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Preparation of the HIV Attachment Inhibitor BMS-663068. Part 1. Evolution of Enabling Strategies

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ABSTRACT: The development of two enabling routes that led to the production of >1000 kg of BMS-663068 (**3**) is described. The route identified for the initial 100 kg delivery to support development activities and initial clinical trials involved the conversion of 2-amino-4-picoline to the parent active pharmaceutical ingredient (API), followed by pro-drug installation and deprotection. To eliminate the problematic isolation of the parent API and synthesis of di-*t*-butyl(chloromethyl)phosphate, a second-generation pro-drug installation route was developed which involved the conversion of a late-stage common intermediate to an N(1)-thioether derivative followed by chloromethylation, displacement with di-*t*-butylpotassium phosphate, and deprotection. This second strategy resulted in the multikilogram scale preparation of the API in 14 linear steps and ∼7% overall yield.

INTRODUCTION

Despite continued advances in HIV treatment, the development of new antiretroviral drugs and treatment regimens continues to represent an important area of unmet medical need due to long-term tolerability concerns and the emergence of viral strains resistant to current therapies.[1] To date, the approved therapies to treat HIV infection fall into four general classes: (1) entry inhibitors, (2) reverse-transcriptase inhibitors, (3) integrase inhibitors, and (4) protease inhibitors. HIV-1 entry is a complex, multistep process involving the interaction between the viral gp120 envelope glycopeptide and the host cell CD4 receptor, followed by coreceptor binding and membrane fusion.[2] While two antiretroviral drugs, maraviroc and enfuvirtide, inhibit viral entry by preventing binding of HIV-1 to the CCR5 coreceptor and inhibiting gp41-mediated fusion, respectively,[3] currently there are no approved drugs that inhibit the initial binding between CD4 and gp120 (i.e., HIV attachment inhibitors).

A proof-of-concept for the attachment inhibitor target was first achieved with BMS-488043 (**1**).[4] While subsequent optimization efforts led to the discovery of the more potent BMS-626529 (**2**), due to the low solubility and short half-life of **2**, the pro-drug BMS-663068 (**3**) was selected as the active pharmaceutical ingredient (API); see Figure 1 for the structures of **1**, **2**, and **3**. In a recent eight day monotherapy study, BMS-663068 (**3**) was shown to produce substantial reduction in plasma HIV-1 RNA, supporting the continued clinical development of BMS-663068 as a treatment for HIV.[5]

Herein, we describe the evolution of two synthetic routes which enabled the production of >1000 kg of BMS-663068 (**3**) to support preclinical development and ongoing clinical trials. The initial route closely followed the reported medicinal chemistry synthesis and involved conversion of 2-amino-4-picoline to the parent API (**2**) followed by pro-drug installation.

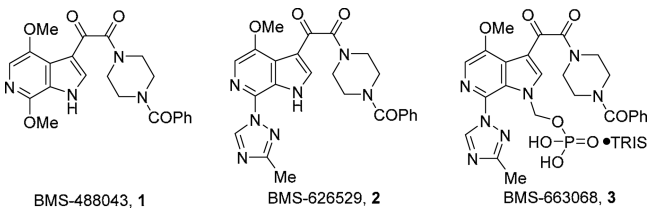

Figure 1. Structures of BMS-488043 (**1**), BMS-626529 (**2**), and BMS-663068 (**3**).

The development of a second-generation route which leveraged the nucleophilicity of the thioether moiety in **4** to enable pro-drug installation will also be discussed (Scheme 1). We also recently published the development of a third-generation route to **3**,[6] and the process development for these transformations is described in the series of papers immediately following this manuscript.

RESULTS AND DISCUSSION

Medicinal Chemistry Synthesis. The medicinal chemistry route to **1**–**3** proceeded through the common 6-azaindole intermediate **7** (Scheme 2). Dimethoxy azaindole **7A** was first accessed from **5** via a low-yielding Bartoli indole cyclization (**5** to **6**)[7] followed by copper catalyzed C(4) methoxylation.[8] An alternative approach to HCl salt **7B**, starting from **8** and involving bromination, diazotization/methoxylation, and a stepwise Leimgruber–Batcho indole synthesis (**9** to **7**),[9]

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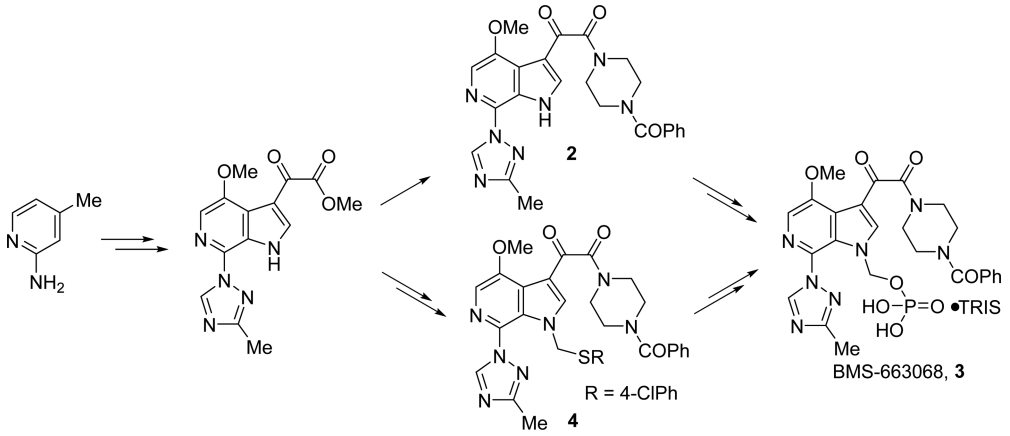
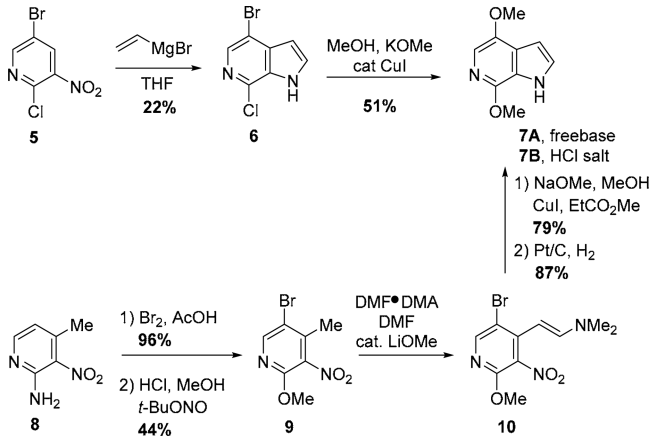
Scheme 1. Initial Routes to BMS-663068 (3)



Scheme 2. Medicinal Chemistry Synthesis of 7A and 7B



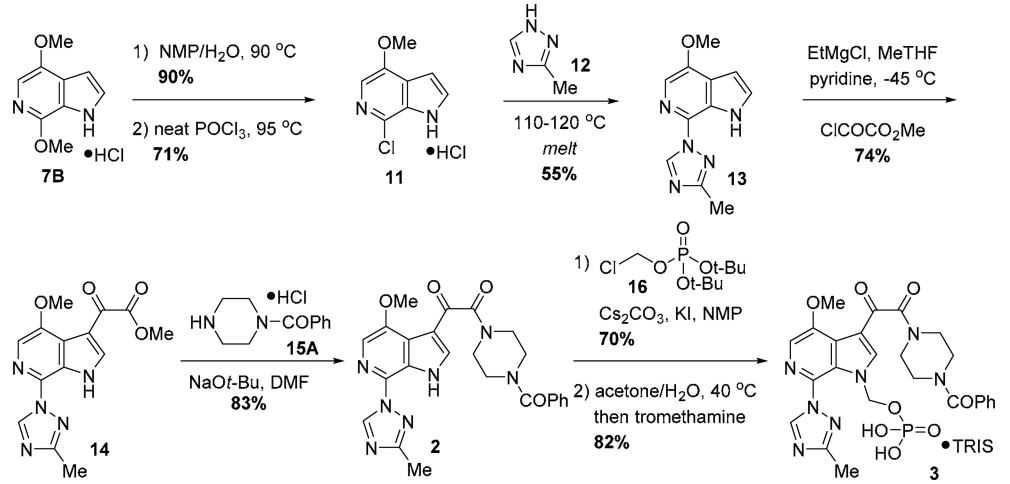
interrupted by copper catalyzed methoxylation, has also been reported.[10]

The synthesis of **3** was then completed via chemoselective hydrolysis of the C(7) methoxy moiety, followed by chlorination with neat $POCl_3$ to give **11** (Scheme 3). Triazole installation was then achieved by heating **11** and **12** as a melt between 110 and 120 °C to afford **13** in a modest 55% yield. Acylation with methyl chlorooxoacetate gave **14** in 74% yield, followed by amidation with **15A** to furnish **2** in 83% yield. Final alkylation with neat **16**, followed by *t*-butyl ester solvolysis and isolation of **3** as the tromethamine [i.e., TRIS, $(HOCH_2CH_2)_3CNH_2$)] salt led to **3** in 57% yield over the two steps. Overall the medicinal chemistry synthesis of **3** was achieved in 12 steps from 2-amino-3-nitropicoline and proceeded in 3−4% overall yield.[11]

Alternate Route Scouting. On the basis of the challenges envisioned with the medicinal chemistry route, specifically the lengthy sequence to convert **8** to **11**, the use of neat $POCl_3$ to prepare **11**, and triazole incorporation involving a melt, we explored additional routes before committing to an approach for an initial 100 kg delivery. As shown in Figure 2, three alterative disconnection strategies were investigated, namely, (1) activation or annulations of a tri- or tetra-substituted pyridine, (2) C(7) activation or (3) hydroxylation or methoxylation of a 4-bromo-6-azaindole substrate. Unfortunately, none of these approaches proved successful.

First Scale-up Campaign. While recognizing the challenges, due to the time constraints of the program, we decided to generally follow the medicinal chemistry route for the first 100 kg delivery. Restraints on the commercial availability of 2-amino-3-nitropicoline (**8**, Scheme 2) necessitated starting from 2-amino-4-picoline (**17**) (Scheme 4). *N*-Acetylation, bromination, and a challenging, highly exothermic nitration[12] led to pyridine **18** in good yield. Development efforts for the

Scheme 3. Medicinal Chemistry Synthesis of 3



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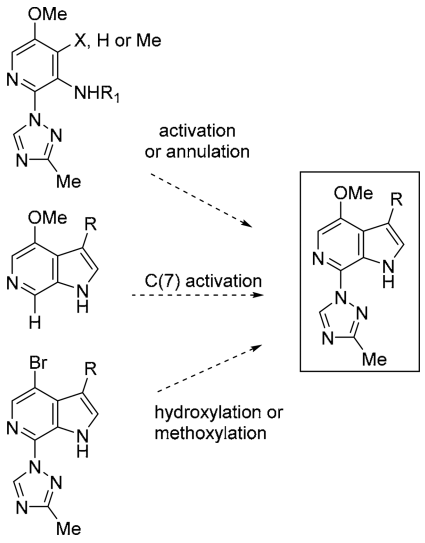


Figure 2. Alternative strategies to access a functionalized 6-azaindole core.

