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Development an Efficient Route to the 5-Lipoxygenase Inhibitor PF-04191834

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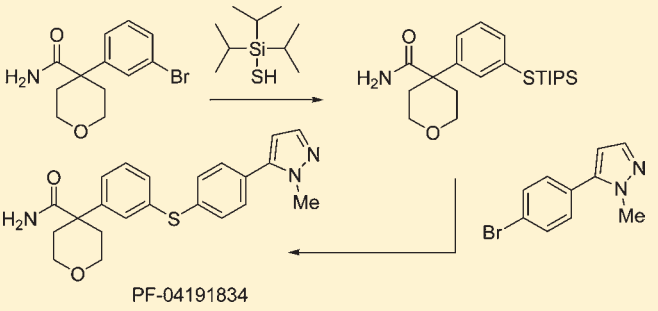
ABSTRACT: A convergent six-step process for the synthesis of PF-04191834 (**1**), a potent and selective 5-lipoxygenase inhibitor, has been developed and used to deliver over 20 kg of API. The process uses the same bond-forming steps as the initial medicinal chemistry route, including the use of two consecutive Pd-catalyzed Ar−S couplings to form the key diaryl thioether linkage. The reaction conditions and downstream processing have been optimized to eliminate column chromatography and aqueous work-ups and to minimize disproportionation of **1**, to ensure successful scale-up.



INTRODUCTION

Leukotrienes are a family of highly potent lipid pro-inflammatory mediators that play a significant role in a number of allergic and inflammatory diseases.[1] These bioactive lipids are generated by metabolism of arachidonic acid, initially to leukotriene A4 (LTA4), by the enzyme 5-lipoxygenase (5-LO)[2] and its accessory activating partner protein, 5-LO-activating protein (FLAP).[3] Subsequently LTA4 may be further metabolized by LTA4 hydrolase to form LTB4, a potent chemoattractant for neutrophils, macrophages and other inflammatory cells. Alternatively, metabolism of LTA4 by LTC4 synthase enzyme leads to the cysteinyl leukotrienes, LTC4, LTD4 and LTE4, which increase vascular permeability, contract smooth muscles cells and increase mucus production. Inhibiting the production of these pro-inflammatory mediators generated by the 5-LO pathway has potential therapeutic benefit in numerous indications, including asthma, COPD, atherosclerosis,[4] pain[5] and cancer.[6] The key role of 5-LO in catalyzing the first step of the metabolism of arachidonic acid has therefore made it an important pharmacological target for a number of disease areas.

As part of a 5-LO drug discovery program, the potent and selective 5-LO inhibitor PF-04191834 (**1**) was identified[7] and progressed into development. From an inspection of the medicinal chemistry route (Scheme 1), it was evident that the convergent synthesis developed would be an appropriate strategy to assemble the active pharmaceutical ingredient (API); however, the possibility of reversing the step order and/or telescoping the two Pd-catalyzed steps were obvious areas for exploration. The use of chromatography to separate the pyrazole regioisomers **4** and **5**, as well as to purify the API, was also addressed in our development program.

Another initial concern was the use of TIPS-thiol **7** as the hydrogen sulfide surrogate.[8] However, while recognizing the poor atom economy[9] and potential long-term challenges associated with this reagent (unpleasant odor, limited number of vendors, long leadtime), we were able to source adequate supplies for early phase development,[10] and thus no alternative sources of sulfur were examined.

RESULTS AND DISCUSSION

The original synthesis of pyrazole **4** entailed heating a mixture of 4-bromoacetophenone **2** and dimethylformamide dimethyl acetal (DMFDMA) in DMF at 125 °C for 3 h.[7] The cooled reaction mixture was concentrated to a thick oil, redissolved in DMF and treated with methyl hydrazine (3 equiv) at 75 °C. Crude **4** (containing 5% of the regioisomer **5**) was isolated by concentration to dryness and purified by chromatography on silica gel. While this was suitable for small-scale preparations, it was not appropriate for our scale-up facilities and required some modification.

