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

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Supporting Information

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

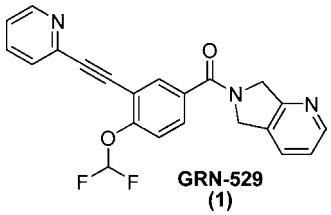


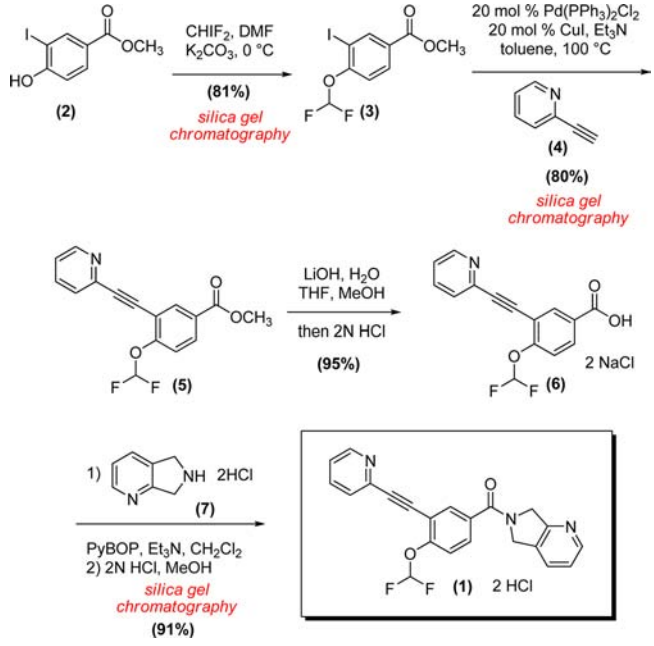
Figure 1. Lead mGluR5 NAM identified by Wyeth Medicinal Chemistry.

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 difluoroiodomethane in DMF with potassium carbonate. The subsequent reaction is a Sonogashira coupling of the aryl iodide (**3**) with 2-ethynylpyridine (**4**) under Pd and Cu catalysis. Following the coupling step, hydrolysis of the methyl ester produces acid **6** containing two equivalents of

Scheme 1. Medicinal Chemistry route to 1



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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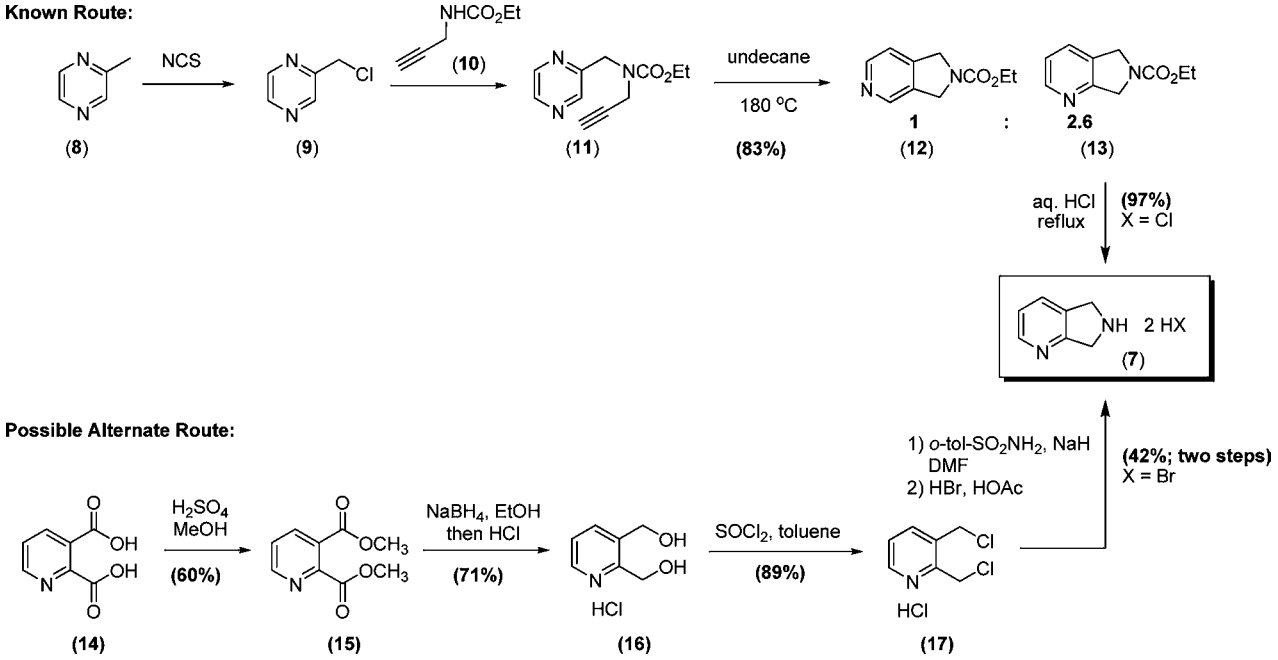
Scheme 2. Two routes employed to generate 7



