A Robust Process for an mGluR5 Negative Allosteric Modulator: Difluoromethylation and Sonogashira Coupling on Large Scale

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ABSTRACT: The development of the potent and selective mGluR5 negative allosteric modulator (NAM) 1 is described. Key features in the process, which has been implemented on a multikilogram scale, include a high-temperature difluoromethylation reaction, a Sonogashira coupling, and careful control of residual Pd and Cu in the final API. Due to the relative nonpolar nature of the intermediates, water-miscible solvents were employed in all four steps to allow for direct crystallizations upon reaction completion. In addition, several crystalline morphologies of the API were discovered, and the isolation of the desired form II will be discussed.

INTRODUCTION
GRN-529 (1) was the third in a series of mGluR5 negative allosteric modulators (NAMs)1 identified by Wyeth Medicinal Chemistry (see Figure 1) that possess high affinity for the mGluR5 allosteric binding site. 1 also exhibits >100-fold selectivity for mGluR5 versus the other group I (mGluR1) and group II mGluRs (mGluR2 and mGluR3) in functional assays. 1 was preferentially advanced over other mGluR5s due to improved hERG therapeutic index.2 During the predevelopment phase, 1 was also successfully evaluated by Drug Safety and Metabolism in a dog cardiovascular study. After 1 entered development phase, a planned 4-kg cGMP campaign was initiated to provide material for phase 0 toxicology studies and, potentially, phase 1 clinical needs.

MEDICINAL CHEMISTRY ROUTE
The Medicinal Chemistry route to 1 is illustrated in Scheme 1. The first step is a difluoromethylation of phenol 2. This transformation was facilitated either by the use of chlorodifluoromethane or difluoromethylidene in DMF with potassium carbonate. The subsequent reaction is a Sonogashira coupling of the aryl iodide (3) with 2-ethylpyridine (4) under Pd and Cu catalysis. Following the coupling step, hydrolysis of the methyl ester produces acid 6 containing two equivalents of NaCl. The final step in the Medicinal Chemistry route is the amidation of 6 and isoindoline dihydrochloride 7 with PyBOP.

RESULTS AND DISCUSSION
The major issues that needed to be addressed by the Chemical and Pharmaceutical Development (CPD) team were: (1) securing a supply of the isoindoline 7, (2) finding a source for the difluorocarbene for the difluoromethylation reaction, (3)

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finding more “process friendly” conditions for the Sonogashira reaction, and (4) using silica gel chromatography for three of the four steps. After performing an evaluation of the Medicinal Chemistry synthesis, it was decided to improve the current route for the first phase 0 and phase 1 deliveries in lieu of developing a new route.3

The Synthesis of Dihydropyrrolopyridine (7). The isoindoline for the Medicinal Chemistry efforts was either externally sourced or prepared in small batches in-house using literature4 conditions. As seen in Scheme 2, the sequence begins with the chlorination of 2-methylpyrazine (8) and nucleophilic displacement with 10 to generate the cyclization precursor 11. After thermal cyclization and loss of HCN, a 1:2.6 mixture of isomers 12 and 13 are formed and must be separated by chromatography. Deprotection of the carbamate with refluxing HCl provided the dihydropyrrolopyridine 7 as the dihydrochloride salt.

Although this procedure proved effective at generating small quantities of 7 for initial development work, the multistep synthesis, separation of the isomers from the key [4 + 2] cyclization reaction, and stoichiometric generation of HCN required us to develop a proof-of-concept for an alternative route amenable to scale-up.

The backup method for the generation of 7 closely followed work previously published by Johnson & Johnson5 to generate compound 17. The plan was to follow the reliable route to 17 and develop cyclization conditions with an appropriate amine to produce 7 after deprotection. In this fashion, preparation of the diester 15 with standard Fisher esterification conditions was carried out on 2 kg scale (60% isolated yield) and provided sufficient intermediate to fund further screening work. Reduction of the diester was first explored using borohydrides (NaBH₄ and LiBH₄) as well as LiAlH₄. While in-process assay data were encouraging, the isolation of the diol 16 and borate removal proved to be problematic. However, treatment of the borane reaction mixture with alcoholic HCl enabled precipitation of the diol as the HCl salt 16, free of inorganic contaminants. Adopting the chlorination conditions outlined in the Johnson & Johnson paper provided a reasonable approach to 17.

