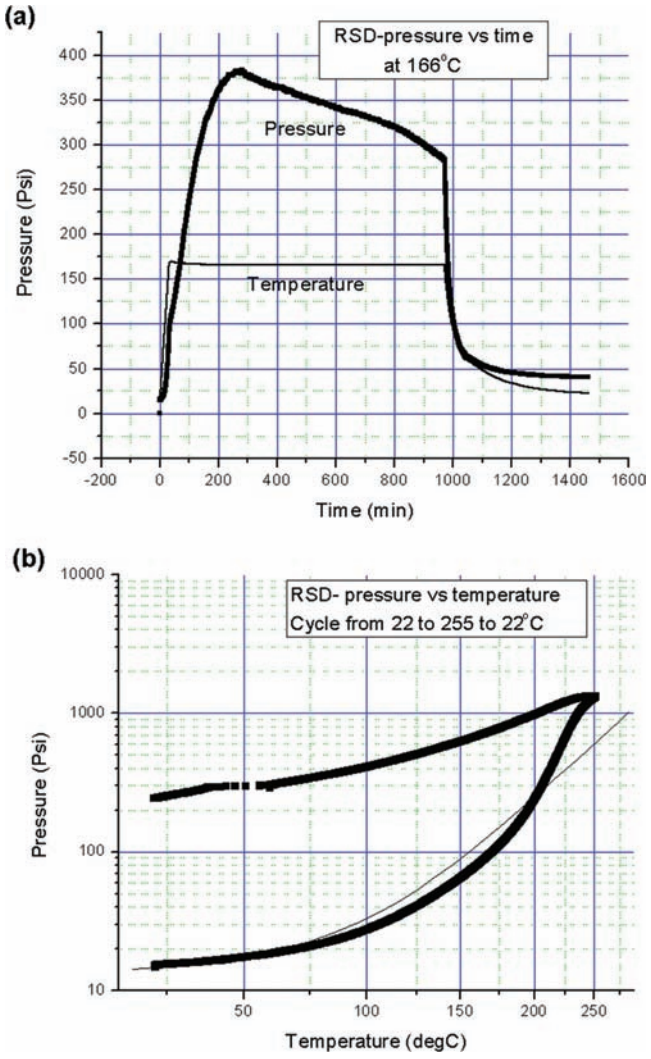

Figure 2. RSD testing of hydrazine displacement reaction: (a) isothermal age at 166 °C; (b) temperature cycling.

be used,[21] and they showed that the reaction was safe to run under the conditions described.[22]

The conversion of chloride **17** to hydrazine **18** was run in 3 × 1.1 kg batches, each of which proceeded to >99% conversion. The highest pressure generation was 1450 psi, at a maximum rate of 7.6 psi/min, in excellent agreement with the extrapolation from the RSD testing. At the end of each reaction, the product slurry was diluted with water to minimize product liquor losses and reduce the concentration of residual NH_2NH_2. The batches were combined for filtration, affording 2.6 kg of hydrazine **18** in 98% purity and 84% yield. The small amount (0.7%) of unreacted chloride starting material **17** was not rejected during this isolation but could be purged during downstream steps.

The optimum conditions for the subsequent triazole formation employed 3 equiv of difluoroacetic anhydride and 5 equiv of Hünig's base in MeCN at 5−20 °C. The use of less than 3 equiv of the anhydride gave inconsistent results with long reaction times or stalled reactions. MeCN was preferred to DMF as solvent due to a slightly cleaner reaction profile and better impurity rejection. Although the conversion of hydrazine **18** to triazole **19** is a slurry-to-slurry process, it behaved reproducibly on scale, with the reaction completing within 2 h. Water was then added to quench excess anhydride reagent and reduce product liquor losses. The product cake that was first isolated was subsequently reslurried in MeCN/water to upgrade the purity, with triazole **19** being isolated in 91% overall yield from hydrazine **18**. This upgrade was necessary for satisfactory performance of the material in the subsequent triflation step.[23]

The conversion of triazole **19** to aryl chloride **2** could only be effected, with any modest degree of success, using $POCl_3$ under microwave conditions at temperatures above 100 °C. We proposed that the corresponding triflate **4** (Scheme 4) could be generated under milder conditions and would serve as a viable coupling partner in the Suzuki coupling. Treatment of triazole **19** with Tf_2O (1.5 equiv) in the presence of a base indeed led to the clean formation of the desired triflate **4** in good yield. A small, focused screen of reaction conditions identified pyridine, MeCN, and 40−50 °C as the optimum base, solvent, and reaction temperature, respectively. Under these conditions, >98% conversion of pyridone **19** was achieved within 2 h on scale, with the product **4** then being crystallized by the addition of water and isolated in 91% yield. A total of 3.4 kg of triflate **4** was produced in 7 steps, and 18% overall yield, from 3-amino-6-chloropyridine **8**. Notably, in five of these steps, the desired product could be isolated directly from the reaction mixture, with no aqueous workup or other purification procedures needed.

Preparation of *trans*-Hydroxy Acid 27. The cyclobutane ring was constructed in a one-pot operation involving sequential *C*-alkylations of the dianion of 4-chlorophenylacetic acid **20**, generated using *i*-PrMgCl as base in THF, with epichlorohydrin as the 1,3-bis-electrophile (Scheme 5). On 20 kg scale the *cis*-hydroxy acid product was isolated in 59% yield and 96% purity following aqueous workup and crystallization from toluene (PhMe).[24] A small amount of dechlorination occurred during the reaction. The resulting des-chloro impurity **22** (4%) cocrystallized with the desired product **21**; however, sufficient rejection of des-chloro impurities was observed during later isolations. Esterification of acid **21** under standard conditions (MeOH, cat. H_2SO_4) proceeded smoothly to give methyl ester **23** (90% yield), which was used crude in the subsequent bleach/TEMPO oxidation to afford cyclobutanone **7** in quantitative yield. Due to the fact that ketone **7** is a low-melting solid, it was not isolated but instead carried forward as a solution in PhMe into the methyl addition step.

Initial gram scale experiments evaluating the addition of MeMgBr to ketone **7** were not promising. At 0 °C in THF the diastereoselectivity was poor (**24**:**25** ∼1.6:1), reactions would stall at ∼80% conversion (due to competing enolate formation), and chromatographic purification was required to isolate samples of the desired *trans*-hydroxy ester **24** (since this material is an oil). A breakthrough was found when the reaction was performed under cryogenic conditions in a less polar solvent mixture (10:1 PhMe/THF, a small amount of THF was necessary to maintain solubility of the ketone starting material **7** at low temperatures); the addition proceeded to >95% conversion and with an improved diastereoselectivity of ∼2.5:1. A difference in the relative rates of hydrolysis of the ester groups in compounds **24** and **25** was observed, with *cis*-isomer **25** undergoing saponification much more rapidly. This allowed for separation of the resulting undesired *cis*-acid **26** from the desired *trans*-ester **24** by simple aqueous extraction.

On scale, the addition of MeMgBr to ketone **7** at −70 °C proceeded to 98% conversion and with a diastereoselectivity of

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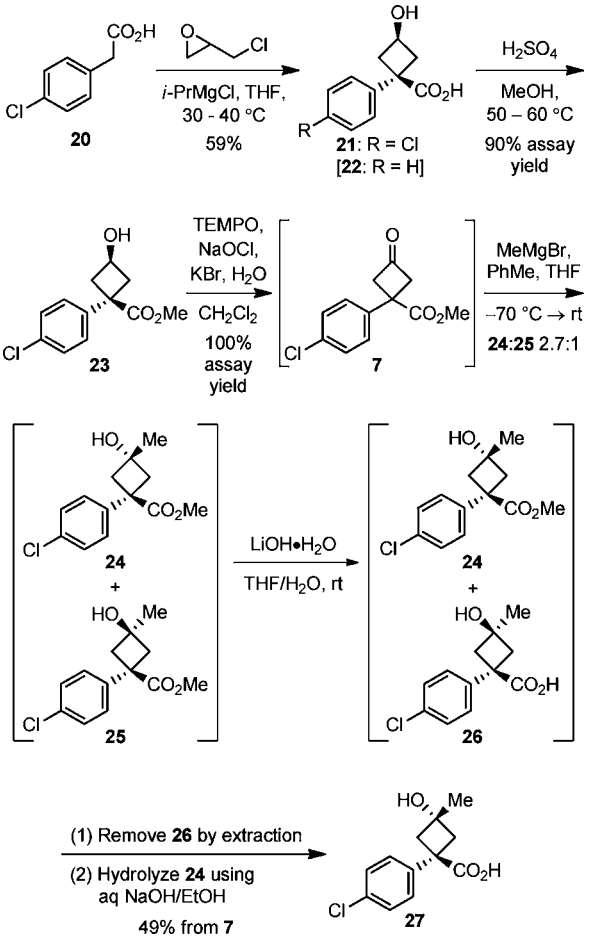
Scheme 5. Preparation of *trans*-Hydroxy Acid 27

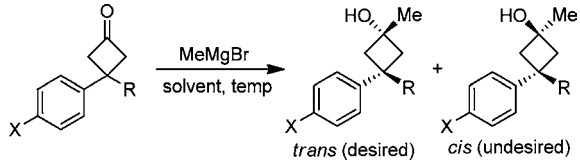


2.7:1. After selective hydrolysis of the product mixture using LiOH in aq THF (5% of the desired *trans*-ester **24** was also hydrolyzed under these conditions) and removal of the resulting *cis*-acid **26**, the resulting organic stream containing *trans*-ester **24** was saponified under more forcing conditions (aq NaOH, ethanol) to generate *trans*-acid **27**.