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 literature[4] 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 & Johnson[5] 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 ($NaBH_4$ and $LiBH_4$) as well as $LiAlH_4$. 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 DMF[6] 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 chlorodifluororomethane)[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 chlorodifluoroacetate[9] (SCDA) (**18**) due to its stability and

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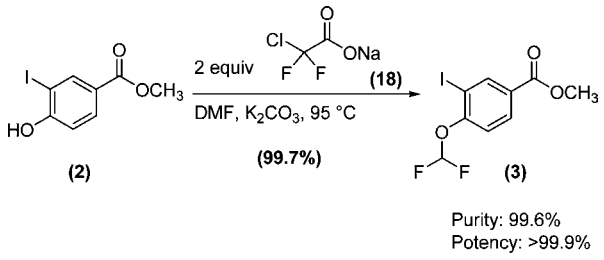
availability in bulk.[10] Difluoromethylation reactions are typically run in polar aprotic solvents such as DMF with sodium, potassium, or cesium carbonate as the base. This process proved highly efficient and was essentially complete once addition of the SCDA/**2** solution to the base was finished. 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[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



The Sonogashira Reaction. As seen in Scheme 1, the Medicinal Chemistry conditions for the Sonogashira cross-coupling reaction[12] between **3** and **4** utilized $Pd(PPh_3)_2Cl_2$ (20 mol %) as the source for *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 achieve phase separation. The original goal was to keep **5** in the organic layer, perform aqueous cysteine washes to remove residual Pd, and end with a crystallization from 2-MeTHF/heptanes.

Although this method was successful for earlier compounds in this series, several issues with this procedure forced alternative solvents to be explored. First, both the organic and aqueous layers were so black that observing the phase split was near impossible, even on small scale. The difficulty in observing the phase split lead to product losses, and residual water interfered with the crystallization during initial development on this process. Even when a good phase split was achieved, the crystallization from 2-MeTHF/heptanes proved to be ineffective. 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[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 $Pd(PPh_3)_2Cl_2$ 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.[14] Attempts to drive reactions to completion with 0.4 mol % $Pd(PPh_3)_2Cl_2$ 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 % of $Pd(PPh_3)_2Cl_2$ 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).

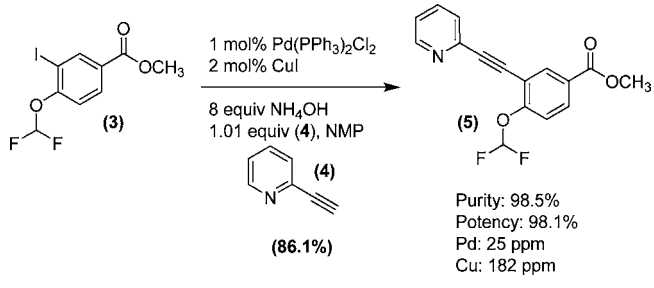
Table 1. Selected Sonogashira yields

scale (g)	Pd (mol %)	time (h)	conversion (%)	isolated yield (%)
10[a]	0.8	0.5	99	94[c]
258[a]	0.8	0.5	99	93[c]
425[b]	0.4	2.5	99	91[c]
7250[a]	1.0	1.0	98	86

[a]These reactions were degassed using an evacuate and refill method. [b]This entry was degassed via subsurface sparging. [c]These yields are higher because no cake washes (*vide infra*) were performed to remove residual Pd (~6% loss per wash).