The purpose of the first concentration to dryness was to remove excess DMFDMA to avoid reaction with methyl hydrazine. Postulating that the condensation product(s) of DMFDMA and methyl hydrazine should be water-soluble and therefore purge upon aqueous quench, we optimized the relative amounts of both DMFDMA (2.0 equiv) and methyl hydrazine (4.0 equiv) to ensure complete consumption of **3**. As anticipated, any DMFDMA-methyl hydrazine related byproducts were purged in the aqueous work-up.[11]

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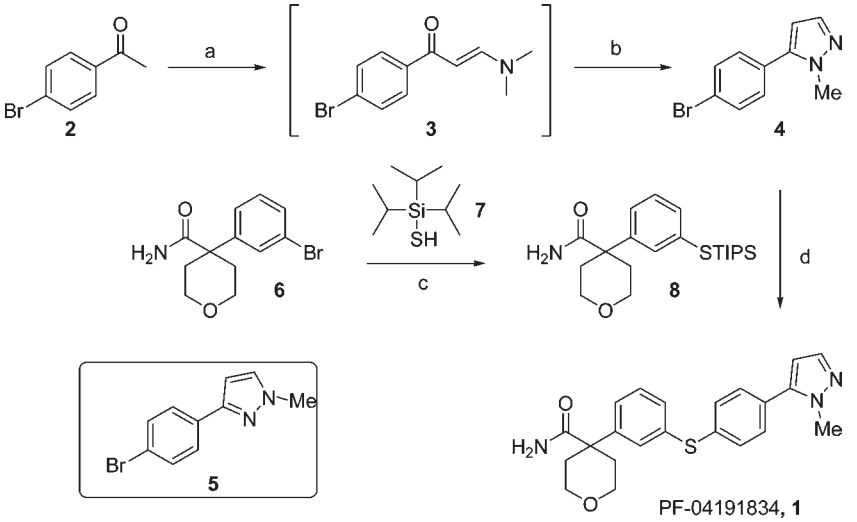
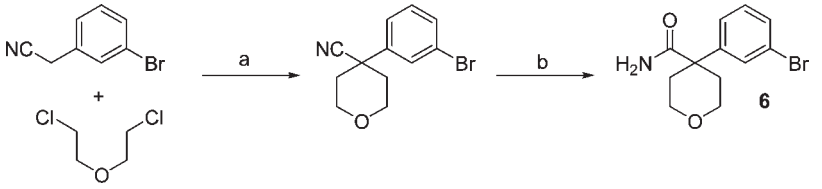
Scheme 1. Medicinal Chemistry Route to PF-04191834 (1)[a]



[a] Reagents and conditions: (a) *N*,*N*-dimethylformamide dimethylacetal, DMF, reflux, 4−5 h; (b) methylhydrazine, DMF, 75 °C, 4 h, 68%; (c) NaO^{t}Bu, $Pd(OAc)_2$, 1,1-bis(diisopropylphosphino) ferrocene, 1,4-dioxane, reflux, 1 h, 84%; (d) $(Ph_3P)_4Pd$, bis[(2-diphenylphosphino)]phenylether, 1 M KO*t*-Bu in THF, *i*-PrOH/5% H_2O, 90 °C, 4 h, 86%.

Scheme 2. Literature Synthesis of Amide 6 (from ref 13a)[a]



[a] Reagents and conditions: (a) aqueous NaOH, *n*-Bu_4NHSO_4, THF, reflux; then IPA/water cryst, 68%; (b) KOH, IPA, reflux; then water, 89%.

We then examined the effect of temperature on the condensation of **3** with methyl hydrazine, in the hope that lower temperatures would reduce the level of regioisomer **5** formed. Fortunately this proved to be the case; when the reaction was conducted at 25 °C, the level of **5** was halved (to around 2.5%), although the reaction took ∼16 h to reach completion (compared to 3 h in the original procedure). Given the challenges of separating the regioisomer **5** from **4**, this was an acceptable compromise. In order to simplify the work-up, MTBE was used as solvent for the condensation reaction (in conjunction with DMF from the first stage), and this had no effect on the regioselectivity or reaction rate.

