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A Robust Kilo-Scale Synthesis of Doravirine

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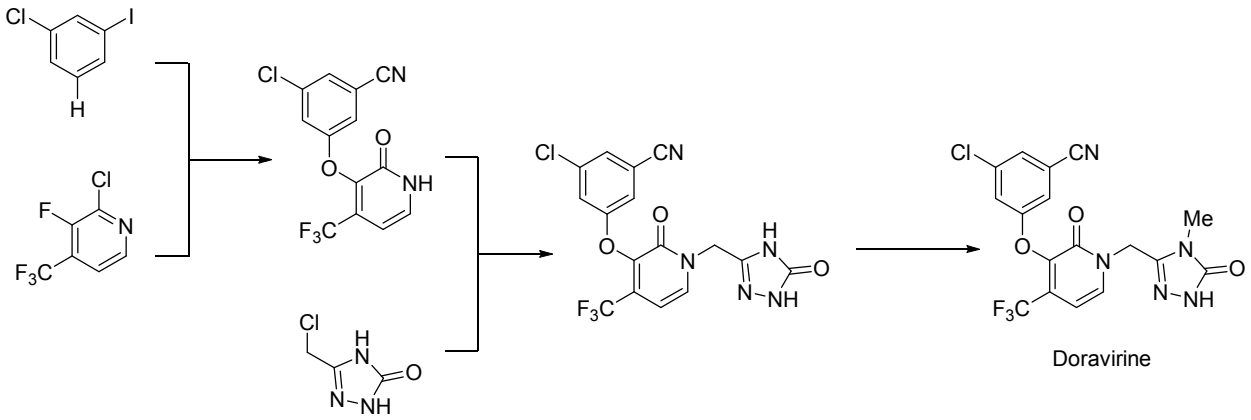
TOC Abstract



ABSTRACT Doravirine is non-nucleoside reverse transcriptase inhibitor (NNRTI) currently in phase III clinical trials for the treatment of HIV infection. Herein we describe a robust kilo-scale synthesis for its manufacture. The structure and origin of major impurities were determined and their downstream fate-and-purge studied. This resulted in a re-design of the route to introduce the key nitrile functionality via a copper mediated cyanation which allowed all impurities to be controlled to an acceptable level. The improved synthesis was scaled to prepare ~100 kg batches of doravirine to supply all pre-clinical and clinical studies up to phase III. The synthesis affords high quality material in a longest linear sequence of 6 steps and 37% overall yield.

Keywords: non-nucleoside reverse transcriptase inhibitor (NNRTI), Doravirine, C-H Borylation, Cyanation

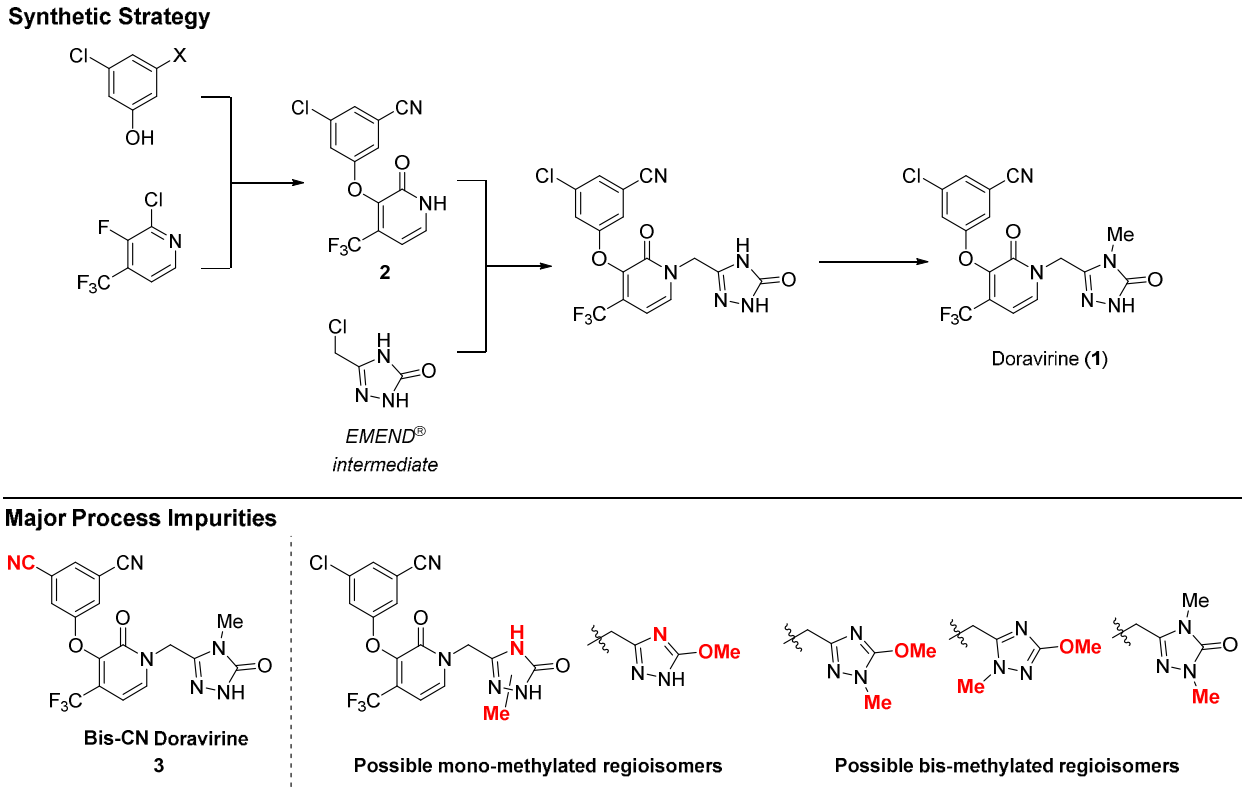
Introduction. Highly active antiretroviral therapy (HAART) is the standard of care for the treatment of HIV infection.[1] A critical component of this treatment is often a non-nucleoside reverse transcriptase inhibitor (NNRTI).[2] Efavirenz is a first generation NNRTI[3] which has been co-formulated with tenofovir disoproxil fumarate and emtricitabine both nucleoside reverse transcriptase inhibitors (NRTI), as a once-a-day fixed-dose combination (Atripla®). This first-line therapy reached a premier market position given its proven efficacy, tolerability and convenient dosing regimen.[4] However, neurocognitive side effects,[5] teratogenicity,[6] and complications of hyperlipidemia[7] have been associated with efavirenz treatment. Coupled with the emergence of clinical resistance to first generation NNTRIs, there is a critical need for the development of a superior, second generation of these life-saving medications.[8]

