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Route Design and Development of a MET Kinase Inhibitor: A Copper-Catalyzed Preparation of an *N*1-Methylindazole

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Supporting Information

ABSTRACT: The synthesis of a MET kinase inhibitor in an overall yield of 22% was achieved over eight steps starting with 3-hydroxybenzaldehyde, an improvement from the initial 12-step process with a 5.4% yield. Highlights of the process chemistry design and development are a Cu-catalyzed cyclization to form an important *N*1-methylindazole ring, a selective nitro reduction in the presence of an aryl bromide, a late-stage Suzuki cross-coupling, and a base-promoted Boc deprotection to form the desired drug candidate.

INTRODUCTION

MET is a member of the receptor tyrosine kinase family. MET expression occurs in normal tissues such as endothelial, epithelial, and mesenchymal cells. Binding of the endogenous ligand, hepatocyte growth factor (HGF), to MET promotes cell migration, proliferation, and invasion in embryogenesis. The MET pathway has been implicated in the progression of certain tumors, and MET overexpression has been shown in many tumor types, including colon, renal, lung, head and neck squamous cell carcinoma, and gastric cancer. Activation of MET receptors enhances tumor cell proliferation, invasion/metastasis, and resistance to apoptosis and cytotoxic therapies. Aberrant activation of MET can increase the tumorigenicity and metastatic potential of tumor cells.[1]

MET kinase inhibitors are a class of small molecules that inhibit the enzymatic activity of MET tyrosine kinase. These inhibitors may have therapeutic application in the treatment of various types of cancers.[2] Various amidophenoxyheteroaryl MET inhibitors have been reported. The novel amidophenoxyindazole compound LY2801653 (**1**), a type-II ATP competitive slow-off inhibitor[3] of MET, is currently undergoing early-phase clinical investigation in cancer patients.

The challenges of the medicinal chemistry route for large-scale implementation include a long linear synthesis with a low overall yield (5.4%), lack of regioselectivity in the formation of *N*1-methylindazole **2** (Figure 1), and utilization of a thermally unstable diazonium intermediate for the preparation of indazole intermediate **7**, which raised safety concerns for long-term production. We report herein an efficient and practical alternative synthesis of **1** that is amenable to multikilogram operations.

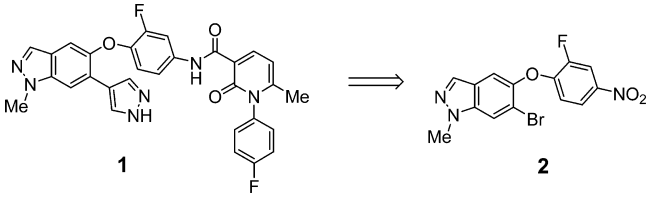

Figure 1. Retrosynthetic analysis of **1**.

RESULTS AND DISCUSSION

First-Generation Synthesis of 1. Indazole derivative **2** served as a critical advanced intermediate for structure−activity relationship (SAR) studies leading to **1** (Scheme 1). In order to identify a drug candidate, the original synthetic route was optimized to enable the kilogram-scale synthesis of intermediate **2** for support of late-stage SAR studies. Acylation of 4-methoxy-2-methylaniline followed by selective bromination of amide **3** under acidic conditions with Br_2 in acetic acid provided the corresponding brominated amide **4** in good yield. However, a significant level of the undesired regioisomer (15%) was present after bromination and was difficult to remove by chromatography. A trituration method using EtOAc at ambient temperature or EtOAc/THF mixed solvent at 60 °C was developed to eliminate the undesired isomer without chromatography. Free amine **5** was then obtained in good yield by acid hydrolysis with concentrated aqueous HCl in MeOH under refluxing conditions. The formation of diazonium salt **6** was cautiously carried out while maintaining the temperature below 20 °C to avoid possible thermal decomposition. Jacobsen indazole synthesis[4] with KOAc/18-crown-6 in $CHCl_3$ afforded indazole **7** in 50% yield from intermediate **5**. Preparation of **7** on a multikilogram scale was successfully accomplished. Upon further scale-up of these steps, indazole **7** was prepared in THF using tetrabutylammonium bromide in place of 18-crown-6.

Demethylation of **7** using BBr_3 in CH_2Cl_2 proceeded smoothly to yield hydroxyindazole **8** in 77% yield. In the larger-scale synthesis of **8**, the CH_3Br off gas was effectively trapped using a PPh_3/DMF scrubber to avoid any environmental release.[5] Phenol **9** was prepared by selective protection of the indazole nitrogen in **8** with 3,4-dihydro-2H-pyran (DHP). Phenol **9** was successfully coupled with 1,2-difluoro-4-

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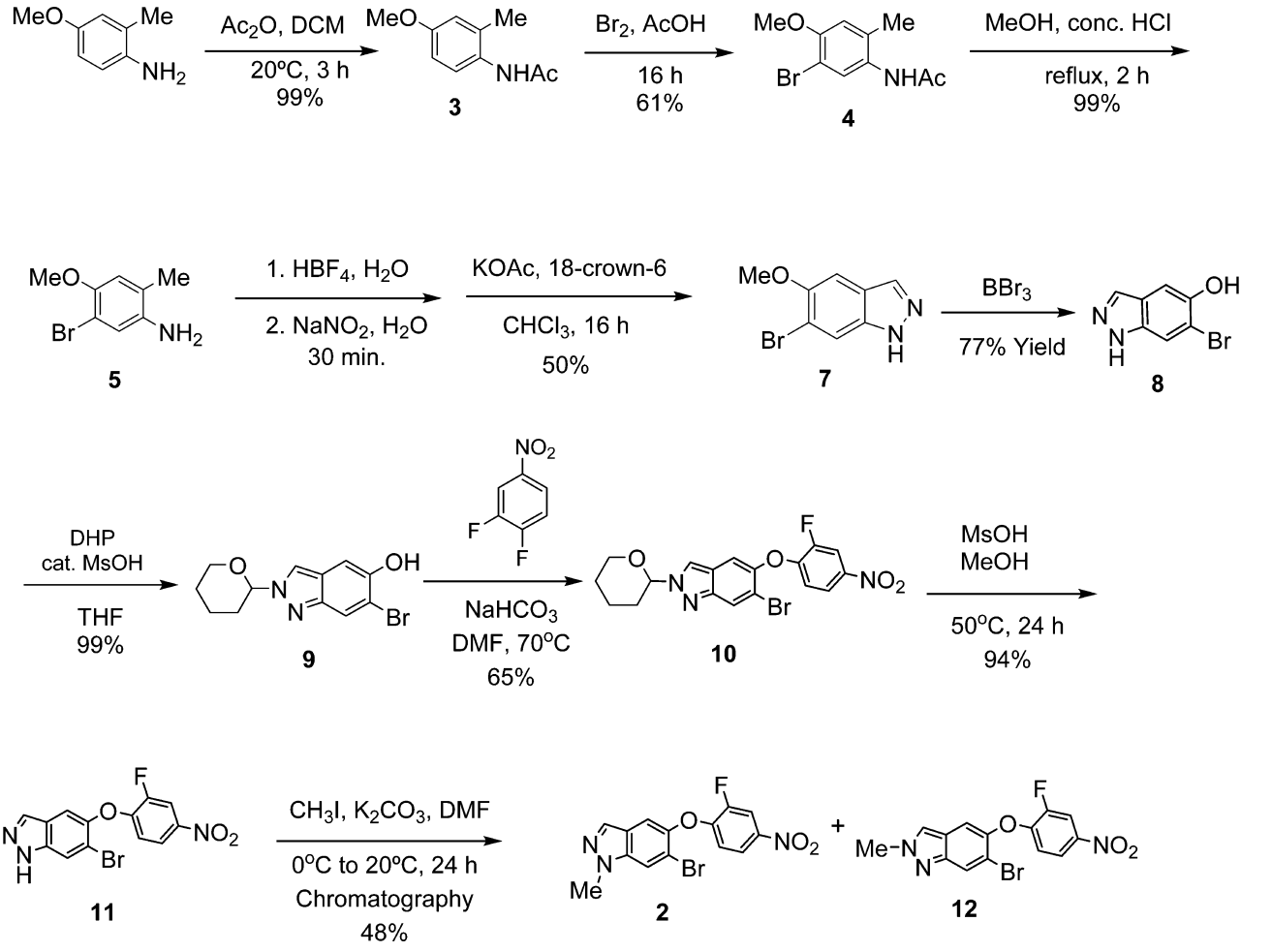
Scheme 1. Synthesis of Advanced Intermediate 2