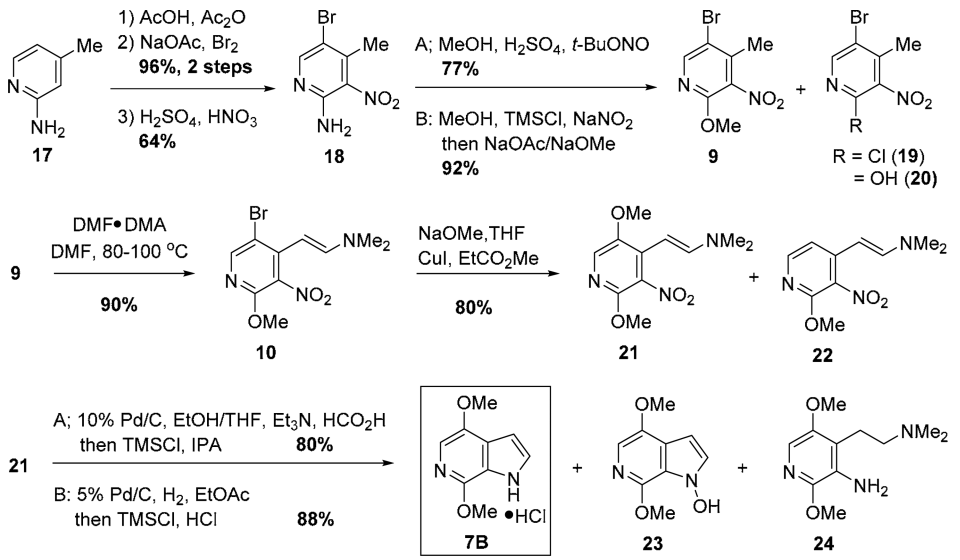
Sandmeyer methoxylation using *t*-BuONO led to a significant yield improvement (increased from 44% to 77%); however, 15−17% of hydroxyl byproduct **20** was also generated. Fortuitously, **20** was readily removed during the crystallization of **9** from methanol/1 M aqueous Na_2CO_3. To improve the overall yield, an alternative process using sodium nitrite and in situ generated HCl was developed. This modification eliminated the potential for formation of **20**, and while up to 25% of **19** was initially generated, workup with NaOAc/NaOMe converted this intermediate to the desired product in high yield.[13]

During the preparation of **10**, we found that catalytic LiOMe was not required, and it was optimal to add the DMF·DMA at 80 °C in a controlled fashion. For the formation of **21**, while the reduction product **22** was the main byproduct [5−10 liquid chromatography area percent (LCAP) in-process], it was readily removed during the crystallization (Scheme 4). Most importantly, since high levels of copper in **21** led to poisoning in the downstream hydrogenation, we implemented an aqueous NH_4Cl workup to consistently afford **21** with <200 ppm of Cu without the need for recrystallization. We also found that temperature control during the aqueous NH_4Cl phase separation was critical. Specifically, while we obtained 80% yield when the temperature was kept <0 °C, the yield dropped to 50−65% at >10 °C due to the formation of multiple hydrolysis byproducts. For the formation of **7B**, we opted to investigate replacing Pt/C with less expensive Pd/C, as well as both high-pressure and transfer-hydrogenation processes (Scheme 4). For the transfer-hydrogenation process, the most critical parameter was the addition rate of the formic acid/THF solution to the 50 °C mixture of **21**, Pd/C, THF, EtOH, and Et_3N. For instance, while the optimal addition time was 45 min, faster addition rates led to increased levels of **24**, while slower rates led to increased levels of **23**. Fortunately, after filtration and solvent swap to MTBE, washing with aqueous NaOH removed **23**, and a subsequent wash with aqueous acetic acid not only removed **24**, but also the Et_3N which caused gumming of **7B** during its isolation as the HCl salt. While both Pd/C high-pressure and transfer hydrogenation procedures were successfully implemented on 100 kg scale, the high-pressure process (1.8 bar) afforded improved isolated yields (88% vs 80%).

With robust access to **7B**, our next challenge was to develop scalable processes to enable the triazole incorporation at C(7). While we were not able to avoid running the chlorination in neat $POCl_3$, we were able to combine the demethylation and chlorination into a single transformation (Scheme 5). The key issues associated with this chemistry resulted from the requirement to isolate and handle intermediate phosphate salt **26**. Specifically, **26** did not remain a free-flowing solid upon storage for >12 h, and it was critical to remove the residual $POCl_3$ in **26** to prevent oiling of **11** due to the formation of $PO(OMe)_3$ upon addition of MeOH to the wet cake of **26**.[14]

To eliminate the previous melt conditions at 110−120 °C to install triazole **12**, we first explored the transition-metal catalyzed conversion of **11** to **13**. Unfortunately, all of these efforts, as well as our attempts to convert **25** to the 7-bromo derivative of **11**, were not viable. Gratifyingly, we were able to carry out the addition with triazole **12**[11] in 6 L/kg 4-methyl-2-pentanol at reflux (132 °C). Under these conditions, **13** was

Scheme 4. Conversion of 2-Amino-4-picoline to 7B



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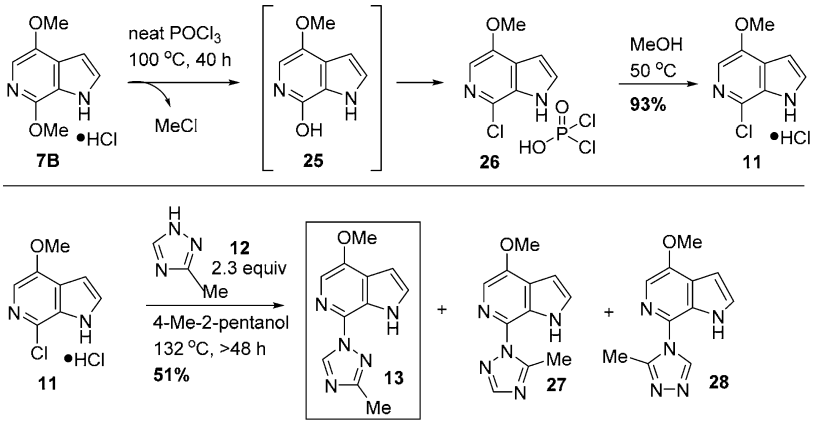
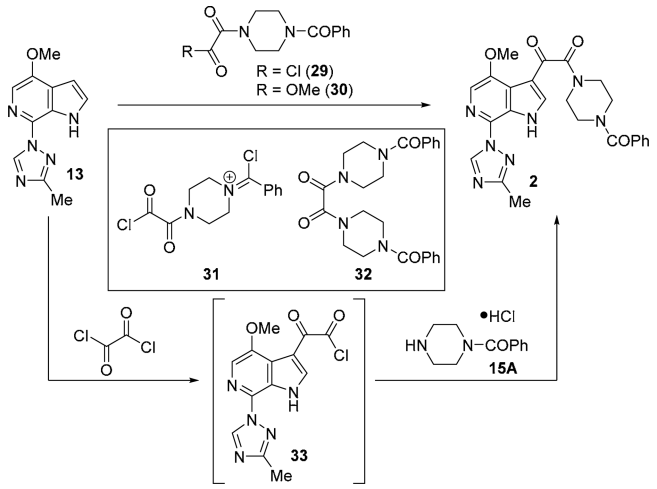
Scheme 5. C(7) Chlorination and Triazole Incorporation



generated in ~65 LCAP, along with a combined 22 LCAP of triazole isomers **27** and **28**.[15] Following an initial crude isolation, recrystallization from MeOH afforded **13** in 51% yield with >99 LCAP purity. We also screened a variety of protic and Lewis acids, as well as additives, but none of these modifications impacted the overall rate or product distribution.

In an attempt to improve the overall convergency as compared to the medicinal chemistry route, we next prepared both acid chloride **29** and ester **30** and attempted to couple directly to **13** under basic, Lewis acid, and/or ionic liquid conditions (Scheme 6). Unfortunately, only ~50% conversion

Scheme 6. Approaches To Directly Convert 13 to 2



could be achieved using **29**, and **30** was unreactive. In addition to the poor conversion, three steps were required to prepare **29** from methyl chlorooxoacetate (i.e., amidation, hydrolysis, chlorination), and **29** was highly moisture sensitive. Furthermore, attempts to prepare the corresponding benzotriazole derivative of **29** led only to dimer **32**, and the evaluation of the direct reaction of **15A** with oxalyl chloride led to the formation of Vilsmeier reagent **31**. While we did achieve proof-of-concept (~55% yield) for the conversion of **13** to **2** via reaction with oxalyl chloride, followed by telescoped displacement with **15A** (Scheme 6), this approach was not further explored since **33** was highly moisture sensitive, >5 equiv oxalyl chloride was required to prevent over-reaction of **33** with **13**, and the excess oxalyl chloride needed to be removed via distillation prior to the addition of **15A**.

Returning to the two-step conversion of **13** to **2** utilized in the medicinal chemistry route (Scheme 3), the key issue in the initial conversion of **13** to **14** was the requirement for −45 °C cryogenic reaction conditions. Toward this end, during our development work for the acylation, five important observations were made: (1) magnesium (vs Li, Na, Zn) bases were uniquely effective for this transformation with *i*-PrMgCl leading to the cleanest purity profile, (2) mechanistically, since **14** is more acidic than **13**, >2 equiv base was required, (3) deuterium incorporation studies verified that dianion **35** was generated in the presence of 2 equiv *i*-PrMgCl, (4) pyridine significantly accelerated the rate of the acylation but did not affect the outcome of the metalation, and (5) inverse addition of the dianion solution to methyl chlorooxoacetate in MeTHF dramatically minimized the exotherm during the acylation and enabled the reaction to be executed between −25 and −10 °C (Scheme 7). Overall, conducting the metalation with 3.5 equiv of *i*-PrMgCl and 0.5 equiv of pyridine in MeTHF, followed by addition to a solution of 4 equiv of methyl chlorooxoacetate in MeTHF between −25 and −10 °C and aqueous workup, led to the isolation of **14** in 76% yield after crystallization.