The product solution was then washed with aqueous ammonium chloride to remove DMF and any DMFDMA-methyl hydrazine adducts. The resulting solution was filtered through silica gel (∼3 g silica/g of **2**; eluting with MTBE) to remove polar impurities that adversely affected the crystallization. Solvent exchange to heptane via distillation and controlled crystallization, seeding at 40−45 °C, efficiently removed the regioisomer, affording the desired pyrazole **4** in an acceptable 68% overall yield from bromoacetophenone **2**. This procedure was then successfully outsourced. All batches of **4** were analyzed to ensure that the level of residual methyl hydrazine was below the threshold of toxicological concern (TTC).[12]

The other half of the API, amide **6**, is a known compound,[13] prepared in a relatively straightforward fashion by base-mediated condensation of commercially available 2-(3-bromophenyl)acetonitrile and bis(2-chloroethyl)ether, followed by nitrile hydrolysis (Scheme 2). As an alternative to the literature procedure (KOH in refluxing IPA), refluxing with KOH in *tert*-butanol or treatment with sulfuric acid[7] could also be used to hydrolyze the nitrile. This process was outsourced to support all manufacturing campaigns. Analysis of **6** showed that the level of residual bis(2-chloroethyl)ether was below the TTC.

The crux of the synthesis was the two consecutive Pd-catalyzed carbon−sulfur bond-forming steps (occasionally referred to as the Migita reaction).[14] In addition to a careful evaluation of the existing route, both the alternative step-reordered sequence (first reacting bromopyrazole **4** with TIPS-thiol **7**, followed by amide **6**) and the completely telescoped process were examined. While in the long term a telescoped sequence would offer the opportunity for streamlined processing, at this early stage, the importance of having a crystalline late-stage intermediate (namely, **8**) to control impurities was paramount, and therefore the telescoped process was not developed beyond the initial, successful proof of concept experiments. Since the intermediate S-TIPS pyrazole in the step-reordered sequence was not crystalline, the route via **8** was selected.

The initial synthetic procedure for the coupling between bromide **6** and TIPS thiol **7** (1.1 equiv) used the Buchwald conditions,[15] namely, sodium *tert*-butoxide (1.2 equiv) in refluxing 1,4-dioxane in the presence of palladium(II) acetate (2 mol %) and 1,1′-bis(diisopropylphosphino)ferrocene (2.4 mol %). After an aqueous work-up, **8** was crystallized in excellent purity from

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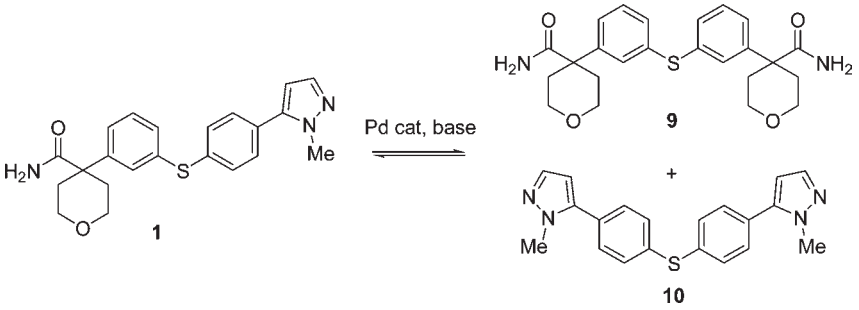
Scheme 3. Palladium-Mediated Equilibration of 1



ethyl acetate−hexanes (80% yield). While this procedure had been successfully demonstrated on a 300-g scale,[7] the yield dropped significantly on further scale-up, and the process therefore required modification prior to transfer into our kilo laboratory or pilot plant facilities. The main concern was the stability of the product **8** towards the aqueous work-up employed. An investigation showed that protracted work-up times, as would be expected on scale-up, led to significant degradation of **8**, primarily through loss of the TIPS protecting group and subsequent side reactions (e.g., disulfide formation). A detailed investigation showed that the aqueous stability of **8** was linked to pH and especially to temperature (with greatest stability around pH 7 and at low temperature). A pH-controlled, low temperature (10 °C) aqueous work-up was developed, but notwithstanding a successful demonstration thereof at laboratory scale, the decision was made to develop a nonaqueous work-up protocol to avoid the hydrolytic instability altogether.

