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# Development of an Expedient Process for the Multi-Kilogram Synthesis of Chk1 Inhibitor GDC-0425

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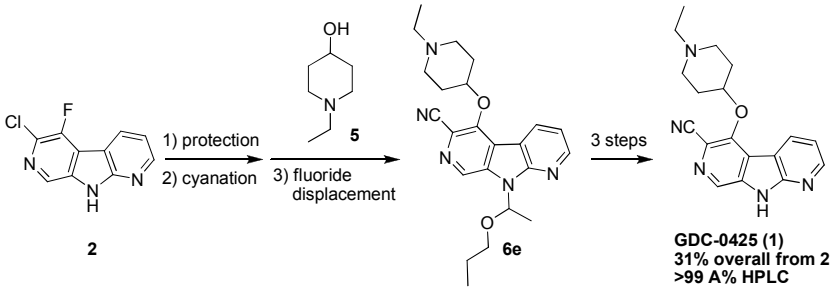
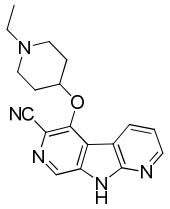


ABSTRACT

A process leading to the multi-kilogram GMP synthesis of Chk1 inhibitor **GDC-0425 (1)** was developed. Highlights of the synthesis include protection of the pyrrole ring of a 1,7-diazacarbazole as propyl ethyl ether, an efficient Pd catalyzed cyanation of an aryl chloride, aryl ether formation by SNAr fluoride displacement and development of a controlled crystallization providing the API with the required polymorphic form. The process delivered high quality **GDC-0425** with low levels of impurities and residual metals in 5 steps and 31 % overall yield.

KEYWORDS: Carbazole, Cyanation, Propyl Vinyl Ether, Aromatic Fluoride Displacement.

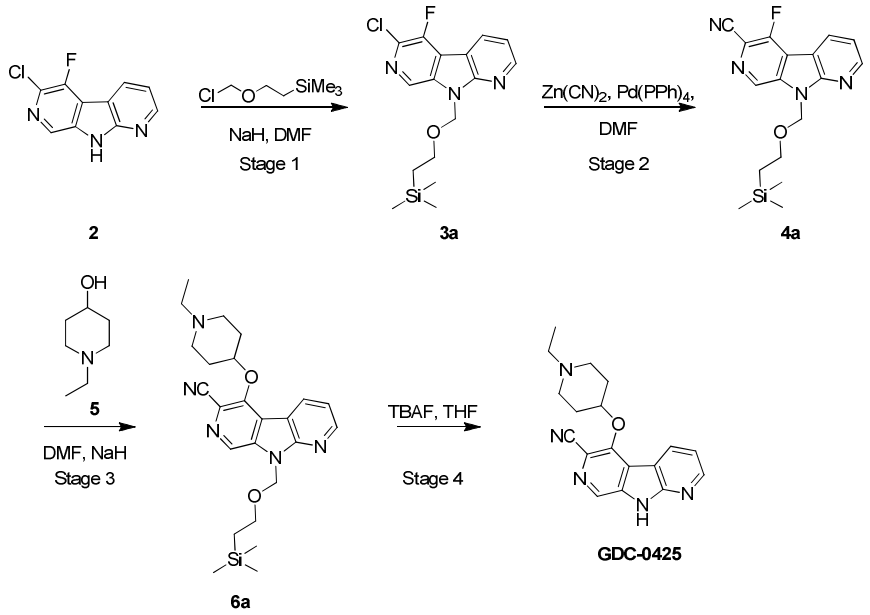



GDC-0425

INTRODUCTION.

**GDC-0425** is an orally bio-available small molecule inhibitor of Chk1 that has been developed as a treatment for various cancerous malignancies. As part of a recent drug development program, we required multi-kilogram amounts of API to support human clinical studies. The initial discovery chemistry synthesis[1a-d] involved a multi–step conversion from **2** to **GDC-0425**. This route (Scheme 1) provided initial quantities of API but could not be scaled up because it used undesirable reagents (SEM-chloride, NaH, TBAF), high catalyst loadings and required tedious workup and isolation procedures. We needed to develop a phase-appropriate fit-for-purpose 1st generation process that would overcome these issues and allow expeditious scale-up to multi-kilograms of **GDC-0425**. In addition to chemistry optimization, the removal of residual heavy metals and the development of a crystallization process for the isolation of the penultimate API also needed to be addressed. The process development of the end game chemistry will be discussed in detail.

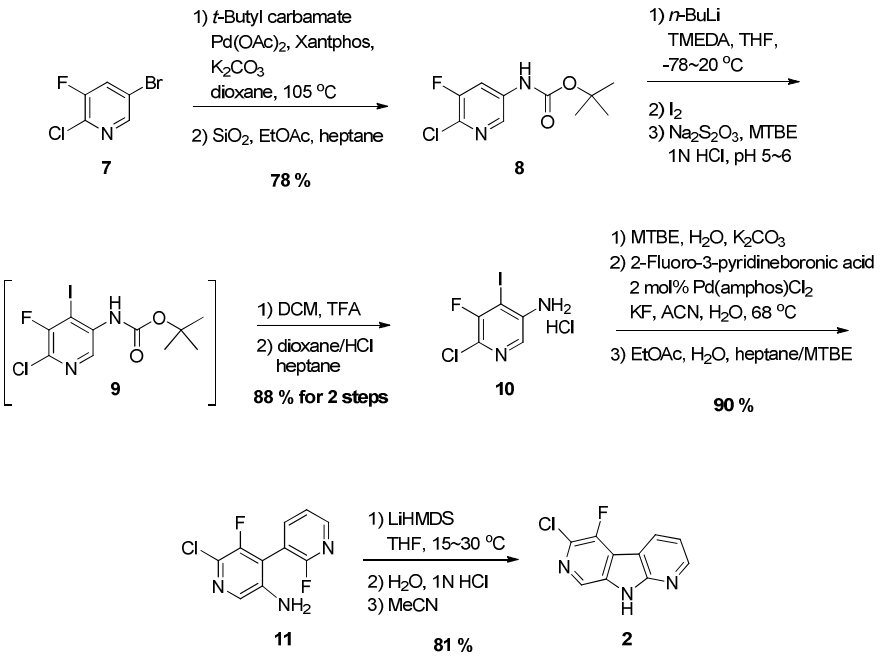
**Scheme 1.** *Discovery Route to* ***GDC-0425***




RESULTS AND DISCUSSION.

**Manufacture of the GMP starting materials 2 and 5.** GMP starting material **2** was made on 30 kg scale via the synthetic route shown in Scheme 2 with an overall yield of 50 % (see Supporting Information). Because of time constraints at this stage of development, no major process development was performed on the synthesis of carbazole **2** and the discovery chemistry route was implemented with only minor modifications for scale up.

**Scheme 2.** *Manufacture of carbazole* ***2***




Amination of bromo-pyridine **7** (59 kg) via Buchwald coupling with *t*-butyl carbamate in dioxane with 2 mol % $Pd(OAc)_2$/Xantphos, provided the Boc protected amino pyridine **8.** The major issue for this step was the purification of **8**. When crude **8** was used directly in the next step, a severe emulsion was observed during work up. It was assumed that the remaining Pd/xantphos, catalyst which was difficult to remove via crystallization, affected the workup. Thus, a silica plug was applied on scale and the product **8** was eluted with 10 % ethyl acetate in cyclohexane. 59 kg of **8** were isolated after concentration of the eluents to 2 volumes and crystallization from heptane in 78 % yield and 91 HPLC A % purity (~9 A % of residual *t*-butyl carbamate). Compound **8** was then first de-protonated with *n*-BuLi in THF/TMEDA at -78 °C, and then treated with iodine to obtain the iodocarbamate **9.** The reaction mixture was acidified with aqueous 1M HCl and extracted with MTBE, followed by an aqueous sodium thiosulfate solution wash to remove excess iodine. Iodocarbamate **9** could be isolated after concentration

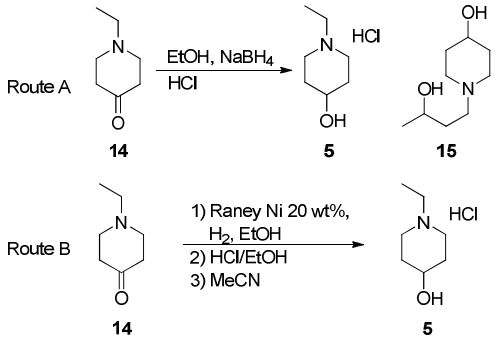
and trituration with ethanol, but 9 % of material was lost in the mother liquors. To increase the yield, the ethanol trituration was eliminated and the crude suspension of **9** was telescoped directly into the de-protection of the amino group. Initial de-protection conditions with 37 % aqueous HCl in MeOH were tried and the HCl salt of **10** could be isolated, however, we observed that a significant amount of the iodide of **10** was exchanged with chloride. Thus alternate de-protection conditions were investigated and we were pleased to find that TFA in DCM at ambient temperature led to clean reaction. Solvent exchange from DCM to dioxane was then performed, and the HCl salt of **10** was crystallized by addition of 4N HCl in dioxane followed by trituration from heptane. 59 kg of **10** HCl salt were isolated in 88 % yield over 2 steps and 96 HPLC A % purity. The following Suzuki coupling with 2-fluoro-3-pyridine boronic acid using $Pd(t\text{-}Bu_2PC_6H_4NMe_2)_2Cl_2$ (AMPHOS) and excess KF in MeCN to give the bi-pyridine intermediate **11** was initially tried directly with the HCl salt of **10** but the reaction worked very slowly. Thus, **10**·HCl salt was free based with aqueous $K_2CO_3$ and extracted into MTBE, followed by a solvent exchange from MTBE to MeCN. Lowering the catalyst loading from 5 mol % to 2 mol %, and lowering reaction temperature from the original 90 $^oC$ to 65 $^oC$ resulted in complete conversion of **10** to **11**. 40 kg of **11** were isolated by crystallization after extraction into EtOAc followed by solvent exchange to heptane and addition of MTBE in 90 % yield and 93 HPLC A %. The amount of loss to the mother liquors was around 4 %.