When we initially examined the medicinal chemistry conditions to convert **14** to **2** with **15A** and NaO*t*-Bu we discovered that the reaction was very sensitive to water, observing significant hydrolysis to acid **34** (Scheme 7). While we did achieve proof-of-concept for the chemical dehydration of the reaction mixture using trimethylorthoformate prior to the addition of the base, we also observed significant levels of **15A** formylation; hydrolysis to **34** was also observed during the azeotropic distillation of the **14**/**15A** mixture. As a result of this liability, we developed a two-stage process in which **14** was initially converted to acid **34** using 3 equiv of KO*t*-Bu in *N*-methyl-2-pyrolidone (NMP)/water, followed by the sequential addition of **15A**, 37 wt % HCl, and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDAC). While this solved the hydrolysis challenge, we discovered that the EDAC coupling was very sensitive to pH, with an HCl overcharge leading to reaction stalling, and an HCl undercharge generating up to 20 AP of hydantoin byproducts **36a/b**. Furthermore, due to the high level of organic solvent after the HCl charge, pH readings were not accurate, and an in-process control (IPC) could not be implemented prior to adding the EDAC. Taken together, these observations led us to set the HCl charge = 2.12 ± 0.05 equiv and then determine if additional HCl or 1 M KOH was required prior to adding the

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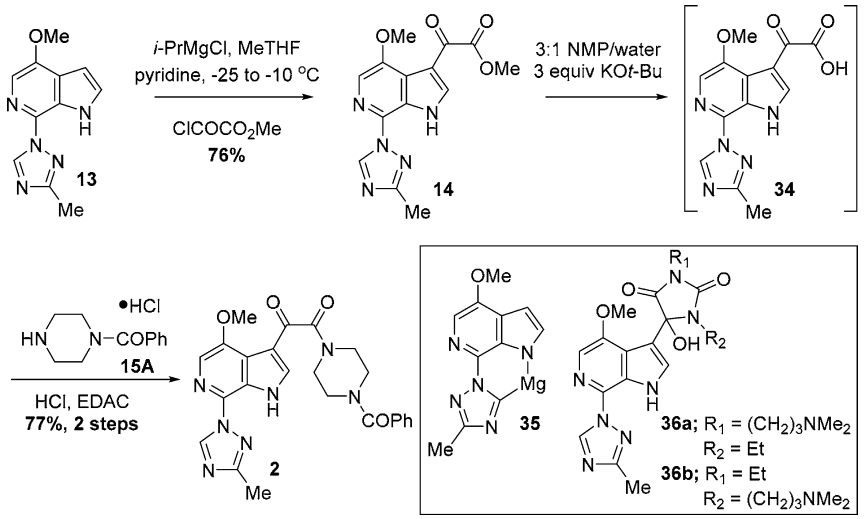
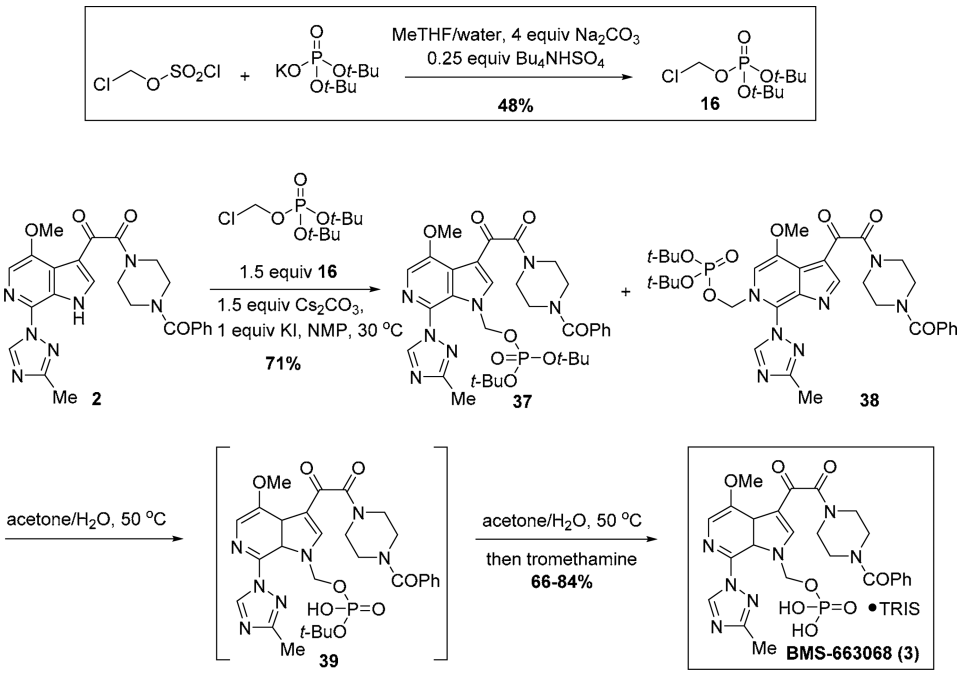
Scheme 7. Installation of C(3) Side Chain



Scheme 8. Endgame for the First Large-Scale Campaign



EDAC via a lab-scale use-test for each pilot-plant run. The final challenge in the amidation was the isolation of **2**. Despite extensive experimentation, including the addition of two heat cycles, due to its very low solubility and needle-like morphology, the filtration of **2** was extremely slow; on 26 kg scale using *two* Nutsche filters in parallel the filtration required >2 weeks! Nonetheless, 159 kg (77% yield, 2 steps) of **2** with 99.9 LCAP was successfully prepared via this process.

The endgame for **3** involved the alkylation of **2** with **16** followed by deprotection and TRIS salt formation (Scheme 8). The synthesis of **16** from chloromethyl chlorosulfate (CMCS) and di-*t*-butyl potassium phosphate had been previously reported,[16] and the process to prepare **16** was not optimized for this campaign.[17] On 44 kg scale, **16** was prepared in 48% in-process yield as a solution in NMP which was used directly due to the known instability of **16** as a neat oil.[18] The alkylation conditions for **2** (i.e., Cs_2CO_3, KI, NMP, 30 °C) were also largely unchanged as compared to the medicinal chemistry route and led to an ~10:1 mixture of **37** and its N(6) isomer **38**. The main modifications implemented on scale were: (1) heat cycling of the starting **2**/NMP mixture to 90 °C to delump **2**,[19] (2) use of a continuous nitrogen blow through the bottom valve of the reactor to maintain adequate Cs_2CO_3 suspension,[20] and (3) development of a modified MTBE:DCM (4:1/v:v) antisolvent addition protocol to improve the filtration rate as compared to the original DCM to IPA distillative crystallization procedure.

While the modified crystallization protocol led to significantly improved filtration rates (i.e., 500 vs 25 L/m^2/h), variable levels of **38** removal were observed, leading to **37** with 91.3–97.5 LCAP and 0–6 LCAP **38**; the isolated **37** also contained 0.3–1.0 LCAP **2** and ~1 LCAP **39**. Despite the variable purities, the yield of **37** was not affected (i.e., 71%), and all batches led to API **3** meeting specifications (vide infra).

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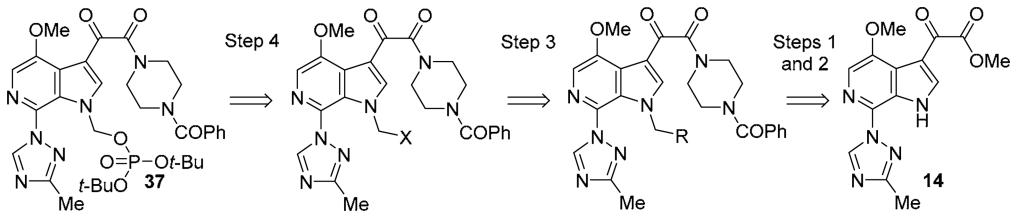
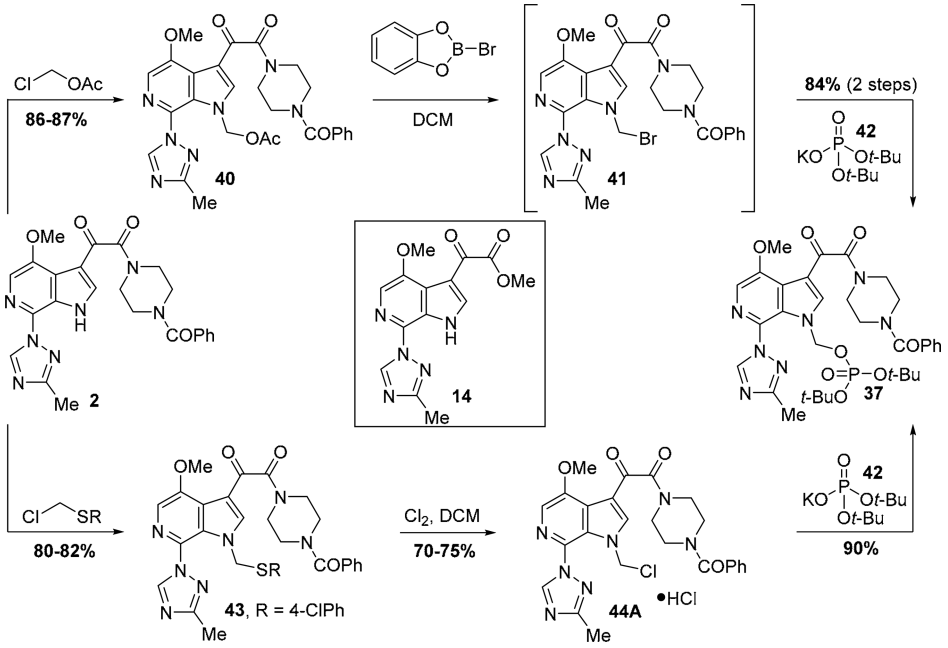
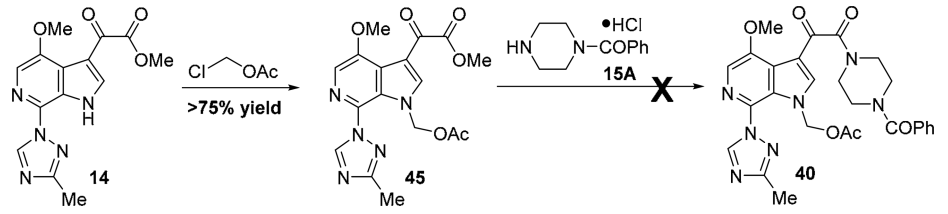
Scheme 9. Proposed Retrosynthetic Analysis for the Second Campaign



Scheme 10. Proof-of-Concept for Alternative Strategies To Convert 2 to 37



Scheme 11. Challenges with Chloromethyl Acetate Endgame



We conducted the final solvolysis of **37** in acetone/water at 50 °C in close analogy to the medicinal chemistry route. As mentioned above, while all batches of **37** led to API meeting our specifications, the isolated yield of **3** was 15−20% lower using batches of **37** containing the N(6) isomer **38**. These lower yields were due to the conversion of **38** to **2** under the solvolysis conditions, and the increased level of **2** led to blinding of the polish filters. This required their replacement multiple times during processing and increased the yield loss due to material remaining in the filter housings. Despite the lower than expected yields in the API step,[21] the overall campaign afforded 108 kg of BMS-663068 (**3**) with >99.6 LCAP.