The net effect of the steps from *cis*-acid **21** to *trans*-acid **27** is only to convert a secondary alcohol group into a tertiary alcohol plus one carbon unit (methyl). For the immediate needs of the delivery, this sequence provided a timely, low-tech solution that could be telescoped into a through process and which proceeded in a serviceable 43% overall yield with no chromatography required. It did not, however, solve the fundamental problem of the low diastereoselectivity of the methyl addition step. With a view to enabling subsequent larger deliveries of API **1**, this addition was subsequently screened against a number of substrates on small scale using high-throughput experimentation techniques.[25] Selected data is presented in Table 1.

As described above, moderate diastereoselectivity in the direction of the desired *trans*-adduct was observed with ketoester substrate **7** (entries 1 and 3–5) but could not be improved further. Indeed, performing this addition in the presence of a stoichiometric amount of CuI resulted in a switch in selectivity to strongly favor the *cis*-isomer (entry 2). Addition to ketoacid **28** using MeMgBr (entry 6) or MeLi (entry 7) was nonselective. Marginal selectivity in favor of the undesired *cis*-adduct was found with *N*-Boc substrate **29** (entries 8 and 9).

Table 1. Screening of MeMgBr Addition to Cyclobutanone Substrates



entry	substrate	R	X	solvent	temp (°C)	dr[a]
1	7	CO_2Et	Cl	THF	0	1.6:1
2	7			THF	0	1:10[b]
3	7			THF	−78	2.1:1
4	7			PhMe	0	1.6:1
5	7			PhMe	−78	2.5:1
6	**28**	CO_2H	Cl	THF	0	1:1
7	**28**			THF	0	1:1[c]
8	**29**	NHBoc	Br	THF	0	1:1.5
9	**29**			PhMe	0	1:2
10	**30**	CN	Cl	THF	0	>20:1
11	**30**			PhMe	0	>20:1

[a]Ratio of *trans*/*cis*-adducts determined by ^{1}H NMR analysis of crude product mixtures. [b]CuI (1 equiv) used as an additive. [c]MeLi used instead of MeMgBr.

Interestingly, a ratio of >20:1 in favor of the desired *trans*-isomer was obtained when nitrile **30** was employed (entries 10 and 11). This promising screening hit could not be evaluated further due to the timeline constraints of the kilogram-scale delivery, but it clearly represents an opportunity that could be investigated to favorably impact future API campaigns.

Completion of the Synthesis. The procedure developed in the lab for the Curtius rearrangement of acid **27** involved the initial generation of acyl azide intermediate **31**, using diphenylphosphoryl azide (DPPA) in THF, followed by the addition of aqueous hydrochloric acid (HCl) at reflux to induce rearrangement.[26] In the pilot plant this step performed poorly (Scheme 6), giving a low conversion to the desired amine **32** and a large amount of the urea byproduct **33**. Urea **33** could be separated and then hydrolyzed under very forcing conditions to recover an additional quantity of amine **32**, which was all processed forward into the Boc protection step. The resulting protected compound **34** was isolated by crystallization from *tert*-butyl methyl ether (MTBE)/heptane. Noteworthy is the fact that carbamate **34** is the first crystallized intermediate since acid **21** (Scheme 5). At this stage carbamate **34** still contained 2.5% of the des-chloro impurity **35**, which had been carried over since the first step in the synthesis. Recrystallization of carbamate **34** from acetone/water (95% recovery) reduced the level of des-chloro impurity **35** to 0.4%, and improved the purity of the product **34** to 99.3%.

A total of 2.87 kg of carbamate **34** was procured from an input of 7.1 kg of acid **27** into the Curtius rearrangement step. This modest amount of product was sufficient for the presently described delivery. However, the low yield for this overall transformation (30%) would not be sustainable in the longer term. The root cause for the generation of urea **33** was identified as being the prolonged (4 h) addition time of the aq HCl that was required to control the rate of gaseous N_2 and CO_2 evolution on scale. Subsequent lab-scale development showed that inverse addition of the solution of acyl azide **31** into the aq HCl would provide a method to minimize the formation of urea **33**.

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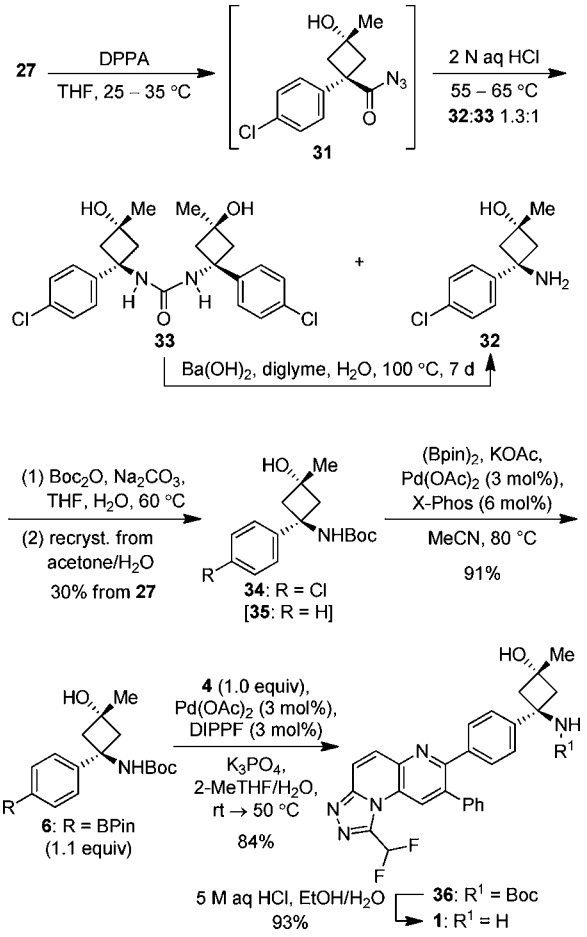
Scheme 6. Conversion of Acid 27 to Akt Inhibitor 1

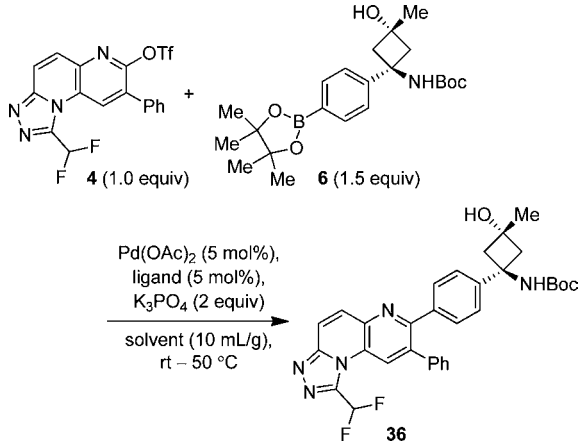


A palladium-catalyzed borylation of carbamate **34** afforded boronate **6** in 91% isolated yield. During the aqueous workup, removal of the pinacol byproduct by successive water washes was necessary to ensure a reproducible crystallization of the product **6** from heptane. A total of 3.4 kg of boronate **6** was produced as a free-flowing white powder in 8 steps (7% overall yield) from 4-chlorophenylacetic acid **20**.

The reaction conditions for the Suzuki coupling between triflate **4** and boronate **6** were screened in an effort to identify a milder alternative to using an unoptimized method of 20 mol % $Pd(PPh_3)_4$ at 140 °C in a microwave.[6] Key results are summarized in Table 2. Electron-rich bidentate phosphines outperformed monodentate ligands (compare entry 1 to entries 2–5), allowing for good conversion at or slightly above room temperature. Ferrocene derivatives (entries 4 and 5) proved superior to acyclic (entry 2) or binaphthyl analogues (entry 3). Ethereal solvents, e.g. THF (entry 5) or 2-methyltetrahydrofuran (2-MeTHF) (entry 6), gave better product yields than more strongly dipolar aprotic solvents, such as dimethylacetamide (DMAc) (entry 7). The presence of water cosolvent in the reaction was found to be crucial, with the yield dropping substantially under anhydrous conditions (entry 8). Ultimately, 2-MeTHF was chosen over THF due to the relative ease of product isolation, since the coupled penultimate **36** could be crystallized directly from the reaction mixture using the former solvent.