nitrobenzene in DMF under basic conditions to provide aryl ether **10** in 65% yield. Deprotection of **10** with MsOH followed by methylation with MeI in the presence of K_2CO_3 in DMF gave a 50/50 mixture of **2** and its *N*2-methylated regioisomer **12**. The desired compound **2** was obtained by normal-phase chromatography separation. Screening was performed to explore reaction conditions that could provide the desired *N*1-methylated product with better regioselectivity. This screening proved to be unsuccessful, but an equilibration process applied to the methylation of **7** ultimately solved this problem.

Suzuki reaction of bromide **2** with Boc-protected pyrazole **13** using catalytic 1,1′-bis(di-*tert*-butylphosphino)ferrocene (Di-tBPF) and $Pd_2(dba)_3$ gave a mixture of the coupled product **14** and 40% unprotected pyrazole product in a 15 h reaction at 60 °C using 4 mol % Pd (Scheme 2). Because of the rate of deprotection of the Boc-protected pyrazole under the Suzuki reaction conditions, more catalyst was required since the unprotected pyrazole poisoned the catalyst. The mixture was then subjected to protection conditions to give **14** in 60% yield. Selective hydrogenation of the nitro moiety of compound **14** in THF gave complete reduction to the corresponding aniline **15** in high yield. Reaction of **15** with **16** under peptide coupling conditions using HOBt/EDCI followed by HCl deprotection of the pyrazole provided **1** in 51% yield from **2**.

Alternative Synthesis of 16. The initial synthetic route for the synthesis of **16** via a three-step procedure is shown in Scheme 3. Reaction of cyanoacetic acid with *p*-fluoroaniline at room temperature using EDCI/HOBt coupling provided amide **18** in low yield. Ring formation using DBU as the base in the subsequent step gave **19** in low yield as well. An alternative route was then developed to produce the desired intermediate **16** using ethyl malonyl chloride and 4-fluoroaniline as starting materials (Scheme 4). Amide **20** was formed in quantitative yield and was then reacted with 4-methoxybut-3-en-2-one under basic conditions followed by neutralization to give the desired compound **16** in 56% yield.

Initial Improvements in the Preparation of 2. Given the lack of regioselectivity in the preparation of **2**, we were pleased to find that **7** could be methylated and that the mixture of methylated products could be equilibrated with catalytic methyl iodide in DMAc at 150 °C for 2 h via the dimethylimidazolium salt,[6] resulting in a 63% isolated yield of **21** on a kilogram scale (Scheme 5). In the deprotection of **21**, aluminum chloride was preferred over BBr_3, which was used in the analogous deprotection in the first route. The S_NAr reaction with 1,2-difluoro-4-nitrobenzene provided **2** in an overall yield of 49% from **7** and avoided the chromatography needed in the first route. Moreover, this approach avoided the tetrahydropyran (THP) protection and deprotection, though it still relied on the hazardous diazo chemistry in the preparation of the indazole.

Improved Preparation of 1. Though the route from key intermediate **2** to **1** remained the same in the subsequent delivery (Scheme 6), there were several improvements that

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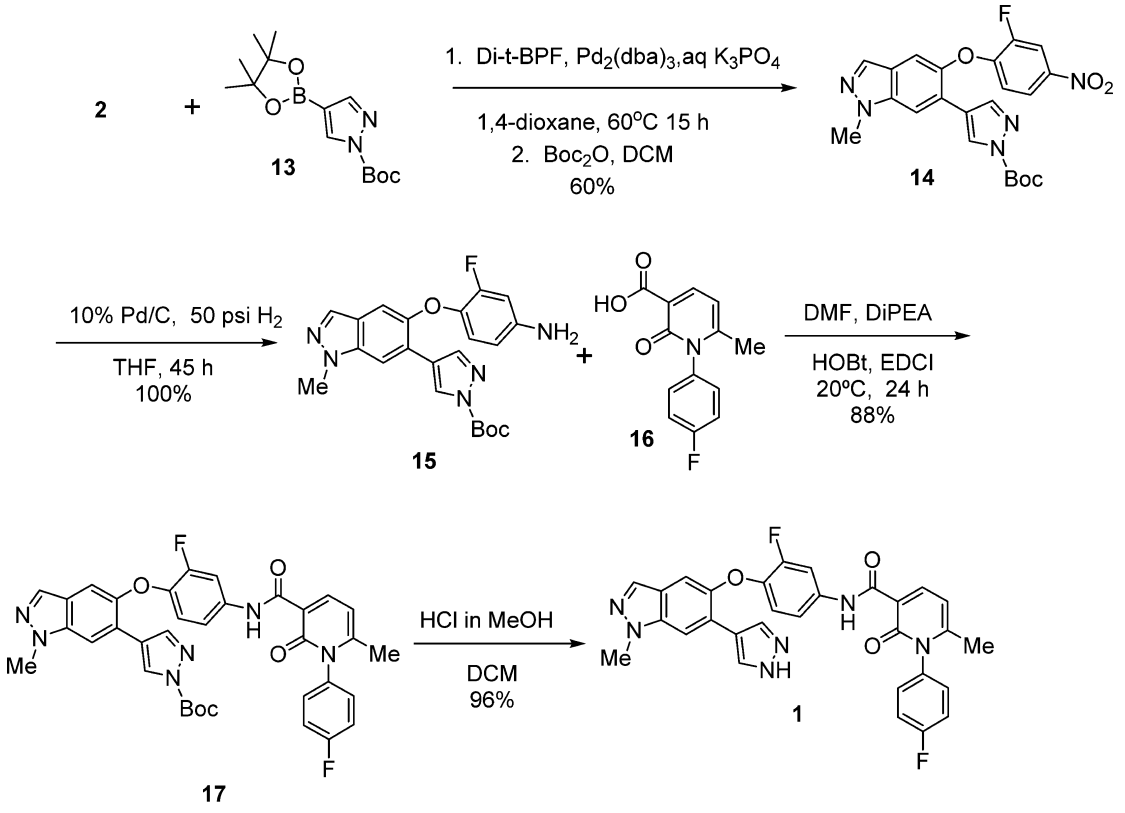
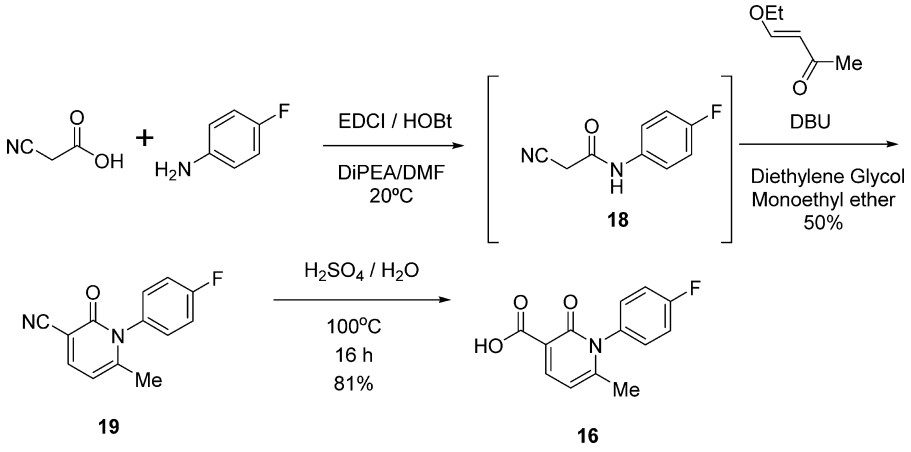
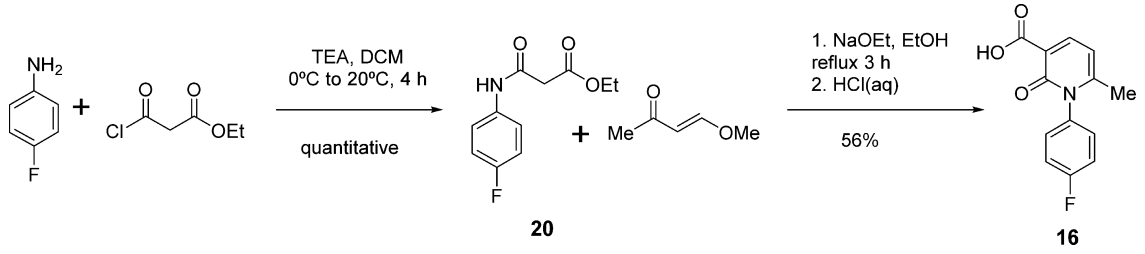
Scheme 2. First-Generation Synthesis of 1