Results and Discussion. Our discovery efforts toward this goal identified doravirine (**1**) as a potential second generation NNRTI, and this compound has advanced into Phase III clinical trials.[9] To support its preclinical and early clinical development, we required a robust and practical synthesis suitable for kilo-scale deliveries. Our retrosynthetic approach to **1** leveraged the discovery chemistry strategy used to establish the triazolinone pharmacophore via late-stage alkylation of pyridone intermediate **2**. Early synthetic evaluation of a late-stage methylation of readily accessible penultimate revealed formation of several distinct impurities in the active pharmaceutical ingredient (API) which would have to be reduced to meet our target specifications (Scheme 1). For milligram-scale synthesis, this was only possible using tedious HPLC purification. LCMS revealed that these impurities fall into two classes; those resulting from mono- and bis-methylation. Only two isomers of the mono-methylated impurities, along with two bis-methylated impurities were typically observed and the extent to which each formed largely depended on the methyl iodide charge and reaction conditions. However, one impurity

was identified as a bis-CN doravirine **3**, which we tracked to the upstream pyridone synthesis. In fact, close examination of the lot of pyridone **2** which had been used to synthesize the material in discovery chemistry, revealed presence of bis-cyanopyridone **2-CN** (Scheme 2). After extensive crystallization studies at the penultimate and final steps failed to identify adequate conditions for the removal **3**,[10] we set out to develop a route to pyridone **2** in which formation of this bis-cyano impurity would be limited to <0.5% area by HPLC.

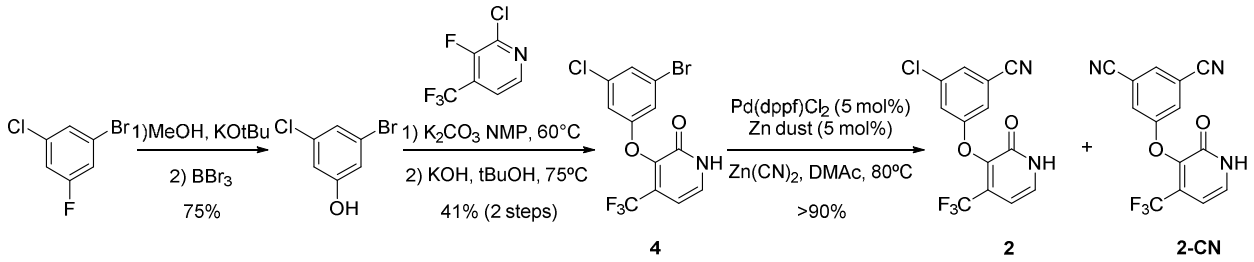
With this critical knowledge, we first set out to address the robustness of the sequence and develop a process which could be rapidly scaled to kilogram quantities to help accelerate the development of doravirine.