With further optimization, >99% conversion of triflate **4** could be achieved at lower catalyst and ligand loadings of 3 mol

Table 2. Suzuki Coupling Screening



entry	ligand[a]	solvent[b]	assay yield (%)[c]
1	X-Phos	THF/H_2O	52
2	DPPB	THF/H_2O	71
3	(*R*)-BINAP	THF/H_2O	70
4	DPPF	THF/H_2O	76
5	DIPPF	THF/H_2O	84
6	DIPPF	2-$MeTHF/H_2O$	82
7	DIPPF	$DMAc/H_2O$	57
8	DIPPF	2-MeTHF	22

[a]DIPPF = 1,1′-bis(di-*i*-propylphosphino)ferrocene. [b]10% v/v H_2O in mixed solvent systems. [c]HPLC yield relative to internal standard.

% each, with only a very slight excess of the valuable boronate coupling partner **6** (1.1 equiv) needing to be employed. On kilogram scale the coupling proceeded to completion within 1 h while warming from rt to 50 °C (Scheme 6). At the end of the reaction, a biphasic mixture was formed, and the product **36** began to crystallize from the organic layer as the mixture was cooled to ambient temperature. After addition of MTBE antisolvent to reduce liquor losses, filtration and drying afforded penultimate **36** in good yield (84%) and with excellent rejection of Pd impurities (residual Pd in the product cake was only 30 ppm).[27] Treatment of penultimate **36** with 5 M aq HCl (5 equiv) in ethanol (EtOH) at 50 °C for 24 h resulted in clean deprotection of the Boc group; upon pH adjustment to 10–11 using aq NaOH, the desired polymorph of the API free base crystallized directly from the reaction mixture. The target compound **1** (2.6 kg) was isolated in 93% yield and met all required purity specifications.

■ CONCLUSION

A fit-for-purpose, kilogram scale synthesis of Akt kinase inhibitor **1** has been developed. The convergent route consisted of 17 total steps (10 steps longest linear sequence), required no chromatographic purifications, and could be performed safely on multikilogram scale. Key transformations included a high temperature and pressure hydrazine displacement reaction, and separation of a diasteromeric mixture of Grignard addition products through chemoselective ester hydrolysis. Proof-of-concept was established on kilogram scale for a key dianion formylation reaction under flow conditions in which yield and practicality improvements over batch mode were demonstrated, providing a further example of the utility and potential of continuous flow processing as an enabling technology in process chemistry.

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EXPERIMENTAL SECTION

2-Bromo-6-chloropyridin-3-amine (10).[10] 2-Chloro-5-aminopyridine (**8**; 8.0 kg, 62.2 mol) was dissolved in DMF (32 L) in a 100 L jacketed cylindrical vessel, and the resulting solution was cooled to 15 °C. NBS (10.85 kg, 61.0 mol, 0.98 equiv) was added in portions over 2 h below 25 °C. The mixture was stirred for a further 2 h, then water (48 L) was added over 1 h below 25 °C, and the resulting slurry was aged at rt for 16 h (liquors assayed for 13.3 mg/mL of product **10** at this point, ∼10% of theoretical yield). The slurry was filtered, and the resulting product was washed with 2:1 water/DMF (20 L) and then dried under vacuum with a N_2 sweep at rt and then 40 °C for 3 days to afford the title compound (10.50 kg, 50.6 mol, 81% yield) as a brown solid.

***tert*-Butyl (2-Bromo-6-chloropyridin-3-yl)carbamate (11).** Bromide **10** (4.9 kg, 23.6 mol, 1.0 equiv), Boc_2O (5.05 kg, 23.1 mol, 0.98 equiv), and THF (20 L) were charged to a 100 L jacketed cylindrical vessel, and the resulting solution was cooled to −5 °C. NaHMDS (43.32 kg of a 40 wt % solution in THF, 47.2 mol, 2.0 equiv) was added over 2.5 h below 0 °C. The solution was warmed to 20 °C, at which point HPLC analysis indicated complete conversion of bromide **10**. The reaction was quenched by addition of water (24 L) and isopropyl acetate (IPAc) (24 L). The layers were separated, and the organic layer was washed with 1 N aq HCl (1 × 24 L) and then 10% aq NaCl (1 × 24 L). The organic layer was held in plastic drums while a second reaction of the same batch size was run. The combined organic layers from both batches were concentrated under vacuum to a low volume and switched to approximately 35 L of IPA (∼60 L total of IPA was used). ^{1}H NMR analysis was used to confirm that all THF and IPAc had been removed. Water (20 L) was added slowly, and the resulting slurry was aged at rt for 16 h (liquors assayed for 6.6 mg/mL of product **11** at this point, ∼6% of theoretical yield). The slurry was filtered, and the resulting product was washed with 2:1 water/IPA (20 L) and then dried under vacuum with a N_2 sweep at 40 °C for 24 h to afford the title compound (12.0 kg, 39.0 mol, 83%) as a pink solid. mp 95−96 °C; IR (neat) 3349, 2984, 1717, 1497, 1249, 1156, 1143, 1128, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, d, J = 8.5 Hz), 7.23 (1H, d, J = 8.5 Hz), 6.98 (1H, br s), 1.50 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 142.3, 133.5, 129.6, 129.1, 123.7, 82.1, 28.1; HRMS calcd for $C_{10}H_{13}BrClN_2O_2$ $[MH]^+$ 306.9849, found 306.9854.

***tert*-Butyl (6-Chloro-2-formylpyridin-3-yl)carbamate (5).** *a. Flow Preparation.* The flow reactor was constructed of stainless steel tubing, maintained at low temperature by immersion in a dry ice/acetone bath. Feed lines to/from the pumps, and from the reactor to the quench solution, were Teflon-coated, and each pump was followed by a pressure indicator and check valve. A 22 L round-bottomed flask was charged with THF (4.5 L) and bromide **11** (1.0 kg, 3.25 mol, 1.0 equiv) at rt, and the resulting solution was cooled to −55 °C. MeLi (1.07 L of a 3.19 M solution in diethoxymethane, 3.41 mol, 1.05 equiv) was added over 30 min below −40 °C (note—mild effervescence, methane).[28] The resulting solution was stirred for a further 15 min, and then the flask was equipped with the feed line for FMI pump 1. Concurrently, *n*-BuLi (1.43 L of a 2.5 M solution in hexanes, 3.58 mmol, 1.1 equiv) was charged at rt to a 5 L round-bottomed flask equipped with the feed line for FMI pump 2, and a solution of DMF (0.38 L, 4.88 mol, 1.5 equiv) in THF (2.06 L) was charged at rt to a separate 5 L round-bottomed flask equipped with the feed line for FMI pump 3. The solution of anion **13** was pumped by FMI pump 1 at a rate of 114 mL/min. *n*-BuLi was pumped by FMI pump 2 at a rate of 24 mL/min. The anion **13** and *n*-BuLi streams were mixed in a Swagelok T (0.125 in. internal diameter) followed by a temperature indicator (T1), static mixer (0.25 in. internal diameter, 6 mL volume, 2.0 s residence time), and second temperature indicator (T2), to generate dianion **14**. The DMF solution was pumped by FMI Pump 3 at a rate of 37 mL/min. The dianion **14** and DMF solutions were mixed in a Swagelok T (0.125 in. internal diameter) followed by a static mixer (0.25 in. internal diameter, 6 mL volume, 2.5 s residence time) and a third temperature indicator (T3). During the kilogram run the temperatures recorded at T1, T2, and T3 were −70, −65, and −55 °C, respectively, and the pressure on the pumps was in the range of 40−50 psi. The mixture then exited the flow reactor. The first 30 s of product stream was discarded (while the system reached steady-state) and then the remainder was fed into a stirred quench solution (0.72 L acetic acid (AcOH), 1.5 L MTBE, and 6 L water) in a 30 L jacketed cylindrical vessel at rt. After 1 h, all the solution of anion **13** had been processed. The layers in the quench solution were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ (1 × 3 L) and then water (1 × 3 L). The organic layer (10.1 kg, 707 g assay **5**, 85% assay yield) was collected and stored in a plastic drum.