Second Scale-up Campaign. Due to success in delivering >100 kg API, coupled with the aggressive timelines for the project, it was decided for the second scale-up campaign to continue to utilize the existing chemistry to convert 2-amino-4-picoline **17** to **14**, but focus optimization efforts on identifying alternative C(3) side-chain and pro-drug installation strategies. The goals of a revised endgame sequence were: (1) to eliminate the use of **16**, due both to the low yield of its synthesis[17] and the challenges associated with sourcing the chloromethyl chlorosulfate starting material,[22] (2) to avoid the isolation of **2** due mainly to its poor filtration properties, and (3) to maintain the isolation of **37** as our quality gate intermediate. Toward this end, we envisioned a strategy from **14** that would entail: (1) N(1) alkylation, (2) benzoyl piperazine side-chain installation, (3) conversion of the N(1) substituent to a halomethylderivative, and (4) reaction with di-*t*-butyl potassium phosphate to afford **37** (Scheme 9).[23]

While the goal of our final modified endgame was to not include the isolation of **2**, to simplify our route-scouting efforts, we first achieved proof-of-concept for two approaches involving the initial reaction of **2** with chloromethyl acetate or 4-chlorophenylchloromethyl sulfide (Scheme 10).[24] With respect to **40**, after extensive screening we discovered that *B*-bromocatechol borane[25] was uniquely effective in converting acetate **40** to bromomethyl intermediate **41**. The telescoped

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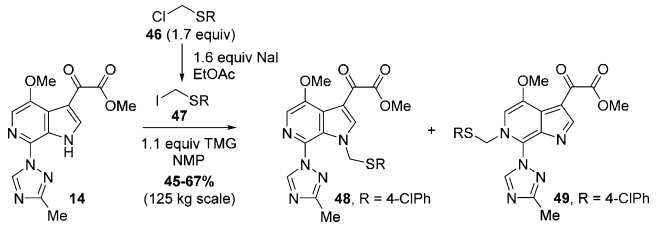
conversion of **40** to **37** was then effected via addition of di-*t*-butyl potassium phosphate (**42**) to afford **37** in 84% yield over two steps. In the second approach, thioether derivative **43** reacted instantaneously with Cl_2[26] to afford **44A** in 70−75% yield via a direct-drop process. In analogy to **41**, the addition of **42** readily converted **44A** to **37** in 90% yield.

While both routes were potentially viable, since they started with the undesirable intermediate (**2**), and we were unable to telescope the conversion of **14** to either **40** or **43** via **2**, it became necessary that N1 alkylation of **14** occurred prior to amidation. Due to the instability of the acetate moiety of **45** under a variety of amidation conditions (Scheme 11), we selected the thioether endgame for further development.[27]

With this basic bond disconnection strategy, we screened a variety of solvents, bases and additives, from which we selected and rapidly developed an initial set of alkylation conditions. These conditions entailed the initial Finkelstein conversion of **46** to **47** using stoichiometric NaI in ethyl acetate, followed by the addition of a solution of **14** and tetramethylguanidine (TMG) in NMP (Scheme 12).[28] Under these conditions, an

Scheme 12. Conditions for the Conversion of 14 to 48 in the Second Campaign

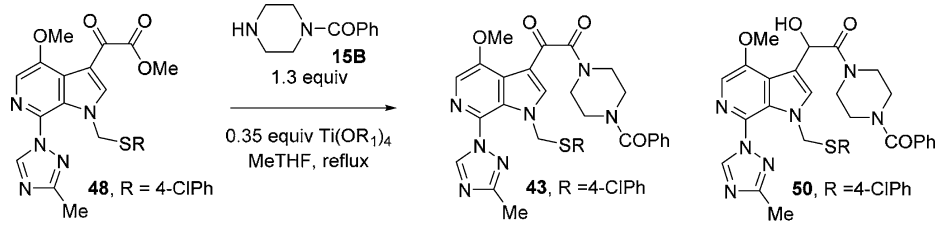


∼4:1 ratio of **48**:**49** was observed. Serendipitously, during our workup studies to examine NMP removal, we found that washing the reaction stream with 0.5 M aqueous HCl also led to selective partitioning of **49** to the aqueous phase; the optimized workup entailed addition of 15 L/kg EtOAc, followed by 3 × 0.5 M HCl and 2 water washes. Crystallization via solvent exchange from EtOAc to IPA then led to **48** with >97.7 LCAP in 45−67% yield on 125 kg scale. It is important to note that five aqueous washes were necessary to remove both the NMP and **49** prior to crystallization, and these phase separations were challenging due to the formation of emulsions.

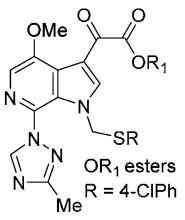
In analogy to the observations during the preparation of **2**, direct amidation between **48** and **15A** under basic conditions, with or without various drying protocols, led to significant hydrolysis. Fortunately, we discovered that the desired amidation could be achieved under Lewis acid catalyzed conditions.[29] As shown in Scheme 13, our initial optimization with $Ti(OMe)_4$ supported the coupling of **48**, and **15B** proceeded readily in MeTHF at reflux; the only new requirement for this approach was the need to utilize the piperazine freebase (i.e., **15B**) instead of the more readily available HCl salt. A further screen of titanium alkoxides indicated that $Ti(O\textit{i}\text{-}Pr)_4$ increased conversion; however, it also increased the level of reduction byproduct **50**, generated via a Meerwein−Ponndorf−Verley reduction,[30] and led to low levels of the transesterified starting material. We proposed that the use of a straight chain titanium alkoxide would decrease the level of **50**, and to our delight, executing the amidation with inexpensive and commercially available $Ti(O\textit{n}\text{-}Bu)_4$ maintained the high reaction rate, but led to decreased levels of both **50** and the transesterification byproduct.

Following the identification of amidation conditions, we next turned our attention to defining a workup/isolation protocol to address titanium removal. Initially, we observed that washing the MeTHF reaction mixture with 1 M aqueous $NaHSO_4$, followed by addition of 1:1 EtOH:heptane as antisolvent, reproducibly led to **43** with <10 ppm Ti. However, after extensive development work, we identified a new thermodynamically favored crystal form of **43** which, due to its significantly lower solubility in MeTHF (i.e., 11 mg/mL vs >110 mg/mL for initial form), crystallized directly from the reaction mixture below 65 °C and prevented the implementation of the planned MeTHF/1 M aqueous $NaHSO_4$ workup.[31] Fortunately, we were able to rapidly develop a direct-drop isolation of **43** from the MeTHF reaction mixture, recognizing that a critical aspect of this strategy would be the strict control of water to prevent titanium contamination. Overall, the final combined procedure entailed: (1) free-basing of **15A** in MeTHF with aqueous NaOH, followed by azeotropic distillation, (2) because of yield variability (75−90%), quantitation of the dry MeTHF/**15B** solution to determine the amount required to achieve 1.3 equiv of **15B** for the reaction, and (3) sequential addition of **48** and $Ti(O\textit{n}\text{-}Bu)_4$, followed by heating to reflux (Scheme 14). Upon reaction

Scheme 13. Identification of a Titanium Alkoxide Mediated Amidation



R_1	43 (prdt)	48 (sm)	50 (red)	OR_1 ester
Me	81.7	9.8	0.6	
i-Pr	88.5	0.9	2.9	2.0
n-Bu	91.8	0.6	0.8	1.0



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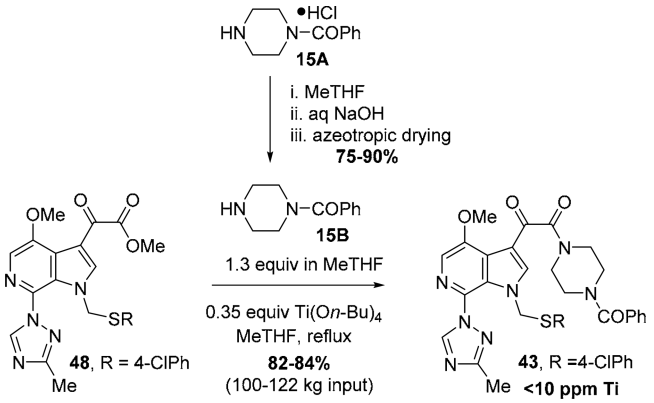
Scheme 14. Amidation Conditions Implemented in the Second Campaign



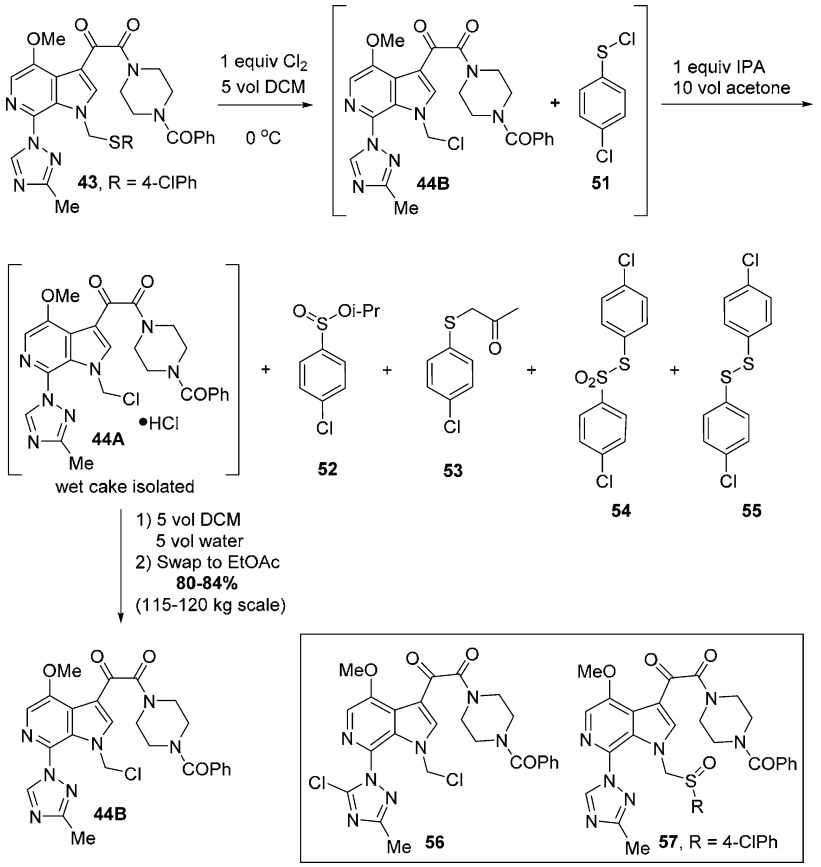
completion, the mixture was cooled to 65 °C, seeded with the desired crystal form, and then slowly cooled to 15 °C. The execution of this process on 100−122 kg scale led to **43** in 82−84% yield with >99.6 LCAP and <10 ppm titanium.

Continuing with the synthesis, our attention shifted to optimizing the process for the conversion of **43** to chloromethyl derivative **44** (Scheme 15). As previously mentioned in our initial studies (Scheme 10), this was accomplished by addition of gaseous Cl_2 to a DCM solution of **43** at 0 °C. Further development work identified that the two most critical process variables were the equivalents of chlorine and the water content of the DCM/**43** solution. For example, in the presence of a slight excess of Cl_2 (i.e., 1.1 equiv), ∼3 LCAP of the dichloro byproduct **56** was generated, while the use of a DCM/**43** solution with a water content = 0.3 wt % led to >6 LCAP of sulfoxide **57**. We also found that after the reaction was complete, the addition of 1 equiv of IPA in 10 L/kg of acetone quenched the intermediate 4-chlorophenylchlorosulfide (**51**) and led to crystallization of **44A**. The main byproducts **52**−**55** all remained in the mother liquor, and **44A** was isolated in >85% yield with excellent purity. However, stability studies of **44A** demonstrated that the material was highly susceptible to hydrolysis.[32] Fortunately, the corresponding freebase (**44B**) did not hydrolyze under identical storage conditions.