In parallel with these initial work-up investigations, a small catalyst/solvent screen for the reaction was conducted, from which [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium-(II) [$PdCl_2$(dppf)] in toluene emerged as a suitable alternative.[16] Replacing the undesirable solvent, 1,4-dioxane, with toluene and using a readily available, preformed metal complex resolved two other concerns with the initial synthesis.

Having identified a suitable solvent/catalyst combination, attention returned to the work-up process. Upon reaction completion, the mixture consists of a solution containing the product, excess thiol **7** (1.2 equiv used) and catalyst, plus suspended inorganic salts (primarily sodium bromide). Since the purpose of the aqueous work-up was largely to remove these inorganic salts, this was readily replaced by a simple filtration through Celite. The filtrate was then diluted with heptane to induce crystallization of **8**. To ensure that **8** remained in solution during the filtration, ethyl acetate was added beforehand, and the Celite was washed with ethyl acetate.

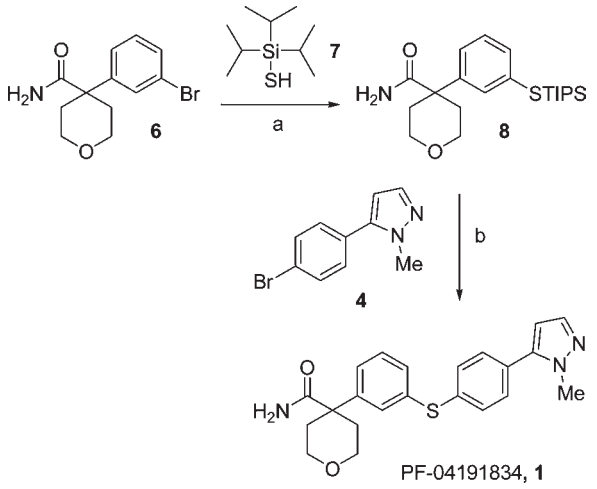
This process was then scaled up, and reproducibly delivered good quality **8** in ∼80% yield (up to 20-kg scale). Key points essential to success were to ensure that the water level was <0.01% (easily achieved by azeotropic distillation with toluene) and to rigorously exclude oxygen from the reactor by a thorough degassing process prior to addition of the catalyst; high oxygen levels led to catalyst poisoning and incomplete reaction. The presence of water resulted in the formation of symmetrical sulfide **9** (Scheme 3), through TIPS cleavage and reaction of the resulting thiol with bromide **6**. The use of high quality sodium *tert*-butoxide was essential for reliable conversion, with best results obtained using material containing less than 0.5% NaOH (as measured by KF titration).

Importantly, we found that addition of catalyst to the reaction mixture at room temperature followed by a slow heating ramp to mimic potential scale-up conditions resulted in incomplete conversion. This was interpreted as resulting from catalyst degradation by the TIPS thiolate prior to the mixture reaching a temperature at which the coupling proceeded. The coupling was not exothermic, and optimal results were obtained if the catalyst was charged at reaction temperature (75 °C), rather than prior to heating. A small excess of TIPS thiol (1.2 equiv) was used to ensure complete consumption of bromide **6** as this did not purge well in the crystallization of **8**. Any residual **6** reacted in the subsequent step, forming sulfide **9**, which was also challenging to purge (vide infra).

In the initial synthesis, the second Ar−S coupling between S-TIPS amide **8** and bromo pyrazole **4** was conducted under basic conditions in aqueous isopropyl alcohol (5% water) using a mixture of tetrakis(triphenylphosphine)palladium (0) (10 mol %) and bis[(2-diphenylphosphino)]phenyl ether (10 mol %). The product (**1**) was crystallized by addition of aqueous acid and purified by chromatography on silica gel. Our enabling work was focused on optimizing the reaction conditions, reducing the catalyst level and developing a suitable isolation that removed the need for chromatography while still controlling the level of residual palladium to below 50 ppm. One unexpected complication was that the oxidized ligand proved difficult to separate from **1**, even via chromatography, and therefore an alternative catalyst was highly desirable.