Scheme 1. Synthetic Strategy and Impurities for doravirine Chemical Process



Pyridone Synthesis. The original route to pyridone **2** (scheme 2), was largely limited by the availability of 1,3,5-substituted benzene raw materials. To achieve differentiated substitution, 1-bromo-3-chloro-5-fluorobenzene was selected. This arene underwent a selective S_NAr reaction with methoxide, the product of which was converted to the phenol using boron tribromide.[9] Elaboration to the cyanation precursor **4** was then straightforward via two successive substitution reactions on 2-chloro-3-fluoro-4-trifluoromethyl pyridine. Several palladium catalysts were screened for the cyanation of **4**,[11] some of which showed ~1 % bis-cyano impurity in a small-scale controlled glove-box environment. This protocol called for reduction of the Pd (II) pre-catalyst with zinc dust and use of $Zn(CN)_2$ as the cyanide source. However, while these optimal conditions led to a high yield, >1% HPLC of bis-cyanation impurity **2-CN** on laboratory scale, outside the glove-box environment. Given that we intended to target a specification <1% of **2-CN** and that this impurity tended to enrich in the end-game an alternative approach was sought.

Scheme 2. Original Route to Pyridione **2**

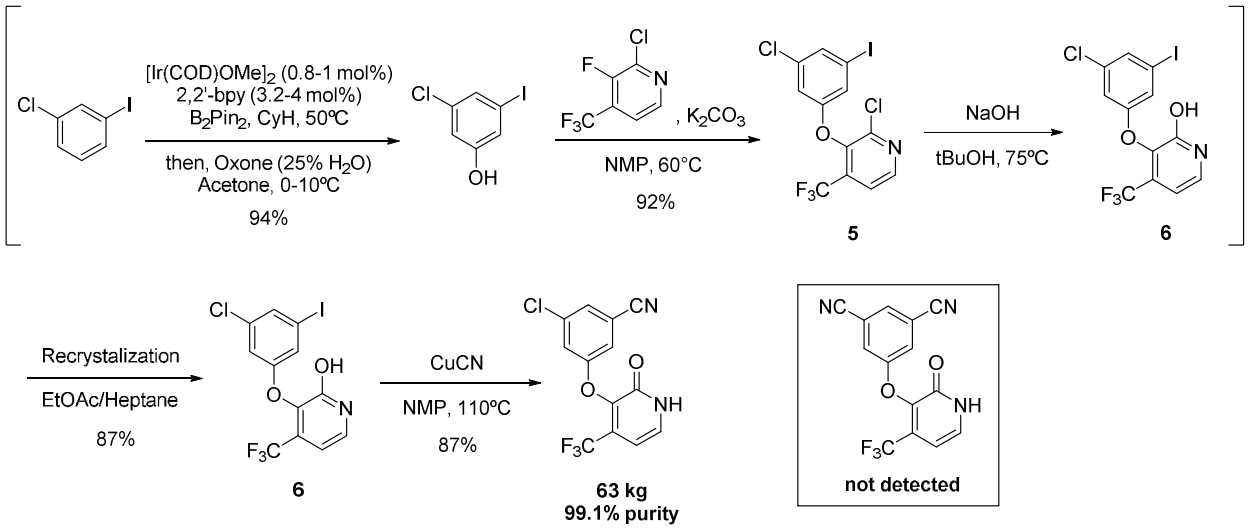


We then explored copper mediated cyanation reactions, hoping to achieve better selectivity; however attempts at cyanation of the aryl bromide with copper cyanide underscored the difficulty of this transformation. Screening of solvent and temperature revealed that at <90 ºC, no reaction occurred. Increasing the temperature to >130 ºC afforded ~70% conversion overnight with formation of several impurities including the bis-cyano **2-CN**.