b. Batch Preparation. A 100 L round-bottomed flask was charged with THF (36 L) and bromide **11** (4.8 kg, 15.6 mol, 1.0 equiv) at rt, and the resulting solution was cooled to −65 °C. MeLi (5.14 L of a 3.19 M solution in diethoxymethane, 16.4 mol, 1.05 equiv) was added over 1 h below −55 °C (note—mild effervescence, methane).[28] The resulting dark solution was cooled to −65 °C over 20 min and then *n*-HexLi (7.46 L of a 2.3 M solution in hexane, 17.2 mol, 1.1 equiv) was added over 50 min below −55 °C. The dark orange solution was aged at −55 °C for a further 5 min and then a solution of DMF (1.93 L, 25.0 mol, 1.6 equiv) in THF (2 L) was added over 30 min below −45 °C. A separate 100 L cylindrical vessel was charged with the quench solution of water (28 L), AcOH (3.87 L, 60.4 mol, 3.9 equiv), and MTBE (8 L) at rt. The reaction mixture was then transferred over 15 min into the quench solution. The resulting biphasic mixture was aged at 15 °C for 15 min, and then the layers were allowed to settle. The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ (1 × 15 L) and then water (1 × 15 L). The organic layer (43.2 kg, 3.16 kg assay **5**, 76% assay yield) was collected and stored in plastic drums while a second formylation batch was run using 4.7 kg of bromide **11**.

c. Product Isolation. The organic layers from both batches were combined with the organic stream from the flow preparation described in section a above, obtaining a total of 6.82 kg assay **5**. The combined organic layers were then concentrated under vacuum at 35−40 °C in a 100 L round-bottomed flask to a volume of ∼30 L. The solution was then flushed with IPA (30 L), maintaining the batch volume at ∼30 L, during which time the product began to crystallize. The resulting slurry was then allowed to cool from 38 °C to rt over 2 h. Water (16 L) was then added over 1.5 h. By the end of the water addition, the slurry had changed consistency, and a small amount of the product had begun to oil out. Additional IPA (14 L) was added, and the batch heated to 65 °C over 1 h. The resulting thin slurry was allowed to cool to rt over 3 h. The

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mixture was then filtered and the product was washed with 3:2 IPA/water (2 × 8 L) and then dried under vacuum with a N_2 sweep at rt for 2.5 days to afford the title compound (5.99 kg, 95 wt % purity, 22.2 mol, 63% corrected yield) as a light beige powder. mp 98−98.5 °C; IR (neat) 3294, 2985, 2843, 1735, 1680, 1492, 1227, 1137, 898 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.16 (1H, br s), 9.95 (1H, d, J = 1.0 Hz), 8.85 (1H, d, J = 9.0 Hz), 7.45 (1H, d, J = 9.0 Hz), 1.51 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6, 152.4, 143.2, 138.2, 135.7, 129.8, 129.6, 82.1, 28.1; HRMS calcd for $C_{11}H_{14}ClN_2O_3$ $[MH]^+$ 257.0693, found 257.0685.

6-Chloro-3-phenyl-1,5-naphthyridin-2(1*H*)-one (17). A 100 L jacketed cylindrical vessel was charged with MeCN (33 L) and aldehyde **5** (5.8 kg, 21.5 mol, 1.0 equiv) at rt. Methyl phenylacetate (3.46 L, 24.0 mol, 1.1 equiv) was added to the thin slurry, rinsing with MeCN (1 L). Cs_2CO_3 (24.5 kg, 75 mol, 3.5 equiv) was then added in portions over 10 min to the orange solution, rinsing with MeCN (1 L). The resulting slurry was aged at rt for 1 h (during which time the temperature had risen slowly by 5 °C, from 22 to 27 °C). The slurry was then heated to 50 °C over 1.5 h, aged at that temperature for a further 1 h, then heated to 70−75 °C over 3 h, aged at that temperature for a further 5 h, and then allowed to cool to rt overnight (~16 h). The slurry was then cooled to 10 °C, and water (35 L) was added over 1 h below 25 °C. The resulting biphasic slurry was aged at 20 °C for 1 h and then filtered. The product cake was washed with 1:1 MeCN/water (2 × 8 L) and then dried under vacuum with a N_2 sweep at rt for 24 h and then at 35 °C for 3 days to give the title compound (3.57 kg, 92 wt % purity, 60% corrected yield) as a cream-colored powder. mp 262−264 °C (dec); IR (neat) 2781, 1652, 1591, 1443, 1113, 918, 694, 669 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.28 (1H, br s), 8.01 (1H, s), 7.80−7.77 (2H, m), 7.73 (1H, d, J = 9.0 Hz), 7.59 (1H, d, J = 9.0 Hz), 7.47−7.39 (3H, m); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.3, 143.7, 136.7, 136.6, 136.5, 135.2, 133.8, 128.9, 128.6, 128.1, 126.2, 125.2; HRMS calcd for $C_{14}H_{10}ClN_2O$ $[MH]^+$ 257.0482, found 257.0477.

6-Hydrazinyl-3-phenyl-1,5-naphthyridin-2(1*H*)-one (18). *a. Vessel Cleaning and Conditioning.* A 5-gal Hastelloy C autoclave,[29] fitted with a rupture disk rated for 3100 psi, was cleaned and rinsed to neutral pH with deionized (DI) water. The autoclave was charged with additional DI water (12 L) and heated to 155 °C. Samples of the final DI water rinse were submitted for metals analysis (Pd, Pt, Ru, Rh < 1 ppb; Ni 1 ppm; Cr 0.18 ppm; Mo 0.38 ppm; W 0.22 ppm). The vessel was then conditioned for 1 h at 155 °C with 1% aq NH_2NH_2 (10 L) prior to carrying out the reaction.

b. Hydrazine Displacement Reaction. Chloride **17** (1.11 kg, 92 wt %, 4.0 mol, 1.0 equiv) was slurried in DMI (4.5 L) and charged by residual vacuum into the 5-gal autoclave. A 1 L follow flush of DMI was used to rinse the lines. Hydrazine (6.5 L of a 35% aq solution, 72.0 mol, 18.0 equiv) was charged into the autoclave by residual vacuum and the charge line rinsed into the vessel with DI water (200 mL). Nitrogen pressure (80 psi) was placed on the vessel, and the batch temperature was heated to 155 °C over 1.5 h. The batch was aged at 155 °C for 4 h and then cooled to 40 °C. The batch was discharged from the vessel in two equal portions into two 5-gal polyjugs which each contained 3 L DI water. The autoclave vessel was rinsed with DMI (14 L), and the DMI was agitated overnight and then discharged from the vessel into a third 5-gal polyjug.

This reaction was repeated twice more on the same scale (note—the vessel pressure at the end of the reaction age at 155 °C ranged from 1450 psi for the first batch to 900 psi for the third batch). After the third batch the DMI vessel rinse slurry (note—the same DMI rinse was used for all three batches) was transferred into a 30 L extractor. The stirred slurry was diluted with water (8 L) and agitated for 1 h. This slurry and the three reaction mixture batches were then filtered together to isolate the product. The cake was washed with water (1 × 8 L) and EtOH (2 × 8 L), and it was then dried under vacuum with a N_2 sweep for 16 h at rt and then 2 days at 35 °C to give the title compound (2.585 kg, 98.4 wt % purity, 10.1 mol, 84% corrected yield) as a muddy yellow powder. mp 255−258 °C (dec); IR (neat) 3321, 3201, 2785, 1662, 1621, 1477, 1447, 687, 620 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.85 (1H, br s), 7.79−7.75 (3H, m), 7.65 (1H, s), 7.48 (1H, d, J = 9.0 Hz), 7.45−7.35 (3H, m), 6.95 (1H, d, J = 9.0 Hz), 4.18 (2H, br s); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.7, 157.8, 137.1, 136.3, 134.2, 133.9, 128.7, 128.2, 128.0, 127.9, 124.7, 112.0; HRMS calcd for $C_{14}H_{13}N_4O$ $[MH]^+$ 253.1089, found 253.1080.