A small screen of catalyst/solvent/base combinations was conducted, from which $PdCl_2$(dppf), sodium methoxide (in methanol) and 2-methyl THF (MeTHF) were identified as the optimal conditions. The presence of a nucleophilic base and an alcohol proved essential for the initial in situ deprotection of **8** to generate the requisite thiolate. A slight excess of bromopyrazole **4** (1.1 equiv) was used to ensure complete consumption of **8**. The choice of MeTHF as solvent has the added advantage that the product **1** is not particularly soluble and precipitates upon cooling, with good purge of most impurities (apart from sulfide **9**). This initially isolated crude **1** still contains large quantities of inorganic salts (notably sodium bromide) and significant levels of palladium (>5000 ppm). The inorganic salts were removed by slurrying crude **1** in water; however, removing the palladium was more challenging. Since **1** has poor solubility in most organic solvents, the selected approach was to dissolve crude **1** in THF (70 mL/g), add a suitable scavenger resin (we chose to use SiliaBond thiol, based on prior experience) and stir at reflux until the palladium was removed. The palladium purge took up to 24 h, and to ensure that acceptable levels were achieved, in-process monitoring of the Pd level by ICP-MS analysis of samples was used on scale. After filtration to remove the resin, **1** was crystallized by

Scheme 4. Enabled Route to 1[a]



[a] Reagents and conditions: (a) (i) NaO*t*-Bu, $PdCl_2$(dppf), toluene, reflux 1 h; (ii) filtration, EtOAc; (iii) heptane cryst, 80%; (b) (i) $PdCl_2$(dppf), NaOMe (25% w/w in MeOH), 2-MeTHF, 70 °C; (ii) water reslurry; (iii) SiliaBond thiol, THF, reflux; then heptane; (iii) MeOH reflux; 70% overall.

partial concentration and addition of heptane. However, this process provided the wrong polymorph, and consequently an additional reslurry in refluxing methanol was required to convert the material to the correct polymorph. While this work-up process was laborious and rather inefficient, we were unable to identify an alternative in the time available, and therefore it was used on scale.

The process above was scaled to provide 4 kg of suitable quality **1** in 73% yield from **8**. However, when the process was scaled up to ~15 kg, high levels of the sulfides **9** and **10** were observed (around 5% of each, Scheme 3). The bis-pyrazole sulfide **10** purged in the initial crystallization from MeTHF, but the bis-amide sulfide **9** did not purge through the work-up, resulting in API (**1**) that failed to meet purity specifications. While we were unable to identify crystallization conditions to purge this impurity, an efficient chromatographic procedure was developed to purify the batch to an appropriate standard; see the Experimental Section for details thereof.

The key difference between this batch and previous, successful batches was that the reaction mixture had been held at temperature (70 °C) for an extended period (40 h, instead of the more normal 2−3 h). In addition, at this stage of development the reaction protocol had been to charge everything to the vessel prior to heating, and therefore the slower heat-up time on larger scale might have had an effect. This suggested that the product (**1**) was degrading under the reaction conditions, possibly through a Pd-mediated C−S bond cleavage, and the resulting species were recombining to generate the symmetrical sulfides **9** and **10** (Scheme 3). The formation of symmetrical sulfide byproducts has been previously observed in both Ni-[17] and Pd-catalyzed[18] processes, and a mechanism involving Ni-mediated Ar−S cleavage of a diaryl thioether by a thiolate has been proposed for the Ni-catalyzed process.[17] In the case of the Pd-catalyzed process, formation of the symmetrical byproducts was suppressed by increasing the catalyst loading and conducting the reaction at a higher temperature.[18]

A purified sample of **1** (>99% purity) was subjected to the reaction conditions (NaOMe, $PdCl_2$(dppf), 2-MeTHF), and after 6 h about 3% of the symmetrical sulfides **9** and **10** was observed, increasing to 5% after 18 h. A control experiment in which the Pd catalyst was omitted showed no symmetrical sulfides. Repeat experiments confirmed this result; however, there was some variability in the levels of **9** and **10** observed, in some cases requiring 24−48 h to reach 3%. This suggests that these symmetrical sulfide impurities can also be formed in the absence of an external thiolate, in contrast to the literature mechanism, but due to time constraints we were unable to conduct further investigations.