In light of the challenges associated with the synthesis of **2,** we elected to evaluate an alternative substrate for cyanation which would enable the use of milder and hopefully more selective cyanation conditions. Early proof-of-concept for this strategy was quickly achieved using commercially available 3-chloro-5-iodo-phenol. Treatment of iodo-pyridone **5** with CuCN in DMF or NMP at 120ºC readily afforded complete conversion to the desired pyridone with no observed formation of the bis-cyano impurity.[12] The corresponding palladium-catalyzed protocol led to significant amounts of a des-chloro impurity so we opted to move forward with the copper-mediated protocol. Due to its limited availability on bulk scale, the development of a scalable synthesis of 3-chloro-5-iodo-phenol was required, which we envisioned via meta-selective C-H borylation-oxidation of 3-iodo-chlorobenzene.[13] Initially, we employed 4,4´-di-*tert*-butyl-2,2´-bipyridyl (dtbpy) as the ligand in the iridium-catalyzed borylation.[14] The high cost and long lead time for this ligand led us to examine alternative bipyridyl ligands for this transformation and we were delighted to find that the simple 2,2´-bipyridyl was a suitable replacement. Moreover, we were also able to reduce the iridium loading from the initial 1.5-3.0 mol% to 0.8-1.0 mol%. By running the borylation as a concentrated solution in cyclohexane, the subsequent oxidation step could be run as a through-process. After a solvent switch from cyclohexane to acetone, the pinacol boronate intermediate solution is cooled and a 25 wt% aqueous oxone solution is added while maintaining the temperature between 0-10ºC.[15] After work-up and carbon treatment, the phenol could be directly used in the subsequent step as a solution in NMP. This process was readily executed on an 85 kg batch to afford the desired phenol in 94% assay yield. The two subsequent steps were adapted from the original route, continuing as a through process. First, 3-chloro-5-iodophenol was coupled with pyridine 2-chloro-3-fluoro-4-trifluoromethylpyridine by carbonate-mediated SNAr , affording **5** in 91%

assay yield on 65 kg scale. Hydrolysis of chloropyridine **5** to pyridone **6** could be accomplished using either sodium or potassium hydroxide but the latter resulted in agglomeration of potassium salts and was not amenable to large scale synthesis. In contrast, the use of sodium hydroxide provided a reaction mixture that remained a well-agitated slurry throughout the course of the reaction. Pyridone **6** could then be isolated directly by addition of aqueous HCl to the mixture, and the crude solid was re-crystallized from ethyl acetate and *n*-heptane to provide compound **6** in 87% yield and 99% purity over the 3-step through process. Cyanation of of iodopyridone **6** using the aforementioned CuCN process in NMP at 105-110 °C provided full conversion to nitrile **2**. We found that controlling the temperature below 110 ºC was beneficial to the overall impurity profile of **2**. Following a buffered ammonia work-up to remove copper salts, the pyridone could be isolated via crystalization from an NMP solution by addition of water. The process was successfully executed on 92 kg scale and final pyridone **2** was isolated in 87% yield from **6** and 99.1% purity. The bis-cyano pyridone impurity **2-CN** could not be detected in material obtained from this route.

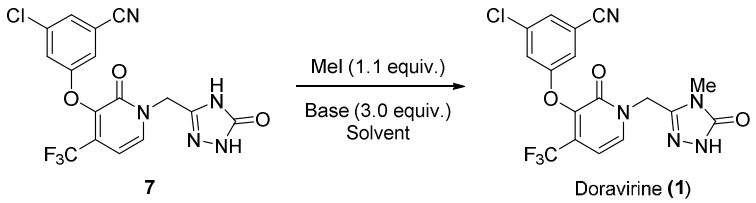
Scheme 3. Improved Synthesis of Pyridone **2**.



Triazolinone and End-Game. When considering options for incorporation of the *N*-methyltriazolinone moiety, we were mindful of the fact that we could readily procure large quantities of des-methylated triazinolinone which is an intermediate in the manufacturing process of another Merck product, EMEND®.[16] The bulk availability of this intermediate for early deliveries prompted us to explore a two-step process, where we first introduced the heterocycle and then affixed the methyl group in the final step. Des-methyl doravirine **7** was readily prepared by alkylation of pyridone **2** with triazolinone chloride and potassium carbonate in DMF at -10 ºC.[17] Material which meets specifications, including complete rejection of the triazolinone chloride, can be obtained by re-crystallization from acetonitrile/water in 81% isolated yield. This protocol was executed on 122 kg scale batches.

Screening of base and solvent for the final methylation step immediately revealed that the highest levels of conversion to product could be obtained in DMAc or DMSO (Figure 1). This is most likely due to the very low solubility of pyridone **2** in many organic solvents. Closer examination of reaction profile led us to choose potassium carbonate as the base for the final coupling which provided end-of-reaction streams with 76% purity on screening scale at room temperature. Moving from DMAc to NMP as the reaction solvent further enhanced the process, providing a similar reaction profile while enabling direct isolation of the crude compound after addition of water, and obviating the need for an aqueous work-up. To reach an optimal balance between yield and formation of the bis-methylated impurities, we elected to not drive the reaction to completion and instead opted to quench the reaction once >90% conversion was reached. Additional bis-methylated impurities were observed when the reaction was carried out at 40 ºC, keeping the reaction between 5-10 ºC provided optimal balance of reaction time and purity profile.