1-(Difluoromethyl)-8-phenyl[1,2,4]triazolo[4,3-*a*][1,5]-naphthyridin-7(6*H*)-one (19). A 50 L jacketed cylindrical vessel was charged with MeCN (24.5 L), hydrazine **18** (2.45 kg, 9.5 mol, 1.0 equiv), and *i*-Pr_2NEt (8.31 L, 47.6 mol, 5.0 equiv) at rt. The yellow slurry was cooled to 5 °C over 20 min, and difluoroacetic anhydride (3.19 L, 28.6 mol, 3.0 equiv) was added over 45 min below 15 °C. The resulting yellow slurry was warmed to rt and aged until <1% starting material **18** (as measured by HPLC area count) remained (~2 h). The thin yellow slurry was cooled to 10 °C over 20 min, and water (400 mL) was added over 10 min below 17 °C. The mixture was allowed to warm to rt, and additional water (5.6 L) was added over 75 min. The yellow slurry was aged for a further 30 min (liquors assayed for 1.3 mg/mL of product **19** at this point) and then filtered. The product cake was washed with 7:2 MeCN/water (1 × 10 L) and then with EtOH (1 × 10 L), and it was then dried under vacuum with a N_2 sweep at rt for 2 days to afford the title compound (3.2 kg, 88 wt % purity by ^1H NMR analysis) as a yellow solid. The solid was reslurried in 7:2 MeCN/water (12.25 L) in a 30 L jacketed cylindrical vessel at rt for 4 h. The slurry was filtered, and the product cake was washed with 7:2 MeCN/water (1 × 12 L) and then with EtOH (1 × 12 L) and finally with MTBE (1 × 12 L). The product was dried under vacuum with a N_2 sweep at rt for 4 days to give the title compound (2.72 kg, 100 wt % purity, 8.7 mol, 91% yield from **18**) as a yellow solid. mp >300 °C; IR (neat) 2777, 1644, 1577, 1128, 1018, 789, 699, 651 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.77 (1H, br s), 8.37 (1H, s), 8.10 (1H, d, J = 9.5 Hz), 8.01 (1H, t, J = 51.5 Hz), 7.80−7.78 (2H, m), 7.64 (1H, d, J = 9.5 Hz), 7.52−7.48 (2H, m), 7.46−7.43 (1H, m); ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.3, 149.4, 140.7 (t, J = 27.5 Hz), 135.4, 132.6, 131.6, 128.7, 128.4 (2C), 127.6 (t, J = 6.0 Hz), 121.9, 118.1, 115.9, 110.0 (t, J = 234.5 Hz); ^{19}F NMR (471 MHz, DMSO-d_6) δ −115.1; HRMS calcd for $C_{16}H_{11}F_2N_4O$ $[MH]^+$ 313.0901, found 313.0899.

1-(Difluoromethyl)-8-phenyl[1,2,4]triazolo[4,3-*a*][1,5]-naphthyridin-7-yl Trifluoromethanesulfonate (4). A 50 L jacketed cylindrical vessel was charged with MeCN (17.2 L), triazole **19** (2.65 kg, 8.5 mol, 1.0 equiv), and pyridine (1.72 L, 21.2 mol, 2.5 equiv). The resulting yellow slurry was cooled to 5 °C over 15 min, and Tf_2O (2.15 L, 12.7 mol, 1.5 equiv) was added over 40 min below 15 °C. The slurry was warmed to 40 °C over 80 min, by which point an orange solution had formed and <2% triazole starting material **19** remained (as measured by

HPLC area count). The solution was cooled to 7 °C over 45 min, and water (300 mL) was added over 15 min below 25 °C. The resulting reddish brown solution (15 °C) was transferred under vacuum through a 1 μm in-line filter into a 50 L jacketed cylindrical vessel at rt. Water (0.93 L) was then added in one portion. The solution was aged for 5 min and then seeded and aged for a further 30 min. Additional water (20.3 L) was added over 2 h to the resulting slurry, which was then aged for a further 30 min (liquors assayed for 3.7 mg/mL of product **4** at this point). The slurry was filtered, and the product cake was washed with 4:5 MeCN/water (2 × 8 L) and then dried under vacuum with a N_2 sweep at rt for 40 h to give the title compound (3.41 kg, 100 wt % purity, 7.7 mol, 91% yield) as a beige solid. mp 130.5−131.5 °C; IR (neat) 1521, 1421, 1209, 1121, 1037, 849, 838, 831, 602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (1H, s), 7.66 (1H, d, J = 9.5 Hz), 7.53 (1H, d, J = 9.5 Hz), 7.22−7.09 (5H, m), 7.05 (1H, t, J = 52.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 150.3, 142.7 (t, J = 28.5 Hz), 138.8, 132.2, 131.0 (t, J = 8.0 Hz), 131.0, 130.1, 129.9, 129.2 (2C), 127.2, 119.6, 118.2 (q, J = 321.0 Hz), 110.0 (t, J = 237.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ −73.6, −115.7; HRMS calcd for $C_{17}H_{10}F_5N_4O_3S$ $[MH]^+$ 445.0394, found 445.0404.

***cis*-1-(4-Chlorophenyl)-3-hydroxycyclobutanecarboxylic Acid (21).** (4-Chlorophenyl)acetic acid (**20**; 21.0 kg, 123 mol, 1.0 equiv) and THF (110 kg) were charged into a 1000 L glass-lined reactor, and the solution was concentrated under vacuum below 45 °C to a final volume of ∼55 L, and a KF spec of 200 ppm was met. The resulting solution was transferred into a clean drum. *i*-PrMgCl (134.4 kg of a 2 M solution in THF, 276 mol, 2.24 equiv) was charged into the reactor at rt, and then the THF solution of starting material **20** was added below 40 °C. The mixture was stirred at 30−40 °C for 70 min, then epichlorohydrin (20.5 kg, 221 mol, 1.8 equiv) was added at 35−40 °C, and the resulting mixture was aged at this temperature for a further 3.5 h. The mixture was cooled to 20−25 °C, and additional *i*-PrMgCl (122.1 kg of a 2 M solution in THF, 250 mol, 2.03 equiv) was added below 32 °C. The resulting mixture was stirred at 25−32 °C for 18 h and then was cooled to 0−5 °C and quenched by the addition of 5 N aq HCl (120 kg) below 40 °C. The resulting biphasic mixture was cooled to 23−28 °C (pH of aqueous layer was 2) and aged for 30 min. The layers were then separated, and the organic layer was washed with 25% w/v aq NaCl solution (1 × 79 kg) and then concentrated under vacuum below 45 °C to a volume of ∼100 L. The resulting solution was solvent-switched into PhMe under vacuum below 45 °C until a final volume of ∼100 L and residual THF and water levels of 0.6% and 0.1%, respectively, were achieved (target specifications: THF ≤1.0%, water by KF analysis ≤0.3%). The resulting slurry was cooled to 10−15 °C, aged for 1 h, and then filtered using a centrifuge. The product cake was washed with PhMe (32 L) and dried under vacuum at 55−60 °C for 10.5 h to give the title compound (16.95 kg, 96.8 wt % purity, 72.4 mol, 59% corrected yield) as a white solid. mp 181−182 °C; IR (neat) 3316, 2948, 1697, 1261, 1240, 1129, 819, 629 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.05 (1H, br s), 6.03 (4H, s), 3.84 (1H, br s), 1.40−1.35 (2H, m), 1.18−1.13 (2H, m); ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.0, 141.1, 131.3, 128.9, 128.3, 60.2, 43.6, 42.5; HRMS calcd for $C_{11}H_{15}ClNO_3$ $[MNH_4]^+$ 244.0740, found 244.0734.

Methyl *cis*-1-(4-Chlorophenyl)-3-hydroxycyclobutanecarboxylate (23). To a 500 L glass-lined vessel were charged acid **21** (16.8 kg, 72 mol, 1.0 equiv) and MeOH (72 kg), and the resulting mixture was stirred for 30 min at 20−30 °C. Conc H_2SO_4 (2.2 kg, 22 mol, 0.03 equiv) was added, and the mixture was aged for 30 min before being heated to 50−60 °C and aged at this temperature for 2.5 h (<2% acid starting material **21** remained at this point, as measured by HPLC area count). The solution was cooled to 0−10 °C, then 8% w/v aq K_2HPO_4 (180 kg) was added below 30 °C, and the mixture was aged for a further 1.5 h. The solution was then concentrated under vacuum below 50 °C to a volume of ∼160 L. PhMe (99 kg) was then added at rt, and the resulting biphasic mixture was stirred for 1 h. The layers were separated, and the organic layer was concentrated to dryness under vacuum at 45−60 °C to give the title compound (23.65 kg, 66.2 wt % purity by HPLC analysis, 65 mol, 90% corrected assay yield) as a crude oil which was used directly in the next step. Residual solvent levels for PhMe, water, and MeOH were 21.3%, 0.01%, and not detected, respectively.

Data for an authentic sample of ester **23** purified by column chromatography on silica gel: colorless oil; IR (neat) 3402, 2991, 2950, 1728, 1492, 1235, 1130, 1094, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.27 (4H, m), 4.16−4.09 (1H, m), 3.61 (3H, s), 3.51 (1H, br s), 2.89−2.84 (2H, m), 2.73−2.68 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 139.5, 132.7, 128.4, 128.3, 61.9, 52.5, 44.1, 42.4; HRMS calcd for $C_{12}H_{17}ClNO_3$ $[MNH_4]^+$ 258.0897, found 258.0894.