On the basis of this result and the literature evidence for the generation of symmetrical sulfides during extended reaction periods,[17,18] the reaction conditions were modified to minimize the reaction time (Scheme 4). In practice, the catalyst loading was increased, in this case to 2 mol % (added in two 1 mol % portions 1 h apart), and the catalyst was charged while the reaction mixture was at the required reaction temperature (70 °C). As a further precaution, all in process analyses were conducted promptly (within 15 min of the sample being taken). Under these conditions, the reaction proceeded to completion in around 2 h on scale. The work-up procedure used previously was retained, and we were able to prepare 20 kg of suitable quality **1** in around 70% yield, without requiring chromatographic purification.

In conclusion, a robust, convergent, four-step process to prepare PF-04191834 (**1**) has been developed and has been used to deliver over 20 kg of **1** in 37% overall yield from 4-bromoacetophenone. Optimal catalyst, base and solvent combinations were identified for the two consecutive palladium-catalyzed carbon−sulfur couplings, and an effective strategy to purge palladium residues and deliver the correct polymorph was developed. Palladium-mediated disproportionation of **1** was observed, but this could be suppressed by adding the catalyst to the reaction at 70 °C and minimizing the reaction time.

EXPERIMENTAL SECTION

General Procedures. Intermediates were analyzed by reverse phase LC−MS on an Agilent 1100 series instrument, coupled to a Waters Micromass ZQ mass spectrometer according to the following conditions: column Extend-C18 3.0 mm × 50 mm i.d., 1.8 μm; eluent A, 5% v/v acetonitrile in 10 mM aqueous ammonium acetate; eluent B, acetonitrile; flow rate 1.2 mL/min; wavelength, diode array (190−400 μm); column temperature, 50 °C; injection volume, 10 μL; at t = 0 min, 5% eluent B; at t = 3.5 min, 100% eluent B; at t = 4.5 min, 100% eluent B; at t = 4.6 min, 5% eluent B. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus spectrometer at 400 and 100.6 MHz, respectively. The quoted melting points for all materials are the onset temperatures observed by DSC.

5-(4-Bromophenyl)-1-methyl-1*H*-pyrazole 4. A reactor was charged with DMF (12 mL), 4-bromoacetophenone **2** (20 g, 0.1 mol) and *N*,*N*-dimethylformamide dimethylacetal (29 mL, 0.2 mol). The mixture was heated to 110 °C for 4 h, with the methanol and water generated during the reaction being removed by distillation. The mixture was then cooled to 25 °C, MTBE (100 mL) and methylhydrazine (21 mL, 0.4 mol) were added, and the mixture was stirred overnight at room temperature. The reaction mixture was then washed with 1 M aqueous ammonium chloride (3 × 40 mL) and water (40 mL). The organic phase was dried by azeotropic distillation using a Dean−Stark apparatus. The solution was filtered through a silica

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gel cartridge (60 g), eluting with MTBE. The fractions containing product were combined and concentrated by distillation (to approximately 70 mL). Heptane (120 mL) was added, and distillation was continued until the pot temperature reached 98 °C (approximately 100 mL of distillate was collected). The mixture was cooled to 40 °C and seeded, and the temperature was maintained at 40 °C for 30 min while crystallization was initiated and then slowly chilled to 0 °C over 90 min. The mixture was held at 0 °C for 30 min, and the mixture was then filtered. The solid was washed with chilled (0 °C) heptane (3×) and dried on the filter to give the product **4** as a cream-colored, crystalline solid (16.3 g, 68% yield). Mp 58 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.68 (2H, dt, J = 8.4, 1.8 Hz), 7.49 (3H, m), 6.43 (1H, d, J = 2.0 Hz), 3.86 (3H, s). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 141.5, 137.7, 131.4, 130.6, 129.6, 121.8, 106.0, 37.5. LC−MS: found m/z 237.05/235.02 $[M + H]^+$. Anal. Calcd for $C_{10}H_9BrN_2$: C, 50.66; H, 3.83; Br, 33.70; N, 11.82. Found: C, 50.62; H, 3.78; Br, 33.94; N, 11.77.