Scheme 3. Medicinal Chemistry Synthesis of 16



Scheme 4. Improved Synthesis of 16



aided its manufacture. Adding 0.25 equiv of di-*tert*-butyl dicarbonate minimized the amount of Boc group that was removed during the Suzuki reaction of **2** with Boc-protected pyrazole **13** to 0.4%, which allowed less catalyst (2 mol %) to be used and the reaction to be performed at a lower temperature (40 °C, 3 h). As noted earlier, the deprotected pyrazole poisoned the catalyst. Second, the addition of catalytic ammonium vanadate[7] helped drive the nitro reduction to

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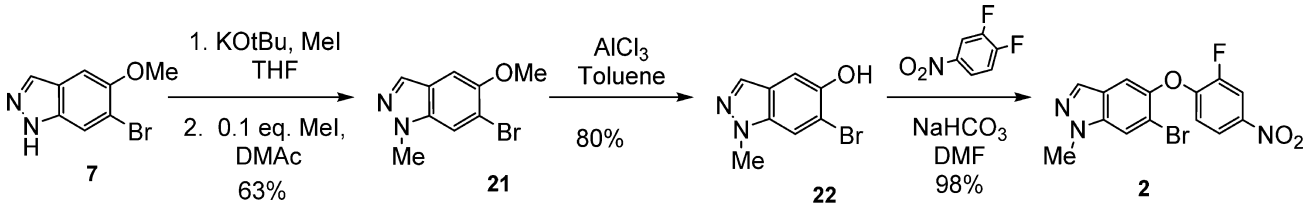
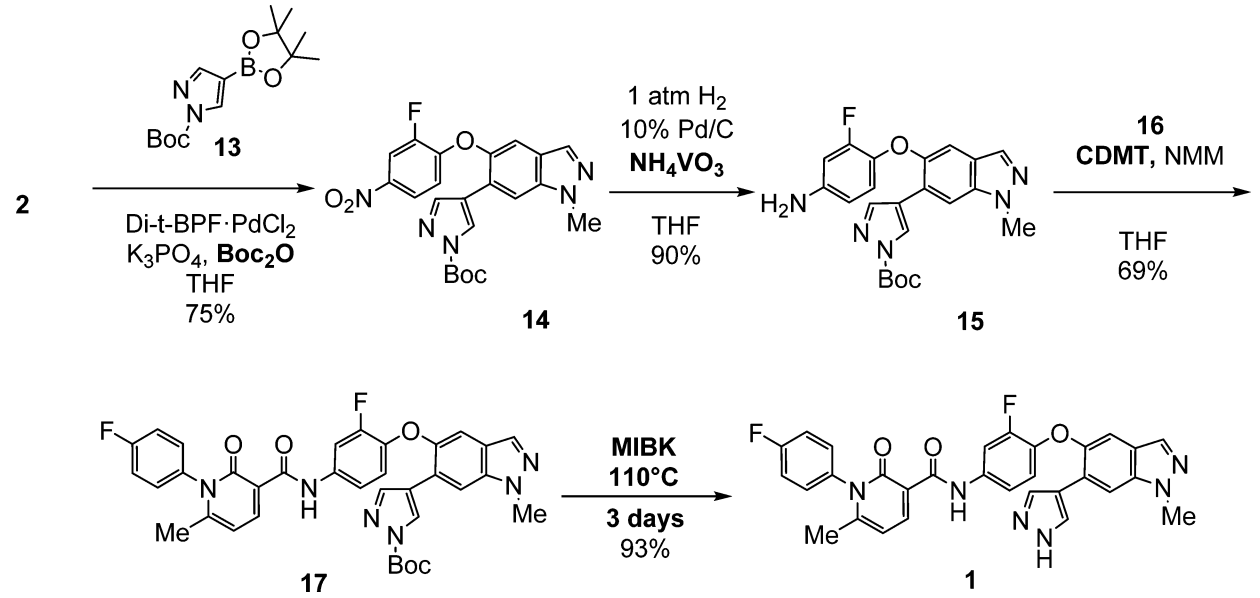
Scheme 5. Improved Preparation of 2 from Indazole 7

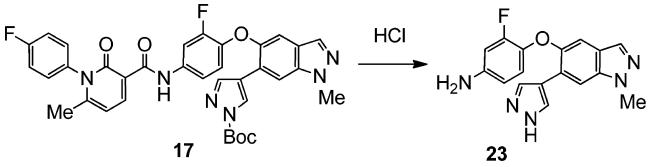


Scheme 6. Improved Preparation of 1



completion, allowing the reduction to be performed with 1 atm H_2. The amide coupling reagent was switched to 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), minimizing the safety concerns about use of HOBt on the manufacturing scale.[8] Finally, the HCl deprotection was switched to thermal deprotection[9] in 4-methyl-2-pentanone (MIBK). This was necessitated by the discovery that HCl deprotection of **17** led to unacceptable levels of mutagen **23** by amide hydrolysis (Scheme 7), which was obviated by the thermal deprotection.