Figure 1. Base and Solvent Screen for Final Methylation Step.[a]

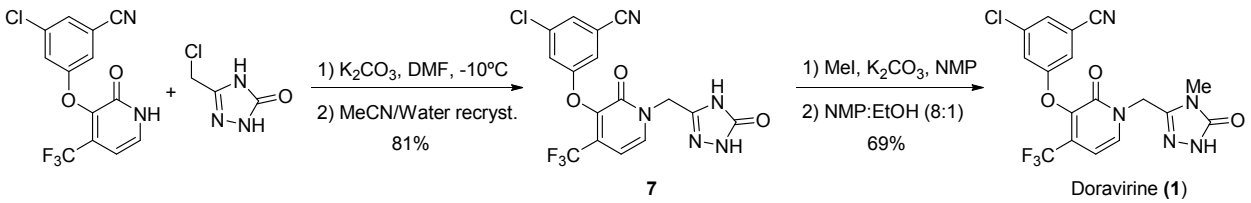


	K_2CO_3	Cs_2CO_3	K_3PO_4	*t*BuOK
DMSO	40	40	70	90
DMAc	98	98	90	80
MeCN	1	25	2	5
***i*PrOH**	2	2	1	2
$MeNO_2$	1	12	3	3
Sulfolane	3	3	4	1

[a]% conversion measured by HPLC analysis using 1.05 equiv. of MeI and 3.0 equiv. of base at 0.2 M.

At the end of reaction, filtration of the heterogeneous base followed by direct crystallization of the API by addition of ~1.5 volumes of water afforded the crude API (**1**) with 89-90% HPLC purity. The main impurity in the crude material is a bis-methylated impurity at ~5% HPLC. There are three other main impurities, 1 bis-methylated and 2 mono-methylated region-isomers. The API could then be recrystallized from NMP:EtOH (~8:1) at ~75 ºC which yields doravirine in 69% yield and high purity (99.1%). This improved end-game process was executed on 130 kg batches to afford >92 kg of API per batch.

Scheme 4. Doravirine End-Game and Final Recrystallization.



Conclusion. In summary, we developed a robust, scalable synthesis of doravirine. The focus of our strategy was to enable rapid acceleration of doravirine into preclinical and clinical development. With this in mind, we developed a process that leveraged existing knowledge for the triazolinone fragment. We identified the structure and origin of major impurities and were able to develop a robust process which either eliminated or purged these to acceptable levels, delivering material in greater than 99% purity. The process was quickly developed on lab-scale to supply initial preclinical drug substance and was then scaled up to provide material on >90 kg batches of final API.

EXPERIMENTAL PROCEDURES

Preparation of 3-chloro-5-iodo phenol. 1-chloro-3-iodobenzene (75.0 kg, 314.5 mol) was dissolved in cyclohexane (950 L) in a glass-lined vessel under nitrogen and the mixture was degassed by reducing pressure and back-fillingwith nitrogen. Bis(pinacolato) diboron is then charged (96.0 kg 468.2 mol) along with bis(1.5-cyclooctadiene) di-μ-methoxydiridium(I) (1.0 kg, 1.6 mol, 0.005 equiv.) and 4,4'-bypyridine (0.98 kg, 6.3 mol, 0.02 equiv.). The mixture is further degassed for 20 minutes before raising the temperature between 50-55 ºC. The mixture is aged for 12-20h until HPLC analysis showed less than 2% remaining starting material. The reaction mixture is then solvent switched to acetone keeping the temperature below 40 ºC to final volume of ~1000 L. After cooling back to 0-10 ºC, 20.5 w% aqueous oxone solution (718.0 kg, 237.5 mol) is added slowly over 9-10h keeping the temperature between 0-10 ºC. After addition, the reaction was complete and an aqueous 10% $NaHSO_3$ quench is then added over 30 minutes at the same temperature. Upon further stirring for 30 minutes, the reaction was concentrated to ~1200 L. Ethyl acetate (750 L) is added to the mixture which is stirred for 30 minutes between

20-30 ºC. Stirring was stopped and the aqueous layer was separated. The organic layer was filtered via 9.0 kg of activated charcoal. The charcoal was further washed with ethyl acetate (200 L). The organic layer was then washed with water (400 L) and concentrated and azeotroped with *n*-heptane. The solution in finally solvent switched to NMP resulting in a 10.4 weight % NMP solution of known 3-chloro-5-iodo phenol (75.3 kg, 94.1% assay yield, 98.5% LCAP) which could be used directly in the next step. Spectral data was consistent with what is already reported.