4-(3-(Triisopropylsilylthio)phenyl)-tetrahydro-2*H*-pyran-4-carboxamide 8. A nitrogen-purged reactor was charged with toluene (349.6 L), amide **6** (26 kg, 91.5 mol) and sodium *tert*-butoxide (10.55 kg, 109.8 mol), followed by tri-isopropylsilanethiol **7** (20.91 kg, 109.8 mol) and a toluene wash (10.4 L). The mixture was heated to 75 °C, [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (0.67 kg, 0.92 mol) was added under nitrogen, and the mixture was stirred at reflux until reaction completion was confirmed by HPLC analysis (approx 2 h). The reaction mixture was cooled to 22 °C, ethyl acetate (780 L) was added, and the mixture was stirred at this temperature for at least 30 min. The slurry was filtered through Celite (39 kg), and the Celite cake was washed with ethyl acetate (260 L). The combined filtrates were distilled under vacuum to one-fifth of the volume, heptane (520 L) was added to the slurry, and the mixture was cooled to 5 °C and stirred at this temperature for at least 1 h. The product was isolated by filtration, and the cake was washed with heptane (260 L), to afford the title compound **8** as a white solid (28.45 kg, 79% yield) after drying at 50 °C under vacuum. Mp 141 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.45−7.23 (4H, m), 7.05 (1H, m), 5.10 (1H, s), 3.72 (2H, m), 3.47 (2H, t, J = 10.8 Hz), 2.40 (2H, br, d, J = 13.3 Hz), 1.77 (2H, m), 1.04−0.87 (21H, m). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 174.5, 145.7, 135.9, 129.4, 125.8, 125.2, 125.0, 64.6, 47.9, 33.9, 17.8, 12.1. LC−MS: found m/z 394.24 $[M + H]^+$. Anal. Calcd for $C_{21}H_{35}NO_2SSi$: C, 64.07; H, 8.96; N, 3.56; S, 8.15. Found: C, 64.13; H, 8.97; N, 3.55; S, 8.20.

4-(3-([4-(1-Methyl-1*H*-pyrazol-5-yl)phenyl]thio]phenyl)-tetrahydro-2*H*-pyran-4-carboxamide 1. A reactor was charged with 2-methyltetrahydrofuran (256 L), S-TIPS amide **8** (28.45 kg, 72.3 mol) and pyrazole **4** (18 kg, 75.9 mol), the reactor was evacuated and repressurized with nitrogen, and the mixture was heated to 60 °C. Sodium methoxide in methanol (25 wt %; 32.8 kg, 151.8 mol) was added, the reactor was evacuated and repressurized with nitrogen and stirred at 60 °C for a minimum of 30 min. The reaction mixture was then heated to 70 °C, and [1,1′-bis-(diphenylphosphino)ferrocene] dichloropalladium(II) (0.530 kg, 0.73 mol) was added; the reaction mixture was stirred at this temperature for 1 h, whereupon a further charge of [1,1′-bis-(diphenylphosphino)ferrocene] dichloropalladium(II) (0.530 kg, 0.73 mol) was added, and the mixture was stirred at 70 °C until reaction completion was confirmed by HPLC analysis (approx 1 h). The mixture was cooled to 0 °C and stirred at this temperature for a minimum of 1 h; the slurry was filtered, and the filter cake was washed with 2-methyltetrahydrofuran (3 × 71.1 L). The filter cake was then suspended in water (569 L), stirred at 23 °C for a minimum of 2 h, and filtered, and the solid was washed with water (2 × 142 L) to afford crude **1** as an off-white solid (23.2 kg) after drying at 70 °C under vacuum.