Conversion of 17 to 7 was envisioned to proceed through a two-step process: displacement of the two chlorine atoms with a suitable amine followed by deprotection, if necessary. This theory led us to examine a range of amines (ammonia, benzylamine, tritylamine, tert-butyl carbamate, and o-toluenesulfonamide). Benzylamine readily reacted with 17; however, hydrogenolysis of the benzyl group without concomitant reduction of the pyridine ring proved challenging. Typically up to 50% of over-reduced product was observed with Pd/C as the catalyst. In addition, separation of two closely related amines via chromatography at the penultimate stage was not attractive, and the benzylamine approach was quickly abandoned.

Ammonia and alkyl amines were equally unsuccessful. Tritylamine underwent initial alkylation only partially and failed to undergo cyclization. tert-Butylcarbamate did not undergo alkylation, and reaction with tert-butylcarbazate gave decomposition. Somewhat surprisingly, only the sulfonamides gave acceptable conversion. o-Toluenesulfonamide with sodium hydride in DMF6 afforded the product in 46% yield after chromatography. Removal of the sulfonamide with HBr in acetic acid produced 7 as the dihydrobromide salt in 88% yield, albeit on small scale (<100 mg). During the course of this development work, a reliable supply of 7 from an outside vendor using the known route in Scheme 2 was secured, and no further developmental work was required.

The Difluoromethylation Reaction. The difluoromethylation of phenol 2 posed several challenges. First, the reagents employed in the Medicinal Chemistry route (difluoroiodomethane or chlorodifluoromethane)7 are environmentally toxic. They are also inconvenient for a process since difluoroiodomethane is a low-boiling liquid (bp 21.6 °C) and chlorodifluoromethane is a hydrochlorofluorocarbon (HCFC) gas which is also listed in the Montreal Protocol.8 The reagent of choice for the difluoromethylation reaction was sodium chlorodifluoroacetate9 (SCDA) (18) due to its stability and

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availability in bulk.\textsuperscript{10} Difluoromethylation reactions are typically run in polar aprotic solvents such as DMF with sodium, potassium, or cesium carbonate as the base. This process proved highly efficient and was essentially complete once addition of the SCDA/2 solution to the base was finished. With a slow addition of the SCDA/2 solution, the formation of impurities was minimized and provided 3 in near quantitative yield and 99.6\% HPLC purity (Scheme 3). We recently reported\textsuperscript{11} on this transformation and provided an in-depth discussion of the safety issues we encountered with the scale-up of this highly exothermic reaction.

**Scheme 3. Large-scale difluoromethylation conditions and results**

![Scheme 3](image)

The Sonogashira Reaction. As seen in Scheme 1, the Medicinal Chemistry conditions for the Sonogashira cross-coupling reaction\textsuperscript{2} between 3 and 4 utilized Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (20 mol \%) as the source for \textit{in situ} generated Pd(0). CuI (20 mol \%) and triethylamine (2 equiv) were also selected to facilitate the coupling reaction. The reaction was performed with 1.5 equiv of 2-ethynylpyridine (4) in toluene at 100 °C for 6 h. Once complete, the reaction was concentrated to dryness and purified by chromatography. Although acceptable for the generation of small quantities of intermediate 5, several variables needed to be addressed before scale-up could commence.