Final ring closure of **11** to GMP starting material **2** was easily accomplished using 2.5 equiv LiHMDS in THF. After quench with water, the pH was adjusted to 2~3 with aqueous 1N HCl, and crude **2** was isolated by filtration, followed by recrystallization from MeCN. The recrystallized **2** showed high residue on ignition (ROI) (~8 wt %) and necessitated a rework to be suitable for use in the subsequent GMP step to **GDC-0425**. Therefore, **2** was reslurried with

water to remove the inorganic salt residue (presumably potassium carbonate), and finally 30 kg of **2** were obtained in 81 % yield and 99 HPLC A % purity. We also explored an alternative route to **2** to shorten the lengthy synthetic sequence, but this effort was not successful[2].

GMP starting material **5** was manufactured in two batches via the two synthetic routes shown in Scheme 3.

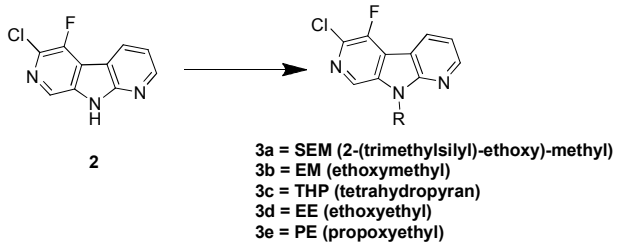
**Scheme 3.** *Manufacture of alcohol **5***




Initially 5 kg of 5 was made in 83 % yield and 98 % purity using route A. Reduction of ketone 14 to 5 was accomplished with sodium borohydride in ethanol. Route A produced small amounts of impurity 15, which was carried through downstream chemistry and later detected in the API[13]. The impurities formed from 15 were hard to purge, so in order to avoid formation of 15, route B was implemented where 14 was hydrogenated with Raney Ni in ethanol to form alcohol 5, which was then converted to the HCl salt. After a solvent exchange from ethanol to acetonitrile and distillation, the product was isolated by filtration and 9 kg of 5 HCl salt was obtained in 76 % yield and > 98 % purity. See supporting information for further experimental detail for the synthesis of GMP starting materials 2 and 5.

**Process development and optimization of the GMP steps.**

**Scheme 4.** *Process Development of 1,7-Diazacarbazole **2** Protection.*




We initiated our process development by re-examining the chemistry developed for the protection of 1,7-diazacarbazole **2** in which the 2-(trimethylsilyl)-ethoxy)-methyl (SEM) group was initially selected in order to avoid dimerization of the 1,7-diazacarbazole motif during the later fluoride displacement in stage 3 of the synthesis[3]. We reasoned that the use of high cost 2-(trimethylsilyl)-ethoxymethylchloride and the use of hazardous[4] and unnecessarily strong base (pKa = ~35)[5] sodium hydride, with subsequent hydrogen gas evolution and the formation of formaldehyde, a volatile, toxic and carcinogenic side product, was a serious cause of concern in a scale-up operation. Also, multiple washes, trituration and chromatography were required for the isolation and purification of the protected product. We initially considered protecting groups that were similar to SEM in terms of electronegativity and steric environment yet have minimal potential safety risks.

**Table 1.** *Protection Group Screen for Stage 1*

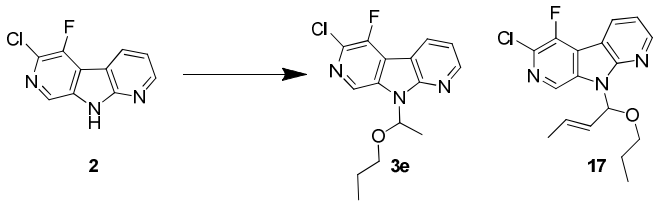
| Entry | Protective Group | Conditions | Conversion (A%)[a] |
|---|---|---|---|
| 1 | Ethoxymethyl (EM) | 1.3 equiv KOtBu, 1.3 equiv chloro-methylethyl ether, rt, THF | 64 |
| 2 | Tetrahydropyran (THP) | 3.0 equiv dihydropyran, 5 mol% PPTS, 60 $^{o}$C, THF | 0 |

| | | | |
|---|---|---|---|
| 3 | Ethoxyethyl (EE) | 18 equiv ethyl vinyl ether, 5 mol % PPTS, 70 °C, THF | 95 |
| 4 | Propoxyethyl (PE) | 3.2 equiv propyl vinyl ether, 5 mol % PPTS, 66 °C, THF | 86 |

[a]Conversion of **2** to **3(b-e)** after 3 h as measured by HPLC area%.

First, ethoxymethyl ether (EM) protection of **2** was examined (Table 1, entry 1). Reacting **2** with chloro-methylethyl ether led to the major desired product **3b** alongside with the formation of a major impurity (36 A % by HPLC), where alkylation on the pyridine nitrogen had occurred. Next it was attempted to install the THP group (Table 1, entry 2) by reacting **2** with DHP and pyridinium p-toluenesulfonic acid (PPTS) in THF but no conversion to the desired protected product was observed. We then turned our attention to the ethoxy ethyl (EE) protecting group, which traditionally is hydrolyzed by HCl at elevated temperature[6]. Reacting **2** with ethyl vinyl ether and 5 mol % PPTS in THF at 70 °C in a closed system resulted in up to 95 % conversion to **3d** (Table 1, entry 3). However, the degree of conversion was inconsistent, presumably because of loss of some of the ethyl vinyl ether due to its low boiling point (33 °C). Continuously dosing a minimum of 18 equiv of ethyl vinyl ether via a syringe pump helped to drive the reaction to completion, but it was reasoned that using the higher boiling propyl vinyl ether (PVE, 65 °C) would avoid this problem altogether. Indeed, we found that the use of PVE in the protection reaction enabled us to lower the amount of ether from 18 to 3 equiv. A solvent screen was then performed on the reaction (Table 2).

**Table 2**[a]**.** *Selected Solvent Screen for Reaction of **2** with PVE*




| Entry | Solvent | **3e** (A%)[a] | **17** (A%) |
|---|---|---|---|
| 1 | Tetrahydrofuran | 84 | 12 |
| 2 | 2-methyl THF | 68 | 9 |
| 3 | Dichloromethane | 53 | 8 |
| 4 | Ethyl acetate | 40 | 6 |
| 5 | Acetone | 37 | 9 |
| 6 | Toluene | 36 | 4 |
| 7 | Dimethylformamide | 22 | 7 |

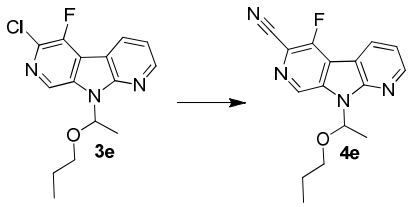
[a]Conversion of **2** to **3e** as measured by HPLC area%. All reactions were run with the following conditions: 1.4 mmol of **2**, 5 mol% PPTS, 3 equiv propyl vinyl ether, 70°C, 10 vol solvent for 3 h.

Results from this screen indicated that THF was the best solvent and led to complete conversion (Table 2, entry 1) of **2** to **3e** although with concomitant formation of 12% of an unknown side product which was subsequently isolated and identified as impurity **17**[7]**.**

Next, the influence of various acids on the activation of PVE and conversion of **2** to **3e** was examined. It was found that *p*-toluenesulfonic acid (PTSA) was superior to all other acids examined and resulted in conversion of **2** to **3e** even at room temperature while the reaction with PPTS proceeded only at 70 °C. On the other end of the reactivity spectrum, acetic and citric acid proved to be completely ineffective catalysts. Further lowering the temperature from 25 °C to 0 °C with PTSA as catalyst caused the reaction to not proceed at all. We therefore established a reaction protocol with a reaction temperature of 25 °C.

We also wanted to understand the impact of the PVE dosing rate on the formation of impurity **17**. Using a syringe pump, PVE was charged to **2** in THF over 2 hours, but reaction was similar to the semi batch mode addition, and no impact on the amount of **17** generated was observed. While a second charge of 0.5 equiv PVE was usually necessary in the lab setting, at the 5 kilogram scale, the reaction went to completion when 3.5 equiv was added in one portion, possibly due to more effective agitation. Quenching the reaction mixture with aqueous $NaHCO_3$ was necessary to prevent de-protection of **3e** caused by residual acid. To avoid a work up operation, direct isolation of **3e** from the reaction mixture by addition of water was attempted but resulted in the product oiling out. A solvent switch from THF to acetone, methanol or acetonitrile followed by addition of water also resulted in the formation of oily material. We next tried to extract **3e** from the reaction mixture using EtOAc, but this resulted in an emulsion. At this point it was hypothesized that polymeric impurities generated from PVE were the cause for the oiling out and emulsion formation and to remove these impurities, the THF solution was solvent switched to EtOAc and then treated with a combination of 20 wt. % of charcoal and 1 wt. % of celite. After filtration, the EtOAc solution was solvent exchanged to MeOH, from which, after further concentration by distillation, product **3e** crystallized. At multi-kilogram scale, we substituted MeOH for higher boiling EtOH to more effectively remove EtOAc during the solvent switch. After further concentration of the reaction mixture by distillation and cooling to 25 °C, the product **3e** crystallized. Addition of water as an anti-solvent was necessary to increase recovery and **3e** was isolated after drying as a free flowing solid in 97 % yield and 80 % purity. A further recrystallization from MeOH resulted in 5.32 kg of **3e** in a 71 % overall yield and with a purity of 96 A % by HPLC.

**Scheme 5.** *Process Development of Pd catalyzed Cyanation of **3e**.*

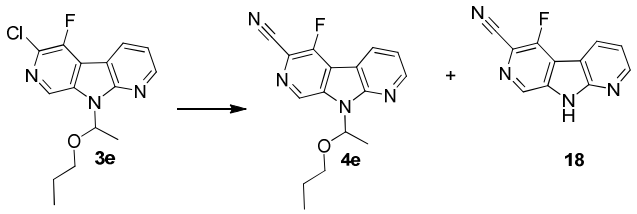



With acceptable protection conditions in hand, we turned our attention to the cyanation of **3e**. The initial chemistry for the palladium catalyzed cyanation of **3a** used a high loading of tetrakis triphenylphosphine palladium(0) (15 wt %) and zinc cyanide (2.4 equiv) adding to overall cost, waste disposal and heavy metals removal issues. In the work up phase, multiple washes, trituration of the crude product, and a column chromatography were necessary to provide the product in acceptable purity. The first step in our optimization was to seek a more efficient catalyst system that could be applied towards the cyanation of **3e**, reducing catalyst loading and offering better work-up conditions.