Methyl 1-(4-Chlorophenyl)-3-oxocyclobutanecarboxylate (7). An aq KBr solution was prepared by dissolving KBr (1.7 kg, 14.2 mol, 0.22 equiv) in water (15.6 kg). An aq $Na_2S_2O_3$ quench solution was prepared by dissolving $Na_2S_2O_3$ (8.0 kg, 50.6 mol, 0.78 equiv) in water (51.5 kg). An aq NaOCl solution was prepared by dissolving NaOCl (106.7 kg of a 10% w/w solution in water, 144.0 mol, 2.2 equiv) and $KHCO_3$ (81.9 kg, 818 mol, 12.6 equiv) in water (330 kg). A 1000 L glass-lined reactor was charged with CH_2Cl_2 (211 kg) and the crude solution of ester **23** from the preceding step (23.65 kg, 66.2 wt % purity by HPLC analysis, 65 mol, 1.0 equiv) at rt. The solution was cooled to 0−5 °C, and the aq KBr solution was added below 5 °C. After a further 15 min, TEMPO (0.94 kg, 5.4 mol, 0.08 equiv) was added. After a further 30 min, the aq NaOCl quench solution was added below 5 °C. After a further 30 min (HPLC analysis showed complete conversion of ester starting material **23** by this point), the aq $Na_2S_2O_3$ solution was added below 5 °C. The mixture was then warmed to 23−28 °C and aged for 40 min at this temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 105 kg). The combined organic layers were washed with water (1 × 105 kg) and concentrated to dryness under vacuum below 20 °C. THF (47 kg) was then added, and the mixture was concentrated to dryness under vacuum again to give the title compound (18.05 kg, 87.7 wt % purity, 66.3 mol, ∼100% assay yield) as a crude oil, which was diluted with PhMe (15.2 kg) for use directly in the next step.

Data for an authentic sample of ketone **7** purified by column chromatography on silica gel: white solid; mp 46−47 °C; IR (neat) 2934, 1773, 1725, 1218, 1125, 1088, 821, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.35 (2H, m), 7.32−7.29 (2H, m), 3.95−3.88 (2H, m), 3.71 (3H, s), 3.57−3.50 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1, 174.1, 139.0, 133.6, 128.8, 128.6, 57.6, 53.0, 42.9; HRMS calcd for $C_{12}H_{15}ClNO_3$ $[MNH_4]^+$ 256.0740, found 256.0738.

***trans*-1-(4-Chlorophenyl)-3-hydroxy-3-methylcyclobutanecarboxylic Acid (27).** *a. MeMgBr Addition.* A 1000 L glass-lined reactor was charged with PhMe (168 kg) and the

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crude solution of ketone **7** from the preceding step (18.05 kg, 87.7 wt % purity by HPLC analysis, 66.3 mol, 1.0 equiv) at rt. The mixture was concentrated under vacuum below 50 °C, azeotroping with additional PhMe (170 kg), until a final volume of ~70 L was reached (residual THF and water levels at this point were 0.001% and 0.02%, respectively). THF (6.9 kg) was added, and the solution was cooled to between −60 and −70 °C. MeMgBr (25.85 kg of a 3.0 M solution in diethyl ether, 76.3 mmol, 1.15 equiv) was added between −60 and −70 °C, and the mixture was stirred for a further 3 h at that temperature, by which point HPLC analysis showed 98% conversion of ketone starting material **7**. The solution was warmed to 20−30 °C and aged for 2 h, after which time the degree of conversion had not increased. The solution was cooled to 0−5 °C and quenched by the addition of MeOH (5.0 kg) below 10 °C. The quenched reaction mixture was transferred to a 500 L glass-lined reactor, followed by a rinse of the 1000 L reactor with PhMe (47 kg). To the combined solutions was added 2 N aq HCl (50 kg) below 10 °C. The resulting biphasic mixture was warmed to 20−30 °C and aged for 30 min, and then the layers were separated. The organic layer was washed with water (1 × 60 kg) and then concentrated under vacuum below 50 °C to a volume of ~40 L. The resulting solution was solvent-switched into THF (a total of 323 kg THF was used) under vacuum below 50 °C and concentrated to a final volume of ~100 L (residual PhMe at this point was 5.9%; target specification ≤10%). HPLC analysis of this solution indicated a 2.7:1 ratio of *trans*-ester **24**/*cis*-ester **25**.

Data for an authentic sample of *trans*-ester **24** purified by column chromatography on silica gel: colorless oil; IR (neat) 3397, 2951, 1727, 1250, 1125, 1090, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (2H, d, J = 8.5 Hz), 7.07 (2H, d, J = 8.5 Hz), 3.78 (1H, br s), 3.49 (3H, s), 2.87 (2H, dd, J = 10.5, 2.5 Hz), 2.40 (2H, d, J = 10.5 Hz), 1.21 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 142.1, 132.2, 128.1, 127.5, 67.7, 52.3, 47.4, 42.7, 27.2; HRMS calcd for $C_{13}H_{19}ClNO_3$ $[MNH_4]^+$ 272.1053, found 272.1048.

*b. Hydrolysis and Removal of Undesired cis-Ester **25**.* To this THF solution were added $LiOH·H_2O$ (0.548 kg, 13.1 mol, 0.2 equiv) and water (70 kg) at rt. The resulting mixture was periodically analyzed by HPLC to monitor the conversion of *cis*-ester **25** to *cis*-acid **26**, as measured by the corresponding increase in the ratio of *trans*-ester **24**/remaining *cis*-ester **25**. After 2 h the ratio had increased from 2.7:1 to 3.8:1. A total of 0.905 kg (21.6 mol, 0.33 equiv) additional $LiOH·H_2O$ was then added in 4 portions over 6 h. After a further 2 h the ratio of *trans*-ester **24**/remaining *cis*-ester **25** was 143:1, and MTBE (168 kg) was added to the reaction to give a biphasic mixture. The layers were separated, and the organic layer was washed with 25% w/v aq NaCl (2 × 78 kg) and then concentrated under vacuum below 50 °C to a target volume of ~40 L.

*c. Hydrolysis of Desired trans-Ester **24**.* To the resulting solution was added EtOH (150 kg), water (70 kg), and NaOH (13.2 kg, 330.0 mol, 5 equiv) at rt, and the mixture was stirred for 3 h. The mixture was then concentrated under vacuum below 50 °C to a target volume of ~70 L, and solvent-switched under vacuum below 50 °C from EtOH into ~100 L of water (achieved 0.02% residual EtOH, target specification <5% EtOH). The resulting solution was diluted with water (32 kg) and MTBE (48 kg). The layers were separated, and the aqueous layer was washed with MTBE (1 × 76 kg). The resulting aqueous layer was diluted with water (47 kg), then 35% aq HCl (75 kg) was added, and the mixture was stirred for 2.5 h. IPAc (156 kg) was then added, and the layers were separated. The organic layer was concentrated under vacuum below 50 °C to a final volume of ~70 L, to afford the title compound **27** (66.9 kg, 10.9 wt % purity, 30.2 mol, 49% corrected overall yield) as a crude solution in IPAc, which was used directly in the next step.

Data for an authentic sample of *trans*-acid **27** purified by column chromatography on silica gel: off-white solid; mp 136−139 °C; IR (neat) 3404, 2945, 1693, 1244, 1132, 1092, 945, 819, 630 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.56 (1H, br s), 7.40−7.37 (2H, m), 7.28−7.24 (2H, m), 5.06 (1H, br s), 2.85 (2H, dd, J = 10.5, 2.5 Hz), 2.42 (2H, dd, J = 10.5, 2.5 Hz), 1.25 (3H, s); ^{13}C NMR (101 MHz, DMSO-d_6) δ 176.2, 143.7, 130.7, 127.9, 127.8, 66.5, 47.7, 42.5, 27.5; HRMS calcd for $C_{12}H_{17}ClNO_3$ $[MNH_4]^+$ 258.0897, found 258.0897.

