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Development of practical syntheses of potent non-nucleoside reverse transcriptase inhibitors

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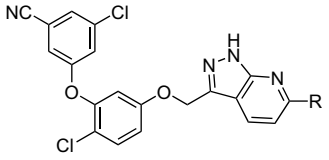
ABSTRACT

The development of practical and efficient syntheses of the potent non-nucleoside reverse transcriptase inhibitors **1** and **2** is described. The preparation of **1** proceeded in four synthetic steps and in 48% overall yield from **3**. The long-term synthesis of **2** proceeded in nine synthetic steps and in 47% overall yield from commercially available 2,6-diflurorpyridine. The route to **2** was highlighted by the three-step synthesis of intermediate **22** and the high yielding coupling between **18** and phenol **8**. The overall sequence required no chromatography and has successfully been utilized for the manufacture of **2** on large scale.

1. Introduction

Representing a key component of highly active antiretroviral therapy, non-nucleoside reverse transcriptase inhibitors (NNRTIs) target an allosteric binding pocket on the reverse transcriptase enzyme giving rise to a broad spectrum of activity against HIV RT mutations. Although there are currently three marketed NNRTIs (efavirenz, nevirapine, and delavirdine) that demonstrate clinical efficacy against HIV-1 RT mutations,[1] treatment-related failure due to the emergence of clinical resistance remains a recurring issue with these therapies. The discovery of second generation NNRTIs, such as the very recently approved etravirine,[2] that have a broader spectrum of activity against mutant viruses and have a high genetic barrier to the selection of new resistant strains, has been an intensive area of investigation. As part of a program to develop potent, orally active NNRTIs possessing a broader spectrum of activity against HIV RT mutations, Merck has recently reported the discovery of a novel class of second generation NNRTIs from which both **1** and **2** were brought forward for development.[3] The key structural features of these molecules are the pyrazolo[3,4-*b*]pyridine fragment and the pendant biaryl ether moiety. In particular, the amino substituent on the pyrazolo[3,4-*b*]pyridine fragment of compound **2** presented formidable synthetic challenges that were not initially obvious in the deceptively simple structure of **2**. Herein, the preparation of **1** and the evolution of a robust and long-term scaleable synthesis of **2** will be discussed.



1 R = H
2 R = NH_2

2. Results and discussion

2.1. Preparation of compound 1

Compound **1** was the first second generation NNRTI that Merck brought forward for development. The synthesis of **1** closely paralleled the initial synthesis and began with the known 3-methyl-pyrazolo[3,4-*b*]pyridine **3** (Scheme 1).[4] Conversion of **3** to **4**[5] was effected by reaction of **3** with Boc_2O in the presence of 20 mol% DMAP in MeCN at 45 °C for 6 h. In the initial stages of the reaction, formation of intermediate **5** was observed by HPLC. However, further heating led to the nearly complete conversion of **5** to **4** (99.5:0.5). Although compound **4** could be isolated, it was found that isolation of **4** was not necessary. Crude **4** was carried forward in the next step without further purification after an acidic aqueous workup with 1 N

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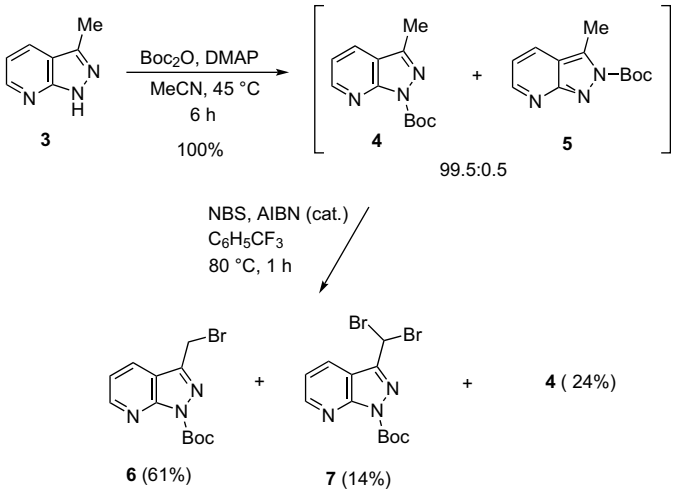


Scheme 1.

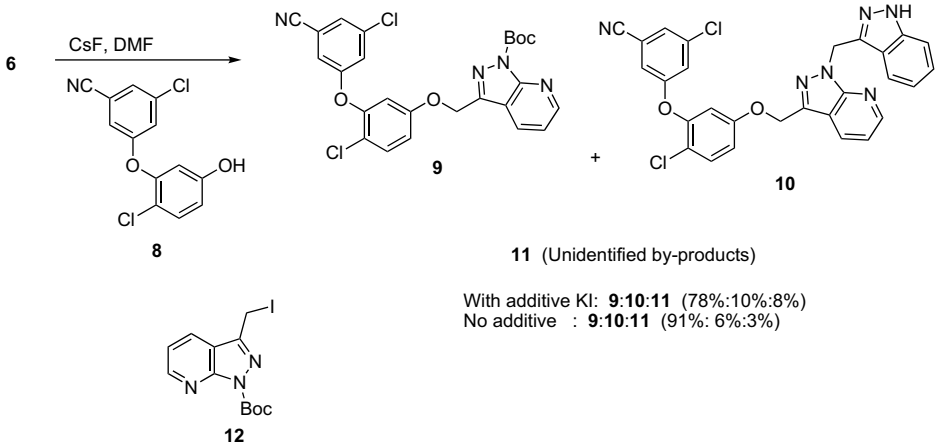
KH_2PO_4, which effectively removed all traces of DMAP from the organic layer. After the solvent was switched to trifluorotoluene, reaction of crude **4** with NBS in the presence of catalytic amount of AIBN at 80 °C for 1 h gave a statistical ratio of the desired bromide **6** (61%), dibromide **7** (14%), and starting material **4** (24%). All efforts to drive the reaction to completion led to significant amounts of dibromide **7** and substantial degradation of both **6** and **7**. Fortunately, bromide **6** could be isolated in 42% yield from **3** after purification by silica gel chromatography followed by recrystallization from MTBE/heptane. It should be noted that storage of bromide **6** at room temperature for prolonged periods of time led to significant degradation and the formation of multiple unidentifiable products. This was mitigated by storage of **6** at 0–5 °C where it had good stability with no loss of chemical purity for up to 2 years.

The preparation of **1** from bromide **6** and phenol **8**[3] required considerable optimization of the initial route due to both the instability of **6** at room temperature and the use of NaH. The initial route involved deprotonation of **8** with NaH followed by reaction with **6** in DMF. Subsequent Boc deprotection with TFA gave **1** in 67% yield for the two-step procedure. The use of NaH in conjunction with DMF raised serious concerns in terms of safety associated with scale-up since reports of thermal runaway in large-scale processes, the pyrophoric nature of NaH, and issues associated with rapid release of hydrogen gas upon deprotonation.[6] Therefore our efforts were focused on alternative safer reaction conditions for the coupling of **6** and **8**. Our initial experiments revealed that reaction of 1 equiv of **6** and 1 equiv of **8** in the presence of 6 equiv of CsF as the base and 1.5 equiv of KI as an additive afforded **9** in 70–78% yield (Scheme 2). The mass balance of the reaction was found to contain up to 10% of over-alkylated by-product **10** and approximately 8% of a mixture of unidentified by-products **11**. The formation of **10** and other by-products **11** arise from the fact that bromide **6** was unstable to the reaction conditions, presumably due to the presence of adventitious water, which competitively cleaves the Boc group. This was confirmed in subsequent experiments where treatment of bromide **6** under the identical reaction conditions in the absence of phenol **8** led to extensive decomposition of bromide **6**. The addition of KI to the reaction resulted in a dramatic increase in the rate of reaction where the rapid formation of iodide intermediate **12** could be observed by HPLC. However, the use of super-stoichiometric amounts of KI also resulted in extremely thick reaction mixtures, which were difficult to stir. After extensive optimization of the initial reaction parameters, better conditions for the alkylation involved the portion-wise addition of 1.08 equiv of bromide **6** to a preformed mixture of 1 equiv of **8** and 3.00 equiv of CsF in DMF at room temperature and stirring for 2 h. Analysis of the crude reaction mixture by HPLC after workup revealed that **9** was obtained in 90% yield with <9% combined amounts of both **10** and **11** present. Elimination of KI from the initial conditions was found to slightly decrease the reaction rate, but also gave stirrable reaction slurries. Intermediate **9** was not isolated but was directly used in the deprotection step without further purification.

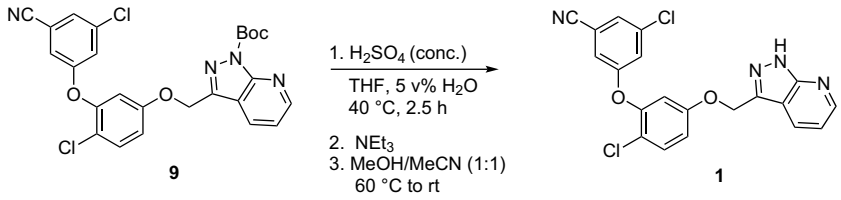
Deprotection of crude **9** to **1** was effected at 35–40 °C in aqueous THF using 2.5 equiv of concd H_2SO_4 for 2.5 h to give quantitative conversion to **1** (Scheme 3). Direct filtration of the crude reaction mixture provided **1** as a crystalline hemi sulfate salt. The freebase of **1** was obtained by distilling the THF from the crude reaction mixture prior to filtration followed by the addition of water. Alternatively, neutralization with NEt_3 to a pH of 8–9 also provided the freebase of **1**. The purity of **1** was upgraded by recrystallization from 1:1 MeOH/MeCN to provide analytically pure **1** in 78% overall yield from **8**.