Several examples of cyanation of aryl halides have been described in the literature, some of which have been performed on multi-kilogram scale[8]. Notably, aryl bromides have been subjected to Pd catalyzed cyanation on large scale using catalytic $Pd_2(dba)_3$, dppf, and $Zn(CN)_2$. This protocol has been applied to the cyanation of aryl chlorides with the incorporation of Zn powder[10f]. In this case Zn metal takes on the role of reducing $Pd^{II}$ to $Pd^0$ rendering the reaction more robust. This example was of particular interest to us since it describes the cyanation of a less active aryl chloride as with our substrate **3e**. We first performed a solvent screen for the $Pd(PPh_3)_4$ catalyzed cyanation of **3e** to **4e** using $Zn(CN)_2$ and Zn powder (Table 3, entry 1-5) and found DMA to be the best solvent in terms of reaction rate and minimal side product formation. The main side product, **18**, resulted from de-protection of **4e** during prolonged heating of the reaction mixture[9]. A Pd catalyst screen was then performed in DMA with screening results for

the effects of different Pd precursors, ligands, and catalyst loadings on conversion of **3e** to **4e** are shown in Table 5. The $Pd(OAc)_2$, dppf, Zn catalyst system (Table 3, entry 15) was found to be superior to all other catalysts examined in terms of conversion and minimal side product formation[10].

**Table 3.** *Pd Catalyst Screen for Cyanation of **3e** to **4e***



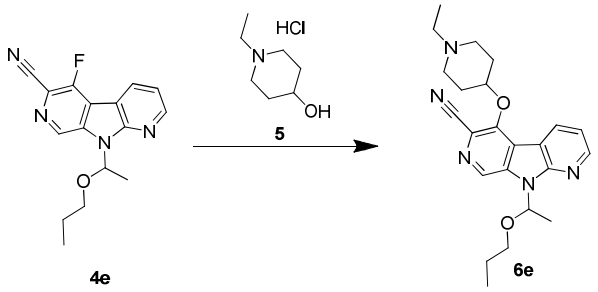

| Entry | Catalyst | mol% catalyst | Ligand | Solvent (vol) | Time (h) | **4e** (A%)[a] | **18** (A%)[a] |
|---|---|---|---|---|---|---|---|
| 1[b,e] | $Pd(PPh_3)_4$ | 15 | N/A | DMA (20) | 18 | 83 | 25 |
| 2[b,e] | $Pd(PPh_3)_4$ | 15 | N/A | NMP (20) | 18 | 57 | 43 |
| 3[b,e] | $Pd(PPh_3)_4$ | 15 | N/A | DMF (20) | 18 | 44 | 56 |
| 4[b,e] | $Pd(PPh_3)_4$ | 15 | N/A | Toluene (20) | 18 | 5 | N/A |
| 5[b,e] | $Pd(PPh_3)_4$ | 15 | N/A | Dioxane (20) | 18 | 3 | N/A |
| 6[b,f] | $Pd_2(dba)_3$ | 5 | Xantphos[g] | DMA (20) | 21 | 77 | 23 |
| 7[b,f] | $Pd_2(dba)_3$ | 5 | Dppf | DMA (20) | 18 | 79 | 21 |
| 8[b,f] | $Pd(OAc)_2$ | 5 | Dppf | DMA (20) | 21 | 79 | 21 |
| 9[c,f] | $Pd(OAc)_2$ | 5 | Dppf | DMA (20) | 3 | 94 | 6 |
| 10[c,f] | $Pd(OAc)_2$ | 5 | Dppf | DMA (10) | 3 | 93 | 7 |
| 11[c,f] | $Pd(OAc)_2$ | 5 | Dppf | DMA (5) | 3 | 88 | 12 |
| 12[c,f] | $Pd(OAc)_2$ | 1 | Dppf | DMA (10) | 3 | 96 | 4 |

[a]Conversion of **3e** to **4e** and **20** as measured by HPLC (area%). Reactions were run with the following conditions: [b]0.3 mmol scale. [c]3 mmol scale. [d]Ratio of ligand to catalyst = 2:1. [e]$Zn(CN)_2$ 1.2 equiv, zinc 10 mol %. 120 °C. [f]$Zn(CN)_2$ 0.6 equiv, zinc 10 mol %. 120 °C. [g]4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

In order to minimize decomposition of **4e** to **18** we investigated different parameters. Reducing the volume of DMA from 20 vol to 5 vol resulted in an increase of **18** from 6 to 12 A % (Table 3, entries 9-11). Reduction of catalyst loading from 5% to 1% resulted in a slight decrease of **18** from 7 to 4 A % (Table 3, entries 10 and 12)[9]. At the several hundred gram scale, complete conversions (> 99 %) were consistently obtained with 4 mol % of Pd. Based upon these results, the optimal parameters to ensure a complete conversion were set at 4 mol % $Pd(OAc)_2$, 8 mol % dppf, 10 mol % Zn and 8 vol DMA. Next, a work-up procedure was developed. After reaction completion, the mixture was filtered over celite to remove residual Zn and water was added to precipitate the product. The filterability of the solids was markedly improved when water was added at 40 °C as opposed to addition at 0 °C which resulted in very slow filtration. These solids were usually obtained with ~90 A % purity by HPLC and required further purification. Enrichment of impurities in the mother liquors was only found in toluene and MTBE at elevated temperature (50 °C), but purification of the crude product **4e** by hot trituration in MTBE and hot filtration would be difficult to implement on kilogram scale. Earlier solubility studies showed poor solubility of product in various solvents (toluene, MTBE, IPAC, MeCN and 2-butanol), but good solubility in DMF. For this reason crystallization in DMF was further examined. A good purity upgrade (90 % to 98 %) in 75 % yield was observed when **4e** was crystallized from DMF (2 vol) and isolated by filtration at 5 $^{o}$C. In order to increase the recovery of **4e**, the isolation temperature was lowered to -5 $^{o}$C and -10 $^{o}$C, with isolated yields increased to 90 % and no negative impact on product purity (98 A %). We also tried to remove residual Pd, Zn and Fe at this step, but treatment with various metal scavengers (florisil, quadrasil MP and Si-Thiol; 20 wt % each) resulted in significant degradation of product and loss of yield. Therefore, metal removal was postponed to the next step. The optimized conditions were then applied to the

kilogram-scale production, **4e** was recrystallized from DMF at -10 $^{o}$C resulting in 3.5 kg of **4e** being obtained after filtration and drying in 72 % yield and > 99 A % purity by HPLC. The impurity **18** was completely purged during crystallization from DMF.

**Scheme 6.** *Process Development of Stage 3a/3b Penultimate Coupling Step*




A major safety concern in the discovery route was the use of NaH to deprotonate the piperidine alcohol HCl **5**. We set out to explore alternative bases and solvents to optimize fluoride displacement of the electron deficient **4e**, which presumably proceeds via a SNAr mechanism[11]. As a first option we explored $K_2CO_3$ and DMF. We found no conversion of **4e**[12] to **6e** even after heating at higher temperatures (75 °C and 120 °C) (Table 4, entries 1 and 2). However, 70 % conversion was observed when 4 equiv of potassium *t*-butoxide was used at 25 °C (Table 4, entry 3). In order to drive the reaction to completion, the amount of base was doubled from 4 to 8 equiv, but this caused the formation of a significant amount of impurities (Table 4, entry 4).

**Table 4.** *Base Screen For $S_NAr$ Fluoride Displacement of **4e** with Piperidine Alcohol HCl **5***

| Entry | Base | Base (equiv) | Temp ($^{o}$C) | Solvent | **6e** (A%)[a] | Impurities (A%) |
|---|---|---|---|---|---|---|
| 1 | $K_2CO_3$ | 4 | 75 | DMF | 0 | 0 |
| 2 | $K_2CO_3$ | 4 | 120 | DMF | 0 | 0 |
| 3 | KOtBu | 4 | 25 | DMF | 70 | 0 |

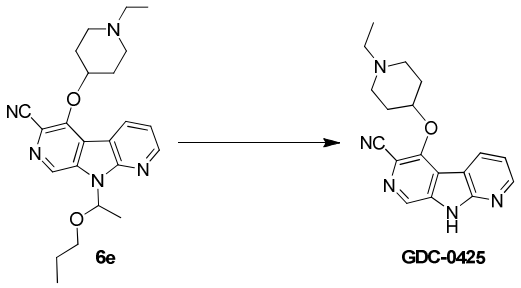
| | | | | | | |
|---|---|---|---|---|---|---|
| 4 | KOtBu | 8 | 25 | DMF | 47 | 32 |
| 5 | KOtBu | 6 | 40 | DMF | 77 | 20 |
| 6 | KOtBu | 6 | 75 | DMF | 71 | 27 |
| 7 | $K_2CO_3$/KOtBu | 2.5/3 | 75 | DMF | 86 | 12 |
| 8 | KOtBu | 6 | 75 | THF | 28 | 70 |
| 9 | KOtBu | 6 | 75 | NMP | 30 | 70 |
| 10 | LDA | 6 | 0 | THF | 0 | 85 |
| 11 | NaHMDS | 6 | 25 | THF | 83 | 17 |
| 12[b] | NaHMDS | 3 | 25 | THF | 85 | 15 |
| 13[b] | NaHMDS | 3 | 0 | THF | 96 | 4 |

[a]Conversion to **6e** as measured by HPLC. All reactions were run with the following conditions except noted otherwise: 2.5 equiv **5**, reaction time 1 h.
[b]Reactions were run with the following conditions: 1.5 equiv **5**, reaction time 1 h.