With a new solvent and reduced catalyst amounts, the next issue to be addressed was the excess of 2-ethynylpyridine (1.5

Scheme 4. Large-scale Sonogashira reaction conditions and results



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equiv) reported in the Medicinal Chemistry route. A minor pathway in the Sonogashira catalytic cycle involves homocoupling of the terminal alkyne moiety, the so-called Glaser–Hay coupling.[15] The coupling of 2-ethynylpyridine led to the formation of diyne **19**, which tended to contaminate the isolated crystals of **5**. **19** also proved challenging to remove at 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.

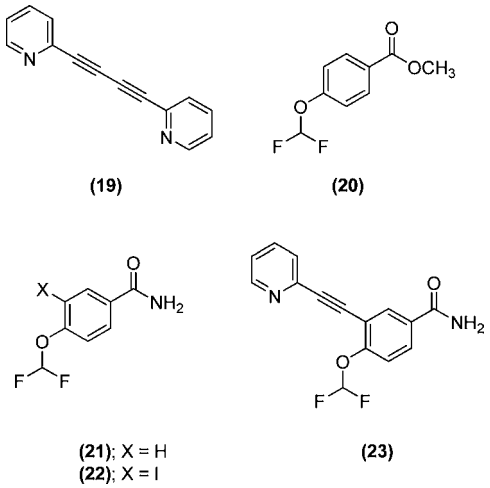


Figure 2. Impurities observed in Sonogashira reaction.

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 **3**) cysteine dissolved in a 4:1 water:28% ammonium hydroxide to the reaction mixture at 35 °C. The ammonium hydroxide is used to achieve complete cysteine solubility. As seen in Table 2,

Table 2. Operations that Reduce Pd Levels After Crystallization

entry	operation	residual Pd level (ppm)
1	crystallization from water	>1900
2	aqueous cysteine treatment	600–900
3	1.5:1 water:methanol cake wash	0–50

entry 2, this treatment resulted in a 2–3 fold reduction in the level of Pd in the isolated solids, generally in the range of 600–900 ppm. Although not at a level deemed acceptable for this step (<100 ppm), this significant reduction contributed an excellent starting point for further development.

In addition to lowering the level of Pd in the isolated material, the aqueous cysteine treatment also initiated the crystallization of **5**. After stirring at 35 °C for 2 h, the reaction cooled and formed a thin slurry. Complete crystallization was 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).

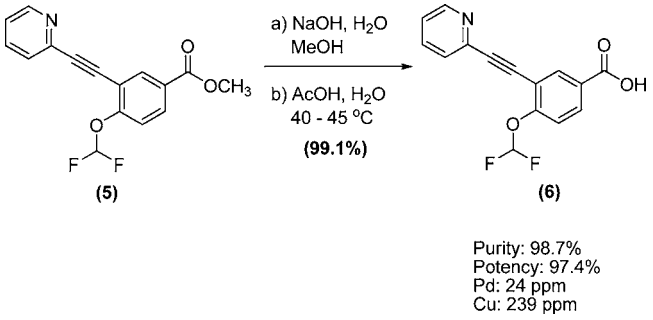
The Ester Hydrolysis Reaction. Initial attempts to repeat the Medicinal Chemistry hydrolysis conditions revealed the formation of impurities during the neutralization reaction with 2 N HCl. Although the impurities were not fully identified, they were the result of additional hydrolysis as determined by HPLC–MS analysis. Careful monitoring of the HPLC purity versus pH revealed instability at a pH of less than pH 2. Without access to a pH probe for the kilo-lab campaign, the aqueous HCl neutralization procedure was replaced with an aqueous acetic acid solution. This small change prevented the pH of the system from falling below pH 4 and the corresponding formation of hydrolysis impurities. Other changes included switching from LiOH to NaOH, reducing the number of equivalents of base from 5 equiv to 1.2 equiv, and removing THF from the reaction mixture.