2.2. Preparation of compound 2 (first generation synthesis)

Pre-clinical evaluation of compound **1** revealed that compound **1** was only orally bioavailable when dosed as a solution. Given the low solubility of **1** and the higher doses/exposures needed to support dosing in safety assessment and clinical studies, the development of compound **1** was halted. Compound **2** was ultimately brought forward for development as it was equally as potent and compound **1** displayed excellent pharmacokinetic properties and



Scheme 2.



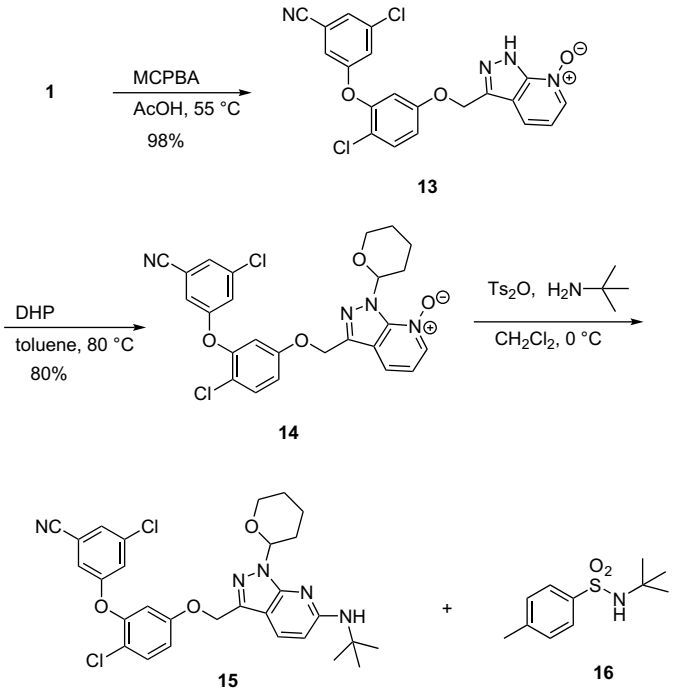
Scheme 3.

was several orders of magnitude more soluble at relevant pH. With sufficient quantities of compound **1** in hand, the first generation synthesis of **2** was focused on conversion of **1** to **2**. It was reasoned that appropriate activation of the pyridine nitrogen toward nucleophilic addition of a protected amine would allow for the rapid preparation of **2**. A recent report from these laboratories has demonstrated that reaction of pyridine *N*-oxides with Ts_2O in the presence of *tert*-butylamine followed by cleavage of the *tert*-butyl group with TFA is an attractive method for preparation of 2-aminopyridines and 2-aminoquinolines.[7] Therefore, we elected to fully investigate this approach for the preparation of **2**.

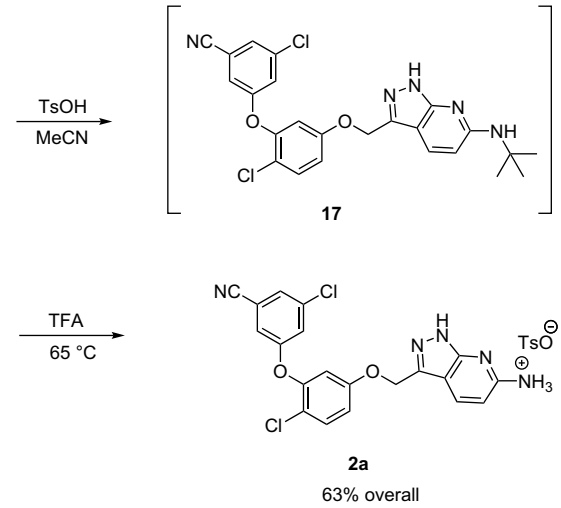
Oxidation of the pyridine nitrogen of **1** was conducted with MCPBA (1.7 equiv) in EtOAc at 55 °C (Scheme 4). While the reaction mixture was a slurry throughout the course of the reaction, near complete conversion to **13** was observed. Upon cooling and filtration, **13** was isolated in analytically pure form and essentially quantitative yield. While these conditions appeared to perform well on small scale, they were found to be unacceptable upon scale-up leading to incomplete conversion of **1** to **13**. It was believed that entrainment of **1** by the product was the source of incomplete reaction. Solubility experiments were conducted in order to find an effective solvent where the starting material **1** was soluble and the product was not. It was finally established that AcOH was the optimal solvent for conducting the oxidation. The optimal conditions involved addition of an AcOH solution of MCPBA to a solution of **1** in AcOH at 55 °C over 1 h and stirring for an additional 3 h at 55 °C. Upon cooling the reaction mixture was diluted with aqueous sodium bisulfite, which not only quenched remaining MCPBA but also aided in the removal of 3-chlorobenzoic acid. The product was filtered providing **13** in 98% isolated yield.

Installation of the amino substituent on the pyridine ring was next examined. Treatment of **13** with Ts_2O in the presence of *tert*-butylamine resulted in complex reaction mixtures due to competitive tosylation of the pyrazole nitrogen atom. Therefore, protection of the pyrazole nitrogen atom was required prior to amination. Due to the lability of the Boc group seen in bromide **6**, the use of a more robust protecting group was required. After evaluation of several common protecting groups, the THP-protected pyrazole **14** was selected for further development. Compound **14** was prepared by reaction of **13** with 4.7 equiv of 3,4-dihydro-2*H*-pyran (DHP) in toluene at 80 °C in the presence of catalytic TsOH. After cooling to room temperature, crystalline **14** was isolated in 80% yield. Addition of a preformed mixture of **14** and 4 equiv of *tert*-butylamine in CH_2Cl_2 to a solution of 2.1 equiv of Ts_2O in CH_2Cl_2 keeping the internal temperature between 0 and 5 °C afforded **15** and *tert*-butylsulfonamide **16** as a reaction by-product. Compound **16** was insoluble in CH_2Cl_2 and was easily removed by filtration upon completion of the reaction. The filtrate containing **15** was washed with water and the solvent switched to MeCN for global deprotection of both the THP and *tert*-butyl groups. Since compound **15** was not a crystalline intermediate, it was not isolated and was used crude in the deprotection step without purification.

It was envisioned that removal of the THP group of **15** would be trivial and that cleavage of the *tert*-butyl group from the aminopyridine nitrogen would require more forcing conditions.[8] It was initially discovered that deprotection of **15** in the presence of a combination of 5 equiv of dry TsOH and 25 equiv of TFA in MeCN at 70 °C for 3 h afforded tosylate salt **2a**, which crystallized from the crude reaction mixture and was isolated in 55–60% yield for the one-pot process (Scheme 5). However, these investigations also revealed that the product **2a** appeared to be decomposing over



Scheme 4.



Scheme 5.

time. For example, treatment of crude **15** with TsOH·H_2O at room temperature resulted in rapid cleavage for the THP group giving intermediate **17**. The rapid removal of the THP group also resulted in the formation of an extremely dark reaction mixture, presumably due to the formation/polymerization of the THP by-products. In order to prevent potential hydrolysis of the cyano group under the extremely acidic reaction conditions, water from the TsOH was azeotropically removed prior to the addition of TFA (25 equiv) and the reaction mixture heated to 70 °C for 3.5 h. The course of the reaction was monitored by HPLC analysis. Conversion of the des-THP intermediate **17** to **2** stalled at 90% at the end of 3.5 h. As shown in Figure 1, maximum HPLC assay yield[9] of 65% was achieved after 2.5 h and the yield of **2a** dropped to 60% after prolong heating. Attempts to either lower the reaction temperature to 50–55 °C or number of equivalents of TFA did not improve the reaction profile. It is also important to note, that the use of TsOH or TFA alone only resulted in the formation of **17** and failed to proceed to **2a**.

For further scale-up of the reaction, it was estimated that azeotropic distillation of water after the addition of TsOH·H_2O to **15** would take several hours. Due to the instability of the reaction intermediates, it was decided to examine azeotropic drying the TsOH prior to addition of **15**. In addition, the reaction was further refined in terms of reaction time and number of equivalents of TsOH employed. The conditions that were finally selected involved addition of 4 equiv of dry TsOH in MeCN to a solution of **15** in MeCN followed by the addition of 25 equiv of TFA. The reaction mixture was stirred at 65 °C for 4 h and monitored by HPLC. As outlined in Figure 2, a dramatic increase in HPLC assay yield to near 80% was realized. Although these slightly improved conditions were beneficial, conversion of **17** to **2a** still stalled at 90% conversion. After 4 h, the reaction mixture was cooled to room temperature and seeded with pure tosylate salt **2a** resulting in the crystallization of **2a** from the crude reaction mixture. After addition of water, **2a** was isolated in 63% overall yield from **15**. The first generation synthesis of **2** including the preparation of **3**[10] required nine linear steps and proceeded in 13% overall yield.