The first issue selected for attention was the choice of solvent. With the desire to incorporate an aqueous workup to remove excess base and possibly some heavy metals, 2-methyltetrahydrofuran (2-MeTHF) was explored primarily on the basis of previous work in this series of APIs. 2-MeTHF was also an attractive possibility due to its excellent ability to deoxygenate. During initial development work, the amount of Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} was dropped from 20 mol \% to 0.4 mol \% (Table 1). Although this was a great improvement in terms of catalyst loading, this modification required subsurface sparging with nitrogen to effect reaction completion. Although acceptable on laboratory scale, this operation was less practical for use in large fixed vessels.\textsuperscript{14} Attempts to drive reactions to completion with 0.4 mol \% Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} through degassing the solvent mixture by evacuating and filling with nitrogen were unsuccessful. Increasing the amount of the Pd catalyst to 0.8 mol \% greatly improved the reaction conversion without the need for subsurface sparging. The plan was to use 0.8 mol \% Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} during the scale-up campaign; however, after performing a use-test with the available lot of catalyst, it was decided to increase the loading to 1 mol \% to ensure reaction completion. The quantity of CuI was dropped from 20 to 2 mol \%, an amount typical for Sonogashira couplings. No efforts were made to explore lower Cu loadings as the results from these studies were sufficient for an initial 4 kg manufacture (Scheme 4).

With a new solvent and reduced catalyst amounts, the next issue to be addressed was the excess of 2-ethynylpyridine (1.5 equivalents). A slow addition of the SCDA/2 solution to the base was required. During the crystallization, black “tar” from residual Pd would coat the inside of the vessel and the crystallizing solids. As a result, the residual Pd levels for the isolated solids tended to be >1900 ppm.

In an attempt to keep the black tar in solution, the reaction solvent was changed from 2-MeTHF to N-methylpyrrolidinone (NMP). NMP was an attractive choice of solvent because it allowed the catalyst (and impurities) to remain solubilized, even during crystallization from water. Once the solids were collected, residual NMP can simply be washed from the cake with water. The low solubility of 5 in water meant product losses would be minimal. Switching to NMP and substituting ammonium hydroxide\textsuperscript{13} for triethylamine also allowed for the reaction temperature to be dropped from 100 °C to between 30 and 40 °C, presumably due to increased solubility of the catalysts or a solvent-stabilized intermediate in the catalytic cycle.

Having selected NMP as the solvent, the next issues to be addressed were the equivalents of the two catalysts. Care had to be taken in reducing the equivalents of Pd. Lowering the amount of Pd catalyst also required the reaction to be sufficiently deoxygenated. During initial development work, the amount of Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} was dropped from 20 mol \% to 0.4 mol \% (Table 1). Although this was a great improvement in terms of catalyst loading, this modification required subsurface sparging with nitrogen to effect reaction completion. Although acceptable on laboratory scale, this operation was less practical for use in large fixed vessels.\textsuperscript{14} Attempts to drive reactions to completion with 0.4 mol \% Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} through degassing the solvent mixture by evacuating and filling with nitrogen were unsuccessful. Increasing the amount of the Pd catalyst to 0.8 mol \% greatly improved the reaction conversion without the need for subsurface sparging. The plan was to use 0.8 mol \% Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} during the scale-up campaign; however, after performing a use-test with the available lot of catalyst, it was decided to increase the loading to 1 mol \% to ensure reaction completion. The quantity of CuI was dropped from 20 to 2 mol \%, an amount typical for Sonogashira couplings. No efforts were made to explore lower Cu loadings as the results from these studies were sufficient for an initial 4 kg manufacture (Scheme 4).

**Table 1. Selected Sonogashira yields**

<table>
<thead>
<tr>
<th>scale (g)</th>
<th>Pd (mol %)</th>
<th>time (h)</th>
<th>conversion (%)</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10\textsuperscript{a}</td>
<td>0.8</td>
<td>0.5</td>
<td>99</td>
<td>94\textsuperscript{b}</td>
</tr>
<tr>
<td>258\textsuperscript{a}</td>
<td>0.8</td>
<td>0.5</td>
<td>99</td>
<td>93\textsuperscript{c}</td>
</tr>
<tr>
<td>425\textsuperscript{b}</td>
<td>0.4</td>
<td>2.5</td>
<td>99</td>
<td>9\textsuperscript{d}</td>
</tr>
<tr>
<td>7250\textsuperscript{a}</td>
<td>1.0</td>
<td>1.0</td>
<td>98</td>
<td>86</td>
</tr>
</tbody>
</table>

\textsuperscript{a}These reactions were degassed using an evacuate and refill method.