On the basis of these observations, the final process developed for the second campaign entailed a careful subsurface addition of Cl_2 to minimize overchlorination. The addition of IPA and acetone then led to the quenching of **51** and isolation of HCl salt **44A**. Wet cake **44A** was then freebased by addition of DCM and water, with no additional base required, and solvent swap to EtOAc led to the isolation of **44B** in 80−84% yield on 115−120 kg scale with 97−98 LCAP purity. It is important to note that both **44** and **52** were shown to be Ames positive and thus needed to be monitored as genotoxic impurities (GTI) (vide infra).

To complete the synthesis, all that remained was the displacement of the chloride in **44B** by di-*t*-butyl potassium phosphate (**42**), followed by the subjection of **37** to the known solvolysis conditions. During our initial development work using **44A** we discovered that the portionwise addition of **42** was necessary to prevent gelling of the reaction mixture, and the selection of phase-transfer catalyst (PTC) impacted both

Scheme 15. Chloromethylation Process Implemented in the Second Campaign



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the reaction rate and the partitioning of the PTC into the aqueous layer during the workup. Specifically, as shown in Table 1, we observed that the reaction rate increased according to the nature of the counterion (Cl < Br < I) and length of the alkyl chain (ethyl < propyl < butyl), with the tetramethyl phase-transfer catalysts leading to almost no conversion irrespective of the counterion (Table 1). Both the nature of the counterion and length of the alkyl chain also dictated the partitioning of the PTC to the aqueous phase, roughly following the trends of iodide < bromide < chloride and butyl < propyl < ethyl, respectively. These latter observations were of particular importance as residual PTC present in the DCM layer post aqueous workup was observed to precipitate during the crystallization of **37**.

Table 1. Impact of PTC on the Conversion of 44A to 37 and Partitioning into the Aqueous Layer

entry	PTC	conversion (%)[a]	% PTC in org layer[b]
1	Bu_4NCl	45	45
2	Bu_4NBr	83	80
3	Bu_4NI	98.5	>95%
4	Pr_4NCl	47	5%
5	Pr_4NBr	77	5%
6	Pr_4NI	97	50%
7	Et_4NCl	36	0
8	**Et_4NBr**	**77**	**0**
9	Et_4NI	82	<5%
10	Me_4NCl	4	nd[c]
11	Me_4NBr	4	nd
12	Me_4NBr	6	nd

[a]Calculated by HPLC. [b]Calculated from ^{1}H QNMR of organic layer after aqueous workup with trimethylphosphate as the internal standard. [c]nd = not determined.

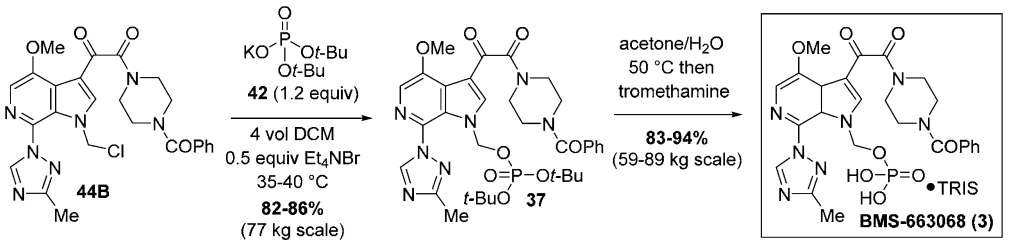
As a result of the data in Table 1, we selected Et_4NBr as the PTC for the preparation of **37** using **44B**, as it afforded the best combination of reaction rate and partitioning into the aqueous layer. As depicted in Scheme 16, our final processing conditions entailed heating a solution of **44B** and 0.5 equiv of Et_4NBr in 4 L/kg DCM to 35 °C. Di-*t*-butyl potassium phosphate (**42**) was then added in four portions over 1 h followed by heating the resulting mixture to reflux. After cooling and conducting a single water wash, a 20:1 mixture of MTBE:IPA was charged as the antisolvent to induce crystallization. Execution of this process on 77 kg scale led to **37** in 82−86% yield with 98 LCAP purity.[33] We also verified that our process embodied a robust GTI control strategy; affording **37** with <0.2 ppm **46** and **47**, <0.3 ppm **52**, and 4−16 ppm **44B**.[34] While no major processing changes were implemented in the API step for the second campaign, due to the improved and more consistent purity of **37**, we did not observe significant yield losses during the polish filtration and isolated a total of 218 kg of API (**3**) in 83−94% yield meeting all acceptance criteria, including the GTI specifications (Scheme 16).[21]

Third Scale-up Campaign. While the delivery of an additional 218 kg API was a significant milestone for the program, we were almost immediately charged with executing a larger campaign. To meet these demands as efficiently as possible, multiple aspects of the alkylation, amidation, and chlorination processes were targeted for improvement. Starting with the alkylation to convert **14** to **48**, our optimization focused on developing an improved process to address three issues: the requirement for a separate, mixing-sensitive Finkelstein reaction using NaI; the need for a large excess (1.7 equiv) of 4-chlorophenylchloromethyl sulfide (**46**); and the multiple challenging phase separations. After extensive experimentation, modified alkylation conditions were developed to address all of these concerns. Specifically, replacing TMG and NMP with K_2CO_3 and CH_3CN, respectively, led to a one-pot process using catalytic tetrabutylammonium iodide (TBAI) (Scheme 17); the in-process ratio of **48**:**49** remained ∼4:1. In addition to eliminating the separate heterogeneous Finklestein reaction, these conditions enabled the equivalents of **46** to be reduced from 1.7 to 1.2.[35] While 4 × 0.5 M HCl washes were still required to remove the undesired isomer **49**, the phase separations were extremely rapid and clean due to the lack of NMP. The crystallization conditions from IPA were not changed and led to more consistent isolated yields ranging from 60 to 64%.[36] Overall, this process delivered >1000 kg of **48**.

Turning to the amidation, the goals for the third campaign were (1) to decrease the variability in yield for free-basing **15A** and (2) to replace MeTHF with a less expensive solvent. This latter goal was readily achieved by changing the reaction solvent to toluene. However, free-basing **15A** was problematic using toluene/aq NaOH. Alternatively, we found that free-basing **15A** in CH_3CN with 0.95 equiv of K_2CO_3, followed by an azeotropic solvent swap into toluene and polish filtration, reproducibly led to a toluene solution of **15B** in >95% yield. To our delight, we successfully executed both the modified free-basing and the amidation processes to afford a total of 1200 kg of **43** in 82−84% yield with >99 LCAP purity and <10 ppm Ti (Scheme 18).

Finally, when considering the previous chlorination and phosphate displacement reactions, specifically the liabilities associated with the isolation of the **44A** wet cake, and the observation that both the chlorination and phosphate displacement were executed in DCM, we sought to develop a telescoped process to convert **43** to **37** (Scheme 19). Toward this end, after the standard chlorination conditions, **51** was quenched with IPA in the absence of the acetone antisolvent. This was followed by two aqueous washes and an azeotropic

Scheme 16. Endgame for the Second Campaign



DOI: 10.1021/acs.oprd.7b00134
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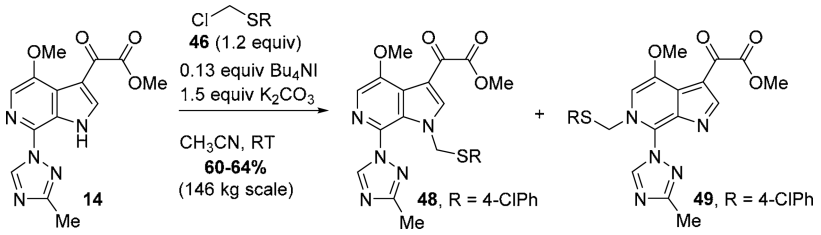
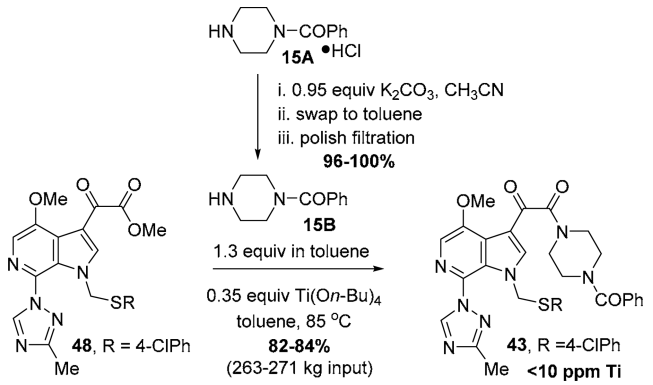
Scheme 17. Improved Conditions To Convert 14 to 48 in the Third Campaign



Scheme 18. Improved Conditions To Convert 48 to 43



distillation to afford a crude solution of **44B** in DCM. Direct addition of 0.5 equiv Et_4NBr and 1.2 equiv **42**, followed by the same aqueous workup and crystallization protocol utilized in the second campaign, furnished **37** in 73−78% yield with 97 LCAP. While the purity of the isolated **37** was ∼1 LCAP lower compared to the previous process, due to slightly increased levels of **2** and **43**, and the level of residual **52** (GTI) was slightly higher (i.e., 64−86 ppm vs <0.3 ppm), these byproducts did not impact the purity of the resulting API, and the average yield for the conversion of **43** to **37** via the telescoped process was 14% higher than the two-step procedure. Following the removal of both *t*-butyl groups and TRIS salt formation, we obtained 720 kg of API meeting all quality specifications.

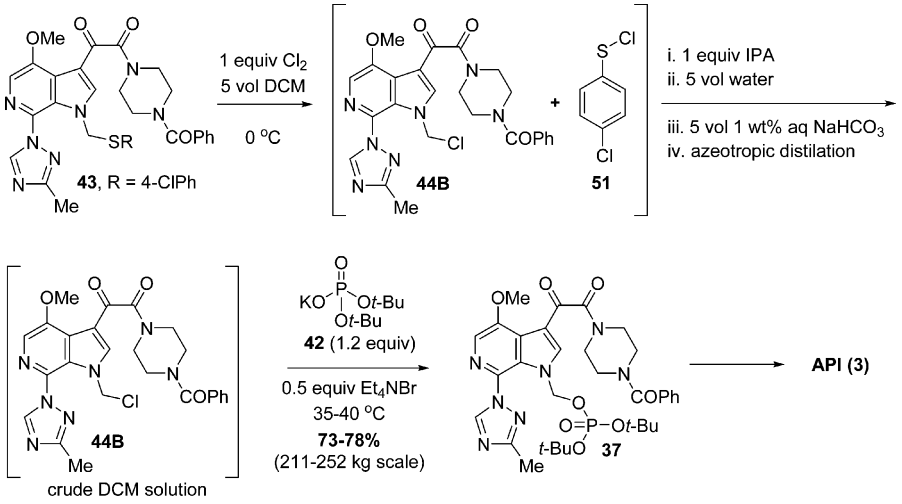
CONCLUSION

We have described the evolution of two enabling routes that led to the production of >1000 kg of BMS-663068 (**3**). Specifically, the first-generation route closely followed the reported medicinal chemistry synthesis and involved the conversion of 2-amino-4-picoline to the parent API (**2**), followed by phosphonooxymethyl prodrug installation and deprotection. To eliminate the problematic isolation of **2** and preparation of **16**, a second-generation pro-drug installation route was developed which involved the conversion of common intermediate **14** to thioether derivative **43** followed by conversion to the chloromethyl derivative **44**, displacement with di-*t*-butyl potassium phosphate, and deprotection. Optimization led to robust processing conditions which afforded the desired API in 14 linear steps and ∼7% overall yield. While the processes described herein represent scalable protocols for the preparation of **3**, due to both the high number of synthetic steps and the significant GTI burden in the route beginning from 2-amino-4-picoline, we continued our route-scouting efforts,[6] and the evolution and optimization of the envisioned commercial synthesis will be discussed in the subsequent papers.