2.3. Preparation of compound 18 (second generation synthesis)

The first generation synthesis of **2** described above was only suitable for the short-term. In order to support further clinical trials with this drug candidate, a longer-term route for the synthesis of **2** with improved overall yield and efficiency was required. Key liabilities that needed to be addressed included elimination of the unstable bromide **6**, which was only obtained in 42% yield from **3**, and streamlining the final deprotection step. It was reasoned that installation of the amino group at an early stage of the synthesis would allow for a more convergent synthesis of **2**. Our retrosynthetic approach was centered on preparation of alcohol **18** (Scheme 6). It was reasoned that appropriate activation of the fully elaborated benzylic alcohol **18** would eliminate the low-yielding transformations of the previous route and shorten the synthesis. Since THP-protection of the pyrazole nitrogen proved successful in the first generation synthesis, retention of this protecting group became a key design feature and imparted a significant degree of stability to synthetic intermediates.

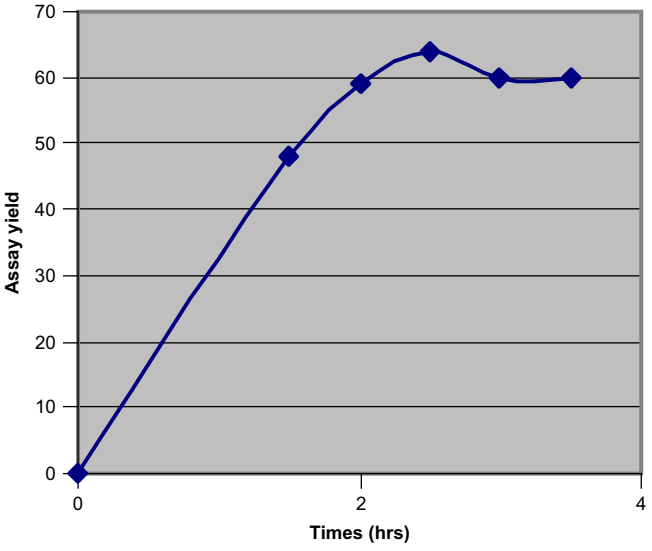


Figure 1.

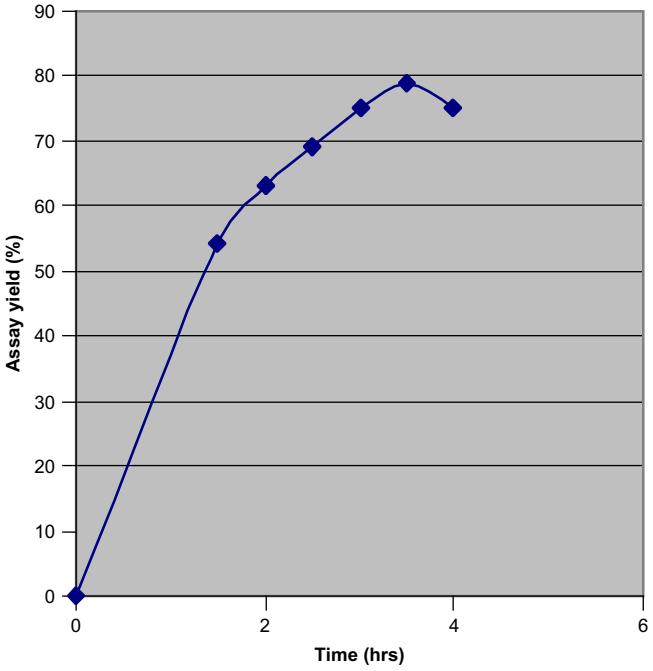
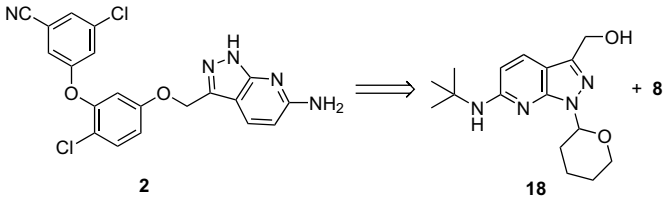


Figure 2.



Scheme 6.

The second generation synthesis of **18** began with pyrazole **20**. Recently we outlined an effective strategy for the preparation of **20** from 2-fluoropyridine, which proceeded in 50% overall yield.[11] N-Oxidation of **20** was accomplished by treating **20** with 1.3 equiv of MCPBA in isopropyl acetate (IPAc) at 35 °C for 2 h (Scheme 7). Due to the increased solubility of **20** in IPAc at 35 °C, the complications encountered in the first generation synthesis for the conversion of **1** to **13** were not observed. Compound **21** began to crystallize from the reaction mixture during the oxidation, and upon cooling to room temperature, compound **21** was isolated by direct filtration of the crude reaction mixture in 82% yield.

THP-protection of pyrazole **21** and subsequent conversion to *tert*-butylamine **22** was developed as a one-pot procedure. Reaction of **21** with 5 equiv of DHP in the presence of catalytic amount of

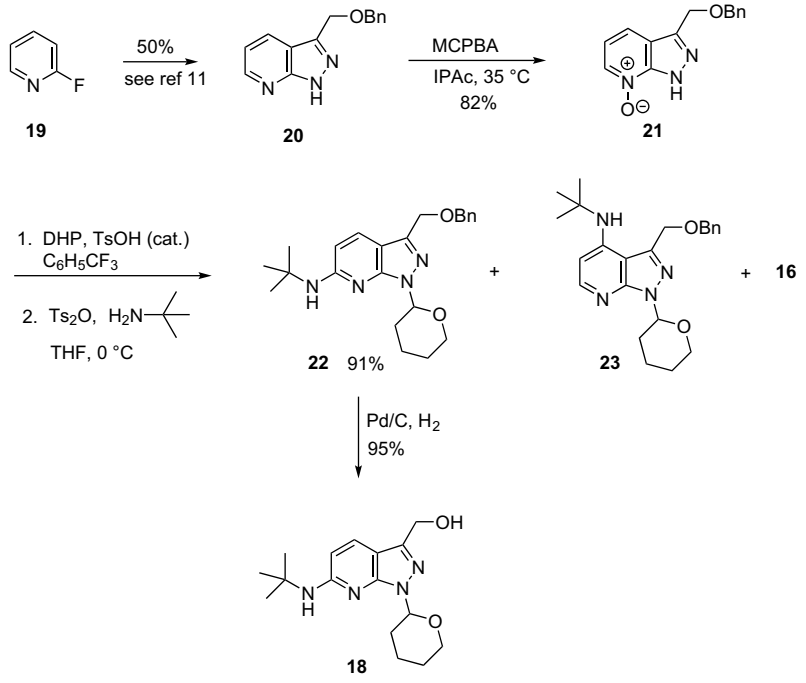
pyridine *p*-toluenesulfonate (PPTS) at 80 °C in trifluorotoluene for 5 h gave crude THP-protected pyrazole in near quantitative yield. Conversion of the THP-protected *N*-oxide intermediate to **22** was initially conducted in trifluorotoluene. Cooling the crude reaction mixture to −15 to −10 °C and adding 5.6 equiv of *tert*-butylamine was followed by the portion-wise addition of 2.5 equiv of Ts_2O while keeping the internal temperature <−5 °C. Analysis of the crude reaction mixture by both HPLC and NMR revealed that the undesired 4-regioisomer **23** was also formed. The ratio of **22**/**23** was ~6.5:1 as determined by NMR. After warming to 0 °C the reaction mixture was diluted with heptane and filtered to remove precipitated **16**. The filtrate was then treated with 10 N NaOH to precipitate the remaining sulfonamide **16** as a sodium salt that was removed by filtration. The use of an aqueous NaOH workup to remove **16** was found to be ineffective as little of **16** was found in the aqueous layer. The organic layer was then concentrated under reduced pressure and purified by silica gel chromatography to give the desired regioisomer **22** in 65–67% isolated yield.

In an effort to improve the regioselectivity of this step, the reaction was further investigated in terms of solvent, temperature, and order of addition of reagents. It was found that formation of the THP intermediate was best performed in trifluorotoluene and subsequent conversion of **22** was done in THF. After THP-protection in trifluorotoluene, the reaction solvent was switched to THF by distillation under reduced pressure. To the solution was directly added 10 equiv of *tert*-butylamine. The resulting solution was then added drop-wise to a cold slurry (−10 to −15 °C) of 5 equiv of Ts_2O in THF. After stirring for 1 h at −10 °C, the reaction was worked up as described above to give a 10.5:1 mixture of **22**/**23**. Unfortunately, all attempts to completely remove both **16** and regioisomer **23** without recourse to chromatography were unsuccessful. Purification by silica gel afforded **22** in 91% yield for the improved amination step.