The reaction begins as a slurry of **5** in MeOH:water (1:1) and slowly becomes homogeneous as the reaction progresses. The aqueous solution of **6** (as the sodium salt) provided an opportunity to further remove residual Pd (if level is >100 ppm). Two toluene washes of the reaction mixture can effectively remove 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 1,1′-carbonyldiimidazole (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 multikilogam delivery. Sodium *tert*-butoxide was employed

Scheme 5. Large-Scale Ester Hydrolysis Conditions and Results



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*-diisopropylethylamine (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 solution 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 **1** 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 **1** (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 **1** 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 **1** 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 **1** (87% from crude as form II, 100% HPLC purity, >100% potency[16]) 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 **1** with very high purity after final conversion to the desired form II.

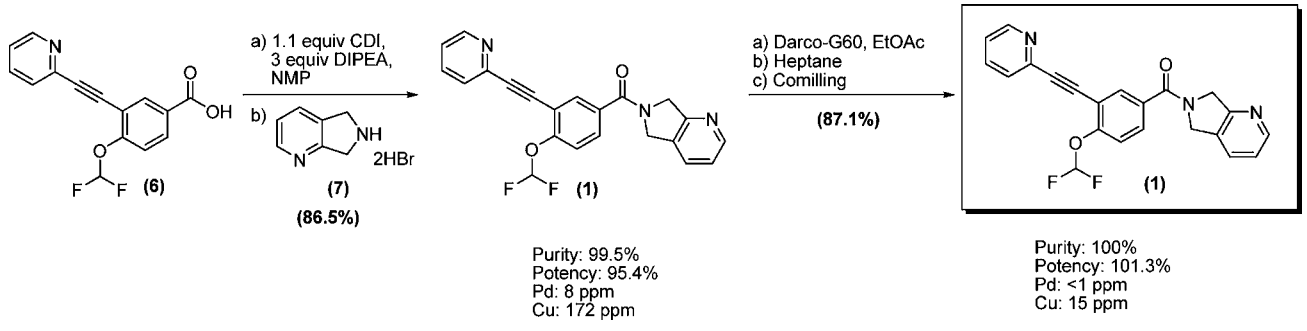
EXPERIMENTAL SECTION

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 NH_4OAc 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 = 90%; 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[17] over a period of 4 h to a 95 °C suspension of potassium carbonate (5.2 kg, 47 mmol, 1.5 equiv) in DMF (13.2 kg). The addition was controlled to maintain an internal temperature range of 93−98 °C. After complete addition, the suspension was stirred for 15 min and cooled to 30 °C. Water (17.5 kg) was added, and the contents of the reactor were transferred to a 180 L reactor for further processing. The remaining 52.5 kg of water was added, and the batch was cooled to 10−15 °C. After stirring at this temperature for 1 h, the suspension was filtered on a Nütsche filter. The crystals were washed with water (3 × 22.4 kg) and dried under nitrogen. The material was isolated as a white solid (8.24 kg, 99.7% yield, 99.6% pure, mp = 56 °C). HPLC retention time: 9.09 min. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.31 (d, J = 2.0 Hz, 1H), 7.81 (dd, J = 8.5, 2.0 Hz, 1H), 6.96 (dt, J = 8.5, 1.0 Hz, 1H), 6.39 (t, J = 72.6 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 154.1, 141.4, 131.1, 128.5, 118.2, 115.4 (t, J = 265 Hz), 87.9, 52.4. HRMS calculated for $C_9H_7O_3F_2I$: 328.94807 [M + H]; found: 328.94768.

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).

Scheme 6. Amidation and final form conversion



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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. $Pd(PPh_3)_2Cl_2$ (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 Nütsche 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. ^{1}H NMR (300 MHz, DMSO-d_6) 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 = 72.6 Hz, 1H), 7.45−7.49 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 154.7, 150.3, 141.7, 136.9, 134.6, 132.0, 127.7, 126.5, 124.0, 117.9, 116.0 (t, J = 260 Hz), 113.7, 94.1, 82.0, 52.5. HRMS calculated for $C_{16}H_{11}F_2NO_3$: 304.07798 [M + H]; found: 304.07793.