The conversion of **4e** to **6e** could be improved to 77 % by raising the reaction temperature to > 40 °C and simultaneously increasing the amount of potassium *t*-butoxide from 4 to 6 equiv (Table 4, entries 5 and 6), but the reaction still generated a high level of impurities. The loading of potassium *t*-butoxide was then further decreased by free-basing the piperidine alcohol HCl **5** with $K_2CO_3$ (2.5 equiv) (Table 4, entry 7), followed by addition of potassium *t*-butoxide (3 equiv). Using this approach it was possible to drive the reaction to higher conversion (86 A %), yet, a considerable amount of impurities continued to be formed (12 A % total). Investigation of THF and NMP as alternate reaction solvents (Table 4, entries 8 and 9) gave worse results than DMF. We next examined LDA but to our dismay no product **6e** was formed and the reaction gave a complex mixture. A breakthrough occurred with NaHMDS. When a mixture of **4e** and **5** in THF was reacted with 6 equiv of a 1 M solution of NaHMDS in THF at 25 °C (Table 4, entry 11) we observed a high conversion (83 %) to **6e**. It was further elaborated that complete

conversion could be obtained with 1.5 equiv of **5** and 3 equiv of NaHMDS (Table 4, entry 12). While this still resulted in the formation of a large unknown impurity (15 A % by HPLC), by lowering the reaction temperature from 25 °C to 0 °C we were pleased to find that the impurity level could be reduced to < 4 A %. The excess base was quenched with aqueous $NH_4Cl$, followed by a solvent exchange from THF to EtOAc. In order to remove residual Zn, Pd and Fe from the stage 2 cyanation, an aqueous extraction with trisodium EDTA was employed, followed by a florisil and thiosilicycle treatment. All attempts to isolate **6e** directly from the reaction mixture failed and therefore it was decided to concentrate the product solution and telescope it into the de-protection step.

**Scheme 7.** *Process Development of Deprotection of* ***6e***




In the discovery chemistry route, TBAF was needed for removal of the SEM group. Switching from SEM to the PE group facilitated acidic hydrolysis at elevated temperatures. First, deprotection of **6e** was investigated in 2-propanol using 37% aqueous HCl at 3 different strengths (3, 2, 1.5 equiv) (Table 5, entries 1-3) at 50 °C and it was found that the reaction went to completion with 3 equiv of HCl after 24 h. In order to increase the rate and decrease reaction time the temperature was increased to 60 °C and a solvent screen was performed in EtOH, MeOH, MeCN, MeTHF and THF using 2 equiv of HCl. No crystalline material could be obtained from THF and MeTHF and they were abandoned. The highest rate of de-protection was found in MeCN, which was complete after 1 h (Table 5, entry 6). Conversion of **6e** to **GDC-**

**0425** in EtOH and MeOH (Table 5, entries 4-5) proceeded markedly slower than in MeCN. From these experiments it was also found that de-protection of **6e** using HCl in MeCN resulted in a higher isolated yield and higher HPLC purity of **GDC-0425** than in EtOH. Interestingly, the dihydrochloride salt of **GDC-0425** was obtained from the reaction mixture.

**Table 5.** *Hydrolysis of **6e** to **GDC-0425***

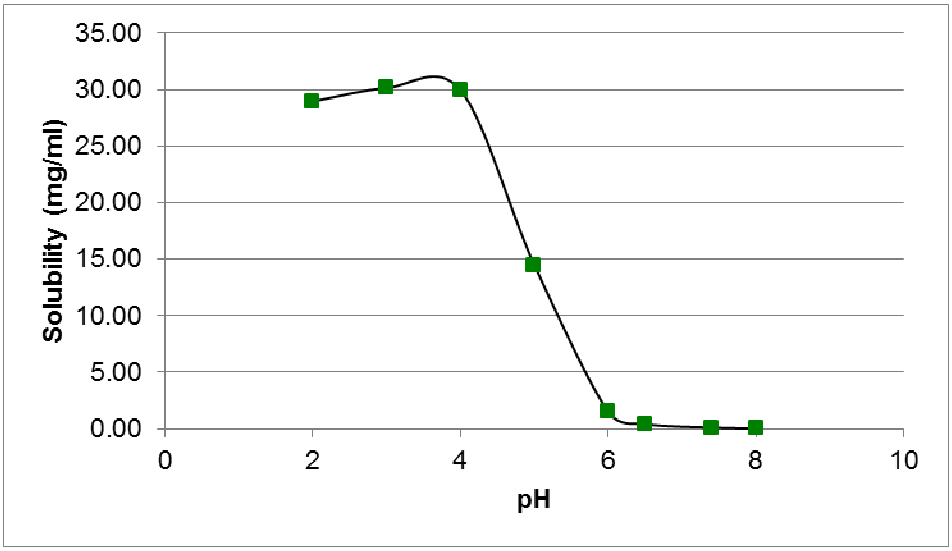
| Entry | Conditions | Acid (equiv) | Time (h) | Conversion (A%)[a] | Impurities (A%) |
|---|---|---|---|---|---|
| 1 | 2-propanol, 50 °C | 3 | 24 | 100 | 13 |
| 2 | 2-propanol, 50 °C | 2 | 24 | 91 | 13 |
| 3 | 2-propanol, 50 °C | 1.5 | 24 | 85 | 12 |
| 4 | EtOH, 60 °C | 2 | 5 | 100 | 13 |
| 5 | MeOH, 60 °C | 2 | 5 | 100 | 13 |
| 6 | MeCN, 60 °C | 2 | 1 | 100 | 11 |

[a]Conversion of **6e** as measured by HPLC. All reactions were run with 37% aqueous HCl in 10 vol of solvent.

The optimized protocol was then applied to the kilogram-scale hydrolysis of **6e** using 37% aqueous HCl in MeCN. In order to optimize yield, 50 % of the solvent was distilled off and, after cooling to 25 °C, **GDC-0425·2HCl** was isolated by filtration in 80 % yield and 97 A % purity.

*Process Development of **GDC-0425** Freebase. The* solubility of **GDC-0425** has been evaluated and found to be poor in most organic solvents. The solubility of **GDC-0425** (Figure 1) in water is pH dependent, with good solubility observed at low pH, but **GDC-0425** is practically insoluble at neutral pH. We made use of the pH solubility dependence of the **GDC-0425** in water for isolation purposes.

**Figure 1:** *pH Solubility of GDC-0425*



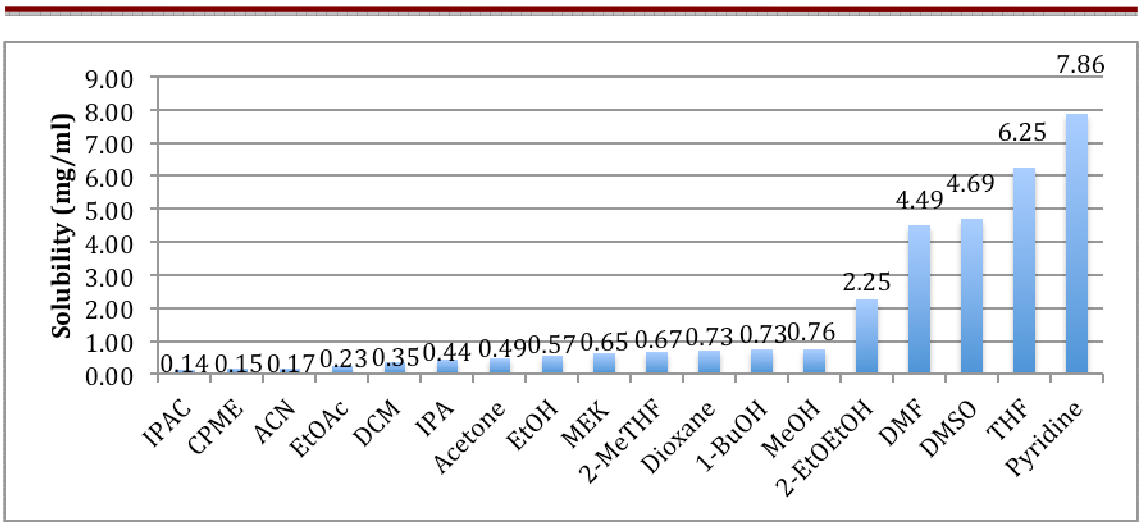

HPLC concentration assays for filtrates from aqueous saturated mixtures of **GDC-0425** at various pH after trituration for 48 h at 37 °C.

Because **GDC-0425·2HCl** is soluble in water, we started out by exploring two solvent systems, IPA-water and THF-water mixtures. Two inorganic bases, sodium hydroxide and sodium bicarbonate were chosen for further evaluation. First, **GDC-0425·2HCl** was suspended in a mixture of water and organic solvent, heated to 55 °C to completely dissolve the salt. The base was then slowly added while the free base **GDC-0425** crystallized out. Filterability of **GDC-0425** was best for the THF-$NaHCO_3$ combination. Finally, we addressed the issue of particulate filtration and came to the conclusion that the reaction mixture could be filtered after addition of 1 mol equiv of base. A purity upgrade from 99.2 % to > 99.9 % could be achieved. For GMP production, $NaHCO_3$ was exchanged with NaOH, in order to avoid foaming of the reaction mixture from $CO_2$ evolution. Due to the occurrence of the dimer impurity **16**[13] in the stage 3 product during the GMP run, a DMF trituration was performed which purged the impurity to < 0.25 % and converted the **GDC-0425·2HCl** to **GDC-0425·HCl**. The mono HCl salt required only

1 mol equiv of base to convert to free-base and NaOH was added as a 0.6 M solution in water. On kilogram-scale crude **GDC-0425** was isolated in 77.7 % yield and >99 A % purity.

*Process Development of Stage 5 Recrystallization of **GDC-0425***. A polymorph study on the free base of **GDC-0425** was performed and only one crystal form was obtained from multiple solvents (MeOH, EtOH, 1-BuOH, EtOAc, MIBK). From earlier studies we knew that **GDC-0425** had poor solubility in most solvents at room temperature (Figure 2).

**Figure 2:** *GDC-0425 Solvent Solubility*




We evaluated solubility of **GDC-0425** in various alcohols at reflux, and 1-BuOH was found to be best in terms of volumetric efficiency (50 vol) due to its high boiling point (118 $^{o}$C). The metastable zone for **GDC-0425** in 1-BuOH was determined and 110 $^{o}$C was selected as the temperature at which seeding would be performed.