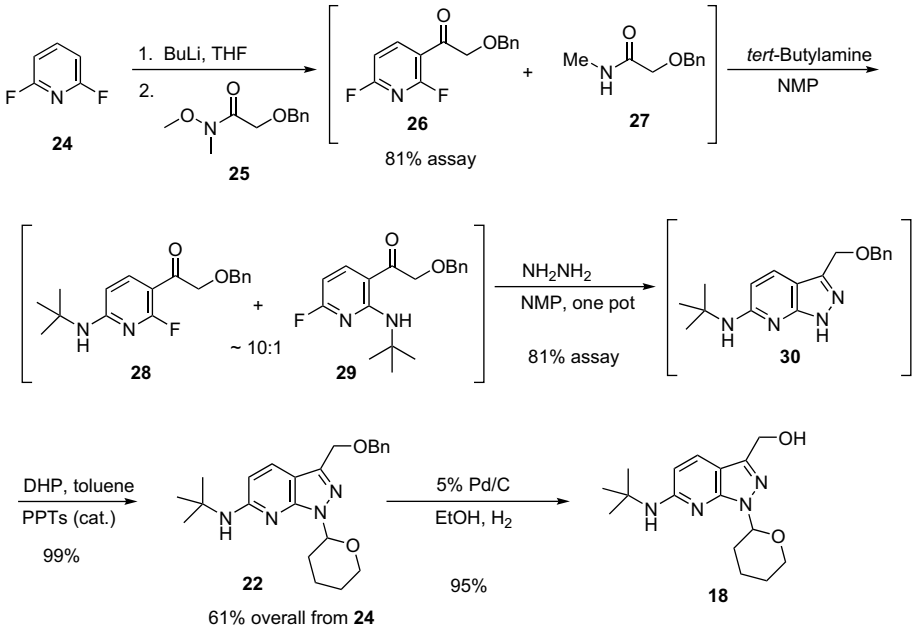
Removal of the benzyl protecting group to give the key alcohol intermediate **18** was next examined. Catalytic hydrogenation of **22** was accomplished under a balloon pressure of hydrogen in the presence of catalytic amount of 5% Pd/C at room temperature for 6 h and gave **18** as a crystalline solid in 95% isolated yield. In an effort to remove the chromatography step for the purification of **22**, the hydrogenation was repeated with crude **22** that contained both regioisomer **23** and sulfonamide **16**. Unfortunately, all attempts to hydrogenate the crude mixture were unsuccessful. To understand the lack of reactivity and identify the source of the catalyst poison, the reaction was repeated with pure **22** that was spiked with either **16** or **23**. It was established that the amount of residual **16** in isolated **22** could be up to 8% and was not detrimental to the hydrogenation of **22** as this experiment gave quantitative conversion to **18**. However, spiking with regioisomer **23** resulted in a complete shut-down of the hydrogenation. It was concluded that **23** was acting as a catalyst poison in the hydrogenation and all traces of this isomer needed to be removed prior to hydrogenation of **22**.[12] Unlike bromide **6**, which needed to be stored at low temperature to prevent decomposition, alcohol **18** was indefinitely stable at room temperature. Conversion of **18** to **2** was successful (vida infra) and will be discussed in detail in the third generation synthesis.

2.4. Preparation of compound 2 (third generation synthesis)

The second generation synthesis of **2** established that benzylic alcohol **18** was the key intermediate required for the final and optimal manufacture of **2**. However, the route needed to be completely overhauled. The obvious liabilities in the synthesis of alcohol **18** would necessitate elimination of both the N-oxidation step and the amination step that required chromatographic removal of the undesired 4-regioisomer **23**. The third generation synthesis of **2** began with 2,6-difluoropyridine **24** (Scheme 8).[13] Lithiation of **24** with 1.1 equiv of BuLi (2.5 M BuLi in hexanes) occurred smoothly below −65 °C and was complete within 60 min. While LDA could also be employed, the use of BuLi was found to be more practical and avoided the use of diisopropylamine. The direct addition of a pre-cooled solution of Weinreb amide **25**[14] in THF to the resulting lithiate and warming to −10 °C was followed by an aqueous workup and gave crude **26** in 81% HPLC assay yield. Also detected in the crude reaction mixture was unreacted **24**, **25**, and amide **27**.[15] Ketone **26** could be isolated in analytically pure form by crystallization from EtOAc/heptane. However, it was found that purification of this intermediate was unnecessary. A one-step process for conversion of crude **26** to pyrazole **30** was developed where the



Scheme 7.

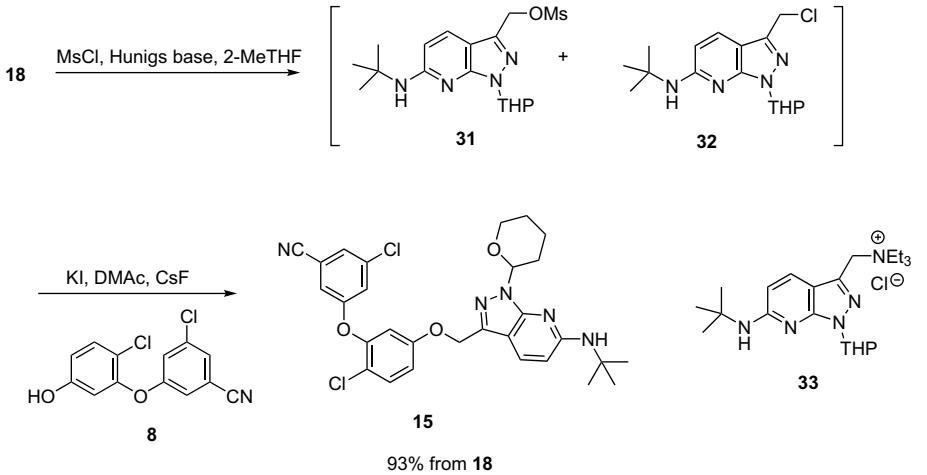


Scheme 8.

presence of impurities **24**, **25**, and **27** was found not to be detrimental to the reaction conditions. Reaction of crude **26** in NMP with 5 equiv of *tert*-butylamine at 0–5 °C afforded a mixture of the desired addition product **28** and the undesired regioisomer **29** as a ~10:1 (determined by ^{1}H NMR) mixture of **28**/**29**.[16] The reaction mixture was degassed and 5 equiv of 64% hydrazine hydrate was added to the reaction mixture. The mixture was stirred at room temperature until complete consumption of **28** was observed and the formation of **30** was complete. The pH of the reaction mixture was adjusted to 5 with 5 N sulfuric acid and **30** was extracted into MTBE. The solvent was then switched to toluene for use in the next reaction without further purification giving pyrazole **30** in 81% HPLC assay yield from **26**. The exact fate of regioisomer **29** was not rigorously determined and only impurities **25** and **27** were still present at this stage.

Conversion of crude **30** to THP-pyrazole **22** was carried out in toluene at 80–85 °C in the presence of 5 equiv of DHP and 5 mol % of PPTS to give nearly quantitative conversion to THP-pyrazole **22**.[17] Isolation of **22** was accomplished following an aqueous workup to remove the PPTS catalyst, solvent switching to cyclohexane, and cooling to 10 °C. Under these conditions, crystalline **22** was isolated in 61% overall yield from difluoropyridine **24**. Catalytic hydrogenation of **22** with 5 mol % Pd/C in EtOH at 20 psi H_2 was complete within 18 h at room temperature and provided **18** in quantitative yield. Compound **18** was isolated in analytically pure form after filtration of the catalyst and concentration to remove the toluene, formed during the removal of the benzyl group, followed by the direct addition of water to give **18** in 95% isolated yield (58% overall yield from **24**).

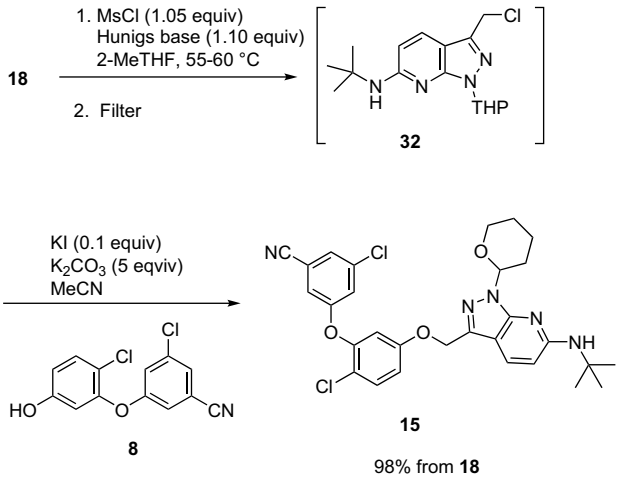
The conversion of **18** to intermediate **15** was extensively examined. For example, activation of alcohol **7** as mesylate **31** was conducted in 2-MeTHF in the presence of 1.10 equiv of Hünig's base by the drop-wise addition of 1.05 equiv of MsCl while maintaining the internal temperature <8 °C (Scheme 9). Also observed in the crude reaction mixture was chloride **32** (3–5%). When the reaction mixture was allowed to warm to room temperature, conversion of mesylate **31** to chloride **32** increased to 20–25%. Interestingly, when NEt_3 was utilized as a base in the mesylation step, the formation of



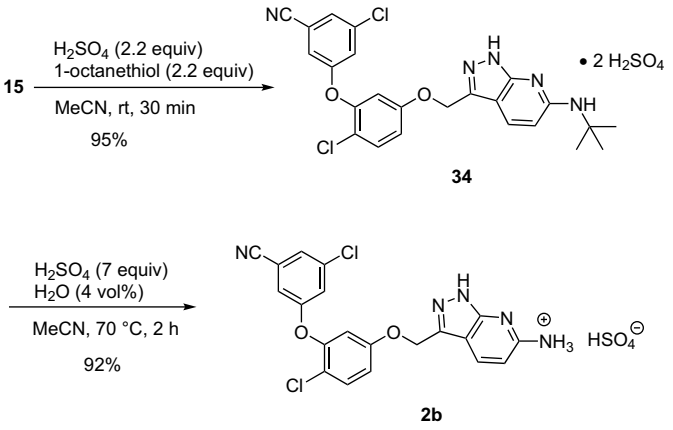
Scheme 9.

chloride **32** was suppressed; however, the formation of ammonium salt **33** was observed during the subsequent alkylation step. Ammonium salt **33** was unreactive toward displacement and resulted in lower conversion to **15**. The use of Hünig's base completely suppressed the formation of ammonium salts in the alkylation step. Mesylate **31** was unstable to aqueous workup and readily converted back to alcohol **18** when exposed to water. Therefore, the crude reaction mixture was filtered to remove the precipitated ammonium salts and the solvent was removed under reduced pressure. The crude mesylate was dissolved in DMAc and 1.7 equiv of KI, 0.93 equiv of phenol **8**, and 5 equiv of CsF were added and the mixture stirred at room temperature for 12 h to give **15** in 93% HPLC assay yield. As described in Scheme 2, the reaction proceeded via the in situ formation of the iodide intermediate, which was observed by HPLC. Chloride **32** reacted at a much slower rate with **8** than the iodide intermediate and required longer reaction times in order to obtain complete conversion to **15**. When KI was eliminated from the reaction, the coupling proceeded to **15**; however, the formation of a number of unidentified impurities resulted in a less desirable reaction profile.