\textsuperscript{b}This entry was degassed via subsurface sparging. These yields are higher because no aqueous washes (vide infra) were performed to remove residual Pd (∼6% loss per wash).

**Scheme 4. Large-scale Sonogashira reaction conditions and results**

![Scheme 4](image)
isolated crystals of formation of diyne 19, which tended to contaminate the isolated crystals of 5. 19 also proved challenging to remove to later stages in the synthesis, so controlling the level at this step was critical to delivering pure API. The first effort to reduce the amount of 4 from 1.5 equiv to 1.01 equiv led to near complete reaction conversion, and only a trace amount (<0.1% by area) of 19 could be observed by HPLC analysis. Several other low-level (NMT 0.5%) impurities were also observed during the reaction (see Figure 2). These include the product from deiodination (20). Several amidation impurities were also observed (21–23), but these were easily removed in downstream crystallizations.

As previously stated, the choice of NMP as the solvent provided an ideal opportunity to crystallize 5 from water. In addition, this solvent also allowed treatment of the mixture with an aqueous cysteine solution in an attempt to lower the residual Pd content of the isolated solids. An aqueous procedure was developed that involved adding 7 wt % (with respect to Pd content of the isolated solids) an aqueous cysteine solution in an attempt to lower the residual toluene is removed as toluene interferes with the reaction mixture. If these optional washes are incorporated, an additional heptane wash must be performed to ensure any residual Pd (if level is >100 ppm) is effectively removed up to 50% of the remaining Pd in the mixture. If these optional washes are incorporated, an additional heptane wash must be performed to ensure any residual toluene is removed as toluene interferes with the crystallization of 6. During this kilo-lab campaign, the optional toluene washes were not performed as the levels of Pd were sufficiently low for further processing. Once deemed complete, the reaction is diluted with water, neutralized, filtered, and washed with water to ensure removal of HOAc before the amidation reaction. As seen in Scheme 5, this reaction was performed on 6.20 kg scale and yielded 5.86 kg of 6 (99.1% yield, 98.75% purity).

The Amidation Reaction. The last synthetic step for the synthesis of 1 is the amidation reaction between 6 and 7. Medicinal Chemistry utilized PyBOP to promote the union. Although this reagent proved successful for the initial delivery, cost and lack of atom economy established 1,′-carbon-ylidimiazole (CDI) as the preferred coupling reagent. Other methods, such as the use of a mixed anhydride and generation of the corresponding acyl chloride (undesired chlorination byproducts observed), proved less successful.

The use of a dihydrochloride or dihydrobromide salt of 7 required the examination of which bases would be most effective for the neutralization. A survey showed that the corresponding salts formed by reaction with triethylamine were too voluminous in laboratory-scale experiments to be used for this multikilogram delivery. Sodium tert-butoxide was employed achieved by an additional charge of water and stirring for 3 h at 5–10 °C. Mother liquor losses for this procedure were generally in the range of 3–4%.

After filtration, the isolated solids were washed with ammonium hydroxide (to aid in the removal of Cu salts), water, and finally one wash with a 1.5:1 water:MeOH solution (Table 2, entry 3). The aqueous MeOH wash proved extremely effective on smaller laboratory scale in reducing the Pd level in the isolated material. Typically, residual Pd in product from lab runs was in the range of 0–50 ppm. This was the target range for scale-up, and gratifyingly the level of Pd in the isolated 4-kg batch was found to be 25 ppm. Care was taken not to perform more than one MeOH wash as each treatment resulted in a 6% loss of material. In the end, this first scale-up effort resulted in the successful production of 6.34 kg of 5 (86.1% isolated yield, 98.5% pure).