EXPERIMENTAL SECTION

Preparation of 18. To glacial acetic acid (336 kg, 2.1 kg/kg) was charged 2-amino-4-picoline (160 kg, 888 mol) in 8 portions at 10 min intervals. Acetic anhydride (181 kg, 1.1 kg/kg) was then added in four portions at 5 min intervals, and the mixture was heated to 85−95 °C. After 5 h, the acetylation was judged complete by HPLC (<0.5 area % 2-aminopicoline), and the reaction mixture was cooled to 40−60 °C. Water (2080 kg,

Scheme 19. Telescoped Conditions To Convert 43 to 37 Utilized in the Third Campaign



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13 kg/kg) was then charged, followed by sodium acetate (182 kg, 2219 mol, 2.5 equiv), and the resulting mixture was stirred at 25−30 °C for 0.5 h. Bromine (260 kg, 1629 mol, 1.8 equiv) was then charged at a rate of 30−40 kg/h, and after an additional 8 h, the bromination was judged complete by HPLC (<5 area % acetylated intermediate). The reaction mixture was then sequentially charged with water (1280 kg, 8.0 kg/kg) and sodium bisulfate (46.2 kg, 384 mol, 0.43 equiv, added in 3−4 portions at 5 min intervals) and agitated at 25−30 °C for an additional 1 h. The resulting slurry was then filtered, washed with water (2 × 480 kg, 2 × 3.0 kg/kg), and dried under vacuum at 50−60 °C. Isolated 325.5 kg (98.2 LCAP, 96% yield) of *N*-(5-bromo-4-methylpyridin-2-yl)acetamide as an off-white solid. To a glass-lined reactor containing concentrated sulfuric acid (832 kg, 6.4 kg/kg) was charged *N*-(5-bromo-4-methylpyridin-2-yl)acetamide (130 kg, 570 mol) in portions while maintaining the internal temperature between 10 and 20 °C. The mixture was then warmed to 25−33 °C and agitated for 1 h. While maintaining the temperature between 25 and 33 °C, fuming nitric acid (39.5 kg, 627 mol, 1.1 equiv) was charged at a rate of 5−6 kg/h. After an additional 7 h, the reaction was judged complete by HPLC (<0.5 area % 5-bromo-4-methyl-2-aminopyridine) and transferred into a new reactor containing ice (832 kg, 6.4 kg/kg) and water (832 kg, 6.4 kg/kg), maintaining the temperature <20 °C. The pH of the reaction mixture was then adjusted to 4−5 with ammonium hydroxide (1234 kg, 9.5 kg/kg), and the resulting slurry was agitated at 15−25 °C for 1 h. After filtration, the crude solids were combined with analogous wet cakes from two additional 130 kg batches for a single isolation/recrystallization. The combined wet cakes were reslurried with 10 wt % aqueous NaOH (2700 kg, 6.9 kg/kg) while maintaining the temperature between 10 and 20 °C, washed with water (2 × 200 kg, 2 × 0.5 kg/kg), isolated by filtration, and dried under vacuum at 50−60 °C. A total of 350 kg of crude **18** was isolated. A mixture of crude **18** (350 kg) in THF (1232 kg, 3.5 kg/kg) was heated to 55−65 °C, aged 1 h, and polish filtered hot. The filtrate was then cooled to 10−15 °C, charged with water (2100 kg, 6.0 kg/kg), and aged for 1 h. The resulting slurry was filtered, washed with water (2 × 175 kg, 2 × 0.5 kg/kg), and dried under vacuum at 50−60 °C. A total of 252 kg (99.6 LCAP, 64% yield) of **18** was isolated as a yellow solid with spectra identical to that previously reported in the literature.[11b]

Preparation of 9: Method A Using *t*-BuONO. To a mixture of **18** (275 kg, 1184 mol) in methanol (4392 L, 16 L/kg) was added concentrated sulfuric acid (25.3 kg, 258 mol, 0.22 equiv) over 60 min maintaining the internal temperature <20 °C. The reaction mixture was then heated to 40 °C, and *t*-butylnitrite (90 wt %, 476 kg, 4158 mol, 3.5 equiv) was added over 7 h while maintaining the internal temperature between 39 and 43 °C. After an additional 2.5 h at ∼40 °C, the reaction was judged complete by HPLC (<1 area % **18**). The reaction mixture was then concentrated to ∼50% volume under vacuum and warmed to 40 °C to dissolve any residual solids. Water (428 L, 1.6 L/kg) and 1 M aqueous sodium bicarbonate (1562 kg, 5.7 kg/kg) were then added, and the resulting slurry was filtered, washed with water (428 L, 1.6 L/kg), and dried at 40 °C to afford 226 kg (99.5 LCAP, 77% yield) **9** as a yellow solid with spectra identical to that previously reported in the literature.[11b,37]

Method B Using $NaNO_2$. To a 0−10 °C solution of methanol (1363 kg, 11.8 kg/kg) was charged TMSCl (215 kg, 1983 mol, 4.0 equiv), maintaining the internal temperature <25 °C. Compound **18** (115 kg, 496 mol) was then added, and the reaction mixture was stirred for 0.5 h before charging sodium nitrite (51.3 kg, 744 mol, 1.5 equiv) in 0.35−0.45 kg/portions every 10 min between 15 and 25 °C. After an additional 18 h, the reaction was judged complete by HPLC (<0.5 area % **18**), and sodium acetate (1623 kg, 1982 mol, 4.0 equiv), followed by sodium methoxide (187 kg, 3469 mol, 7.0 equiv), were added at 20−30 °C. The resulting mixture was then heated to 55−65 °C for 8 h until judged complete by HPLC (<0.5 area % **19**). The mixture was concentrated at 1 atm until 713−759 kg distillate were collected and then transferred into a new vessel containing water (1725 kg, 15 kg/kg) precooled to 0−10 °C. After an additional 1 h at 10−20 °C the slurry was filtered, washed with water (2 × 460 kg, 2 × 4.0 kg/kg), and dried at 40−60 °C to afford 113 kg (96.8 LCAP, 92% yield) of **9** as a yellow solid with spectra identical to that previously reported in the literature.[11b]

Preparation of 10. To a 80−90 °C solution of **9** (340 kg, 1376 mol) in DMF (802 kg, 2.4 kg/kg) was added *N*,*N*-dimethylformamide dimethyl acetal (328 kg, 2753 mol, 2.0 equiv) over 4−5 h maintaining the internal temperature between 80 and 90 °C. The resulting mixture was then heated to 90−100 °C, and after an additional 12 h was judged complete by HPLC (<2 area % **9**). The mixture was then cooled to 20−30 °C, and water (340 kg, 1 kg/kg) was slowly added to maintain the internal temperature <30 °C. Additional water (1020 kg, 3.0 kg/kg) was then added, and after an additional 0.5 h, the resulting slurry was filtered, washed with water (2 × 680 kg, 2 × 2.0 kg/kg), and dried under vacuum at 40−50 °C to afford 375 kg (99.0 LCAP, 90% yield) of **10** as a red solid with spectra identical to that previously reported in the literature.[11b]

Preparation of 21. To methyl propionate (556 kg, 2.8 kg/kg) was sequentially charged **10** (196 kg, 649 mol), CuI (24.7 kg, 130 mol, 0.20 equiv), and THF (541 kg, 2.8 kg/kg). NaOMe (30 wt % in MeOH, 899 kg, 4985 mol, 7.7 equiv) and MeOH (154 kg, 0.78 kg/kg) were then added to the reactor, maintaining the internal temperature <30 °C. The resulting mixture was heated to 65−72 °C and after 21 h was judged complete by HPLC (<0.5 area % **10**). The reaction mixture was then cooled to −15 °C, and aqueous ammonium chloride [prepared by charging 392 kg NH_4Cl (2.0 kg/kg) to 1568 kg water (8.0 kg/kg)] was slowly charged maintaining the internal temperature < −5 °C. After an additional 15 min, the resulting slurry was filtered, washed with water (3 × 784 kg, 3 × 4.0 kg/kg), and dried under vacuum at 50−60 °C to afford 132 kg (99.6 LCAP, 97.5 wt %, 80% yield) of **21** as a red solid with spectra identical to that previously reported in the literature.[11b]

Preparation of 7B. *Method A.* A solution of THF (1902 L, 19 L/kg), ethanol (301 L, 3.0 L/kg), and triethylamine (176 kg, 1734 mol, 4.4 equiv) was warmed to 50 °C. A solution of formic acid (72.8 kg, 1582 mol, 4.0 equiv) in THF (100 L, 1 L/kg) was prepared in a second vessel. To a third vessel was charged **21** (100 kg, 395 mol) and 10 wt % Pd/C (15.5 kg, 0.15 kg/kg), and the jacket was set to 50 °C. The THF/EtOH/Et_3N solution was then quickly charged to the mixture of **21** and catalyst over 15 min. The resulting solution was stirred for an additional 15 min and then charged with the formic acid/THF solution over 40−45 min maintaining the internal temperature between 50 and 55 °C. After an additional 7 h the reaction was judged complete by HPLC (<0.5 area % **21**). The reaction mixture was then cooled to 20−25 °C, filtered through a 1 μm polish filter, and the vessel and transfer line were rinsed with

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THF (2 × 200 L, 2 × 2.0 L/kg). Solvent swap from THF to MTBE was then accomplished under atmospheric pressure at a constant volume using a total of 2668 L (27 L/kg) of MTBE. The resulting solution was washed with 10 wt % aqueous NaOH (375 L, 3.8 L/kg), water (100 L, 1.0 L/kg), 10 wt % aqueous acetic acid (300 L, 3.0 L/kg), and water (100 L, 1.0 L/kg) to remove both **23** and **24**. Isopropanol (100 L, 1.0 L/kg) was then added, followed by TMSCl (43.0 kg, 396 mol, 1.0 equiv) over 20−25 min. The resulting HCl salt was isolated by filtration, washed with MTBE (150 L, 1.5 L/kg), and dried at 45 °C under vacuum to afford 67.5 kg (99.6 LCAP, 99.8 wt %, 80% yield) of **7B** as a white solid with spectra identical to that previously reported in the literature.[11b]