Although the conditions outlined in Scheme 9 for the preparation of **15** were successful, the reaction needed further refinement in order to streamline the approach and allow for a more robust process. Since mesylate **31** was unstable and readily converted to chloride **32**, the decision was made to form **32** quantitatively prior to reaction with **8** (Scheme 10). Reaction of **18** with 1.05 equiv of MsCl in the presence of 1.10 equiv of Hunig's base in 2-MeTHF at room temperature followed by warming the reaction mixture to 55–60 °C for 3–3.5 h resulted in the quantitative conversion to chloride **32**. Upon cooling, the ammonium salts were removed by filtration and the filtrate containing **32** was used in the alkylation step without purification. Chloride **32** was indefinitely stable as a 2-MeTHF solution and as concentrated foam with no apparent loss of purity. The alkylation step was then fully optimized in terms of solvent, base, temperature, and amount of KI using the crude 2-MeTHF solution of **32**. Due to the expense and hygroscopic nature of CsF, a number of other bases were examined with optimal results being obtained with 5 equiv of powdered K_2CO_3 when MeCN was used as the solvent. The use of catalytic amount of KI for the alkylation was also examined where it was found that 10 mol % of KI led to smooth conversion to **15** when the alkylation was performed at 55–60 °C. The alkylation of crude **32** with phenol **8** was conducted by the addition of the 2-MeTHF solution of **32** to a mixture of 1 equiv of **8**, 5 equiv of K_2CO_3, and 0.1 equiv of KI in MeCN at 55–60 °C. After 7–8 h, complete conversion to **15** was observed. Following an aqueous workup, HPLC assay yield of crude **15** was 98%,



Scheme 10.



Scheme 11.

which was used in the final deprotection without further purification.

The deprotection of **15** and conversion to **2** was thoroughly optimized with the aid of high throughput experimentation (HTE) coupled with DOE optimization (Scheme 11).[8] Screening results found that removal of both the THP and *tert*-butyl groups could be effected in a one-pot procedure employing sulfuric acid in MeCN at 70 °C eliminating the use of a combination of TsOH and TFA. Unfortunately, the HPLC assay yields of **2** remained <70%. It was rapidly established that the by-products of the THP cleavage were the cause of the low yields and a two-step protocol was implemented for the final preparation of **2**. The optimized procedure involved treatment of **15** at room temperature with 2.2 equiv of concd sulfuric acid in MeCN in the presence of 1-octanethiol. The use of 1-octanethiol was crucial as it effectively trapped the THP by-products associated with THP removal. During the course of the reaction, des-THP intermediate **34** began to crystallize from the reaction mixture. After dilution with MTBE and then heptane to maximize the recovery, compound **34** was isolated as the bis-sulfate salt in 95% yield. Removal of the *tert*-butyl group was accomplished by reaction of **34** with 7 equiv of concd sulfuric acid in MeCN in the presence of 4 vol % of water at 70 °C for 2 h. During the course of the reaction, sulfate salt **2b** crystallized from the reaction mixture. After being cooled to room temperature, the slurry of **2b** was diluted with water and was filtered to give **2b** in 92% isolated yield. The crystalline freebase of **2** could be obtained by neutralization of either **2a**/**b** with $NaHCO_3$ in EtOAc at 50 °C and subsequent crystallization from EtOH to give **2** in >95% yield.

In conclusion, we have developed a practical, efficient route for the synthesis of the potent non-nucleoside reverse transcriptase inhibitor **2** in 47% overall yield from 2,6-difluoropyridine. The synthetic route is highlighted by a three-step synthesis of the intermediate **22** that does not require isolation of any intermediates, and a high yielding coupling reaction between **18** with phenol **8**. This chromatography-free and scalable route has been used successfully to prepare large quantities of **2**. Furthermore, two other routes for the synthesis of compound **2** and an optimized initial synthesis of compound **1** were discussed.

3. Experimental section

3.1. General

Melting points are uncorrected. All solvents and reagents were used as received from commercial sources. Analytical samples were obtained by chromatography on silica gel using an ethyl acetate–hexane mixture as the eluent unless specified otherwise. Water

content (KF) was determined by Karl Fisher titration on a Metrohm 737 KF coulometer.

3.2. Preparation of 3-bromomethyl-pyrazolo[3,4-*b*]-pyridine-1-carboxylic acid *tert*-butyl ester (6)

In a 100 L round bottom flask equipped with a mechanical stirrer, thermocouple, and reflux condenser was added 6.64 kg (29.3 mol) of **4** and 73 L of trifluorotoluene and the mixture heated to 75 °C. To the mixture was added 2.60 kg (29.3 mol) of NBS as a solid. After 15 min, 481 g (2.93 mol) of AIBN was added and the mixture was heated between 75 and 80 °C for 1 h. The reaction mixture was allowed to slowly cool to room temperature overnight. The resulting slurry was filtered and the solids were washed with 15 L of toluene. The filtrate containing a mixture of **4** (24%), desired product **6** (61%), and dibromide **7** (14%) was concentrated under reduced pressure and diluted to a final volume of ~19 L with toluene. The crude mixture was purified on a 45 (diameter)×100 (height) cm silica gel column (EMD Sciences silica gel 60 40–63 um) using a 42:58 (v/v) mixture of EtOAc/heptane. The fractions containing the desired bromide **6** were combined and concentrated under reduced pressure to give a solid, which was slurried in 18 L of MTBE and 18 L of heptane. The slurry was heated to 55 °C to dissolve all the solids and allowed to cool to room temperature overnight. To the slurry was then added 20 L of heptane and the slurry was stirred for 4 h and filtered. The wet cake was washed with 10 L of heptane/MTBE (4:1) and the solid was dried under vacuum/N_2 sweep to afford 3.84 kg (42%) of **6** as an off-white crystalline solid. Mp 85–86 °C;[18] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.62 (s, 9H), 5.05 (s, 2H), 7.48 (dd, 1H, J=8.0, 4.5 Hz), 8.42 (dd, 1H, J=8.0, 1.5 Hz), 8.74 (dd, 1H, J=4.5, 1.5 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.2, 31.1, 85.0, 116.2, 120.2, 131.1, 146.2, 147.3, 151.4, 152.2.

3.3. Preparation of 3-chloro-5-[2-chloro-5-(1*H*-pyrazolo-[3,4-*b*]pyridine-3-ylmethoxy)-phenoxy]-benzonitrile (1)

In a 400 L reaction vessel was charged 24.9 kg (89.0 mol) of **8** and 33 kg (217 mol) of CsF and 75 L of DMF. The resulting suspension as stirred at room temperature for 15 min followed by the portion-wise addition of 30.0 kg (96.1 mol) of **6** over 30 min. After 20 min post addition of **6**, a final 6.7 kg (46 mol) of CsF was added. After 2 h, the reaction mixture was diluted with 175 L of MTBE and aqueous $NaHCO_3$ (prepared by dissolving 4.5 kg $NaHCO_3$ in 145 L of water). The layers were separated and the organic layer was washed with water (2×100 L). The solvent was concentrated under reduced pressure and solvent switched to THF and a final volume of 250 L. To the crude solution of **9** was added 7.5 L of water and the mixture was warmed to 30 °C. To the solution was added 21.8 kg (62.5 mol) of concd sulfuric acid over 30 min and the mixture was stirred at <40 °C for 2 h. To the reaction mixture was added 130 L of water and the solvent was concentrated under reduced pressure to a final volume of ~90 L. The thick suspension was diluted with 15 L of THF and 150 L of water and the pH of the mixture adjusted to 8–9 by the addition of NEt_3 and warming to 40 °C. The slurry was cooled to room temperature and was filtered. The wet cake was washed with 100 L of 10:1 water/THF and dried under vacuum/N_2 sweep. The crude product was slurried in 223 L of MeCN and 200 L of MeOH and the slurry warmed to 60 °C for 45 min and then cooled to room temperature over 3 h. The slurry was filtered and the wet cake washed with 120 L of 1:1 MeCN/MeOH. The solid was dried under vacuum/N_2 sweep to give 28.6 kg (78%) of **1** as a colorless solid. Mp 164–165 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.47 (s, 2H), 7.08 (m, 2H), 7.20 (s, 1H), 7.36 (s, 1H), 7.45 (s, 1H), 7.54 (d, 1H, J=8.8 Hz), 7.78 (s, 1H), 8.29 (s, 1H), 8.54 (s, 1H), 13.73 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 64.4, 109.9, 113.8, 114.5, 114.6, 117.2, 117.4, 119.5, 122.2, 127.1, 130.1, 131.7, 135.7, 140.5, 149.6, 150.5, 152.8, 158.2, 159.0. Anal. Calcd for $C_{20}H_{12}Cl_2N_4O_2$: C, 58.41; H, 2.94; N, 13.62. Found: C, 58.29; H, 2.75; N, 13.55.