A reactor was charged with tetrahydrofuran (812 L), crude **1** (11.6 kg, 29.5 mol) and SiliaBond thiol (Silicycle Inc., 5.8 kg), the slurry was heated to 60 °C, and the mixture was stirred at this temperature until ICP-MS analysis of a sample confirmed adequate Pd purge, a minimum of 18 h. The mixture was cooled to 22 °C and filtered, and the filter cake was washed with tetrahydrofuran (58 L). The combined filtrate was distilled under vacuum to a volume of 10 L/kg and then cooled to 25 °C. Heptane (58 L) was added to the slurry at this temperature, and the mixture was aged for 30 min before the solid was isolated by filtration, washed with heptane (58 L), and dried under vacuum at 45 °C to afford partially purified **1** as a white solid (11.08 kg, 95% yield). This process was repeated on the remaining crude **1**.

A reactor was charged with methanol (441 L) and partially purified **1** (22.06 kg). The slurry was heated to reflux for 18 h, cooled to 20 °C, and stirred at this temperature for 2 h. The product was then isolated by filtration, washed with methanol (110 L), and dried under vacuum at 70 °C to afford the title compound **1** as a white solid (19.96 kg, 70%). Mp 173 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.52 (2H, m), 7.48 (2H, m), 7.42 (2H, m), 7.35 (2H, m), 7.29 (2H, m), 7.07 (1H, br. s), 6.42 (1H, d, J = 1.8 Hz), 3.85 (3H, s), 3.74 (2H, dt, J = 11.7, 3.7 Hz), 3.47 (2H, br. t, J = 11.7 Hz), 2.41 (2H, br. d, J = 13.3 Hz), 1.80 (2H, m). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 174.6, 146.0, 141.9, 137.9, 136.0, 133.2, 130.1, 129.7, 129.4, 129.3, 128.6, 125.6, 105.9, 64.6, 47.8, 37.6, 33.9. LC−MS: found m/z 394.17 $[M + H]^+$. Anal. Calcd for $C_{22}H_{23}N_3O_2S$: C, 67.15; H, 5.89; N, 10.68; S, 8.15. Found: C, 67.09; H, 5.93; N, 10.69; S, 8.16.

Optional Procedure for Chromatographic Purification of 1. Silica gel (J.T. Baker flash silica, 40−60 μm; 5 kg/kg crude **1**) was slurried in toluene (2.1 kg/kg silica), and the resulting slurry was loaded onto a suitable column. The column was equilibrated with toluene (4.6 kg/kg silica) at a flow rate of 4 L/min. A solution of **1** in a mixture of CH_2Cl_2/EtOH (97:3; 22.6 kg/kg crude **1**) was loaded onto the equilibrated column at a rate of 3 L/min; the feed line was rinsed with additional CH_2Cl_2/EtOH (97:3; 1 kg/kg crude **1**). The product was then eluted from the column with a toluene/*i*-PrOH mixture (10:1 mixture; 4 L/min flow rate). Fractions containing **1** were combined and concentrated under reduced pressure to afford crude **1**, which was taken directly into the next step (Si-thiol purification); see previous experimental procedure for details thereof.

The major impurity removed through this chromatographic procedure is sulfide **9**. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.35 (6H, m), 7.26 (2H, br. s), 7.16 (2H, dt, J = 7.0, 2.0 Hz), 7.04 (2H, br. s), 3.73 (4H, dt, J = 11.7, 3.5 Hz), 3.46 (4H, t, J = 10.6 Hz), 2.38 (4H, br. d, J = 13.5 Hz), 1.77 (4H, ddd, J = 13.5, 10.6, 3.5 Hz). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 174.6, 145.7, 134.5, 129.5, 128.5, 127.8, 124.9, 64.6, 47.8, 33.9. LC−MS: found m/z 441.12 $[M + H]^+$. Anal. Calcd for $C_{24}H_{28}N_2O_4S$: C, 65.43; H, 6.41; N, 6.36; S, 7.28. Found: C, 65.01; H, 6.37; N, 6.41; S, 7.30.

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(10) During early development, the primary focus was to deliver a "fit-for-purpose" process to deliver material for clinical studies. Subsequent work to identify a more suitable long-term process will be the subject of a future publication.

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