Scheme 7. Formation of Mutagen 23



Synthetic Route Concerns in Schemes 5 and 6. Despite the improvements that were made in the synthesis of **1**, long-term manufacture of the indazole core by the hazardous diazo route was undesirable. Additionally, the Boc-protected pyrazole was thermally unstable, leading to yield loss throughout the synthesis and the formation of coupled product **24** as a major impurity. In addition, the three-day thermal deprotection of the Boc group led to high levels of *tert*-butyl impurity **25** (see Figure 2). All of these concerns were addressed in the development of the next-generation route to **1**.

Second-Generation Improved Route to Indazole 2. Given the long route and the safety issues with the diazo route to the core indazole, we sought a safer, more direct route to indazoles. At the time, there were literature precedents in cyclizing phenylhydrazones to indazoles with Cu or Pd.[10] Several *N*-methylhydrazones were prepared from the corresponding bromobenzaldehydes. Attempts to cyclize these with a variety of Pd conditions all failed. Fortunately, copper-catalyzed cyclization[11] in some instances did result in the formation of the desired indazoles, as shown in Scheme 8 and Table 1. Entry 5 was particularly satisfying, since product **2** intersected the existing route.

Therefore, **2** was prepared in four steps starting from commercially available 3-hydroxybenzaldehyde (**26**), as shown in Scheme 9. **26** was dibrominated in dichloromethane,[12] affording **27** in 67% yield. Subsequently, **27** was reacted with 1,2-difluoro-4-nitrobenzene in an S_NAr reaction to form intermediate **28**, which was directly converted to methylhydrazone **29** by reaction with aqueous methylhydrazine. After an extractive workup and crystallization, **29** was isolated in a two-step yield of 78%.

Significant development was required to optimize the cyclization and reject copper and some tarry material to improve the purity. The reaction was accomplished by slow addition of a degassed solution of **29** in DMF to a degassed mixture of catalytic CuCl, potassium carbonate, and DMF at 100 °C followed by heating for an additional 11 h. The mixture was worked up by cooling, addition of 30% H_2O_2 to oxidize residual copper, and filtration of the salts. To the filtrate was added aqueous HCl, precipitating the technical product, which contained 50−200 ppm Cu. This was more effective than resins or washes with NH_4OH or EDTA. Sulfur reagents could lower

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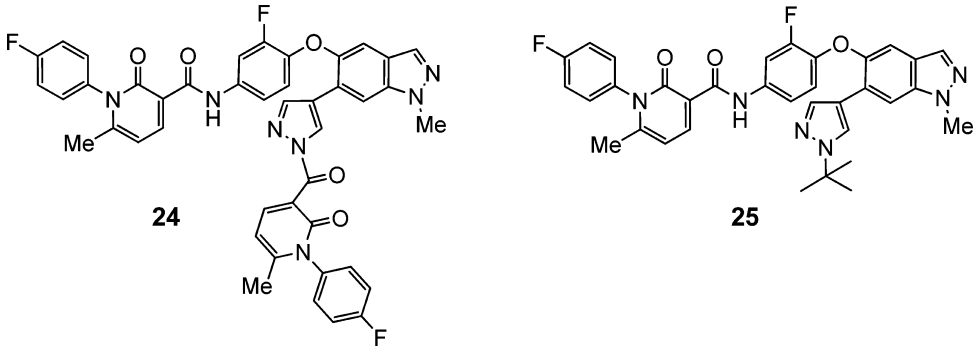


Figure 2. Impurities of concern.

Scheme 8. Preparation of *N*1-Methylindazoles from *N*-Methylhydrazones

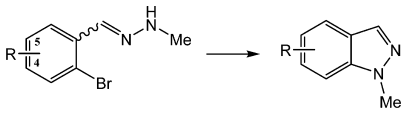


Table 1. Copper-Mediated Cyclization of Hydrazones to Indazoles in DMF

entry	R	CuX	M_2CO_3	conditions[a]	in situ yield (%)
1	H	CuBr	Cs_2CO_3	20V, 100 °C, 4 h	76
2	5-F	CuCl	K_2CO_3	10V, 100 °C, 4 h	31
3	4,5-$(MeO)_2$	CuCl	Cs_2CO_3	10V, 100 °C	33
4	4-Br, 5-MeO	CuI	Cs_2CO_3	20V, 20 °C, 64 h, 60 °C, 3 h	86
5	4-Br, 5-(2-F-4-NO_2PhO)	CuCl	K_2CO_3	10V, 100 °C, 6 h	79

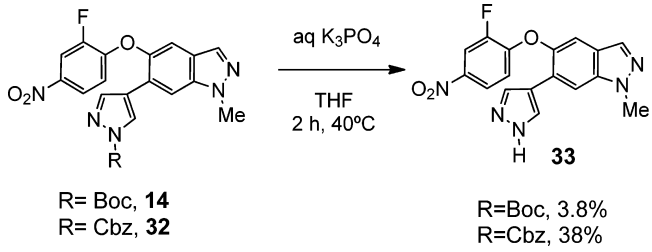
[a]V denotes volumes (i.e., mL of DMF/g of starting material).

the Cu level further, but trace sulfur contamination poisoned the subsequent Pt reduction.

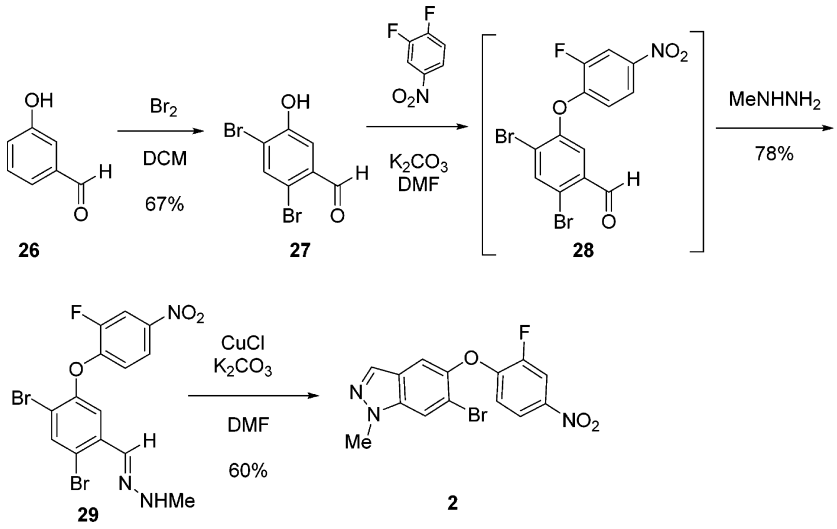
The technical product was purified by dissolution in 2-methyltetrahydrofuran, treatment with 6% aqueous sodium hypochlorite, washing of the mixture with aqueous citric acid and then aqueous HCl, and isolation from ethanol. Subsequent reslurries from ethanol and isopropyl acetate, which were required to improve the potency of the product, resulted in a net 60% yield of **2**. Overall, **2** was produced in 31% yield from **26**, an improvement from the 12% yield in the nine-step diazo route in Schemes 1 and 5.