3.4. Preparation of 3-chloro-5-[2-chloro-5-(7-oxy-1*H*-pyrazolo[3,4-*b*]pyridine-3-ylmethoxy)-phenoxy]-benzonitrile (13)

In a 400 L reaction vessel was added 27.1 kg (110 mol) of MCPBA and 198 L of AcOH. The resulting solution was stirred at room temperature for 20 min to fully dissolve the MCPBA. In a separate 1000 L reaction vessel was added 28.3 kg (68.8 mol) of **1** and 425 L of AcOH and the mixture was heated to 55 °C. To the solution was added the AcOH solution containing MCPBA while maintaining the internal temperature at 55 °C. The reaction mixture was stirred at this temperature for 3 h and was cooled to 30 °C. To the reaction mixture was added aqueous sodium bisulfite (prepared by dissolving 5.01 kg of sodium bisulfite in 8 L of water) over 30 min while maintaining the internal temperature ~30 °C. The reaction mixture was then diluted with 550 L of water and the slurry was stirred for 30 min and filtered. The wet cake was washed with 225 L of EtOH/water (3:2) and dried under vacuum/N_2 sweep at 40 °C for 18 h to afford 32.2 kg (98%) of **13** as an off-white solid. Mp 197–198 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.49 (s, 2H), 7.09 (dd, 1H, J=8.8, 2.8 Hz), 7.12 (d, 1H, J=2.7 Hz), 7.19 (dd, 1H, J=8.0, 6.0 Hz), 7.35 (t, 1H, J=2.2 Hz), 7.45 (dd, 1H, J=2.2, 1.4 Hz), 7.55 (d, 1H, J=8.8 Hz), 7.78 (t, 1H, J=1.4 Hz), 7.89 (d, 1H, J=8.0 Hz), 8.40 (d, 1H, J=6.0 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 64.1, 110.0, 114.5, 114.6, 117.4, 117.5, 118.5, 118.6, 119.6, 120.1, 122.2, 127.1, 131.8, 135.8, 136.0, 150.5, 152.2, 158.5. Anal. Calcd for $C_{20}H_{12}Cl_2N_4O_3$: C, 56.22; H, 2.83; N, 13.11. Found: C, 56.14; H, 2.79; N, 12.99.

3.5. Preparation of 3-chloro-5-{2-chloro-5-[7-oxy-1-(tetrahydro-pyran-2yl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-ylmethoxy]-phenoxy}-benzonitrile (14)

In a 400 L reaction vessel was added 28.4 kg (66.5 mol) of **13** and 284 L of toluene. The slurry was heated to 50 °C and the solvent concentrated under reduced pressure to a final volume of ~200 L to remove residual water. The slurry was re-diluted with 80 L of toluene and 252 g (1.33 mol) of $TsOH\cdot H_2O$ was added followed by 30.8 kg (366 mol) of 3,4-dihydro-2*H*-pyran. The reaction temperature was raised to 80 °C and stirred at this temperature for 2.5 h. The reaction mixture was cooled to 60 °C and seeded with pure **14** (2 g). The resulting slurry was cooled to room temperature over 4 h and filtered. The wet cake was washed with 60 L of toluene and dried under vacuum/N_2 sweep for 18 h at 50 °C to give 27.3 kg (80%) of **14** as a colorless solid. Mp 162–163 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.51 (m, 2H), 1.67 (m, 1H), 1.97 (m, 2H), 2.35 (m, 1H), 3.61 (m, 1H), 3.89 (m, 1H), 5.45 (d, 1H, J=12.5 Hz), 5.50 (d, 1H, J=12.5 Hz), 7.06 (m, 2H), 7.13 (m, 1H), 7.24 (dd, 1H, J=8.3, 6.2 Hz), 7.36 (s, 1H), 7.45 (s, 1H), 7.54 (d, 1H, J=8.8 Hz), 7.78 (s, 1H), 7.91 (d, 1H, J=8.3 Hz), 8.40 (d, 1H, J=6.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 22.9, 25.1, 29.4, 63.9, 67.4, 85.0, 109.9, 114.5, 114.6, 117.4, 117.5, 119.5, 119.6, 120.4, 120.7, 122.2, 127.1, 131.7, 135.8, 138.5, 141.3, 142.8, 150.5, 158.2, 158.8. Anal. Calcd for $C_{25}H_{20}Cl_2N_4O_4$: C, 58.72; H, 3.94; N, 10.96. Found: C, 58.47; H, 4.03; N, 10.99.

3.6. Preparation of 3-{5-(6-amino-1*H*-pyrazolo[3,4-*b*]-pyridine-3-ylmethoxy)-2-chloro-phenoxy}-5-chloro-benzonitrile *p*-toluenesulfonate salt (2a)

In a 400 L reaction vessel was added 27.2 kg (53.2 mol) of **14**, 408 L of CH_2Cl_2, and 22.4 L of *tert*-butylamine and the mixture was cooled to 15 °C. In a separate 1000 L reaction vessel was added 36.5 kg (112 mol) of Ts_2O and 136 L of CH_2Cl_2 and the mixture was

cooled to −5 °C. The mixture containing **14** was transferred to the Ts_2O solution over 1 h keeping the internal temperature <5 °C. The reaction mixture was stirred at this temperature for ~30 min at which point HPLC analysis confirmed the completion of the reaction. The resulting slurry was filtered to remove insoluble **16** rinsing with 55 L of CH_2Cl_2. The filtrate was washed with 82 L of water and the solvent was switched to a final volume of 165 L of MeCN by concentration under reduced pressure. To the crude solution of **15** was added 40.5 kg (212.8 mol) of $TsOH \cdot H_2O$ followed by 243 L of MeCN and 162 L of toluene. The solvent was removed by atmospheric distillation and a final volume of 150 L and KF of <900 ppm water. To the cooled reaction mixture was added 151 kg (1324 mol) of TFA and the mixture was heated to 67 °C for 4 h and was cooled to 5 °C. The black reaction mixture was seeded with pure **2a** and 10 L of water was added and the slurry stirred for 30 min. To the slurry was added 99 L of water over 45 min and the mixture was stirred overnight at room temperature. The slurry was filtered and the wet cake was washed with 100 L of MeCN and was dried under vacuum/N_2 sweep at 45 °C to give 20.2 kg (60%) of **2a** as an off-white solid. Mp 219 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.30 (s, 3H), 5.45 (s, 2H), 6.65 (d, 1H, J=9.2 Hz), 7.07 (m, 2H), 7.13 (d, 2H, J=7.9 Hz), 7.36 (d, 1H, J=1.7 Hz), 7.47 (s, 1H), 7.53 (d, 2H, J=7.9 Hz), 7.58 (d, 1H, J=8.5 Hz), 7.80 (s, 1H), 8.27 (d, 1H, J=9.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.3, 106.7, 109.0, 114.6, 114.7, 117.4, 117.7, 119.7, 122.3, 126.0, 127.2, 128.7, 131.9, 135.8, 138.4, 145.7, 150.6, 156.3, 158.2, 158.5. Anal. Calcd for $C_{27}H_{21}Cl_2N_5O_5S$: C, 54.19; H, 3.54; N, 11.70. Found: C, 53.89; H, 3.22; N, 11.49.

3.7. Preparation of 3-benzyloxymethyl-1*H*-pyrazolo[3,4-*b*]-pyridine 7-oxide (21)

In a 500 mL three-neck round bottom flask equipped with a mechanical stirrer, and a thermocouple was added 4.49 g (18.8 mmol) of pyrazole **20** and 67 mL of IPAc. To the solution was added 6.01 g (24.4 mmol) of 70–77 wt % MCPBA and the sides of the flask were rinsed with 5 mL of IPAc. The reaction mixture was warmed to 35–40 °C and stirred at this temperature for 2 h. During the course of the reaction a thick, yellow slurry of the product formed. After heating for 2 h, the reaction mixture was slowly cooled (5 °C/h) to room temperature. The slurry was filtered and the wet cake washed with 70 mL of IPAc. The solid was dried for 3–12 h under vacuum/N_2 sweep to give 4.47 g (82%) of **21** as a monohydrate and a fluffy white solid that was sufficiently pure for use in subsequent transformations. Mp 210–211 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.54 (s, 2H), 4.83 (s, 2H), 7.18 (dd, 1H, J=8.0, 4.8 Hz), 7.21–7.35 (m, 5H), 7.82 (d, 1H, J=8.0 Hz), 8.39 (d, 1H, J=4.8 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 64.7, 71.6, 117.8, 118.3, 119.7, 127.6, 127.7, 128.3, 135.4, 138.0, 143.6, 144.4. Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.03; H, 5.24; N, 16.49.