***tert*-Butyl [*trans*-1-(4-Chlorophenyl)-3-hydroxy-3-methylcyclobutyl]carbamate (34).** *a. Curtius Rearrangement of Acid **27**.* To a 500 L glass-lined vessel were charged the IPAc solution containing crude *trans*-acid **27** (66.9 kg, 10.9 wt % purity by HPLC analysis, 30.2 mol, 1.0 equiv) and THF (131 kg) at rt. The resulting mixture was solvent-switched into THF by azeotropic distillation under vacuum below 50 °C until the residual IPAc and water levels were ≤5% and ≤0.1%, respectively. The resulting solution (~40 L total volume) was diluted with additional THF (70 kg), and Et_3N (7.4 kg, 73.1 mol, 2.4 equiv) was added. DPPA (7.9 kg, 28.7 mol, 0.95 equiv) was added below 30 °C, and the reaction vessel was then rinsed down with THF (7 kg). The mixture was aged at 25−35 °C, at which point HPLC analysis showed 85% conversion of acid starting material **27** to acyl azide intermediate **31**. An additional portion of DPPA (0.42 kg, 1.5 mol, 0.05 equiv) was added below 30 °C, and the mixture was aged for a further 3 h. The mixture was then heated to 55−65 °C, and 2 N aq HCl (72 kg) was added at this temperature over 4 h. After a further 11.5 h at 55−65 °C, HPLC analysis showed the formation of desired amine **32** and urea **33** in a ratio of 1.3:1. The mixture was concentrated under vacuum below 50 °C to a target volume of ~75 L to remove THF (residual level at this point 0.04%; target specification ≤5%), then IPAc (70 kg) was added, and the biphasic mixture was stirred at 40 °C for 1 h before being cooled to 25−35 °C. The layers were separated. The organic layer, containing urea **33**, was washed with 2 N aq HCl (2 × 30 kg) and processed further as described in section b below. The combined aqueous layers contained amine **32** (as the corresponding HCl salt). These aqueous layers were processed through the Boc protection step, using a procedure analogous to that described in section c below, to provide 900 g of crude carbamate **34**, which was recrystallized as described in section d below.

*b. Hydrolysis of Urea **33**.* To the IPAc organic layer containing urea **33** was charged 30% aq NaOH (26 kg, 195 mol) and water (40 kg) at rt. The mixture was stirred for 2.5 h (to remove residual HCl and DPPA), and then the layers were separated. The organic layer was concentrated under vacuum below 50 °C to a target volume of 50−60 L, during which time urea **33** crystallized. The resulting slurry was filtered and the product cake dried to give 2.3 kg (5.1 mol uncorrected) of crude urea **33** in 92 HPLC area % purity. To a 500 L glass-lined vessel were charged the crude urea **33** (2.3 kg), water (25 kg), diethylene glycol monoethyl ether (25 kg), and $Ba(OH)_2$ (4.5 kg, 26.3 mol). The mixture was heated to 98−103 °C and aged for 7 days. After cooling to 20−30 °C, water (25 kg) and

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MTBE (25 kg) were added, and stirring was continued for 30 min. The layers were separated, and the aqueous layer was back-extracted with MTBE (2 × 25 kg). The combined organic layers were then extracted with 1 M aq HCl (2 × 12 L). The combined aqueous layers contained amine **32** as the corresponding HCl salt (1.64 kg free-base amine by HPLC assay, 7.75 mol) and were processed further as described in section c below.

*c. Boc Protection of Amine **32**.* The aqueous layer from section b above, containing the amine **32** HCl salt (1.64 kg free-base amine by HPLC assay, 7.75 mol, 1.0 equiv), was adjusted to pH 7 using aq NaOH. Na_2CO_3 (0.5 kg, 4.7 mol, 0.6 equiv), THF (15 kg), and Boc_2O (2.8 kg, 12.8 mol, 1.7 equiv) were added, and then the mixture was heated to 60−65 °C and aged at that temperature for 2 h. After cooling to 20−30 °C the layers were separated and the aqueous layer was extracted with MTBE (2 × 15 L). The combined organic layers were concentrated under vacuum to a target volume of 10 L. Heptane (20 L) was added, and the resulting solution was concentrated under vacuum to a target volume of 10 L. To this solution was added heptane (30 L), and the resulting slurry was cooled to 15−20 °C and aged for 3 h. The slurry was filtered, and the product cake was dried under vacuum at rt to give crude carbamate **34** (2.3 kg, 7.4 mol uncorrected).

*d. Recrystallization of Crude Carbamate **34**.* The 0.9 kg of crude carbamate from step a was combined with the 2.3 kg of crude carbamate from step c and recrystallized from acetone/water to give the title compound **34** (2.87 kg, 99.3 wt % purity, 9.2 mol, 30% overall yield from acid **27**) as a white solid.

Data for recrystallized carbamate **34**: mp 144−145 °C; IR (neat) 3275, 2979, 1675, 1364, 1238, 1166, 1075, 1006, 626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.27 (4H, m), 5.51−5.05 (1H, br m), 2.66−2.54 (4H, br m), 2.05 (1H, s), 1.56 (3H, s), 1.39−1.28 (9H, br m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 144.8, 132.2, 128.2, 127.0, 79.7, 68.4, 50.6, 49.3, 29.5, 28.3; HRMS calcd for $C_{16}H_{23}ClNO_3$ $[MH]^+$ 312.1366, found 312.1362.

***tert*-Butyl {*trans*-3-Hydroxy-3-methyl-1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]cyclobutyl}carbamate (6).** A 100 L glass-lined vessel was charged with carbamate **34** (2.87 kg, 99.3 wt % purity by HPLC analysis, 9.2 mol., 1.0 equiv), KOAc (2.7 kg, 27.5 mol, 3.0 equiv), bis(pinacolato)diboron ($(Bpin)_2$) (2.85 kg, 11.2 mol, 1.2 equiv), and MeCN (34.4 kg) at rt. After 20 min, X-Phos (268 g, 0.56 mol, 0.06 equiv) and $Pd(OAc)_2$ (68 g, 0.28 mol, 0.03 equiv) were added, and the resulting mixture was purged with N_2 (vacuum/backfill) 3 times. The mixture was heated to 78−83 °C and aged for 18 h, at which point HPLC analysis indicated no detectable carbamate starting material **34** (target specification: ≥99% conversion). The mixture was cooled to rt and filtered through a pad (600 g) of Celite, rinsing with MeCN (16.8 kg). The combined filtrates were concentrated under vacuum below 50 °C and solvent-switched into a target final volume of MTBE solution by azeotropic distillation (achieved 1.5% residual MeCN; target specification ≤5%). The resulting solution was washed with water (3 × 30 kg) to remove pinacol and *tert*-butanol (*t*-BuOH) byproduct (achieved 0.3% residual pinacol and 0.2% residual *t*-BuOH; target specifications ≤5% for each). The organic layer was dried with Na_2SO_4 (1.0 kg) for 1 h at rt and then filtered. The filtrate was solvent-switched into *n*-heptane by azeotropic distillation under reduced pressure below 50 °C to a final target volume of ∼30 L (achieved 0.02% residual MTBE; target specification ≤5%), during which time the product began to crystallize. The slurry was aged at 20−30 °C for 30 min and then filtered. The product cake was washed with *n*-heptane (1 × 8.6 kg) and then dried under vacuum at rt for 24 h to give the title compound (3.4 kg, 99.0 wt % purity, 8.4 mol, 91% corrected yield) as a white solid. mp 112−115 °C; IR (neat) 3532, 3338, 2980, 1694, 1363, 1164, 1142, 1092, 655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, J = 8.0 Hz), 7.40 (2H, d, J = 8.0 Hz), 5.22−5.04 (1H, br m), 2.67−2.54 (4H, br m), 1.90 (2H, s), 1.57 (3H, s), 1.38−1.26 (21H, br m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 149.3, 134.8, 126.9, 124.8, 83.7, 79.5, 68.5, 51.1, 49.1, 29.4, 28.3, 24.8; HRMS calcd for $C_{22}H_{35}BNO_5$ $[MH]^+$ 403.2645, found 403.2651.