Preparation of 6 (3-(3-chloro-5-iodophenoxy)-4-(trifluoromethyl)pyridin-2-ol). 3-chloro-5-iodo phenol (83.4 kg, 331.7 mol) as a ~10 w% solution in NMP is diluted with further NMP (~250 L) to a final approximate volume of 1000 L. Potassium carbonate (66.8 kg, 483.3 mol) and 2-chloro-3-fluoro-4-trifluoromethylpyridine (65.5 kg, 328.3 mol) are then charged and the reaction is heated between 45-55 ºC for 12 h after which point HPLC analysis showed >99% conversion. The reaction is cooled between 20-25 ºC and water (1000 L) and then n-heptane (~850 L) were added while keeping the temperature constant. This mixture was stirred for 2.5h, the layers were then separated and the aqueous layer was back-extracted with n-heptane (~850 L). The combined organic layers were then washed with water (675 L, twice). The resulting n-heptane solution was assayed to contain compound **5** in 91.6% assay yield (130.4 kg, 301.8 mol) and 92.1 % LCAP. The solution is then concentrated under reduced pressure and finally solvent switched to t-BuOH (to a final volume between 4-6X) keeping the temperature under 45 ºC. To this t-BuOH solution is added solid sodium hydroxide (61.7 kg, 1542 mol) and the mixture is heated between 65-75 ºC for 38h. After cooling, water (~750 L) is added keeping the temperature between 25-35 ºC. The mixture's pH is then adjusted to 6-7 using 2N HCl in two portions while keeping the temperature between 25-35 ºC. More water is then added (900 L) resulting in complete precipitation of crude **6** (supernatant <0.5 LCAP). The solid is filtered and the cake washed with 165 L of water and then 110 L of n-heptane. Analysis of mother liquors revealed only 0.1 LCAP of pyridone **6**. The wet cake was then recharged into the vessel along with ethyl acetate (1400 L). The mixture is heated between 75-80 ºC until all solids were dissolved and then concentrated at atmospheric pressure to a final volume between 280-480 L. The mixture is cooled between 50-70 ºC followed by slow addition of n-heptane (1500 L). The mixture is cooled between 15-25 ºC for 1.5-2 h and filtered. The wet cake was washed with 90 L of n-heptane and was then dried under vacuum at 45-55 ºC for 20h affording 107.8 kg of

pyridone **6** (85.3% yield, 99.9 LCAP). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (br. s., 1H), 7.58 (d, J = 6.8 Hz, 1H), 7.53 (t, J = 1.6 Hz, 1H), 7.29 (dd, J = 1.4, 2.3 Hz, 1H), 7.09 (t, J = 2.0 Hz, 1H), 6.47 (d, J = 6.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.34, 156.78, 140.83, 134.51, 133.83, 130.85, 130.61 (q, J_{C-F} = 31.2 Hz), 123.11, 121.84 (q, J_{C-F} = 274.7 Hz), 115.57, 99.87 (q, J_{C-F} = 5.0 Hz), 95.12; ^{19}F NMR (377 MHz, DMSO-d_6) δ -62.06 (s, 1F); HRMS [M + H]$^{+}$ for $C_{12}H_7ClF_3IINO_2$ calcd, 415.9157; found, 415.9159; mp 221.68-223.25 °C.

Preparation of 2 (3-chloro-5-((2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxy)benzonitrile). Pyridone **6** (92.0 kg, 221.4 mol) is dissolved in NMP (450 L). Copper (I) Cyanide (35.7 kg, 390.8 mol) is then added to the mixture which is then heated between 105-110 ºC for 40h. HPLC analysis revealed >99% conversion. The mixture was cooled between 20-30 ºC and 1800 L of 2-MeTHF is added along with 500 L of MTBE. To this mixture is added ammonia buffer (460 L, $H_2O/NH_4Cl/NH_3$=9.4/4.0/3.8). The aqueous layer was separated and the organics were washed three more times with the ammonia buffer (270-350 L). Finally the organics were concentrated to an approximate volume of 220-300 L (NMP:MTBE:2-MeTHF=16.1:0.5:91.0 w%). 250 L of NMP is added to the mixture which was concentrated further until NMP w% was ~85%. The mixture was then heated between 50-60 ºC to dissolve all solids. After cooling between 30-40 ºC, 130 L of water was added slowly. After the addition, the temperature was dropped to 10-20 ºC and the slurry was stirred for 1h and filtered. The wet caked was rinsed with 0.5 volume of NMP:water (2:1), then 2 volumes of water. Finally the wet cake was charged with 700 L of water into a vessel and the slurry was stirred at 50-60 ºC for 4h. After cooling to 10-20 ºC and aging for 3h, the slurry was filtered and the wet cake washed with 200 L of water. The cake was dried under vacuum at 50-65 ºC for 28h resulting in 63.4 kg (89.6% yield, 99.1 LCAP) of pyridone **2**. Spectral data was consistent with what is already reported.[18]