3.8. Preparation of [6-*tert*-butylamino-1-(tetrahydro-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-yl]-methylene benzyl ether (22)

In a 100 mL round bottom flask was added 3.06 g (12.0 mmol) of **21**, 5.05 g (60 mmol) of DHP, 60 mg (0.24 mmol) of pyridinium *p*-toluenesulfonate, and 30 mL of trifluorotoluene. The mixture was heated to 85 °C for 4 h, cooled to room temperature, and concentrated under reduced pressure while switching the solvent to THF and a final volume of 20 mL. To the resulting solution was added 4.40 g (60.0 mmol) of *tert*-butylamine. In a separate 250 mL round bottom flask was added 9.81 g (30.0 mmol) of Ts_2O and 50 mL of THF. The solution was cooled to −10 °C, and the above mixture was added over 30 min. The reaction mixture was diluted with 70 mL of heptane and the reaction mixture was filtered. The filtrate was cooled to 0 °C and 6 mL of 10 N NaOH solution was added. After stirring at 0 °C for 30 min, the solids were filtered and washed with 1:1 heptane/THF. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography. The first product to elute from the column was identified as compound **22** and was obtained as a colorless solid. mMp 69–70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (s, 9H), 1.59 (m, 1H), 1.73–1.86 (m, 2H), 1.95 (m, 1H), 2.12 (m, 1H), 2.66 (m, 1H), 3.76 (m, 1H), 4.14 (m, 1H), 4.54 (d, 1H, J=11.9 Hz), 4.57 (d, 1H, J=11.9 Hz), 4.62 (br s, 1H), 4.81 (d, 1H, J=12.7 Hz), 4.84 (d, 1H, J=12.7 Hz), 5.87 (dd, 1H, J=12.3, 1.9 Hz), 6.19 (d, 1H, J=8.7 Hz), 7.28–7.35 (m, 5H), 7.72 (d, 1H, J=8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 25.2, 29.3, 29.7, 51.6, 66.5, 68.4, 72.2, 82.6, 106.8, 107.4, 127.6, 128.0, 128.4, 130.4, 138.4, 142.9, 151.6, 157.8. HRMS (ESI) calculated for $C_{23}H_{30}N_4O_2$ (M+H) 395.2447, found 395.2431.

The second product to elute from the column was identified as [3-benzyloxymethyl-1-(tetrahydro-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-4-yl]-*tert*-butylamine **23**, which was obtained as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H), 1.53 (m, 1H), 1.80 (m, 2H), 1.92 (m, 1H), 2.10 (m, 1H), 3.83 (m, 1H), 4.14 (m, 1H), 4.57 (s, 2H), 4.96 (s, 2H), 6.03 (dd, 1H, J=10.8, 2.2 Hz), 6.33 (d, 1H, J=5.8 Hz), 6.93 (br s, 1H), 7.32 (m, 5H), 8.11 (d, 1H, J=5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 25.1, 29.9, 51.2, 67.6, 68.6, 72.3, 81.9, 99.1, 105.5, 128.1, 128.4, 137.0, 142.1, 148.6, 149.8, 153.2. HRMS (ESI) calculated for $C_{23}H_{30}N_4O_2$ (M+H) 395.2447, found 395.2441.

3.9. Preparation of [6-*tert*-butylamino-1-(tetrahydro-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-yl]-methanol (18)

To a solution of 8.50 g (21.6 mmol) of THP-pyrazole **22** in 40 mL of EtOH was added 1.96 g of 10% Pd/C (~50% wet Degussa type E101 NE/W). The stirred solution was placed under an atmosphere of hydrogen (10 psi) and stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of Solka floc (filter agent) eluting with ~40 mL of EtOAc. The filtrate was concentrated under reduced pressure flushing with ~35 mL of EtOH and the final volume adjusted to 30 mL. To the EtOH solution containing **18** was added drop-wise 40 mL of water and the mixture seeded with pure **18**. The slurry was stirred at room temperature for 30 min and 35 mL of water was added over 30 min. The slurry was cooled to 2–5 °C and was filtered. The wet cake was washed with water (2×30 mL) and dried under vacuum/N_2 sweep for 12 h to give 6.23 g (95%) of **18** as a white to off-white crystalline solid. Mp 146–147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 1.59 (m, 1H), 1.76 (m, 2H), 1.91 (m, 1H), 2.11 (m, 1H), 2.20–2.50 (br m, 1H), 2.61 (m, 1H), 3.73 (t, 1H, J=10.8 Hz), 4.12 (d, 1H, J=11.4 Hz), 4.66 (br s, 1H), 4.87 (s, 2H), 5.83 (d, 1H, J=10.8 Hz), 6.19 (d, 1H, J=8.6 Hz), 7.67 (d, 1H, J=8.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4, 25.2, 29.3, 29.6, 51.6, 59.1, 68.4, 82.5, 106.0, 107.4, 130.0, 145.1, 151.6, 157.8. Anal. Calcd for $C_{16}H_{24}N_4O_2$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.91; H, 7.86; N, 18.21.

3.10. Preparation of 2-benzyloxy-1-(2,6-difluoro-pyridin-3-yl)-ethanone (26)

To a 2 L round bottom flask, equipped with an overhead stirrer, thermocouple, addition funnel, and nitrogen inlet, was charged 51.6 g (448 mmol) of 2,6-difluoropyridine **1** and 616 mL of anhydrous THF and the solution was cooled to ~−70 °C. To the mixture was added drop-wise 185 mL (461 mmol) of *n*-butyllithium (2.5 M in hexane) through the addition funnel while maintaining the internal temperature <−65 °C. After the addition of butyllithium was complete, the resulting mixture was stirred at −65 °C for 1 h. In a separate flask was placed 93.7 g (448 mmol) of Weinreb amide **25** in 175 mL of 2-MeTHF and this solution was pre-cooled to −60 to −55 °C. The solution containing **25** was rapidly charged to the lithiate difluoropyridine solution and the resulting reaction

mixture was stirred at −65 °C for 1 h, and slowly warmed to −10 °C over 4 h. The reaction mixture was inversely quenched into a solution of 293 mL of 5 N HCl and 175 mL of THF at −15 to −5 °C. The mixture was extracted with 516 mL of MTBE. The layers were separated and the organic layer was washed with water (2×258 mL) and concentrated under reduced pressure while azeotropically drying to a final KF <250 ppm and then the solvent switched under reduced pressure to a final volume of 266 mL of NMP and used in the next reaction without further purification. HPLC assay yield of **26** was 88.7 g (81%). An analytical sample was obtained by concentration of the crude reaction mixture and crystallized from EtOAc/heptane (1:4) at −10 °C to give pure **26** as colorless needles. Mp 52.3–52.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.69 (d, 2H, J=3.0 Hz), 4.70 (s, 2H), 6.89 (dd, 1H, J=8.4, 1.9 Hz), 7.31–7.52 (m, 5H), 8.54 (dd, 1H, J=16.5, 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 73.8, 75.3 (d, J=10 Hz), 107.7 (dd, J=33, 9 Hz), 115.5 (d, J=33 Hz), 128.1, 128.2, 128.6, 137.0, 146.9 (d, J=9 Hz), 160.3 (dd, J=251, 16 Hz), 163.7 (dd, J=254, 16 Hz), 192.2 (d, J=8 Hz). HRMS (ESI) calculated for $C_{14}H_{11}F_2NO_2$ (M+H) 264.0836, found 264.0807.

3.11. Preparation of (3-benzyloxymethyl-1*H*-pyrazolo-[3,4-*b*]pyridine-6-yl)-*tert*-butylamine (30)

To a 1 L round bottom flask, equipped with an overhead stirrer, thermocouple, addition funnel, and nitrogen inlet, was charged 179 mL (1.68 mol) of *tert*-butylamine and 532 mL of anhydrous NMP. To the resulting solution was slowly added via the addition funnel 88.7 g (337 mmol) of 2,6-difluoropyridine ketone **26** in 266 mL of NMP while maintaining the internal temperature between 0 and 5 °C over 1 h and the mixture as stirred at the same temperature for 2–3 h. The reaction mixture was degassed under vacuum and then placed under an atmosphere of nitrogen. To the resulting mixture was added 83.3 mL (1.68 mol) of hydrazine monohydrate slowly while maintaining the internal temperature between 0 and 5 °C. After complete addition, the reaction mixture was stirred at 0–5 °C for 5 h, and at room temperature for 3–5 h. The reaction mixture was cooled to 0 °C, and the pH was adjusted to 5 by the addition of 5 N sulfuric acid while keeping the internal temperature <20 °C. To the solution was added 700 mL of water and 800 mL of MTBE and the layers were allowed to separate. The aqueous layer was extracted with MTBE (2×300 mL). The combined organic extracts were washed with water (4×300 mL), concentrated under reduced pressure while solvent switching to toluene and azeotropically drying to a final volume of 600 mL of toluene and a KF <150 ppm water. To resulting solution was used as is in the next step without further purification. HPLC assay yield of **30** was 84.7 g (81%). An analytical sample of **30** was obtained by silica gel chromatography (EtOAc/heptane=1:4) to give pure **30** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 4.57 (s, 2H), 4.72 (br s, 1H), 4.83 (s, 2H), 6.22 (d, 1H, J=8.9 Hz), 7.27–7.36 (m, 5H), 7.56 (d, 1H, J=8.9 Hz), 10.24 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.3, 51.7, 66.1, 72.1, 105.9, 107.4, 127.7, 128.0, 128.4, 130.4, 138.2, 143.5, 152.8, 158.1. HRMS (ESI) calculated for $C_{18}H_{22}N_4O$ (M+H) 311.1872, found 311.1854.