Development of the Final Steps. In view of the problems that were identified as concerns in the route shown in Scheme 6, alternative protecting groups were examined. A Cbz group is more base-sensitive than a Boc group and would not survive the Suzuki chemistry, as shown in Scheme 10. A THP ether of the protected pyrazole would be expected to be tolerant of the chemistry, but its removal would require acid, resulting in unacceptable levels of mutagen **23**. A benzyl group would also be tolerant of the chemistry, but surprisingly, removal of the

Scheme 10. Base Instability of the Protected Pyrazole



Scheme 9. An Improved Preparation of Indazole 2



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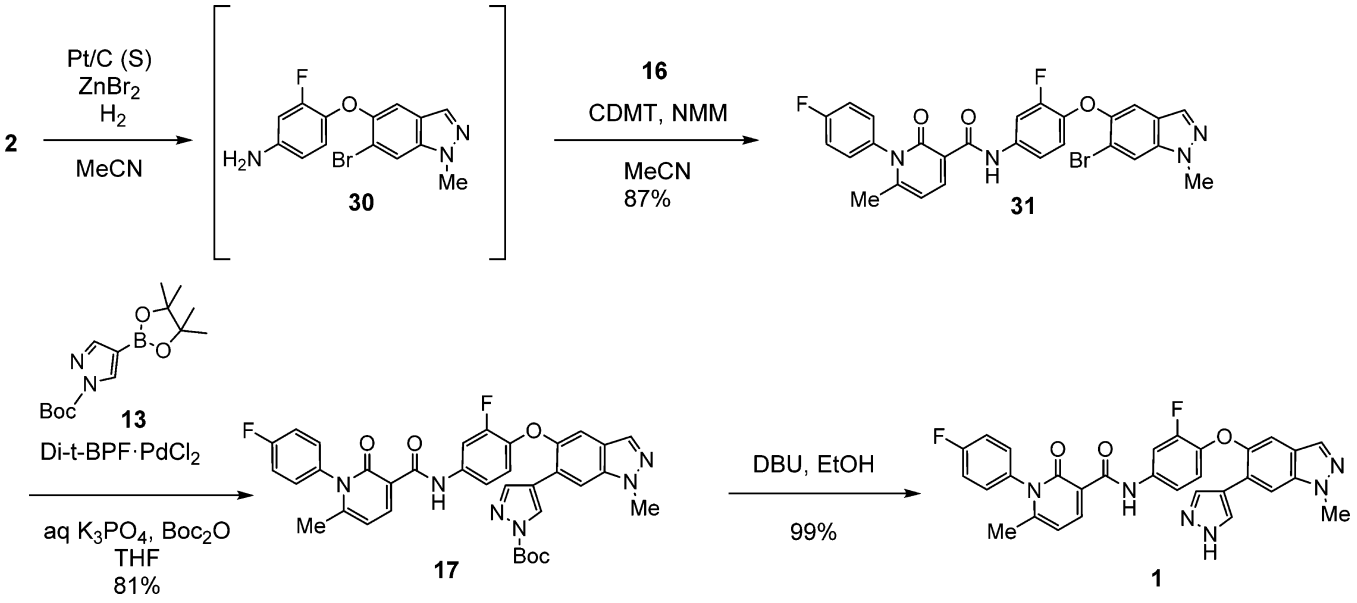
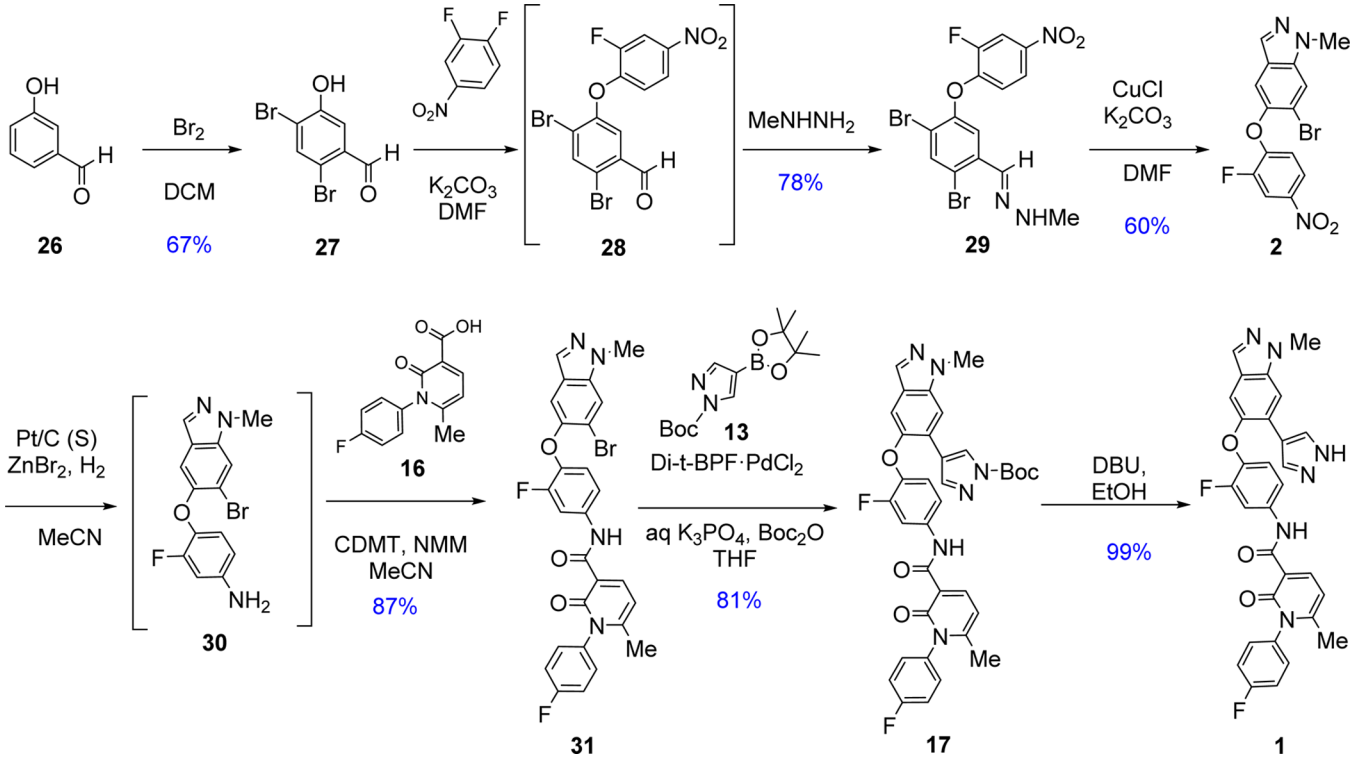
Scheme 11. An Improved Preparation of 1



Scheme 12. Optimized Route for the Manufacture of 1



benzyl group resulted in some over-reduction of the pyridone, which was difficult to remove.

In the end, we decided to continue to use Boc-protected pyrazole **13** in a Suzuki reaction but chose to switch the order of the steps, as shown in Scheme 11. There were several reasons that this was chosen. First, intermediates **2**, **14**, **15**, and **30** were mutagens requiring tight control. In Scheme 11, the final product **1** is three steps removed from the last mutagen, versus only two steps for the previous route in Scheme 6. Second, the Boc-protected pyrazole **13** is expensive, and using it in the last step minimized the quantity required. Finally, performing the Suzuki chemistry last did not lead to additional impurities if some of the Boc group was removed during the Suzuki step.

Therefore, **2** was cleanly reduced with 1 atm H_2 using catalytic sulfided platinum on carbon and catalytic zinc bromide in acetonitrile. This catalyst and additive minimized dehalogenation, which carried through to the final product.[13] After filtration and concentration of the mixture, **30** was coupled with **16** using CDMT. The product **31** was precipitated by the addition of MeOH, resulting in a two-step yield of 87%.