Seeding in the metastable zone and crystal growth was then evaluated. For this purpose, **GDC-0425** was dissolved in 1-BuOH (50 vol) and seed crystals (0.9 % slurried in 10 vol 1-BuOH for 1 h) were introduced at 105 $^{o}$C. Crystal growth was monitored by a FBRM probe[14] while the

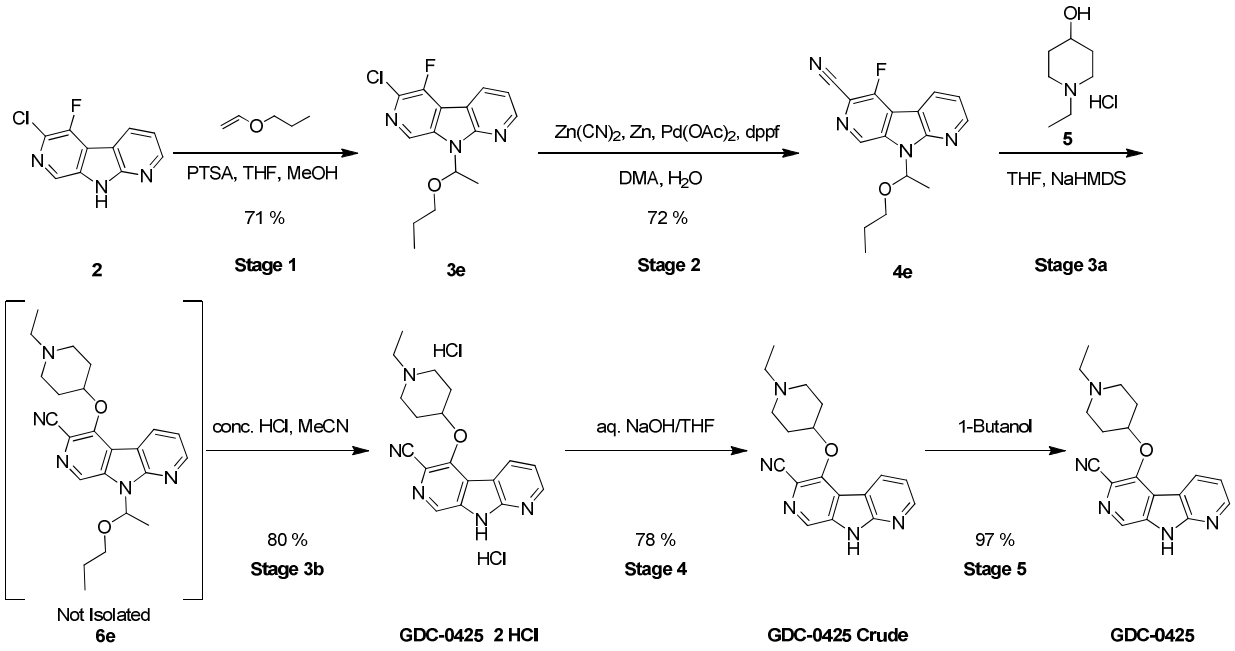
mixture was slowly cooled to room temperature. Maximal crystal growth with particle size range from 46 nm to 158 nm occurred at 97 $^{o}$C. Crystals with smaller particle size solubilize at this temperature, opening up the possibility of growing larger crystals at this temperature and improving filterability. No further change in crystal size was observed below 47 $^{o}$C. Next, drying time was evaluated in order to ensure drying would be feasible on large scale. The amount of 1-BuOH after 14 h drying in a vacuum oven at 60 $^{o}$C was determined by GC analysis as 1700 ppm. The same sample contained 20 ppm THF, which was well below ICH guidelines[15]. To help us determine what amount of residual DMF might be trapped during 1-BuOH crystallization, a run was performed with spiking at 1 % DMF. After crystallization and drying in a vacuum oven at 60 $^{o}$C for 15 h, no residual DMF was detected by GC analysis. The amount of seed crystals was evaluated in two experiments. In one run 20 % of seed crystals was added resulting in 600 ppm of 1-BuOH as opposed to 1700 ppm of 1-BuOH for the other run with 0.9 % seeds (both samples were dried at 60 $^{o}$C for 14 h). Powder XRD analysis of both samples showed better crystallinity with a higher seed loading. At multi-kilogram scale, **GDC-0425** was dissolved in 1-butanol (50 vol) at 115 $^{o}$C, the solution was then cooled to 110 $^{o}$C, where seeding and aging were performed, followed by slow cooling to 20 $^{o}$C (8 h). 1.95 kg of high purity **GDC-0425** (>99 %, with no single impurity ≥ 0.25 %) was isolated after filtration and drying in 97 % yield.

## Conclusion

The optimized kilogram route to **GDC-0425** is shown in Scheme 8. Highlights of the synthesis include (1) an efficient Pd catalyzed cyanation of the aryl chloride **3e**; (2) fluoride displacement of **4e** with 1-ethylpiperidin-4-ol under mild reaction conditions using NaHMDS; and (3) recrystallization of crude **GDC-0425** from 1-butanol. The process delivered 1.95 kg of the

desired crystal form of **GDC-0425** as highly pure material (> 99 A% by HPLC) in five steps with an overall yield of 31 %.

**Scheme 8.** *Optimized Kilogram Synthetic Route to* ***GDC-0425***




## Experimental Section

General. In process methods for (Stages 1-4). Diluent: Acetonitrile. Mobile Phase A: 0.05 % Formic Acid/Water. Mobile Phase B: 0.05 % Formic Acid/Acetonitrile. Column: Phenomenex Onyx Monolithic C18 column, 2x50 mm (CV = 0.157 mL) (Part No. CH0-8373). Column Temperature: 35˚C. Detector Wavelength: 220 nm. Injection Volume: 2µL. Flow Rate: 0.785 mL/minute (5 CV/min). Program: 0.0 min 5.0 % B, 0.4 min 5.0% B, 2.4 min 65.0 % B, 2.8 min 95 % B, 3.0 min 95 % B, 3.2 min 5.0 % B, 4.0 min 5.0 % B. Typical Retention Times: **2** (RT 2.62 min), **3e** (RT 3.50 min), **4e** (RT 3.30 min), **6e** (RT 2.36 min).

*6-chloro-5-fluoro-9-(1-propoxyethyl)-9H-pyrrolo[2,3-b:5,4-c']dipyridine* ***3e***. To a 100 L reactor was charged 6-chloro-5-fluoro-9*H*-pyrrolo[2,3-*b*:5,4-*c'*]dipyridine **2** (5.00 kg, 22.6 mol, 1 equiv.), *p*-toluenesulfonic acid monohydrate (0.22 kg, 1.1 mol, 0.05 equiv.) and

tetrahydrofuran (50 L, 10 vol). Propyl vinyl ether (8.80 L, 79.0 mol, 3.5 equiv.) was charged to the reactor over 21 min while maintaining the temperature at 30 °C. The reaction was maintained at 25 ± 5 °C until HPLC IPC showed **2** to be ≤ 4.0 A % (21 h). The mixture was quenched by addition of aqueous $NaHCO_3$ (0.25 kg, 3.0 mol, dissolved in 4.75 L purified water) over ~ 3 min at 25 ± 5 °C. The organics were distilled under vacuum at ≤ 55 °C (internal temperature) to ~ 20 L and then solvent exchanged to EtOAc (30 L in 3 x 10 L portions) at ≤ 55 °C and concentrated to ~ 20 L. To the solution was added EtOAc (20.0 L), charcoal (Darco G-60, 100 mesh, 1.00 kg, 20 % wt) and celite 545 (5.00 kg, 1 wt) and the slurry was aged for 19 h. The mixture was filtered through celite 545 (5.00 kg, 1 wt) on a filter with the filtrate transferred to a 100 L reactor and the cake washed with EtOAc (40.0 L, 8 vol). The combined organics were washed twice with aqueous $NaHCO_3$ (2 x 0.75 kg, 9.0 mol each, dissolved in 14.25 L purified water) and the batch was concentrated by distillation under vacuum to ~ 20 L and then solvent exchanged to EtOH (40 L in portions: 10.0 L, 10.0 L, 20.0 L) at ≤ 55 °C (internal temperature) and concentrated to ~ 20 L. The mixture was heated to 60 ± 5 °C to ensure dissolution of any solids, cooled to 25 ± 5 °C over ~ 5 h and aged for 11 h to precipitate the crude **3e**. Purified water (20.0 L, 4 vol) was added to aid recovery and the suspension was aged for 30 min. The crude product was filtered and washed with purified water (10.0 L, 2 vol) (MLs assay: total volume 55 L, product concentration 1.93 g/L, 1.5 % product loss). The cake was dried in the filter at 50 ± 5 °C (jacket temperature) under vacuum for 42 h. The crude product was transferred to a 20 L reactor and MeOH (15.0 L, 3 vol) was added and heated to 60 ± 5 °C to ensure dissolution. The mixture was cooled to 0 ± 5 °C over 3.5 h, aged for 2 h, and a small sample of the reaction mixture was filtered. Analysis of the supernatant was used as an IPC to determine that the product concentration in the supernatant was ≤ 15 wt %. The mixture was

filtered at 0 ± 5 °C and washed with cold MeOH (0 ± 5 °C; 5.0 L, 1 vol) (MLs assay: 16 product mol%). The cake was dried on the filter under vacuum at 50 ± 5 °C (jacket temperature) until GC showed the MeOH content to be ≤ 1.0 wt % (63 h). The process gave 5.32 kg of *6-chloro-5-fluoro-9-(1-propoxyethyl)-9H-pyrrolo[2,3-b:5,4-c']dipyridine* ***3e*** (70.9 % yield; 96 A %) as an off-white solid. $^1$H NMR (600 MHz, $CDCl_3$) δ 8.91 (d, *J* = 1.3 Hz, 1H), 8.67 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.51 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.33 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.58 (q, *J* = 6.1 Hz, 1H), 3.45 (dt, *J* = 9.2, 6.4 Hz, 1H), 3.19 (dt, *J* = 9.3, 6.8 Hz, 1H), 1.82 (d, *J* = 6.2 Hz, 3H), 1.58 (dtd, *J* = 13.9, 7.4, 6.5 Hz, 2H), 0.85 (t, *J* = 7.5 Hz, 3H).

$^{13}$C NMR (150 MHz, $CDCl_3$) δ 151.61, 150.58, 149.71, 148.84, 135.04, 135.01, 132.64, 132.62, 129.94, 129.91, 127.51, 127.40, 117.62, 117.49, 117.06, 111.36, 111.35, 81.57, 70.49, 22.59, 20.80, 10.58.