3.12. Preparation of [6-*tert*-butylamino-1-(tetrahydro-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-yl]-methylene benzyl ether (22)

To a 1 L round bottom flask, equipped with an overhead stirrer, thermocouple, addition funnel, and nitrogen inlet, was sequentially charged 84.6 g (273 mmol) of crude **30** in 600 mL of dry toluene–toluene, 126 mL (1.36 mol) of 3,4-dihydro-2H-pyran, and 2.35 g (13.6 mmol) of pyridinium *p*-toluenesulfonate. The resulting mixture was heated at 80–85 °C for 18 h. The reaction mixture was cooled to room temperature, washed with 100 mL of 5% $NaHCO_3$ and with 200 mL of water. HPLC assay yield of the organic layer gave 106 g (99%) of crude **22**. The organic layer was concentrated under reduced pressure, and the solvent switched to cyclohexane and a final volume of 330 mL by distillation at 50 °C. The resulting solution was cooled to 30 °C, and seeded with a few crystals of pure **22**. The resulting slurry was stirred at room temperature for 5 h, and at 10 °C for 1 h. The crystalline solid was filtered, washed with 80 mL of cold cyclohexane, and 150 mL of cold cyclohexane/heptane (2:1) and dried under vacuum/N_2 sweep to afford 99.1 g (93%) of **22** as an off-white solid that was identical to that obtained above.

3.13. Preparation of 3-{5-[6-*tert*-butylamino-1-]tetrahydro-pyran-2-yl}-1*H*-pyrazolo[3,4-*b*]pyridine-3-ylmethoxy]-2-chloro-phenoxy}-5-chloro-benzonitrile (15)

In a 1 L round bottomed flask equipped with a mechanical stirrer and thermocouple was added the 75 g (241 mmol) of **18** and 300 mL of 2-MeTHF. The resulting heterogeneous mixture was cooled to an internal temperature of ∼5 °C and 46.3 mL (266 mmol) of Hunig's base was added in one portion. To the slurry was added drop-wise 19.8 mL (254 mmol) MsCl at such a rate that the internal temperature was maintained <30 °C. The resulting mixture was then heated to an internal temperature of 50–55 °C and stirred at this temperature for 3 h. The resulting hot mixture was cooled in an ice bath to 5 °C and stirred at this temperature for 30 min and filtered. The flask and filter cake were rinsed with 300 mL of 2-MeTHF. The resulting filtrate was concentrated to a final volume of ∼300 mL and used in the next step 'as is'. An analytical sample of 3-chloromethyl-pyrazolo[3,4-*b*]pyridine-1-carboxylic acid *tert*-butyl ester **32** was obtained by purification on silica gel to give **32** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H), 1.56 (m, 2H), 1.75 (m, 2H), 1.94 (m, 1H), 2.10 (m, 1H), 2.58 (m, 1H), 3.76 (m, 1H), 4.12 (m, 1H), 4.60 (s, 2H), 5.87 (dd, 1H, J=10.6, 2.3 Hz), 6.28 (d, 1H, J 8.8 Hz), 7.71 (d, 1H, J=8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2, 25.3, 28.9, 29.3, 38.9, 51.8, 68.2, 86.7, 106.1, 107.7, 129.8, 141.6, 151.4, 157.6. Anal. Calcd for: $C_{16}H_{23}ClN_4O$: C, 59.53; H, 7.18; N, 17.35. Found: C, 59.21; H, 6.89; N, 17.01.

In a separate 3 L round bottom flask equipped with a mechanical stirrer and thermocouple, was added the 67.6 g (241 mmol) of phenol **8**, 4.00 g (24.1 mmol) of KI, 133 g (966 mmol) of K_2CO_3, and 450 mL of MeCN. The resulting mixture was heated to an internal temperature of 55–60 °C and the above solution containing crude chloride **31** in 2-MeTHF was added over 20 min. The reaction mixture was stirred at 55–60 °C for 7–10 h and allowed to cool to room temperature and stirred overnight at room temperature. The reaction mixture was diluted with 600 mL of IPAc and 600 mL of water and the layers well mixed for 15 min and allowed to separate. The organic layer was washed with 375 mL of water and 375 mL of brine. The solvent was concentrated under reduced pressure flushing first with IPAc to bring the KF down and then MeCN to a final volume of 400 mL of MeCN and a KF ∼200 ppm. HPLC assay yield of **15** was 133 g (97%). The MeCN solution containing **15** was used in the next reaction without further purification. An analytical sample of 3-{5-[6-*tert*-butylamino-1-(tetrahydro-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-ylmethoxy]-2-chlorophenoxy}-5-chloro-benzonitrile **15** was obtained by purification on silica gel to give **15** as a colorless foam. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (s, 9H), 1.62 (m, 1H), 1.78 (m, 2H), 1.92 (m, 1H), 2.14 (m, 1H), 2.57 (m, 1H), 3.76 (m, 1H), 4.15 (m, 1H), 4.71 (br s, 1H), 5.29 (s, 2H), 5.88 (dd, 1H, J=10.6, 2.4 Hz), 6.22 (d, 1H, J=8.8 Hz), 6.83 (d, 1H, J=2.9 Hz), 6.94 (dd, 1H, J=8.8, 2.9 Hz), 7.02 (dd, 1H, J=2.4, 1.4 Hz), 7.13 (m, 1H), 7.34 (m, 1H), 7.45 (d, 1H, J=10.6 Hz), 7.66 (d, 1H, J=8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 23.3, 25.1, 29.6, 51.7, 65.2, 68.4, 82.5, 106.3, 108.0, 109.7, 113.6, 114.6, 117.0, 118.1, 118.2, 121.7, 126.1, 129.7, 131.4, 136.4, 140.5, 150.3, 151.5, 157.8, 158.4, 158.7. Anal. Calcd for $C_{29}H_{29}Cl_2N_5O_3$: C, 61.49; H, 5.16; N, 12.36. Found: C, 61.57; H, 5.29; N, 12.29.

3.14. Preparation of 3-{5-(6-*tert*-butylamino-1*H*-pyrazolo-[3,4-*b*]pyridine-3-ylmethoxy)-2-chloro-phenoxy}-5-chloro-benzonitrile bisulfate (34)

In a 1 L flask three-neck round bottom flask equipped with a mechanical stirrer and thermocouple was added 35.9 g (63.4 mmol) of **15** in 100 mL of MeCN and 20.4 g (139 mmol) of 1-octanethiol in one portion. The reaction mixture was cooled to 15 °C and 7.43 mL (139 mmol) of concd sulfuric acid was added drop-wise over 30 min while maintaining the internal temperature <25 °C. The resulting homogeneous solution was stirred at room temperature for 30 min during which time **34** began to crystallize from the crude reaction mixture. The resulting slurry was stirred at room temperature for 30 min at and MTBE (130 mL) was added drop-wise over 45 min. The resulting slurry was stirred at room temperature for an additional 30 min and heptane (65 mL) was added drop-wise over 45 min and the slurry stirred for 3 h and filtered. The wet cake was washed with 125 mL of MTBE and dried under vacuum/N_2 sweep for 8 h to give 40.9 g (95%) of **34** as a colorless solid. Mp 140 °C (DSC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.25 (s, 9H), 4.67 (s, 2H), 6.08 (d, 1H, J=9.4 Hz), 6.17 (d, 1H, J=2.8 Hz), 6.27 (dd, 1H, J=8.9, 2.8 Hz), 6.32 (m, 1H), 6.36 (m, 1H), 6.69 (m, 2H), 7.44 (d, 1H, J=9.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.5, 52.7, 60.7, 105.5, 108.6, 113.0, 113.7, 115.7, 117.4, 120.5, 125.2, 130.6, 135.3, 137.1, 144.9, 149.7, 152.4, 157.4, 157.6. Anal. Calcd for $C_{24}H_{25}Cl_2N_5O_{10}S_2$: C, 42.48; H, 3.71; N, 10.32. Found: C, 42.06; H, 3.66; N, 10.21.

3.15. Preparation of 3-{5-(6-amino-1*H*-pyrazolo[3,4-*b*]-pyridine-3-ylmethoxy)-2-chloro-phenoxy}-5-chloro-benzonitrile sulfate (2b)

To a 1 L round bottom flask equipped with a mechanical stirrer, thermocouple, and reflux condenser was added 53.9 g (79 mmol) of **34** and 350 L of 96:4 mixture of MeCN/water (by volume). To the solution was added 4.23 mL (556 mmol) of concd sulfuric acid and the reaction mixture was heated to 70 °C for 2 h during which point the product begins to crystallize from the crude reaction mixture. The slurry was cooled to room temperature and diluted with 190 mL of water. The slurry was stirred for 3 h and filtered. The wet cake was washed with 150 mL of MeCN/water (2:1, 2×) and dried under vacuum/N_2 sweep for 12 h to give 38.2 g (92%) of **2b** as a colorless solid. Mp 225 °C (DSC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.45 (s, 2H), 6.64 (d, 1H, J=9.2 Hz), 7.07 (m, 2H), 7.37 (dd, 1H, J=2.3, 1.2 Hz), 7.47 (dd, 1H, J=2.3, 1.2 Hz), 7.59 (m, 1H), 7.81 (s, 1H), 8.27 (d, 1H, J=9.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 61.5, 106.7, 109.2, 109.9, 114.5, 114.6, 117.4, 117.7, 119.7, 122.3, 127.2, 131.9, 135.8, 136.9, 137.7, 145.8, 150.6, 156.1, 158.2, 158.4. Anal. Calcd for $C_{20}H_{15}Cl_2N_5O_6S_2$: C, 45.81; H, 2.88; N, 13.36. Found: C, 45.97; H, 2.98; N, 13.33.

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17. In similar fashion as described for the preparation of compound **4**, Scheme 1, the intermediate regioisomeric THP-protected pyrazole could be observed by HPLC. This intermediate converts to THP-pyrazole **22** upon heating.
18. Satisfactory elemental analysis could not be obtained for bromide **6** due to the instability of this intermediate.