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With regard to the Suzuki reaction, it is important to note that the removal of the Boc group led to stalling of the reaction. Therefore, to minimize this loss of the Boc group, the aqueous potassium phosphate was added last to the reaction mixture, resulting in a 70 min reaction at 45 °C using 1.5 mol % catalyst. After the mixture was cooled, the phases were separated, and the organic phase was concentrated, resulting in the precipitation of **17**. The product was then redissolved in a mixture of THF and water and treated with thiol-functionalized silica gel to remove palladium. This treatment was followed by filtration and solvent exchange into 2-propanol, resulting in crystalline **17** in an 81% overall yield with low metal content.

With regard to Boc removal, it was noted earlier (Scheme 7) that acid removal led to unacceptable levels of mutagen **23**. Thermal removal (as in Scheme 6) took over 3 days and led to high levels of *tert*-butyl impurity **25**. Fortunately, the Boc group was able to be removed under basic conditions[14] with negligible quantities of mutagen **23**. We chose to use 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing absolute ethanol to perform the Boc removal. Further investigation indicated that catalytic sodium ethoxide or sodium hydroxide gave comparable results. Upon scale-up, 1.2 equiv of DBU was used, and the mixture was stirred at reflux for 9 h, resulting in >99.9% conversion to **1**. Since **1** crystallizes during the deprotection, a seed of the correct form was added for form control.

■ CONCLUSIONS

A 22% overall yield of **1** was achieved in eight steps (Scheme 12). This was 4 times the yield from the initial 12-step route. Key to this improvement was the four-step route to an important *N*1-methylindazole intermediate via a Cu-mediated cyclization. In addition, a base-promoted Boc deprotection minimized amide hydrolysis in the final step, producing 18.54 kg of high-quality drug candidate.

■ EXPERIMENTAL SECTION

General. In process method for preparations of **16** and **27**. Diluents: acetonitrile for **26** and **27**; 30% acetonitrile/70% water for **16** and **20**. Mobile phase A: 0.05% TFA in water. Mobile phase B: 0.05% TFA in acetonitrile. Column: YMC Pack Pro C18, 4.6 mm × 150 mm, 3.0 μm. Column temperature: 30 °C. Detector wavelength: 220 nm. Injection volume: 10 μL. Flow rate: 2.0 mL/min. Program: 0 min 10% B, 10.5 min 73% B. Typical retention times (RTs): **26** (4.1 min); 4-fluoroaniline (5.3 min); **20** (5.8 min); **16** (6.3 min); **27** (8.7 min).

In process method for preparation of **2**. Diluent: acetonitrile. Mobile phase A: 0.05% TFA in water. Mobile phase B: 0.05% TFA in acetonitrile. Column: YMC Pack Pro C18, 4.6 mm × 150 mm, 3.0 μm. Column temperature: 30 °C. Detector wavelength: 220 nm. Injection volume: 10 μL. Flow rate: 2.0 mL/min. Program: 0 min 30% B, 6.5 min 95% B, 10.5 min 95% B. Typical retention times: 1,2-difluoro-4-nitrobenzene (4.1 min); **27** (4.3 min); **2** (5.7 min); **28** (6.4 min); **29** (7.1 min).

In process and purity method for preparation of **1**. Diluent: acetonitrile/water (1:1). Mobile phase A: 10 mM NH_4CO_3 in water, pH 9. Mobile phase B: Methanol. Column: Waters Xbridge C18, 75 mm × 4.6 mm, 2.5 μm. Column temperature: 35 °C. Detector wavelength: 235 nm. Injection volume: 5 μL. Flow rate: 1.2 mL/min. Program: 0 min 5% B, 5 min 55% B, 11 min 95% B, 13 min 95% B. Typical retention times: **16** (4.1 min); **13** (4.8 min); **30** (7.9 min); **1** (9.2 min); **2** (9.8 min); **31** (10.3 min); **17** (10.7 min).

Ethyl 3-(4-Fluorophenylamino)-3-oxopropanoate (20). A solution of dichloromethane (5000 mL), 4-fluoroaniline (111 g, 96 mL, 1.0 mol, 1.0 equiv), and triethylamine (166 mL, 1.2 mol, 1.2 equiv) was treated with ethyl malonyl chloride (196 g, 167 mL, 1.3 mol, 1.3 equiv) in dichloromethane (500 mL) at 0 °C over 4 h. The mixture was stirred for 0.5 h before water (2 L) was added. The organic phase was washed with saturated $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. The aqueous phase was extracted with ethyl acetate (2 × 1 L). The ethyl acetate phase was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the combined organic solution was concentrated to dryness under reduced pressure. The residue was washed with petroleum ether (1 L) to provide compound **20** (230 g, crude yield 102%) as a yellow solid, which was used for next step without further purification. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.24 (s, 1H), 7.58 (m, 2H), 7.15 (m, 2H), 3.65 (s, 3H), 3.46 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.1, 163.9, 159.3, 156.9, 135.2 (2C), 120.9, 120.8, 115.5, 115.3, 52.0, 43.4. HR-MS: calcd for $C_{10}H_{10}FNO_3$ + H, 212.0717; found, 212.0715.

1-(4-Fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid (16). A solution of ethanol (1500 mL), **20** (139 g, 617 mmol, 1.0 equiv), sodium ethoxide (65.6 g, 925 mmol, 1.5 equiv), and 4-methoxybut-3-en-2-one (103 g, 925 mmol, 1.5 equiv) was prepared and refluxed for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to remove the ethanol. The residue was extracted with dichloromethane (700 mL) and 1 M HCl (1500 mL). The aqueous phase was extracted with dichloromethane (3 × 500 mL). The combined organic phases were washed with brine (1000 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was triturated with ethyl acetate (150 mL) at 10 °C for 1 h. After filtration and washing with ethyl acetate (50 mL), the final product **16** was obtained as a yellow solid (85.3 g, 56% yield, 97 wt %). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 14.21 (s, 1H), 8.40 (d, 1H, J = 7.6 Hz), 7.48 (m. 4H), 6.79 (d, 1H, J = 7.6 Hz), 2.10 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.0, 164.8, 163.4, 160.9, 154.9, 145.5, 133.2 (2C), 129.9, 129.8, 116.8, 116.6, 114.1, 109.3, 21.7. HR-MS: calcd for $C_{13}H_{10}FNO_3$ + H, 248.0717; found, 248.0715.

2,4-Dibromo-5-hydroxybenzaldehyde (27). To a solution of 3-hydroxybenzaldehyde (**26**) (44 kg, 360.3 mol) and dichloromethane (430 L) at 20 °C was added bromine (122.4 kg, 765.9 mol, 2.1 equiv) slowly, and the mixture was stirred for 24 h. Assay showed <0.1% starting material and 65.6 area % product. The mixture was quenched by slow addition with 15% aqueous $Na_2S_2O_3$ (237 kg of solution, 224.8 mol, 0.62 equiv) while maintaining a temperature of <40 °C, resulting in the precipitation of the crude product. The slurry was stirred at 20 °C for 1 h before it was filtered, and the wet cake was washed with water (2 × 220 L). The crude product wet cake was combined with acetic acid (283 L) and water (11 L) and heated to 95 °C, dissolving the product. The mixture was cooled to 50 °C. Water (150 L) was added dropwise, resulting in crystallization of the product. The slurry was cooled to 15 °C, stirred for 4 h, and filtered. The wet cake was washed with water (2 × 220 L) and dried, resulting in **27** (69.8 kg, 98.4 area %, 97.7 wt %, 67.6% yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.11 (s, 1H), 10.07 (s, 1H), 7.96 (s, 1H), 7.37 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 191.0, 154.4, 136.9, 132.9,

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117.6, 115.5, 114.3. HR-MS: calcd for $C_7H_4Br_2O_2$ − H, 276.8505; found, 276.8487.