Preparation of 7(3-chloro-5-((2-oxo-1-((5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxy)benzonitrile). Pyridone **2** (121 kg, 386.5 mol) is dissolved in DMF (475 L) and cooled between -10-10 ºC. To this solution is added potassium carbonate (106.9 kg, 773.5 mol) followed by 5-chloromethyl-2,4-dihydro-[1,2,4] triazol-3-one (54.4 kg, 407.4 mol) as a solution DMF (235 L) over 7-9h. After aging for a futher 0.5-1h, HPLC analysis revealed >97% conversion. 4N HCl is then added (230 L) slowly while keeping the

temperature between 10-30 ºC, followed by 600 L of water. pH analysis revealed the pH to be ~8. The mixture was aged for another 2h at this pH which was then further reduced to between 5-6 by addition of more 4N HCl (100 L) and water (615 L). The resulting slurry was aged at between 10-30 ºC for 10h and then the solids filtered. The wet cake is filtered and washed with 270 L of water. The solids were then dried under vacuum at 65-75 ºC for 12h resulting in 193.7 kg of crude product. The crude solid was then re-dissolved in a 19:1 mixture of MeCN:H2O (3000 L) by heating the mixture to 80-90 ºC. The solution is then concentrated to 330-400 L and another 2500 L of MeCN is added. Distillation is continued back down to a volume of 330-400 L at which point, the slurry is cooled and aged for 10h at a temperature between 10-30 ºC. The slurry is then filtered and the wet cake washed with 100 L of MeCN. The solids were dried under vacuum at 65-75 ºC for 12h affording the desired penultimate triazolone intermediate in 81% yield (130.6 kg, 99.7 LCAP). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (br. s., 1H), 11.40 (s, 1H), 7.93 (d, J = 7.3 Hz, 1H), 7.75 (t, J = 1.5 Hz, 1H), 7.58 (dd, J = 1.2, 2.3 Hz, 1H), 7.51 (t, J = 2.1 Hz, 1H), 6.66 (d, J = 7.3 Hz, 1H), 5.02 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.25, 156.20, 155.97, 142.52, 140.09 (q, J_{C-F} = 2.0 Hz), 137.74, 134.97, 130.17 (q, J_{C-F} = 31.2 Hz), 126.53, 121.70 (q, J_{C-F} = 274.7 Hz), 121.16, 118.37, 116.96, 113.70, 99.96 (q, J_{C-F} = 4.0 Hz), 44.90; ^{19}F NMR (376 MHz, DMSO-d_6) δ -62.24 (s, 1F); HRMS $[M + H]^+$ for $C_{16}H_{10}ClF_3N_5O_3$ calcd, 412.0419; found, 412.0415; mp 148.46-156.11 °C

Preparation of Doravirine (1) (3-chloro-5-((1-((4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl)oxy)benzonitrile). The triazolone intermediate (130.6 kg, 317.2 mol), NMP (850L), potassium carbonate (65.9 kg, 477.5 mol) and water (5 L) were charged to the vessel and degassed with N2. The mixture was cooled to 5-10 ºC and methyl iodide (50.9 kg, 381.2 mol) is added over 0.5h. The mixture is then aged for 34h after which point the reaction had reached ~90% conversion. The mixture was filtered over 15 kg of celite and the cake washed with 375 L of NMP. The resulting filtrate was added over 2.5h to water (2400 L) at 20-25 ºC and the slurry was aged for 24-30h at 20-30 ºC. The slurry is then filtered and the wet cake washed with 2000 L of water. The wet cake is then taken up in 450 L of EtOH and heated to 70-80 ºC for 1.5-2h. After cooling to 5-10 ºC the solid was filtered, rinced with EtOH and dried under vacuum to afford 105.4 kg of crude Doravirine. The crude solid is then recrystallized by slow addition of EtOH (45 L) to a 80-95 ºC solution of 1 in NMP (320 L), then seeding with crystalline 1 (121 g) and further addition of EtOH (13 L).

The mixture was cooled to between 70-80 ºC and aged for 2h. Then 1400 L of EtOH is added. After aging for 1h the mixture is cooled to between 5-10 ºC 7h. The slurry is then filtered and rinsed with cold EtOH (45 L). The solids were dried in a vacuum under reduced pressure between 50-75 ºC for 17h affording pure Doravirine 1 in 68.3% overall yield (92.3 kg, 99.1 LCAP). Spectral data was consistent with what is already reported.[18]

Supporting Information.