4-(Difluoromethoxy)-3-(pyridin-2-ylethynyl)benzoic Acid (6). Water (31.5 kg, 31.5 L) and methanol (27.8 kg, 38.6 L) were charged at 20 °C. Next, **5** (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. The reaction was diluted with water (32.5 kg, 32.5 L) and warmed to 45 °C. A solution of HOAc (6.80 kg, 6.48 L) in water (13.7 kg, 13.7 L) was slowly charged from a pressure can over a period of 3 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 Nütsche 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. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.64 (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); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 154.3, 150.3, 141.8, 136.9, 134.7, 132.1, 128.0, 127.6, 124.0, 117.9, 116.1 (t, J = 260 Hz), 113.5, 93.9, 82.3. HRMS calculated for $C_{15}H_9F_2NO_3$: 290.06233 [M + H]; found: 290.06264.

(4-Difluoromethoxy-3-pyridin-2-ylethynyl-phenyl)-(5,7-dihydro-pyrrolo[3,4-*b*]pyridin-6-yl)-methanone, 1 (1). Into a Hastelloy pressure can was charged **6** (5.61 kg, 1.00 equiv, 19.4 mol) followed by NMP (11.5 kg, 11.2 L) and *N*,*N*-diisopropylethylamine (DIPEA) (2.9 kg, 22.4 mol, 3.9 L). This material was stored at ambient temperature. Into a 100 L fixed vessel at 25 °C was charged NMP (12.4 kg, 12.1 L) followed by 1,1-carbonyldiimidazole (CDI) (3.5 kg, 1.10 equiv, 21.6 mol). This mixture was stirred to dissolve. The solution of (**6**) was charged at 25 °C to the fixed vessel over a period of 60 min. The transfer line was washed with an additional amount of NMP (1.4 kg, 1.4 L). The vessel was aged at 25 °C for 1 h. Generation of the activated intermediate was checked by quenching a small aliquot into a 1 M methylamine solution in THF (HPLC retention time of methylamine adduct: 6.11 min). The reaction was deemed complete when the area percent of acid **6** was less than 3% of the corresponding methyl amide.

Into a 200 L vessel was charged NMP (11.5 kg, 11.2 L) followed by 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrobromide (**7**) (5.7 kg, 1.05 equiv, 20.3 mol). To this was charged DIPEA (4.6 kg, 35.5 mol, 6.2 L) over a period of 25 min, keeping the temperature below 35 °C. The contents from the 100 L vessel were transferred at ambient temperature to the 200 L vessel over a period of 45 min. The reaction was held at 25 °C for a minimum of 4 h. The reaction progress was again checked by quenching a small aliquot into methylamine. Once deemed complete, water (84.0 kg, 84.0 L) was added over a period of 2 h to the mixture at 30 °C. If needed, an additional charge of water (28 kg, 28 L) may be added to aid in crystallization if crystals are not observed after 1h. The mixture was held at 25 °C overnight and filtered. The cake was washed with water (33.6 kg, 33.6 L) followed by MTBE (20.7 kg, 28.0 L), and allowed to dry on the filter overnight. The solids were weighed to provide **1** as a white powder (6.59 kg, 86.5% yield, 99.5% purity, form I mp = 140 °C). HPLC retention time: 6.44 min. ^{1}H NMR (300 MHz, DMSO-d_6, rotomeric mixture) δ 8.65 (d, J = 6.0 Hz, 1H), 8.49 (dd, J = 8.8, 4.7 Hz, 1H), 7.98 (t, J = 2.3 Hz, 1H), 7.90 (td, J = 7.8, 1.8 Hz, 1H), 7.79−7.84 (m, 2H), 7.65−7.68 (m, 1H), 7.43−7.48 (m, 2H), 7.47 (t, J = 73.0 Hz, 1H), 7.28−7.34 (m, 1H), 4.90 (d, J = 14.3 Hz, 2H), 4.85 (d, J = 16.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, rotomeric mixture) δ 167.3, 157.4, 156.6, 150.3, 149.0, 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 $C_{22}H_{15}F_2N_3O_2$: 391.1132 [M^+]; found: 391.1137.

Conversion to Form II. Due to volume restrictions, the clarification process was split into two equal batches. Crude **1** (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 Nütsche 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 **1**. The combined solution of **1** 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, 64.0 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. **1** was isolated as the desired form II (mp = 142 °C) (5.51 kg, 87.1% yield, 100% purity) by filtration.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C 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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Notes

The authors declare no competing financial interest.

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(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.

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(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.

■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on November 7, 2012. A correction has been made in Table 1 and the corrected version was reposted on November 8, 2012.