(*E*)-1-(2,4-Dibromo-5-(2-fluoro-4-nitrophenoxy)-benzylidene)-2-methylhydrazine (29). **27** (69.3 kg, 241.9 mol), DMF (444 L), and powdered potassium carbonate (51.0 kg, 369 mol, 1.5 equiv) were combined, and the mixture was heated to 60 °C. A solution of 1,2-difluoro-4-nitrobenzene (40.4 kg, 253.9 mol, 1.05 equiv) and DMF (117 L) was prepared. This solution was added dropwise at 60 °C, and then the mixture was stirred at 50 °C for 6 h. Assay showed consumption of **27**. Next, 40% aqueous methylhydrazine (31.9 kg, 277 mol, 1.15 equiv) was added dropwise while maintaining a temperature of 55−70 °C. The mixture was maintained at 70 °C for 1 h and then rapidly cooled to 20 °C. Assay showed that only 0.4% of intermediate **28** remained. The salts were filtered off. To the filtrate were added EtOAc (344 L), MTBE (662 L), and water (771 L), extracting the product into the organic phase. The aqueous phase was back-extracted with additional MTBE (662 L). The combined organic phases were washed with water (400 L) and brine (400 L). The washed organic phase was vacuum-distilled below 55 °C to 380 L, and heptane (1396 L) was added. The mixture was again vacuum-distilled below 55 °C to 380 L. The reactor was adjusted to 85 °C, stirred for 2 h, and slowly cooled to 20 °C. The slurry was stirred for 1 h, filtered, and washed with heptane (140 L). The product wet cake was recrystallized from EtOAc (75 L) and heptane (351 L) and dried, resulting in **29** (89.15 kg, 98.1 area %, 94.0 wt %, 77.5% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (dd, 1H, J = 3.0 Hz, J = 10.2 Hz), 7.99 (dd, 1H, J = 2.4 Hz, J = 10.4 Hz), 7.84 (s, 1H), 7.62 (s, 1H), 7.58 (s, 1H), 6.89 (dd, 1H, J = 8.0 Hz, J = 9.0 Hz), 6.00 (br s, 1H), 3.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.9, 150.8, 150.4, 150.2, 150.1, 137.3, 136.8, 129.7, 120.6 (2C), 118.4, 117.9, 117.5, 117.4, 113.8, 113.4, 113.2, 34.2. HR-MS: calcd for $C_{14}H_{10}Br_2FN_3O_3$ + H, 445.9146; found, 445.9142.

6-Bromo-5-(2-fluoro-4-nitrophenoxy)-1-methyl-1*H*-indazole (2). A slurry of DMF (424 L) and powdered potassium carbonate (39.4 kg, 285 mol, 1.5 equiv) was prepared and degassed by bubbling with N_2 for 1 h. Next, copper(I) chloride (1.9 kg, 19.2 mol, 0.10 equiv) was added, and the mixture was heated to 100 °C. A solution of DMF (424 L) and **29** (87.85 kg, 184.7 mol) was prepared, bubbled with N_2 for 1 h, and then added dropwise to the other mixture at 100 °C, and the resulting mixture was stirred for an additional 11 h. Assay showed 0.4% **29** remaining and 90.3 area % product. The mixture was cooled to 20 °C before 30% aqueous H_2O_2 (25.0 kg, 220.5 mol, 1.19 equiv) was added, and the mixture was stirred for 2 h. The slurry was filtered, affording 312 kg of filtrate. To the filtrate was added 1 N aqueous HCl (675 L, 3.6 equiv) dropwise, and the mixture was stirred at 20 °C for 1 h. Again, the mixture was filtered, and the wet cake was washed with water (40 L). To the 624 kg of filtrate was added more 1 N aqueous HCl (1412 L, 7.6 equiv) dropwise, resulting in precipitation of crude product. The mixture was stirred at 20 °C for 8 h and filtered, and the wet cake was washed with water (50 L). The first stage of purification of the product was accomplished by combining the wet cake (69.85 kg) with 2-methyltetrahydrofuran (1534 L) and 6% aqueous sodium hypochlorite (471 L, 417 mol, 2.26 equiv). The mixture was stirred at 40 °C for 1 h before 10% aqueous citric acid (500 L, 260 mol, 1.4 equiv) was added dropwise at 40 °C. The phases were separated. Another quantity of 10% aqueous citric acid (500 L, 260 mol, 1.4 equiv) was added dropwise at 40 °C, and the phases were separated. Then 1 N aqueous HCl (507 L, 2.7 equiv) was added dropwise to the mixture at 40 °C, and the phases were separated. The organic phase was filtered and concentrated in vacuo at <55 °C to 610 L. Absolute ethanol (754 L) was added, and the mixture was concentrated in vacuo at <55 °C to 400 L. The mixture was cooled to 20 °C, stirred for 2 h, and filtered, resulting in product of 96.9 area %. This wet cake was reslurried with absolute ethanol (280 L), and the slurry was stirred at 20 °C for 6 h, filtered, and washed with absolute ethanol (90 L). Drying afforded the product (52.21 kg, 98.0 area %, 89.7 wt %). The final stage of product purification was accomplished by reslurrying the product (52.06 kg) in isopropyl acetate (172 L) at 20 °C for 7 h and then filtering, washing the yellow wet cake with absolute ethanol (175 L). Drying afforded **2** (40.79 kg, 99.3 area %, 99.3 wt %, 59.9% yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.36 (dd, 1H, J = 2.8 Hz, J = 11 Hz), 8.10 (s, 1H), 8.02 (d, 1H, J = 9.2 Hz), 7.85 (s, 1H), 6.88 (t, 1H, J = 8.4 Hz), 4.09 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 151.6, 151.2, 151.1, 149.2, 143.5, 142.0, 141.9, 138.1, 132.9, 123.0, 121.3 (2C), 116.6, 115.2, 114.2, 113.7, 113.2, 113.0, 35.8. HR-MS: calcd for $C_{14}H_9BrFN_3O_3$ + H, 365.9884; found, 365.9882.