Method B. To a solution of **21** (125 kg, 494 mol) in EtOAc (2025 kg, 16.2 kg/kg) was charged activated carbon (12.6 kg, 0.10 kg/kg), and the slurry was warmed to 60−70 °C. After an additional 1 h, the mixture was filtered, and the vessel and transfer line were washed with prewarmed (50−60 °C) EtOAc (225 kg, 1.8 kg/kg). The filtrate was then transferred to an autoclave reactor, and 5 wt % Pd/C (3.2 kg, 0.025 kg/kg) was charged. The autoclave was inerted with nitrogen followed by exchanging to hydrogen (0.17−0.2 MPa) via five pressurization/venting cycles. The reaction mixture was then heated to 25−35 °C for 24 h and was judged complete by HPLC (<0.5 area % **21**). The reaction mixture was then cooled to 10−25 °C, exchanged to a nitrogen atmosphere via five pressurization/venting cycles, and filtered, and the vessel and transfer line were rinsed with EtOAc (2 × 87.5 kg, 2 × 0.70 kg/kg). The filtrate was then charged with water (1250 kg, 10 kg/kg), and after 0.5 h, treated with glacial acetic acid (59.2 kg, 986 mol, 2.0 equiv). After an additional 0.5 h, the layers were split, and the resulting organic phase was washed with water (2 × 1250 kg, 2 × 10 kg/kg). The organic layer was then charged with IPA (129 kg, 1.0 kg/kg), followed by TMSCl (59.0 kg, 543 mol, 1.1 equiv) at a rate to maintain the internal temperature between 10 and 30 °C. After an additional 1−2 h, the slurry was filtered, washed with EtOAc (2 × 113 kg, 2 × 0.90 kg/kg), and dried at 50−70 °C under high vacuum to afford 93.4 kg (98.7 LCAP, 97.5 wt %, 88% yield) of **7B** as a white solid with spectra identical to that previously reported in the literature.[11b]

Preparation of 11. To a reactor containing $POCl_3$ (2188 kg, 12.5 kg/kg), **7B** (175 kg, 815 mol) was added in portions to maintain the internal reaction temperature <40 °C. The resulting mixture was then warmed to 95−102 °C and, after 15 h, was judged complete by HPLC (<3 area % **7B**). The mixture was cooled to 0−5 °C, and after 4 h, the slurry was filtered. The wet cake was then reslurried with toluene (305 kg, 1.7 kg/kg), maintaining the slurry temperature between 0 and 5 °C, and after 0.5 h, the filtrate was removed. This reslurry process was repeated two additional times. The wet cake was then washed with toluene (2 × 152 kg, 2 × 0.87 kg/kg) precooled to 0−5 °C, followed by charging into a new reactor containing toluene (790 kg, 4.5 kg/kg). The mixture was warmed to 45−55 °C and slowly charged with MeOH (180 kg, 1.0 kg//kg) over 3 h to maintain the internal temperature between 45 and 55 °C. After an additional 5 h, the mixture was cooled to 15−25 °C and charged with MTBE (866 kg, 5.0 kg/kg). The slurry was then cooled to 0−5 °C and filtered after an additional 2 h. The wet cake was then reslurried with MTBE (455 kg, 2.6 kg/kg) for 0.5 h, filtered, rinsed with MTBE (228 kg, 1.3 kg/kg), and dried at 40−50 °C to afford 169 kg (98.3 LCAP, 98.2 wt %, 93% yield) of **11** as a white solid with spectra identical to that previously reported in the literature.[11b]

Preparation of 13. To 4-methyl-2-pentanol (772 kg, 3.5 kg/kg) was sequentially charged **11** (218 kg, 995 mol) and **12** (192 kg, 2305 mol, 2.3 equiv). The mixture was then heated to 130−145 °C and after 76 h was judged complete by HPLC (<2 area % **11**). The mixture was then cooled to 60−70 °C and charged with water (575 kg, 2.6 kg/kg), maintaining the internal temperature between 60 and 70 °C. After cooling to 20−30 °C, *n*-heptane (1303 kg, 6 kg/kg) was slowly added to maintain the internal temperature <30 °C. After the *n*-heptane addition was complete, the slurry was cooled to −3 to 3 °C, aged for 5 h, and then filtered. The wet cake was charged to a mixture of water (766 kg, 3.5 kg/kg) and *n*-heptane (651 kg, 3.0 kg/kg), and after agitating for 1.5 h at 15−25 °C was refiltered, washed with water (2 × 383 kg, 2 × 1.8 kg/kg), and dried at 50−60 °C under vacuum to afford 110 kg of crude **13**. Crude **13** was then charged to a new reactor containing MeOH (1043 kg, 9.5 kg/kg), followed by the addition of a premade mixture of MeOH (34.8 kg, 0.32 kg/kg) and activated carbon (5.5 kg, 0.05 kg/kg). The resulting mixture was then warmed to 63−68 °C and after 2−3 h was filtered, and the vessel and transfer line were rinsed with MeOH (139 kg, 1.3 kg/kg) prewarmed to 55−65 °C. The collected filtrate was then concentrated at atmospheric pressure to ∼1/2 volume. The mixture was then cooled to 15−25 °C, and water (1760 kg, 16 kg/kg) was added over ∼12 h. After the addition was complete, the slurry was cooled to −3 to 3 °C, aged for 3 h, filtered, washed with water (2 × 200.0 kg, 2 × 1.8 kg/kg), and dried at 50−60 °C under vacuum to afford 107 kg (99.6 LCAP, 51% yield) of **13** as a white/gray solid with spectra identical to that previously reported in the literature.[11b,38]

Preparation of 14. *Reactor 1.* 2-Methyltetrahydrofuran (50.0 kg, 0.77 kg/kg) was charged to the reactor, and the solvent was tested for water content. If water content was >0.05 wt %, the MeTHF was discarded, and fresh MeTHF was added. If the water content was <0.05 wt %, additional MeTHF (508 kg, 7.8 kg/kg), **13** (65.0 kg, 284 mol) and pyridine (11.2 kg, 142 mol, 0.50 equiv) were added, and the resulting solution was cooled between −25 and −15 °C. Isopropylmagnesium chloride (2 M in THF, 484 kg, 970 mol, 3.5 equiv) was then added, maintaining the internal temperature between −25 and −10 °C, and the resulting mixture was aged for 1−2 h.

Reactor 2. 2-Methyltetrahydrofuran (50.0 kg, 0.77 kg/kg) was charged to the reactor and the solvent was tested for water content. If water content was >0.05 wt %, the MeTHF was discarded and fresh MeTHF was added. If the water content was <0.05 wt %, additional MeTHF (508 kg, 7.8 kg/kg) was added and the solution was cooled between −25 and −20 °C. Methyl oxalyl chloride (139 kg, 1135 mol, 4.0 equiv) was then added to reactor 2. While maintaining the internal temperature in reactor 2 between −25 and −15 °C, the contents of reactor 1 were added to reactor 2 and the vessel and transfer line were rinsed with MeTHF (20.0 kg, 0.31 kg/kg). The resulting reaction mixture was agitated between −20 and −10 °C, and after 3 h was judged complete by HPLC (area **13**/**14** < 10%). Water (130 kg, 2.0 kg/kg) was then added slowly to maintain the internal temperature <5 °C. Additional water (650 kg, 10 kg/kg) was then added to the mixture between 0 and 20 °C. The mixture was warmed to 20−25 °C, and after 1−2 h, the lower aqueous layer was removed. NOTE: some solids also precipitated and should be kept with the upper organic layer. The resulting organic phase was washed with water (2 × 650 kg, 2 × 10 kg/kg) and the solids were isolated by filtration. The wet cake was washed with a solution of IPA (130 kg, 2.0 kg/kg)

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and water (488 kg, 7.5 kg/kg), followed by IPA (154 kg, 2.4 kg/kg), and dried at 50−60 °C to afford 67.5 kg (99.0 LCAP, 101 wt %, 76% yield) of **14** as a white solid with spectra identical to that previously reported in the literature.[11b]

Preparation of 2. To a solution of NMP (431 kg, 17 kg/kg) and water (175 kg, 6.8 kg/kg) at 15−25 °C was charged **14** (25.9 kg, 82.1 mol), followed by a NMP (80 kg, 3.1 kg/kg) rinse. Potassium *t*-butoxide (20 wt % in THF, 138 kg, 247 mol, 3.0 equiv) was then added, maintaining the internal temperature <40 °C, followed by a THF (5.0 kg, 0.19 kg/kg) rinse. After an additional 1 h, the reaction was judged complete by HPLC (<1.5 area % **14**) and charged with **15A** (20.5 kg, 90.4 mol, 1.1 equiv), followed by NMP (45.0 kg, 1.7 kg/kg) as a rinse. HCl (37 wt %, 17.2 kg, 175 mol, 2.12 equiv), water (20.0 kg, 0.77 kg/kg), and EDAC (31.6 kg, 165 mol, 2.0 equiv) were then added sequentially, followed by a NMP (45.0 kg, 1.7 kg/kg) rinse. After 2 h, the reaction was judged complete by HPLC (<8 area % **34**) and was heated to 75 °C and aged for 1 h. The mixture was then cooled to 35 °C over 1.5 h, aged 0.5 h, heated back to 75 °C, aged 1 h, and cooled to 20 °C over 2.5 h. The slurry was filtered, washed with 3:1 v/v NMP−water (133 kg, 5.1 kg/kg) and water (2 × 195 kg, 2 × 7.5 kg/kg), and dried at 55 °C to afford 31.1 kg (99.9 LCAP, 95.4 wt %, 77% yield) of **2** as a white solid with spectra identical to that previously reported in the literature.[11b]

*Preparation of **16** in NMP (First Generation Route).* To a biphasic solution of MeTHF (91.3 kg, 2.1 kg/kg) and water (110 kg, 2.5 kg/kg) was sequentially added di-*t*-butyl potassium phosphate (44.3 kg, 178 mol), sodium carbonate (75.4 kg, 711 mol, 4.0 equiv), Bu_4NHSO_4 (15.1 kg, 44.5 mol, 0.25 equiv), and water (220 kg, 5.0 kg/kg). This mixture was then heated to 50 °C, aged for 2 h to ensure no solids remained coated around the bottom valve of the reactor, and cooled to 25 °C. Chloromethyl chlorosulfate (44.0 kg, 267 mol, 1.5 equiv) was charged, followed by MeTHF (5.0 kg, 0.1 kg/kg) as a rinse, at a rate to maintain the internal temperature <55 °C. After an additional 1 h the reaction mixture was charged with water (531 kg, 12 kg/kg) and agitated for 15 min. The lower aqueous layer was discarded, and the remaining upper MeTHF solution was subjected to a constant-volume solvent swap with NMP (140 kg, 3.2 kg/kg) at 50 mbar to afford 119 kg of the crude solution of **16** in NMP. Raman analysis determined that the concentration of **16** was 0.75 M (density = 1.04 g/mL). Solution yield = 48%. ^1H and ^{31}P of crude solution of **16** in NMP was identical to that previously reported in the literature.[16]