HRMS calcd for $C_{15}H_{15}ClFN_3O$ 308.0960; found $[M+H]^+$ 308.0962.

*5-fluoro-9-(1-propoxyethyl)-9H-pyrrolo[2,3-b:5,4-c']dipyridine-6-carbonitrile* ***4e***. To a 100 L reactor under nitrogen was charged *6-chloro-5-fluoro-9-(1-propoxyethyl)-9H-pyrrolo[2,3-b:5,4-c']dipyridine* ***3e*** (5.28 kg, 17.2 mol, 1 equiv), zinc cyanide (1.20 kg, 10.3 mol, 0.6 equiv), zinc powder (0.11 kg, 1.7 mol, 0.1 equiv), palladium acetate (0.15 kg, 1.0 mol, 0.04 equiv), dppf (0.76 kg, 2.1 mol, 0.08 equiv) and DMA (42.6 L, 8 vol). The mixture was degassed by 3 cycles of vacuum/nitrogen and heated to 120 ± 5 °C. HPLC showed **3e** to be ≤ 2.0 A % after 4.5 h. The reaction was cooled to 40 ± 5 °C, celite 545 (1.59 kg, 0.3 wt) was added and the mixture was aged for 4 h. The mixture was filtered through celite 545 (1.59 kg, 0.3 wt) on a filter with the filtrate transferred to a 100 L reactor. The filter cake was washed with DMA (11.0 L, 2 vol) and the combined organics were cooled to 20 ± 5 °C. Purified water (38.0 L, 7.1 vol) was added over 50 min while maintaining the temperature at ≤ 40 °C to precipitate the crude product. The slurry

was aged for 4 h, filtered and the cake washed with purified water (16.0 L, 3 vol). The crude product was dried in the filter at 60 ± 5 °C (jacket temperature) under vacuum until Karl Fischer analysis showed the water content to be 1.0 wt % (88 h). The crude product (5.85 kg) and DMF (10.25 L, 2 vol) were charged to a 20 L reactor, heated to 70 ± 5 °C to ensure dissolution, aged for 30 min, cooled to 45 ± 5 °C over 2 h, aged for 32 min, cooled to 25 ± 5 °C over 3 h, and cooled to –10 ± 5 °C over 3.5 h. The slurry was aged for 3 h and a small sample of the reaction mixture was filtered and analysis of the supernatant was used to determine that the product concentration in the supernatant was ≤ 30 wt %. The mixture was filtered at -10 ± 5 °C and the cake was washed with cold DMF (0 ± 5 °C; 5.0 L, 0.5 vol) (MLs assay: 26.7 product mol%). After no more filtrate could be collected from the filter, the cake was dried on the filter at 60 ± 5 °C (jacket temperature) under vacuum until Karl Fischer analysis showed the water content to be 0.02 wt % (94 h). The process gave 3.49 kg of 5-fluoro-9-(1-propoxyethyl)-9*H*-pyrrolo[2,3-*b*:5,4-*c'*]dipyridine-6-carbonitrile **4e** (72 % yield, > 99 A %) as a light yellow solid.

$^1$H NMR (600 MHz, $CDCl_3$) δ 9.22 (d, *J* = 2.1 Hz, 1H), 8.74 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.59 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.44 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.63 (q, *J* = 6.1 Hz, 1H), 3.46 (dt, *J* = 9.3, 6.5 Hz, 1H), 3.22 – 3.14 (m, 1H), 1.84 (d, *J* = 6.2 Hz, 3H), 1.58 (ddd, *J* = 14.1, 7.6, 6.7 Hz, 2H), 0.85 (td, *J* = 7.4, 0.9 Hz, 3H).

$^{13}$C NMR (150 MHz, $CDCl_3$) δ 158.60, 156.79, 151.03, 150.22, 137.23, 137.19, 133.29, 133.26, 132.71, 132.70, 118.15, 115.13, 115.02, 114.25, 114.22, 111.27, 111.18, 82.17, 70.84, 22.55, 21.21, 10.53.

HRMS calcd for $C_{16}H_{15}FN_4O$ 299.1303; found $[M+H]^+$ 299.1302.

*Crude 5-(1-ethyl-piperidin-4-yloxy)-9H-dipyrido[2,3-b-4',3'-d]pyrrole-6-carbonitrile dihydro-chloride* ***crude GDC-0425·2HCl****.* To a 100 L reactor inerted with nitrogen was charged

5-fluoro-9-(1-propoxyethyl)-9*H*-pyrrolo[2,3-*b*:5,4-*c'*]dipyridine-6-carbonitrile **4e** (3.44 kg, 11.5 mol, 1 equiv.), 1-ethylpiperidin-4-ol hydrochloride (2.93 kg, 17.7 mol, 1.5 equiv.) and THF (17.7 L, 5 vol). The mixture was cooled to – 5 ± 5 $^{o}$C and 1.0 M sodium bis(trimethylsilyl)amide in THF (35.2 L, 35.2 mol, 3.1 equiv.) was added over 3.5 h, taking care to maintain the temperature at ≤ 5 $^{o}$C. The reaction mixture was warmed to 0 ± 5 $^{o}$C and aged over ~ 15 min and HPLC showed **4e** to be ≤ 2.0 A %. The reaction was quenched by addition of aqueous ammonium chloride (1.82 kg, 34.0 mol, dissolved in 7.0 L water, 20.6 wt%), agitated for 16 min, concentrated by distillation vacuum at ≤ 55 $^{o}$C (internal temperature) to ~ 20 L, solvent exchanged to EtOAc (28 L in 2 x 10 L and 8 L portions) and concentrated at ≤ 55 $^{o}$C to ~ 20 L. EtOAc (3.5 L) and purified water (28.0 L) were added and the mixture was agitated for 16 min. The layers were allowed to separate and the aqueous layer was discarded. The organics were filtered through celite 545 (2.0 kg, 0.3 wt) on a filter with the filtrate transferred to a 100 L reactor and the filter cake washed with EtOAc (3.5 L, 1 vol). The combined organics were washed twice with an aqueous EDTA solution (2 x 1.16 kg EDTA, 2.9 mol each, dissolved in 7.0 L purified water). Florisil (7.0 kg, 2 wt) and Silicycle (Si-Thiol, 1.4 kg, 0.4 wt) were added to the organics and the slurry was aged for 16 h. The mixture was filtered on a filter with the filtrate transferred to a 100 L reactor and the cake washed with EtOAc (14 L, 4 vol). A 30 mL sample of the combined organics was concentrated to an oil **6e**.

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.66 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.61 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.34 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.60 (q, *J* = 6.1 Hz, 1H), 5.01 (dp, *J* = 9.1, 3.9 Hz, 1H), 3.44 (dt, *J* = 9.3, 6.5 Hz, 1H), 3.18 (dt, *J* = 9.2, 6.8 Hz, 1H), 2.99 (dt, *J* = 9.8, 5.9 Hz, 2H), 2.49 (q, *J* = 7.2 Hz, 2H), 2.25 (td, *J* = 11.3, 10.3, 5.2 Hz, 4H), 2.15 – 2.04 (m, 2H), 1.81 (d, *J* = 6.1 Hz, 3H), 1.57 (p, *J* = 7.1 Hz, 2H), 1.12 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H).

$^{13}$C NMR (150 MHz, $CDCl_3$) δ 154.33, 150.98, 149.13, 136.32, 132.62, 132.04, 119.96, 117.55, 117.46, 114.72, 112.93, 81.80, 80.84, 70.65, 52.05, 50.63(2C), 32.13(2C), 22.56, 21.17, 12.20, 10.55.

IPC of the oil by ICP-AES was used to determine the content of Pd, Zn and Fe. After it was determined that all of the specified metals were ≤ 20 ppm (Fe = 8 ppm, Pd ≤ 3 ppm, Zn ≤ 3 ppm), the solution was concentrated by distillation under vacuum at ≤ 55 $^{o}$C to ~ 20 L, followed by solvent exchange to MeCN (35 L in 2 x 10 L and 15 L portions) at ≤ 55 $^{o}$C and concentrated to ~ 20 L. Additional MeCN (21.0 L, 6 vol) and hydrochloric acid (37 % aqueous) (2.32 L, 23 mol, 2.0 equiv) were added, maintaining the temperature at 55 ± 5 $^{o}$C. HPLC showed **6e** to be ≤ 1.0 A % after 3 h. The reaction mixture was concentrated by distillation under vacuum at ≤ 55 $^{o}$C to ~ 23 L. After cooling to 25 ± 5 $^{o}$C over 3 h and aging for 13 h, the slurry was filtered on a filter and the cake was washed with MeCN (20.0 ±, 5.7 vol) (MLs assay: total volume 40 L, product concentration 0.285 g/L, 0.25 product mol %). The filter cake was transferred to drying trays and dried in a vacuum oven at 60 ± 5 $^{o}$C for 46 h giving 3.66 kg of crude 5-(1-ethyl-piperidin-4-yloxy)-9H-dipyrido[2,3-b-4',3'-d]pyrrole-6-carbonitrile dihydrochloride **GDC-0425·2HCl** (80 % yield, 97 A %) as a light yellow solid.