***tert*-Butyl (*trans*-1-{4-[1-(Difluoromethyl)-8-phenyl-[1,2,4]triazolo[4,3-*a*][1,5]naphthyridin-7-yl]phenyl}-3-hydroxy-3-methylcyclobutyl)carbamate (36).** An aq K_3PO_4 solution was prepared by dissolving K_3PO_4 (3.01 kg, 14.18 mol, 2.0 equiv) in water (2.52 L) at rt, followed by degassing via subsurface N_2 sparging for 20 min. A 50 L jacketed cylindrical vessel was charged with 2-MeTHF (12.6 L), triflate **4** (3.15 kg, 7.09 mol, 1.0 equiv), and boronate **6** (3.15 kg, 7.80 mol, 1.1 equiv), and the resulting thin brown slurry was degassed for 20 min. To the vessel was then charged $Pd(OAc)_2$ (48 g, 0.21 mol, 0.03 equiv) and 1,1′-bis-(diisopropylphosphino)ferrocene (DIPPF) (89 g, 0.21 mol, 0.03 equiv), and the mixture was degassed for a further 10 min. The aq K_3PO_4 solution was then added, and the degassing continued for a further 5 min. The mixture was aged for a further 1 h, during which time the batch temperature rose steadily from 25 °C to a maximum of 48 °C. After 1 h the reaction was complete (<0.3% triflate **4** remained). The brown solution was cooled to 20 °C over 35 min, during which time the product began to crystallize. After stirring for 1 h at 20 °C, the liquors were assayed for 31 mg/mL of product **36**. Water (3.78 L) was added in one portion, followed by the addition of MTBE (12.6 L) over 1 h. The resulting yellow slurry was aged for a further 30 min (liquors assayed for 18 mg/mL of product **36** at this point) and then filtered. The product cake was washed with 1:1 2-MeTHF/MTBE (2 × 8 L) and then with 1:1 EtOH/water (2 × 8 L), and it was then dried under vacuum with a N_2 sweep at rt for 4 days to give the title compound (3.66 kg, 93 wt % purity—contains residual EtOH and 2-MeTHF, 5.96 mol, 84% corrected yield) as an off-white solid. mp 147−148.5 °C; IR (neat) 3388, 2968, 1726, 1512, 1164, 1063, 825, 784, 697 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.52 (1H, s), 8.14 (1H, d, J = 10.0 Hz), 8.06 (1H, t, J = 51.5 Hz), 8.04 (1H, d, J = 10.0 Hz), 7.52 (1H, s), 7.40−7.29 (9H, m), 4.97 (1H, s), 2.60 (2H, d, J = 12.5 Hz), 2.35 (2H, d, J = 12.5 Hz), 1.37−1.35 (9H, m), 1.15 (3H, s); ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.0, 154.3, 150.1, 148.2, 142.8 (t, J = 28.0 Hz), 139.1, 138.4, 136.0 (2C), 132.3, 129.3, 129.2, 128.7, 128.2, 127.3 (t, J = 5.0 Hz), 125.8, 125.0, 118.4, 109.8 (t, J = 236.5 Hz), 77.6, 66.5, 50.0, 49.3, 29.2, 28.3; ^{19}F NMR (471 MHz, DMSO-d_6) δ −116.9; HRMS calcd for $C_{32}H_{32}F_2N_5O_3$ $[MH]^+$ 572.2473, found 572.2486.

***trans*-3-Amino-3-{4-[1-(difluoromethyl)-8-phenyl-[1,2,4]triazolo[4,3-*a*][1,5]naphthyridin-7-yl]phenyl}-1-methylcyclobutanol (1).** A 100 L jacketed cylindrical vessel was charged with EtOH (35.9 L) and carbamate **36** (3.59 kg, 93 wt % purity, 5.84 mol, 1.0 equiv). The resulting off-white slurry was cooled to 17 °C over 15 min, and 5 N aq HCl (5.84 L, 29.2 mol, 5.0 equiv) was added in portions over 5 min below 25 °C. The reaction was then heated to 50 °C over 1 h and

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aged at this temperature for 24 h until <1.0% of starting material **36** remained (measured by HPLC analysis). The off-white slurry was then allowed to cool to rt over 12 h and then diluted with water (27.14 L). The mixture was cooled further to 15 °C over 15 min, and 10 N NaOH solution was added over 45 min below 25 °C until a pH of 10−11 was reached (~3.0 L NaOH was added). The faint yellow slurry was aged for a further 30 min at rt and then filtered. The product cake was washed with 2:1 water/EtOH (2 × 8 L) and then with EtOH (2 × 8 L), and it was then dried under vacuum with a N_2 sweep at rt for 40 h to give the title compound (2.57 kg, 99.3 wt % purity, 5.42 mol, 93% corrected yield) as an off-white fluffy solid. mp 260.5−261 °C (dec); IR (neat) 3336, 2961, 2921, 1619, 1516, 1133, 1113, 1039, 882, 821, 772, 793 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.51 (1H, s), 8.14 (1H, d, J = 10.0 Hz), 8.06 (1H, t, J = 51.5 Hz), 8.04 (1H, d, J = 10.0 Hz), 7.45−7.41 (3H, m), 7.40−7.33 (6H, m), 4.77 (1H, s), 2.37 (2H, dd, J = 10.5, 2.5 Hz), 2.16 (2H, dd, J = 10.5, 2.5 Hz), 1.93 (2H, s), 1.51 (3H, s); ^{13}C NMR (126 MHz, DMSO-d_6) δ 156.0, 152.5, 150.1, 142.8 (t, J = 28.0 Hz), 139.9, 138.5, 136.0, 135.8, 132.3, 129.4, 129.3, 128.8, 128.2, 127.3 (t, J = 6.0 Hz), 125.7, 124.6, 118.3, 109.8 (t, J = 235.5 Hz), 66.5, 51.8, 49.3, 29.8; ^{19}F NMR (471 MHz, DMSO-d_6) δ −116.9; HRMS calcd for $C_{27}H_{24}F_2N_5O$ $[MH]^+$ 472.1949, found 472.1948.

■ ASSOCIATED CONTENT

Supporting Information

General experimental information, and copies of ^1H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) Solution assay yields and purity of isolated products reported in the Results and Discussion and Experimental Section were determined by HPLC analysis, unless stated otherwise.

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(16) Lithium-halogen exchange of bromopyridines in flow microreactors without the need for cryogenic conditions has recently been reported; see: Nagaki, A.; Yamada, S.; Doi, M.; Tomida, Y.; Takabaya, N.; Yoshida, J. *Green Chem.* **2011**, *13*, 1110−1113.

(17) Project timeline constraints meant that extension of the flow process to include the generation of anion **13** could not be extensively investigated. Initial attempts to generate dianion **14** directly from bromide **11** in flow using 2 equiv of *n*-BuLi were low yielding.

(18) Structures of intermediates **15** and **16** tentatively assigned based on HPLC-MS and ^1H NMR analysis of reaction mixtures.

(19) There was one major impurity (8 HPLC area %), which appeared to be a dimeric species by HPLC-MS analysis, in the liquors together with numerous other unidentified lower-level impurities.

(20) The 652 psi of pressure included 102 psi from the vapor pressure of water. With the assumption that the sole source of the remaining 550 psi of gas (equal to about 0.077 mol based on the ideal gas law) is hydrazine, then 0.48 mol of gas were generated per mole of hydrazine.

(21) For the process described in this paper, a 5-gal Hastelloy C autoclave rated for 5000 psig was used, fitted with a pressure-venting rupture disk rated for 3100 psig. As described in the Experimental Section, prior to running the main batches, the autoclave was thoroughly cleaned and then conditioned with 1% aq hydrazine.

(22) For subsequent hydrazine displacement reactions, these calculations must be repeated and, if necessary, additional safety evaluation conducted, prior to making any changes to the equipment being used and/or the proposed scale of the process.

(23) Subsequent lab experiments demonstrated that if the product triazole **19** initially isolated from the reaction is washed more thoroughly with organic solvent, then a higher weight % purity is obtained and the reslurry is not required.

(24) Details of the development of this reaction, and the origin of the high *cis*-diastereoselectivity, will be described in a forthcoming manuscript from these laboratories.

(25) For discussion of high-throughput experimentation and selected examples, see: (a) Belyk, K. M.; Xiang, B.; Bulger, P. G.; Leonard, W. R.; Balsells, J.; Yin, J.; Chen, C. *Org. Process Res. Dev.* **2010**, *14*, 692−700. (b) Davies, I. W.; Welch, C. J. *Science* **2009**, *325*, 701−704. (c) Dreher, S. D.; Dormer, P. G.; Sandrock, D.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257−9259. (d) Rubin, A. E.; Tummala, S.;

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(26) For the example of Curtius rearrangement plus carbamate formation on scale, see: Yue, T.-Y.; McLeod, D. D.; Albertson, K. B.; Beck, S. R.; Deerberg, J.; Fortunak, J. M.; Nugent, W. A.; Radesca, L. A.; Tang, L.; Xiang, C. D. *Org. Process Res. Dev.* **2006**, *10*, 262−271.
(27) Target residual Pd specification in the final API **1** for this delivery was 50 ppm.
(28) The methane generated was vented with the stream of N_2, which is sufficient for this scale of synthesis to ensure there is no flammable atmosphere in the reactor or vent piping.
(29) Hastelloy C276 was used in the autoclave. Hastelloy C is typically more robust than 316 Stainless Steel and is compatible with hydrazine. For discussion on a high temperature experiment with 8.5% aq hydrazine in 316 Stainless Steel, see: Brubaker, G. R.; Geoffrey, M. M. *Ind. Eng. Chem. Res.* **1988**, *27*, 1149−1152.