Table 2. Operations that Reduce Pd Levels After Crystallization

<table>
<thead>
<tr>
<th>entry</th>
<th>operation</th>
<th>residual Pd level (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>crystallization from water</td>
<td>&gt;1900</td>
</tr>
<tr>
<td>2</td>
<td>aqueous cysteine treatment</td>
<td>600–900</td>
</tr>
<tr>
<td>3</td>
<td>1.5:1 water: methanol cake wash</td>
<td>0–50</td>
</tr>
</tbody>
</table>

Figure 2. Impurities observed in Sonogashira reaction.
in a smaller 75g batch, however, byproducts arising from attack of tert-butanol on the CDI adduct (to form the corresponding tert-butyl ester) as well as safety concerns with sodium tert-butoxide prompted N,N-disopropylethylamine (DIPEA) to be used as the base for the CDI coupling for the 4-kg batch.

The formation of the activated CDI adduct proceeded in a 97.5:2.5 ratio (by LC area %) to starting carboxylic acid. After addition of the CDI adduct to the isoindoline suspension, the ratio of product to starting acid at 1 h was determined to be 92:8. Even after allowing the reaction to age for an additional hour, the conversion only slightly increased to 94:6. At this point, the activation reaction was deemed complete, and the formation of the activated ester was charged to the free-based point, the activation reaction was deemed complete, and the conversion only slightly increased to 94:6. Even after allowing the reaction to age for an additional hour, the conversion only slightly increased to 94:6. At this point, the activation reaction was deemed complete, and the formation of the activated ester was charged to the free-based slurry of 7 (see Scheme 6). After aging for 4 h, the reaction was quenched with water, and the crude I crystallized after about 1 h. After filtration and a single water wash, the solid was washed with one cake volume of MTBE and dried under a stream of nitrogen. The crude I (as form I hydrate) weighed 6.59 kg for an isolated yield of 86.5%. The mother liquor losses were found to be 9%.

**Recrystallization and Conversion to Final Form II.**

The final step in the synthesis of I involves recrystallization and clarification. Four forms were discovered during development work and can be easily identified by comparing their DSC traces (see Supporting Information). Due to the low solubility of I in most organic solvents few possibilities existed to facilitate the transition from form I hydrate to form II. EtOAc was an attractive option because of its ability to remove water during concentration. The recrystallization from EtOAc was also effective in removing residual Pd, Cu, NMP, and DIPEA, all of which are present in the crude form I hydrate. This process was utilized successfully in the Pearl River kilo-lab on the crude material and produced 5.5 kg of I (87% from crude as form II, 100% HPLC purity, >100% potency) after delumping in a rotary mill.

**CONCLUSIONS**

The first scale-up campaign of the potent and selective mGluR5 NAM GRN-529 (1) has been achieved in 64% overall yield. This five-step process successfully produced 5.5 kg of material for a delivery request of 4 kg. All intermediates were directly crystallized from the reaction mixtures allowing for the production of I with very high purity after final conversion to the desired form II.

**EXPERIMENTAL SECTION**

**General Methods.** Reaction progress and chemical purity were evaluated by HPLC analysis using an Agilent Eclipse XDB-C18 column (4.6 mm × 250 mm) with mobile phases A (25 mM NH₄OAc in water) and B (acetonitrile). Dual detection was at 210 and 254 nm, flow was set at 1.5 mL/min, and the temperature was 30 °C. Gradient: 0 min: A = 10%, B = 90%; 10 min: A = 10%, B = 10%; 12 min A = 90%; B = 10%.

**4-Difluoromethoxy-3-iodo-benzoic Acid Methyl Ester (3).** A solution of sodium chlorodifluoroacetate (9.6 kg, 63 mmol, 2.0 equiv) and methyl 4-hydroxy-3-iodobenzoate (2) (7.0 kg, 31 mmol, 1.0 equiv) in DMF (22.1 kg) was added in two portions over a period of 4 h to a 95 °C suspension of potassium carbonate (5.2 kg, 47 mmol, 1.5 equiv) in DMF (22.3 mol) was charged to a solution of 2-Ethynylpyridine (7.25 kg, 1.00 equiv, 22.1 mol) in N-methylpyrrolidinone (NMP) (30.7 kg, 29.9 L).