Full spectral data for all new compounds (PDF)

ACKNOWLEDGMENT

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REFERENCES

[1] Lohse, N.; Hansen, A.-B. E.; Pedersen, G.; Kronborg, G.; Gerstoft, J.; Sørensen, H. T.; Væth, M.; Obel, N. *Ann. Int. Med.* **2007**, *146*, 87.

[2] Young, S. D. *Perspect. Drug Discov. Des.* **1993**, *1*, 181.

[3] Young, S. D.; Britcher, S. F.; Tran, L. O.; Payne, L. S.; Lumma, W. C.; Lyle, T. A.; Huff, J. R.; Anderson, P. S.; Olsen, D. B.; Carroll, S. S.; Pettibone, D. J.; O'Brien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I.-W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Byrnes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602

[4] Fokunang, C. N.; Hitchcock, J.; Spence, F.; Tembe-Fokunang, E. A.; Burkhardt, J.; Levy, L.; George, C. *Int. J. Pharmacol.* **2006**, *2*, 152

[5] Raffi, F.; Pozniak, A.L.; Wainberg, M. A. *J. Anti-microb. Chemother.* **2014**, *69*, 1742

[6] Hsu, H. E.; Rydzak, C. E.; Cotich, K. L.; Wang, B.; Sax, P. E.; Losina, E.; Freedberg, K. A.; Goldie, S. J.; Lu, Z.; Walensky, R. P. *HIV Med.* **2011**, *12*, 97

[7] Fontas, E.; van Leth, F.; Sabin, C. A.; Friis-Møller, N.; Rickenbach, M.; d'Arminio Monforte, A.; Kirk, O.; Dupon, M.; Morfeldt, L.; Mateu, S.; Petoumenos, K.; ElSadr, S.; de Wit, S.; Lundgren, J. D.; Pradier, C.; Reiss, P. *J. Infect. Dis.* **2004**, *189*, 1056

[8] Tambuyzer, L.; Azijn, H.; Rimsky, L. T.; Vingerhoets, J.; Lecocq, P.; Kraus, G.; Picchio, G.; de Bethune, M.-P. *Antiviral Ther*. **2009**, *14*, 103

[9] Côte, B.; Burch, J. D.; Asante-Appiah, E.; Bayly, C.; Be´ dard,´ L.; Blouin, M.; Campeau, L.-C.; Cauchon, E.; Chan, M.; Chefson, A.; Coulombe, N.; Cromlish, W.; Debnath, S.; Deschenes, D.; Dupont-ˆ Gaudet, K.; Falgueyret, J.-P.; Forget, R.; Gagne, S.; Gauvreau, D.;´ Girardin, M.; Guiral, S.; Langlois, E.; Li, C. S.; Nguyen, N.; Papp, R.; Plamondon, S.; Roy, A.; Roy, S.; Seliniotakis, R.; St-Onge, M.; Ouellet, S.; Tawa, P.; Truchon, J.-F.; Vacca, J.; Wrona, M.; Yan, Y.; Ducharme, Y. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 917.

[10] For some experimental data on early batches of **1** containing elevated levels of **3**, consult Table S1 in the supporting information.

[11] For reviews, see: (a) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513 (b) Takagi, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; J. Wiley & Sons: Hoboken, NJ, 2002; Vol. 1, pp 657-672.

[12] Wen, Q.; Jin, J.; Zhang, L.; Luo, Y.; Lu, P.; Wang, Y.; *Tetrahedron Lett.* **2014**, *55*, 1271

[13] Hartwig, J. F.; Acc. Chem. Res., 2012, 45, 864

[14] (a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N.; Hartwig, J. F., *J. Am. Chem. Soc.* **2002**, *124*, 390. (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056

[15] Maleczka Jr., R. E.; Shi, F.; Holmes, D.; Smith III, M. R. *J. Am. Chem. Soc.*, **2003**, *125*, 7792.

[16] Cowden, C. J.; Wilson, R. D.; Bishop, B. C.; Cottrell, I. F.; Davies, A. J.; Dolling, U.-H.; *Tetrahedron Lett.* **2000**, *41*, 8661

[17] Gomez, R.; Jolly, S.; Williams, T.; Tucker, T.; Tynebor, R.; Vacca, J.; McGaughey, G.; Lai, M. T.; Felock, P.; Munshi, V.; DeStefano, D.; Touch, S.; Miller, M.; Yan, Y.; Sanchez, R.; Liang, Y.; Paton, B.; Wan, B. L.; Anthony, N. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7344

[18] Gauthier, Jr., D. R.; Sherry, B. D.; Cao, Y.; Journet, M.; Humphrey, G.; Itoh, T.; Mangion, I.; Tschaen, D. M. *Org. Lett.* **2015**, *17*, 1353