Crude *5-(1-ethyl-piperidin-4-yloxy)-9H-dipyrido[2,3-b-4',3'-d]pyrrole-6-carbonitrile* ***crude GDC-0425***. To a 100 L reactor inerted with nitrogen was charged crude 5-(1-ethyl-piperidin-4-yloxy)-9H-dipyrido[2,3-b-4',3'-d]pyrrole-6-carbonitrile dihydrochloride **GDC-0425·2HCl** (3.58 kg, 9.1 mol, 1 equiv) and DMF (17.5 L, 4.9 vol). The mixture was heated to 100 ± 5 $^{o}$C and agitated for 2 h. It was then cooled to 25 ± 5 $^{o}$C over 6 h and aged for 13 h. The slurry was filtered on a filter (ID 457 mm) and the cake was washed with DMF (7.0 L, 2 vol) (MLs assay: total volume 40 L, product concentration 7.46 g/L, 10.5 % loss). The filtered solid was

transferred to a 100 L reactor and DMF (28.0 L, 7.8 vol) was added. The mixture was heated to 100 ± 5 °C, aged for 3 h, then cooled to 25 ± 5 °C over 6 h and aged for 12 h. The slurry was filtered on a filter and the filter cake was washed with DMF (7.0 L, 2 vol) and THF (7.0 L, 2 vol) (MLs assay: 1 product mol%). HPLC analysis showed the purity of the cake to be 99.9 A %, with no single impurity ≥ 0.25 A %. The cake was transferred to drying trays and dried in a vacuum oven at 60 ± 5 °C until a GC analysis showed the DMF content to be 0.05 wt % (65 h). The solid was transferred to a 100 L reactor (reactor A), dissolved in purified water (17.2 L, 4.8 vol), and filtered through an inline filter (0.5 micron) into a 100 L reactor (reactor B). Reactor A was rinsed with purified water (3.5 L, 1 vol), followed by THF (17.0 L, 4.8 vol), with both solutions transferred to reactor B via the inline filter. The water/THF solution was heated to 55 ± 5 °C and aged for 20 min. Sodium hydroxide (50 % in $H_2O$, 1.2 L, 22.7 mol, 2.5 equiv) was diluted with purified water (28.0 L) in reactor A and added in portions through the inline filter to reactor B. pH (by pH paper) was 10.5, outside the desired range of 8-10, so hydrochloric acid (37 % aq) (166 mL) was diluted with purified water (3.84 L) and added in portions (2.5 L: 0.5 L, 1.0 L, 1.0 L) through the inline filter to reactor B. The pH value of the contents in reactor B was measured by pH paper to be 8.3. The mixture in reactor B was cooled to 25 ± 5 °C over 2.5 h and aged for 16 h. It was then filtered and washed with purified water (14.0 L, 4 vol) (MLs assay: 4.6 product mol%). The filter cake was dried in the filter at 60 ± 5 °C (jacket temperature) under vacuum until Karl Fischer analysis showed the water content to be 0.02 wt % (91 h). This process gave 2.22 kg of 5-(1-ethyl-piperidin-4-yloxy)-9H-dipyrido[2,3-b-4',3'-d]pyrrole-6-carbonitrile **crude GDC-0425** (77.6 % yield; 99 A %) as an off-white solid.

*5-(1-ethyl-piperidin-4-yloxy)-9H-dipyrido[2,3-b-4',3'-d]pyrrole-6-carbonitrile* ***GDC-0425***. To a 100 L reactor inerted with nitrogen was charged 5-(1-ethyl-piperidin-4-yloxy)-9H-

dipyrido[2,3-b-4',3'-d]pyrrole-6-carbonitrile **crude GDC-0425** (2.01 kg, 99 %, 6.3 mol). 1-butanol (100 L, 50 vol) was added through an inline filter (0.5 micron) and the mixture was heated to 115 ± 5 °C to ensure dissolution. This solution was held at 115 ± 5 °C for 1 h, then cooled to 110 ± 3 °C over 20 min and aged for 30 min, taking care to avoid nucleation. The solution was seeded with a slurry of crystalline GDC-0425 (18.9 g GDC-0425 in 1-butanol(200 mL)). The crystallization was aged at 110 ± 3 °C for 1 h, then cooled to 20 ± 5 °C over 8 h and aged for 7.5 h. A small sample of the reaction mixture was filtered and analysis of supernatant was used to determine that the product concentration in the supernatant was ≤ 25 wt %. The slurry was filtered in a filter dryer and the filter cake was washed with 1-butanol (10.0 L, 5.0 vol). The cake was dried in the filter dryer at 60 ± 5 °C (jacket temperature) under vacuum until GC showed the 1-butanol content to be ≤ 0.5 wt % (15 h). The process gave 1.95 kg of 5-(1-ethyl-piperidin-4-yloxy)-9H-dipyrido[2,3-b-4',3'-d]pyrrole-6-carbonitrile **GDC-0425** (97 % yield; 99 A %) as an off-white solid.

$^1$H NMR (600 MHz, DMSO-$d_6$) δ 12.94 (s, 1H), 8.79 (s, 1H), 8.70 (dd, $J$ = 4.8, 1.6 Hz, 1H), 8.60 (dd, $J$ = 7.9, 1.6 Hz, 1H), 7.47 (dd, $J$ = 7.9, 4.7 Hz, 1H), 4.71 (tt, $J$ = 9.0, 3.9 Hz, 1H), 2.85 (dt, $J$ = 10.3, 4.2 Hz, 2H), 2.34 (q, $J$ = 7.1 Hz, 2H), 2.11 – 2.03 (m, 4H), 1.93 (dddd, $J$ = 14.7, 12.7, 9.3, 3.4 Hz, 2H), 1.00 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 153.43, 151.71, 149.63, 138.08, 132.06, 131.79, 118.83, 117.38, 114.66, 111.67, 81.21, 51.14, 50.01(2C), 31.51(2C), 12.17.

HRMS calcd for $C_{18}H_{19}N_5O$ 322.1662; found $[M+H]^+$ 322.1658.

*3-chloro-N-(6-chloro-5-fluoropyridin-3-yl)pyridin-2-amine **13***. To a 500 mL reactor inerted with nitrogen was charged 5-bromo-2-chloro-3-fluoro-pyridine (10 g, 47.5 mmol, 1 equiv), 3-chloropyridin-2-amine (6.7 g, 52.1 mol, 1.1 equiv), 4,5-bis(diphenylphosphino)-9,9-

dimethylxanthene (1.4 g, 2.4 mmol, 5 mol%), palladium acetate (320 mg, 1.4 mmol, 3 mol%), potassium carbonate (13.2 g, 95.5 mmol, 2.0 equiv) and 1,4-dioxane (200 mL). The mixture was degassed by 3 cycles of vacuum/nitrogen and heated to 115 ± 5 $^{o}$C for 18 h. The mixture was cooled to ambient temperature. Purified water (300 mL) was added to the mixture and agitated for 30 min. The mixture was then filtered and air-dried for 1h. The filtered solid was suspended in acetonitrile (100 mL) and heated to 90 $^{o}$C and acetonitrile (50 mL) was distilled. The mixture was cooled to 0 $^{o}$C over 3 h. The mixture was filtered and the solid was dried under vacuum at 50 $^{o}$C to give a light yellow solid (9.1 g, 74 % yield, 99 A %).

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J = 10.6, 2.4 Hz, 1H), 8.22 (d, J = 2.4 Hz, 1H), 8.18 (dd, J = 4.9, 1.6 Hz, 1H), 7.65 (dd, J = 7.9, 1.6 Hz, 1H), 7.14 (s, 1H), 6.85 (dd, J = 7.8, 4.9 Hz, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$) δ 155.70, 153.12, 149.95, 145.64, 137.38, 137.32, 137.19, 135.06, 135.02, 130.74, 130.53, 116.94, 116.68, 115.27, 115.01.

*6-chloro-5-fluoro-9H-pyrrolo[2,3-b:5,4-c']dipyridine* ***2***. To a 100 mL reactor inerted with nitrogen was charged 6-chloro-N-(3-chloro-2-pyridyl)-5-fluoro-pyridin-3-amine **13** (500 mg, 1.9 mmol, 1 equiv) and tetrahydrofuran (10 mL). The mixture was cooled at - 70 $^{o}$C. n-BuLi (1.6 mol/L in hexanes, 3.6 mL, 5.76 mmol, 3.0 equiv) was added while maintaining temperature < - 50 $^{o}$C. The mixture was agitated at - 50 $^{o}$C for 30 min. After cooling the mixture to - 65 $^{o}$C, zinc chloride (0.5 mol/L in tetrahydrofuran, 13 mL, 6.5 mmol, 3.4 equiv) was added and the mixture was warmed to ambient temperature. The mixture was sparged with nitrogen gas for 30 min. Bis(tri-tert-butylphosphine)palladium(0) (50 mg, 0.1 mmol, 5 mol%) was added to the mixture and heated at 75 $^{o}$C for 18 h. The mixture was cooled to ambient temperature. Aqueous $NH_4Cl$ solution (10 mL, 14 wt %) was added to the mixture and tetrahydrofuran was removed by distillation. Methanol (5mL) was added to the mixture, followed by filtration. The solid was then

triturated in ethyl acetate (5 mL) at 65 $^{o}$C and filtered. The filtered solid was triturated in aqueous 1 N HCl solution (10 mL) and filtered to give an off white solid (130 mg, 30 % yield, 97 A %).

$^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 12.68 (s, 1H), 8.70 (dd, J = 4.8, 1.7 Hz, 1H), 8.59 (d, J = 1.4 Hz, 1H), 8.56 (dd, J = 7.9, 1.7 Hz, 1H), 7.40 (dd, J = 7.8, 4.8 Hz, 1H).

$^{13}$C NMR (101 MHz, DMSO) δ 152.84, 150.85, 150.48, 147.88, 137.33, 137.28, 132.77, 129.86, 129.81, 125.46, 125.29, 117.37, 116.94, 116.76, 110.78.

*5-((1-(3-((6-cyano-9H-pyrrolo[2,3-b:5,4-c']dipyridin-5-yl)oxy)butyl)piperidin-4-yl)oxy)-9H-pyrrolo[2,3-b:5,4-c']dipyridine-6-carbonitrile* ***16***. The mother liquors from trituration of **GDC-0425·2HCl** with DMF (70 mL) were diluted with water (500 mL) and adjusted to pH = 8.6 using 0.6 M aqueous NaOH. The solids were filtered, washed with water (50 mL) and dried in the vacuum oven at 60 $^{o}$C for 16 h. Compound **16** (68 mg) was obtained as an off white solid in a purity of 94 A %.

$^{1}$H NMR (600 MHz, DMSO-$d_6$) δ 12.97 (s, 2H), 8.79 (s, 1H), 8.78 (s, 1H), 8.76 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.72 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.70 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.55 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.0, 4.8, 1.4 Hz, 2H), 5.13 (h, *J* = 6.1 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 2.89 (dd, *J* = 10.5, 4.6 Hz, 1H), 2.72 – 2.60 (m, 1H), 2.60 – 2.53 (m, 1H), 2.48 – 2.35 (m, 1H), 2.20 – 1.75 (m, 9H), 1.38 (d, *J* = 6.1 Hz, 3H).