***N*-(4-((6-Bromo-1-methyl-1*H*-indazol-5-yl)oxy)-3-fluorophenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (31).** Acetonitrile (268 L), **2** (26.8 kg, 73.2 mol), 5% platinum on sulfided carbon (4.01 kg, 1.02 mol, 0.014 equiv), and zinc bromide (0.269 kg, 1.19 mol, 0.016 equiv) were combined, and the mixture was inerted, heated to 55 °C, and then placed under 1 atm H_2 for 12 h, resulting in complete consumption of **2** to afford aniline **30**. The reaction mixture was inerted, cooled to 20 °C, and filtered over Celite (20 kg) in acetonitrile (38 L), and the reactor and wet cake were rinsed with acetonitrile (102 L). The combined filtrates (385 L) were concentrated under vacuum at 60 °C to one-third of the initial volume, resulting in a concentrated organic liquid (117 kg), which was added to **16** (19.21 kg, 77.7 mol, 1.06 equiv) and *N*-methylmorpholine (12 L, 109.4 mol, 1.49 equiv). The reaction mixture was stirred at 20 °C before 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) (14.3 kg, 81.4 mol, 1.11 equiv) was added in two portions, resulting in an exotherm to 43 °C. After complete addition, the mixture was heated to 55 °C for 15 h, resulting in 99.7% conversion to product. Methanol (250 L) was added to the mixture at 55 °C. The mixture was stirred at 55 °C for 2 h, cooled to 20 °C within 3 h, and stirred at 20 °C for 17 h. The slurry was filtered, and the reactor and wet cake were washed with methanol (72 L). The product was dried on a filter dryer under vacuum and N_2 stream, resulting in **31** (37.39 kg, 98.5 area %, 96.7 wt %, 87.4% yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.96 (s, 1H), 8.47 (d, 1H, J = 7.6 Hz), 8.18 (s, 1H), 7.97 (dt, 1H, J = 2.0 Hz, J = 6.8 Hz), 7.46 (m, 5H), 7.32 (d, 1H, J = 8.8 Hz), 6.92 (t, 1H, J = 9.2 Hz), 6.70 (d, 1H, J = 8.0 Hz), 4.04 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 163.0, 161.6, 160.7, 153.3 (2C), 150.9, 146.5, 144.0, 139.8, 139.7, 137.2, 135.0, 134.9, 134.1 (2C), 132.4, 130.1, 130.0, 122.8, 120.0, 116.9, 116.7, 116.4, 116.1, 116.0, 114.7, 113.6, 109.5, 108.7, 108.5, 107.8, 35.7, 21.7. HR-MS: calcd for $C_{27}H_{19}BrF_2N_4O_3$ + H, 565.0681; found, 565.0674.

***tert*-Butyl 4-(5-(2-Fluoro-4-(1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamido)-phenoxy)-1-methyl-1*H*-indazol-6-yl)-1*H*-pyrazole-1-carboxylate (17).** A solution of tribasic potassium phosphate (18.2 kg, 85.7 mol, 2.1 equiv) in water (73 L) was prepared and

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degassed. Separately, THF (339 L), **31** (24.2 kg, 41.4 mol), **13** (15.1 kg, 51.3 mol, 1.24 equiv), and di-*tert*-butyl dicarbonate (2.33 kg, 10.7 mol, 0.26 equiv) were combined, and the mixture was degassed 5 times and heated to 40 °C. Next, the catalyst [1,1′-bis(di-*tert*-butylphosphino)]ferrocene palladium(II) dichloride (Pd-118) (0.40 kg, 0.61 mol, 0.015 equiv) was added, followed by the degassed aqueous potassium phosphate tribasic solution. The mixture was stirred at 45 °C for a total of 70 min, resulting in complete conversion to product. The mixture was cooled to 20 °C, and the phases were separated. The organic layer was vacuum-distilled at 60 °C, and 225 L of distillate was collected. The mixture was stirred at 55 °C for 2 h, cooled to 20 °C within 3 h, and held at this temperature for 19 h. The slurry was filtered, and the reactor and wet cake were washed with a mixture of THF (30 L) and water (30 L). The product was dried on a filter dryer under vacuum and a stream of N_2. This wet cake (14.3% loss on drying) was divided into two equal portions (16.3 kg each), suspended in a mixture of THF (420 L) and water (20 L), and heated to 60 °C. To this mixture was added thiol-functionalized silica gel (3.87 kg). The mixtures were stirred at 60 °C for 6 h and filtered, and the reactor was rinsed with 60 °C THF (20 L). The filtrate (846 L) was vacuum-distilled at 60 °C to one-third of the original volume. To the concentrate was added IPA (223 L), and then the mixture was vacuum-distilled. This step was repeated with additional IPA (223 L) at 60 °C. The resultant concentrate was cooled to 10 °C within 2 h and held at this temperature for 17 h, after which the slurry was filtered and the wet cake was washed with cold IPA. The product was dried in a filter dryer with vacuum and a stream of N_2, resulting in **17** (25.12 kg, 99.7 area %, 86.9 wt %, 80.8% yield) with low metal content (14 ppm Pd; <1 ppm Pt, Zn; 5.5 ppm Fe). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.95 (s, 1H), 8.62 (s, 1H), 8.46 (d, 1H, J = 8.0 Hz), 8.40 (s, 1H), 8.19 (s, 1H), 7.97 (m, 2H), 7.44 (m, 4H), 7.34 (s, 1H), 7.28 (d, 1H, J = 9.2 Hz), 6.92 (t, 1H, J = 9.2 Hz), 6.69 (d, 1H, J = 8.0 Hz), 4.10 (s, 3H), 2.06 (s, 3H), 1.58 (s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 163.0, 161.6, 160.7, 153.3, 147.4, 146.9, 144.0, 143.2, 139.6, 139.5, 137.1, 134.8, 132.1, 130.1, 130.0, 128.9, 122.6, 121.4, 119.8, 117.0, 116.7, 116.5, 109.5, 109.0, 107.8, 85.2, 35.6, 27.4, 21.7. HR-MS: calcd for $C_{35}H_{30}F_2N_6O_5$ + H, 653.2319; found, 653.2313.

***N*-(3-Fluoro-4-((1-methyl-6-(1*H*-pyrazol-4-yl)-1*H*-indazol-5-yl)oxy)phenyl)-1-(4-fluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carboxamide (1, LY2801653).** Absolute ethanol (430 L), **17** (25.0 kg, 33.30 mol), and a seed of the correct form (87 g, 0.005 equiv) were combined. The resultant suspension was heated to reflux, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (6.14 kg, 40.3 mol, 1.21 equiv) was added. The mixture was refluxed for 9 h (resulting in 99.92% conversion), cooled to 10 °C over 14 h, and stirred at 10 °C for 2.5 h. The slurry was filtered on a filter dryer, and the reactor and wet cake were washed with cold ethanol (54 L). The product was dried in a filter dryer by applying vacuum and a stream of N_2, resulting in **1** (18.54 kg, 99.4 area %, 98.75 wt %, 99.5% yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.98 (s, 1H), 11.93 (s, 1H), 8.46 (d, 1H, J = 7.6 Hz), 8.16 (s, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.96 (dd, 1H, J = 2.4 Hz, J = 13.2 Hz), 7.91 (s, 1H), 7.45 (m, 4H), 7.25 (m, 2H), 6.86 (t, 1H, J = 9.6 Hz), 6.68 (d, 1H, J = 8.0 Hz), 4.07 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 163.2, 163.0, 161.5, 160.7, 153.4, 153.2, 151.0, 147.5, 143.0, 140.1, 140.0, 138.0, 137.3, 134.5, 134.4, 134.1, 131.9, 130.1, 130.0, 127.4, 124.1, 121.8, 119.7, 117.0, 116.8, 116.7, 116.4, 116.1, 116.0, 108.9, 108.7, 108.4, 108.2, 107.8, 35.5, 21.7. HR-MS: calcd for $C_{30}H_{22}F_2N_6O_3$ + H, 553.1794; found, 553.1788.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for the compounds in Scheme 12 along with experimentals for Schemes 1, 5, and 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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