**Methyl 4-(Difluoromethoxy)-3-(pyridin-2-ylethynyl)benzoate (5).** 2-Ethynylpyridine (4) (2.30 kg, 1.01 equiv, 22.3 mol) was charged to a solution of 3 (7.25 kg, 1.00 equiv, 22.1 mol) in N-methylpyrrolidinone (NMP) (30.7 kg, 29.9 L).
Next, CuI (0.084 kg, 0.020 equiv, 0.442 mol) was charged in a single portion. The mixture was degassed by evacuating and refilling via nitrogen bleed three times. Pd[PPh3]4Cl2 (0.16 kg, 0.010 equiv, 0.221 mol) was charged in a single portion, and the mixture was heated to 35 °C. Next, ammonium hydroxide (28% solution) (12.6 kg, 8 equiv) was charged via pressure can, carefully maintaining an internal temperature in the range of 35 – 40 °C. The addition time was approximately 45 min. The reaction was held in this range for 1 h and deemed complete by LC analysis (NMT 1% starting material). Next, a solution of l-cysteine (0.5 kg, 0.167 equiv, 3.69 mol) in water (3.0 kg, 3.0 L) and 28% ammonium hydroxide (0.7 kg) was added to the reaction and held for 2 h. The mixture was cooled to 20 °C to effect crystallization. Water (47.3 kg, 47.3 L) was added over a period of 45 min, and the suspension was cooled to 5 °C. After 1 h at this temperature, the solids were filtered on a Nüütsche filter and washed consecutively with water (30.9 kg), two 28% ammonium hydroxide solution portions (14.2 kg each), and water (23.5 kg). To effect further residual Pd removal, the cake was washed with a 2:1 MeOH:water solution (28.6 kg). Finally, the crystals (6.34 kg, 86.1% yield, 98.5% purity, mp = 109 °C) were dried under positive nitrogen flow. HPLC retention time: 8.33 min. 1H NMR (300 MHz, DMSO-d6) δ 8.65 (dt, J = 4.0, 0.8 Hz, 1H), 8.20 (d, J = 2.2 Hz, 1H), 8.09 (dd, J = 8.8, 2.2 Hz, 1H), 7.90 (td, J = 7.8, 1.8 Hz, 1H), 7.70 (d, J = 4.5 Hz, 1H), 7.52 (t, J = 7.26 Hz, 1H), 7.45–7.49 (m, 2H), 3.89 (s, 3H); 13C NMR (100 MHz, DMSO-d6) δ 164.7, 154.7, 150.3, 141.7, 136.9, 134.6, 132.0, 127.7, 117.9, 116.0 (t, J = 260 Hz), 113.7, 94.1, 82.0, 52.5. HRMS calculated for C16H15F3NO4: 304.07798 [M + H]; found: 304.07793.

4-(Difluoromethoxy)-3-(pyridin-2-yethyl)benzoic Acid (6). Water (31.5 kg, 31.5 L) and methanol (27.8 kg, 38.6 L) were charged at 20 °C. Next, $ (6.33 kg, 1.00 equiv, 21.8 mol) was added as a solid, and the suspension was heated to the range of 35–40 °C. To this suspension was added a solution of 50% NaOH (2.10 kg, 26.2 mol, 1.2 equiv) via a pressure can, keeping the temperature in the range of 35–40 °C. Addition time was approximately 30 min. The pressure can and transfer line were rinsed with 1.7 kg of water. The reaction was allowed to react until deemed complete by HPLC analysis (NMT 1% starting material). Typical reaction time was approximately 1 h. After addition of the acetic acid solution, the mixture was cooled to 20 °C and held for one hour, and the solids were collected on a Nüütsche filter. The solids were washed with water (78.0 kg, 78.0 L) and dried under positive nitrogen flow. The solids were weighed to provide 6 as a white powder (5.86 kg, 99.1% yield, 98.8% purity, mp = 240 °C). HPLC retention time: 4.24 min. 1H NMR (300 MHz, DMSO-d6) δ 8.65 (d, J = 6.0 Hz, 1H), 8.18 (d, J = 2.3 Hz, 1H), 8.07 (dd, J = 8.5, 2.3 Hz, 1H), 7.90 (td, J = 7.8, 1.8 Hz, 1H), 7.69 (dd, J = 10.0, 1.7 Hz, 1H), 7.49 (t, J = 73.0 Hz, 1H), 7.44–7.49 (m, 2H); 13C NMR (100 MHz, DMSO-d6) δ 165.7, 154.3, 150.3, 141.8, 136.9, 134.5, 132.7, 131.3, 130.0, 127.6, 123.9, 122.5, 118.5, 117.9, 116.3 (t, J = 260 Hz), 113.7, 93.9, 82.6, 54.3, 52.8. HRMS calculated for C16H13F3N3O2: 391.1132 [M+]; found: 391.1137.