$^{13}$C NMR (150 MHz, DMSO) δ 153.92, 153.35, 151.66, 149.65, 149.56, 138.06, 137.97, 132.33, 131.99, 131.82, 131.49, 118.75, 118.65, 117.40, 117.24, 114.69, 114.57, 111.80, 111.61, 81.10, 78.97, 52.87, 50.56, 50.12, 33.87, 31.46(2C), 20.06.

*(E)-6-chloro-5-fluoro-9-(1-propoxybut-2-en-1-yl)-9H-pyrrolo[2,3-b:5,4-c']dipyridine* ***17.*** 7.2 g of crude **3e** was dissolved in 30 mL dichloromethane. Impurity **17** was isolated by silica gel chromatography with a linear gradient of 0 – 5 v% MeOH/DCM over 40 min.

LCMS method for **17**. Diluent: Acetonitrile. Mobile Phase A: 0.05 % Formic Acid/Water. Mobile Phase B: 0.05 % Formic Acid/Acetonitrile. Column: Ace Excel3 AQ column, 3x50 mm 3.0µm. Column Temperature: 35˚C. Detector Wavelength: 220 nm. Injection Volume: 2 µL. Flow Rate: 1.2 mL/minute. Program: 0.0 min 0 % B, 2.0 min 0 % B, 3.0 min 60.0 % B, 4.0 min 90 % B. Typical Retention Time: **17** (RT 3.69 min).

$^{1}$H NMR (600 MHz, DMSO-$d_6$) δ 8.76 (d, $J$ = 1.2 Hz, 1H), 8.75 (dd, $J$ = 4.8, 1.6 Hz, 1H), 8.60 (dd, $J$ = 7.8, 1.7 Hz, 1H), 7.47 (dd, $J$ = 7.8, 4.7 Hz, 1H), 6.81 (dt, $J$ = 5.3, 1.3 Hz, 1H), 6.02 (ddq, $J$ = 15.3, 4.9, 1.5 Hz, 1H), 5.90 (dqd, $J$ = 14.4, 6.5, 1.2 Hz, 1H), 3.45 (dt, $J$ = 9.4, 6.3 Hz, 1H), 3.11 (dt, $J$ = 9.4, 6.7 Hz, 1H), 1.67 (dt, $J$ = 6.6, 1.4 Hz, 3H), 1.53 – 1.40 (m, 2H), 0.75 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (150 MHz, DMSO-$d_6$) δ 151.25, 150.20, 149.66, 147.92, 135.01, 134.98, 132.76, 132.74, 130.12, 130.09, 130.07, 126.86, 126.11, 125.99, 117.72, 116.94, 116.82, 110.39, 110.37, 83.07, 69.49, 22.01, 17.08, 10.61, 10.38.

HRMS calcd for Chemical Formula: $C_{17}H_{17}ClFN_3O$ 333.79; found $[M+H]^+$ 334.2.

## ASSOCIATED CONTENT

**Supporting Information**.

Additional experimental procedures for the scale-up of the 6-chloro-5-fluoro-9H-pyrrolo[2,3-b:5,4-c']dipyridine **2** . This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

**Author Contributions**

The authors declare no competing financial interest.

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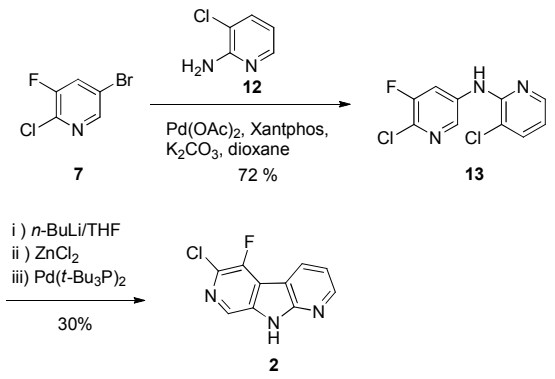
[2] This alternative route also started from bromo-pyridine **7** (Scheme 9).

**Scheme 9.** *Alternate Route to **2***




For the Buchwald reaction, the coupling substrate was replaced with amino pyridine **12** to afford the N-tethered bi-pyridine **13** in 72 % yield. A Negishi reaction was examined to close the ring of **13** and give the desired carbazole **2**. For this purpose a catalyst/ligand screen was performed at 0.4 mmol scale. Only Pd(*tert*-$Bu_3P)_2$ was found to give 74 % conversion of **13** to **2**. All other

catalysts tried were unsuccessful. However, when the reaction using Pd(*tert*-$Bu_3P)_2$ was scaled to 2 mmol scale, extensive decomposition of **13** was observed and the yield dropped to < 30 %. These efforts were not further pursued because it was expected that in a scale-up operation longer cycle would lead to even more decomposition.

[3] Electron withdrawing protecting groups such as BOC, PMB, $SO_2Ph$, Mes were found to inhibit the stage 2 cyanation and the pivaloyl and $CO_2Et$ groups were not stable. THP, TBDMS, $SO_2NMe_2$, $(CH_2)_2SO_2Ph$ could not be introduced.

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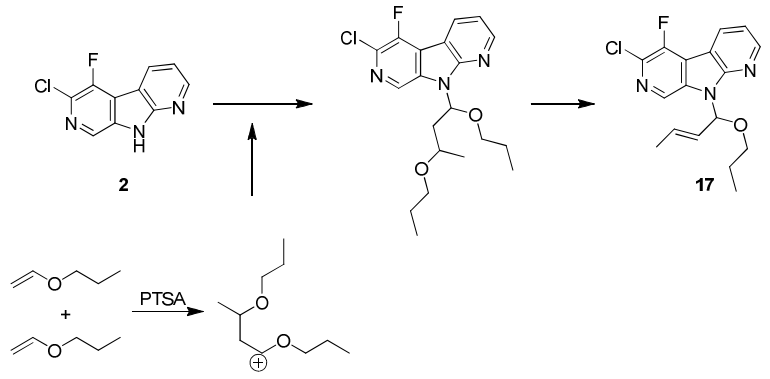
[7] This side product was subsequently isolated and identified as impurity **17.** A plausible explanation for the formation of **17** is the alkylation of the starting material with a dimer of PVE, as is shown in Scheme 10.

**Scheme 10.** *Proposed Mechanism of Formation of Impurity **17***

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[9] Stability of **3e** in the reaction mixture at room temperature was examined and no loss of protecting group or appearance of impurities was observed after several days. When **3e** was refluxed with $Zn(CN)_2$ in DMF in the absence of catalyst for 20 h no loss of protecting group occurred. Premixing of **3e** with $Pd(PPh_3)_4$ in DMF before addition of $Zn(CN)_2$ at 100 $^oC$ to the reaction mixture resulted in formation of a un-reactive catalyst species and no conversion to product was observed. Only small amounts of deprotected **3e** (<1%) were obtained after 21 h reaction time, indicating that **3e** was stable towards Pd species and $Zn(CN)_2$ and thus by-product **18** was generated by the deprotection of **4e**.

[10] An additional benefit of this catalyst system is that all components can be handled under air and it has been shown in a later experiment that the reaction proceeds even in the presence of air, presumably with Zn taking on the role to reduce the $Pd(OAc)_2$ pre-catalyst to the active catalyst species.

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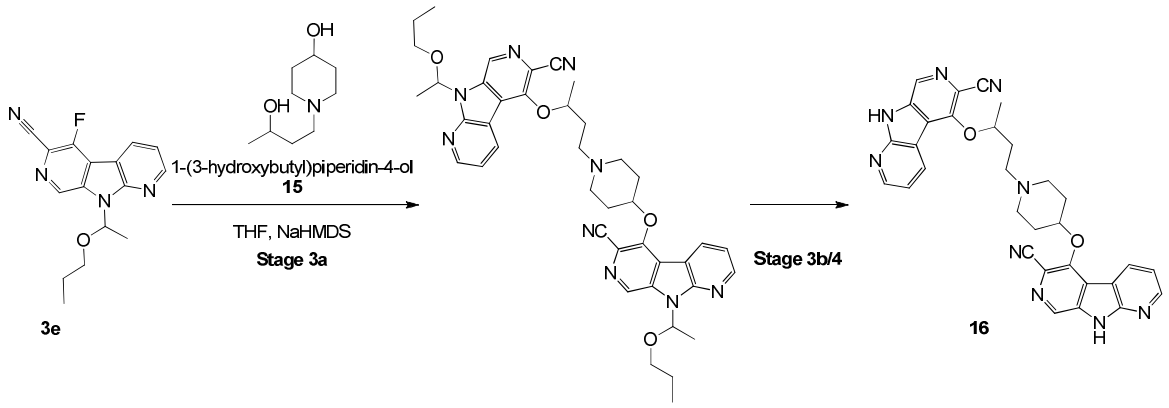
[12] No decomposition of **4** was observed under the applied reaction conditions.

[13] A subsequent use test of converting **3e** to **4e** from the GMP campaign materials unexpectedly showed 1.8 % of a previously not seen dimer impurity **16** (Scheme 11). The dimer impurity did not purge during the subsequent deprotection and was found in the isolated API. This new dimer was traced to the piperidine methanol starting material **2**, which was prepared by reductive

amination of piperidin-4-on **14** with acetaldehyde and sodium borohydride. **15** presumably formed by aldol condensation of acetaldehyde to 3-hydroxybutanal, which then reacted during reductive amination with **14** to generate **15.** Subsequent processing led to the formation of the undesired dimer impurity **16**.

**Scheme 11.** *Formation of Dimer Impurity **16**.*




Dimer **16** was reduced from 1.8 % to 0.20 % by two subsequent triturations in DMF at 100 °C for 2 h. Interestingly, trituration caused the **GDC-0425·2HCl** to convert to monohydrochloride salt of **GDC-0425.**

[14] (a) Adlington, N. K.; Black, S. N.; Adshead, D. L. *Org. Process Res. Dev.* **2013**, 17, 557. (b) Block, S. N.; Quickley, K.; Parker, A. *Org. Process Res. Dev.* **2006**, 10, 241. (c) Liotta, V.; Sabesan, V. *Org. Process Res. Dev.* **2004**, 8, 488.

[15] Impurities: guideline for residual solvents Q3C(R5) Current Step 4 version dated 4 February **2011**.