*Preparation of **37** from **2** (First Generation Route).* A mixture of **2** (20.9 kg, 42.1 mol) in NMP (142 kg, 6.8 kg/kg) was heated to 80 °C, aged for 1 h to disperse the **2**, and then cooled to 30 °C. To this mixture was sequentially charged Cs_2CO_3 (20.7 kg, 63.5 mol, 1.5 equiv), KI (7.0 kg, 42.1 mol, 1.0 equiv), NMP (5.0 kg, 0.24 kg/kg), the solution of **16** in NMP (91.8 kg, 66.2 mol, 1.5 equiv), and NMP (5.0 kg, 0.24 kg/kg). The reaction mixture was then aged at 30 °C for 24 h, continuously blowing nitrogen through the bottom valve to ensure suspension of the solids, followed by kicker charges of Cs_2CO_3 (3.0 kg, 9.2 mol, 0.20 equiv), KI (1.0 kg, 6.0 mol, 0.14 equiv), and NMP (5.0 kg, 0.24 kg/kg). After an additional 6 h the reaction was judged complete (<3.0 area % **2**) and was cooled to 0−5 °C. DCM (200 kg, 9.6 kg/kg) and water (350 kg, 17 kg/kg) were added, maintaining the temperature <20 °C, and the layers were split. The lower DCM layer was washed with water (3 × 350 kg, 3 × 17 kg/kg), maintaining the internal temperature <20 °C with a target temperature of 10 °C. The DCM solution of **37** was warmed to 20−25 °C; MTBE (111 kg, 5.3 kg/kg) was charged, followed by **37** (0.20 kg, 0.01 kg/kg) seeds and MTBE (5.0 kg, 0.24 kg/kg) as a rinse. After aging for 1 h, additional MTBE (328 kg, 16 kg/kg) was charged to the resulting thin slurry over 3 h. After an additional 4 h, the slurry was filtered, and the reactor/cake were washed with 4:1 v:v MTBE:DCM (20.0 kg, 0.96 kg/kg), followed by cake washes with 4:1 v:v MTBE:DCM (85.0 kg, 4.1 kg/kg) and MTBE (74.0 kg, 3.5 kg/kg). The isolated solids were dried at 50 °C under vacuum and afforded 30.0 kg (98.05 LCAP, 99.85 wt %, 71% yield, adjusted for seed charge) of **37** as a white solid with spectra identical to that previously reported in the literature.[26]

Preparation of 48 (Third Generation Route). *Reactor 1.* To a reactor containing CH_3CN (457 kg, 3.1 kg/kg) was charged **46** (107 kg, 554 mol, 1.20 equiv) followed by CH_3CN (114 kg, 0.78 kg/kg) as a rinse. Bu_4NI (22.2 kg, 60.3 mol, 0.13 equiv), K_2CO_3 (96.0 kg, 695 mol, 1.5 equiv), and **14** (73.0 kg, 232 mol) were then added sequentially. After 4 h, a second portion of **14** (73.0 kg, 232 mol) was added. After an additional 12 h, the reaction was judged complete by HPLC (<1.5 area % **14**), and EtOAc (1708 kg, 12 kg/kg) was charged to the reactor.

Reactor 2. The mixture from reactor 1 was charged to a solution of water (1322 kg, 9.0 kg/kg) and 33 wt % aqueous HCl (161 kg, 1.1 kg/kg) in reactor 2, followed by EtOAc (263 kg, 1.8 kg/kg) as a rinse, maintaining the internal temperature between 19 and 25 °C. After 0.5 h the layers were separated, and the upper organic phase was washed with a solution of water (1322 kg, 9.0 kg/kg) and 33 wt % aqueous HCl (161 kg, 1.1 kg/kg). After 0.5 h the layers were separated, and the upper organic phase was first charged with EtOAc (263 kg, 1.8 kg/kg), followed by washing with a solution of water (1322 kg, 9.0 kg/kg) and 33 wt % aqueous HCl (161 kg, 1.1 kg/kg). This process of charging additional EtOAc and washing with the water/HCl solution was repeated once more. The final organic layer was concentrated to 730 L (5.0 L/kg) under vacuum (90−200 mbar), and the distillation was continued under constant-volume conditions while IPA (2295 kg, 16 kg/kg) was added. The mixture was then cooled to 20−25 °C, and after 12 h, the slurry was filtered. The cake was washed with IPA (2 × 574 kg, 2 × 3.9 kg/kg) and dried at 50−55 °C to afford 134 kg (99.1 LCAP, 61% yield) of **48** as a white solid with spectra identical to that previously reported in the literature.[26]

Preparation of 43 (Third Generation Route). *Reactor 1.* To a slurry of **15A** (272 kg, 1199 mol) and CH_3CN (1390 kg, 5.11 kg/kg based on **15A**) at 20−25 °C was charged K_2CO_3 (108 kg, 781 mol, 0.65 equiv based on **15A**). After 2 h, a second portion of K_2CO_3 (50.0 kg, 362 mol, 0.30 equiv based on **15A**) was added. After an additional 2 h, the free-basing was judged complete by HPLC (level of **15B** in solution between 100 and 130 mg/mL). The mixture was then concentrated by distillation at reduced pressure (90−100 mbar) under constant-volume conditions adding toluene (2357 kg, 8.7 kg/kg based on **15A**) until water content <500 ppm. The mixture was then cooled to 20−25 °C, and the inorganic salts were removed by filtration, rinsing the vessel and transfer line with toluene (471 kg, 1.7 kg/kg based on **15A**).

Reactor 2. The filtrate was collected in weighed reactor 2, and a sample was then taken to determine the final concentration of **15B** in solution. Note: the remaining charges were then adjusted such that 1.3 equiv of **15B** was utilized. All

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remaining charges were based on **48** as the limiting reagent. To the toluene solution of **15B** in reactor 2 was sequentially charged **48** (370 kg, 784 mol), titanium tetra-*n*-butoxide (93.4 kg, 244 mol, 0.35 equiv), and toluene (50 kg, 0.14 kg/kg). The reaction mixture was then warmed to 85 °C and after 12 h was judged complete by HPLC (<2 area % **48**). The mixture was then cooled to 50 °C over 4 h, seeded with **48** (0.40 kg, 0.10 wt %), and aged for 8 h. The resulting slurry was then cooled to 20 °C over 6 h, agitated for an additional 10 h, and filtered. The isolated cake was then washed sequentially with toluene (962 kg, 2.6 kg/kg) and ethanol (878 kg, 2.4 kg/kg) and dried at 50 °C to afford 405 kg (99.5 LCAP, 82% yield) of **43** as a white solid with spectra identical to that previously reported in the literature.[26]

Telescoped Preparation of 37 from 43 (Third Generation Route). *Reactor 1.* DCM (1337 kg, 5.3 kg/kg) was charged to the reactor, and the solvent was analyzed for water concentration. If the measured water content was >150 ppm, the DCM was discarded, and fresh DCM was added. If the water content was <150 ppm, **43** (252 kg, 400 mol) was added, and after stirring for 15 min at 20−25 °C, the solution was cooled to −2 °C. Gaseous chlorine (26.9 kg, 380 mol, 0.95 equiv) was then added subsurface over 1 h, maintaining the internal temperature <0 °C. The reaction was aged an additional 1 h after completion of the chlorine addition, and the reaction conversion was checked by HPLC. On the basis of the HPLC results, a kicker charge of chlorine (0.8 kg, 11.3 mol, 0.03 equiv) was added, and after an additional 1 h at −2 °C, the reaction was judged complete by HPLC (<2 area % **43**). IPA (24.1 kg, 400 mol, 1.0 equiv) was then charged, and the reaction mixture was warmed to 20−25 °C. After an additional 16 h, the resulting slurry was cooled to 5 °C, charged with water (1261 kg, 5.0 kg/kg), maintaining the internal temperature <10 °C, and aged for 0.5 h. The layers were then separated, and the lower organic layer was washed with a solution of sodium bicarbonate (12.6 kg, 0.05 kg/kg) in water (1247 kg, 4.95 kg/kg). The organic layer was then azeotropically dried at atmospheric pressure under constant-volume conditions using DCM (2005 kg, 8.0 kg/kg). The final volume was adjusted as needed to equal 1184 L (4.7 L/kg based on **43**) and KF < 200 ppm. At 35 °C, the DCM solution was charged Et_4NBr (42.1 kg, 200 mol, 0.5 equiv), followed by di-*t*-butyl potassium phosphate (119.3 kg, 480 mol, 1.2 equiv) in four portions (29.8 kg each) over 1 h. The resulting slurry was warmed to 40 °C and after 3 h was judged complete by HPLC (<0.5 area % **44B**). The batch was then cooled to 20 °C and charged with water (1261 kg, 5.0 kg/kg). The layers were separated, and the lower DCM phase was transferred to a new reactor via a polish filter. A 20:1 v/v solution of MTBE:IPA (936 kg, 3.7 kg/kg) was charged at 20−25 °C, followed by **37** (0.60 kg, 0.0025 kg/kg) seeds, and the mixture was aged for 0.5 h. To the resulting thin slurry was charged a 20:1 v/v solution of MTBE:IPA (2433 kg, 9.7 kg/kg) over 2.5 h, and the resulting slurry was cooled to 5 °C over 1.5 h and aged for 10 h. The slurry was then filtered and the wet cake washed with 4.5:1 v/v [(20:1 v/v solution of MTBE:IPA):DCM] (1069 kg, 4.2 kg/kg) MTBE (933 kg, 3.7 kg/kg) and dried at 50 °C under high vacuum to afford 204 kg (97.1 LCAP, 95.5 wt %, 73% yield) of **37** as a white solid with spectra identical to that previously reported in the literature.[26]

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Notes

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(33) Isolated product also contained 1.0 LCAP **39** and 0.5 LCAP **2**.
(34) Levels of genotoxic impurities determined by liquid chromatography mass spectroscopy (LCMS).
(35) In the TMG conditions the soluble and nucleophilic amine reacted in a nonproductive manner with the alkylating agent necessitating suprastoichiometric amounts of electrophile. Switching to K_2CO_3 eliminated this side reaction.
(36) We discovered that some KI is generated during the process, which if not removed from the reactor via washing with water and CH_3CN between each batch, was detrimental to the subsequent batch.
(37) DSC supported the onset temperature following *t*-BuONO addition = 181 °C, with the heat of reaction = 368 J/g. Data from RC1 calorimetry supported the adiabatic temperature rise during *t*-BuONO addition = 27.1 °C, with gas evolution = 20.9 L/mol.
(38) DSC supported onset temperatures of the reaction mixture prior to heat up = 112, 175, and 259 °C, with heats of reaction = 15, 44 and 343 J/g, respectively. Data from RC1 calorimetry supported the adiabatic temperature during reaction held at 130 °C for 70 h = −198 °C.

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