Conversion to Form II. Due to volume restrictions, the clarification process was split into two equal batches. Crude I (3.2 kg, 8.2 mol) was dissolved in EtOAc (86.1 kg, 97.0 L) at reflux (77 °C). The solution was allowed to cool to 50 °C in preparation for filtration. The solution was filtered through a pad of Darco G-60 (1.2 kg) and Celite (0.7 kg) on a Nüütsche filter and through a 5-μm in-line filter into a fixed vessel. The reactor, filter, and lines were washed with additional EtOAc (9.51 kg, 10.7 L). The procedure was repeated for the second 3.2 kg portion of I. The combined solution of I was concentrated at atmospheric pressure to a final volume of approximately 50 L and cooled to 55 °C. A 75 mL portion of the batch was removed and sonicated for 10 min at ambient temperature to generate the desired form II seeds. The seeds were added back to the batch at 55 °C. Next, heptane (44.1 kg, 640.0 L) was added to the mixture over a period of 1 h. The mixture was held at 55 °C for 30 min before being cooled to 0 °C over a minimum of 4 h. The contents of the reactor were held at 0 °C for 8 h. I was isolated as the desired form II (mp = 142 °C) (5.51 kg, 87.1% yield, 100% purity) by filtration.
ASSOCIATED CONTENT

Supporting Information

1H and 13C NMR spectra, as well as DSC curves for 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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REFERENCES

(3) The direct conversion of ester 3 to 1 was briefly explored. However, 3 proved unstable to nucleophiles at the elevated temperatures required for this transformation. In addition, conversion to the acid via saponification provided an opportunity to remove Pd (see Experimental Section). If issues were encountered with either the saponification or amidation reactions, the conversion of 3 to 1 would have been further explored.
(8) For additional information on the Montreal Protocol, see: http://ozone.unep.org/Publications/MP_Handbook/Section_1.1_The_Montreal_Protocol/.
(13) Ammonium hydroxide and triethylamine both provided similar reaction profiles; however, ammonium hydroxide also provided an additional means to control the exotherm associated with the Sonogashira reaction. The dose-controlled addition of ammonium hydroxide proved superior to triethylamine for keeping the reaction in the range of 35–40 °C. As expected, removing ammonia also proved more facile than removing triethylamine without the need for elevated drying temperatures.
(14) For future deliveries, the pilot plant would have been piped to handle this type of operation, but the kilo-laboratory did not have subsurface tubes for sparging. After a couple of experiments, the evacuate and refill method proved efficient for this delivery.
(16) The >100% potency for the isolated (1) from the kilo-lab batch is a result of the isolated solids having a greater purity than the material used as a reference standard.
(17) For the difluoromethylation reaction, the large-scale addition of the SCDA/2 solution was charged through a pressure can. Due to the limited capacity of the pressure can two batches of SCDA and (2) in DMF were generated and added consecutively. Once the first charge was complete, the second batch was dissolved and charged to the same pressure can. The time between the completion of the first charge and the beginning of the second charge was about 10 min.

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