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Development of a Scalable Process for DG-041, a Potent EP_3 Receptor Antagonist, via Tandem Heck Reactions

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Abstract:

DG-041 is a small molecule antagonist of the EP_3 receptor for prostaglandin E_2 that is in clinical development for treatment of peripheral artery disease (PAD). Originally produced using a six-step synthetic procedure, process optimization led to development of a four-step sequence that is readily scalable. The key step in the optimized sequence contains two sequential Heck reactions, involving an intramolecular Heck cyclization followed by an intermolecular Heck coupling, performed in one pot to produce a highly substituted indole core.

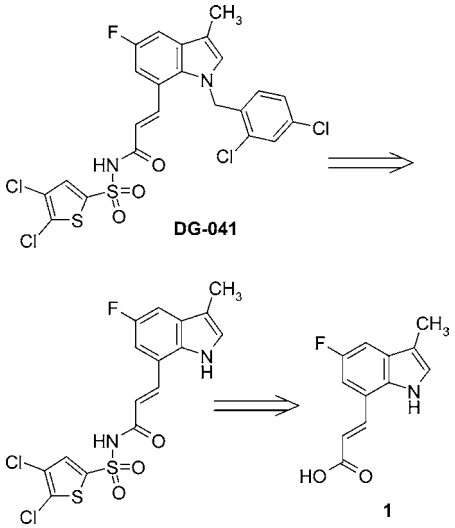
Background

Peripheral artery disease (PAD) is an atherosclerotic condition of the extremities, typically of the legs, that affects up to 20% of people older than 55 years.[1] Development of PAD is predictive of other cardiovascular diseases, such as myocardial infarction and stroke. PAD can lead to narrowing of the peripheral arteries, resulting in pain upon walking that is relieved by resting (claudication), ischemic ulcers, and, in extreme cases, amputation of the affected limb.

A population-based genome-wide scan of PAD patients in Iceland identified a statistically significant correlation between risk of disease and variants of a gene on chromosome 1p31,[2] later identified as the EP_3 receptor. The EP_3 receptor is one of four related GPCRs activated upon binding to prostaglandin E_2.[3] The other three receptors, EP_1, EP_2, and EP_4, all couple through G_s, resulting in increased levels of cAMP, while EP_3 couples through G_i, resulting in decreased levels of cAMP.[4] EP_3, which is present on the platelet, has been implicated in atherothrombosis.[5] The interplay between the EP_3 receptor and a related receptor, the IP receptor, regulates the homeostatic response to platelet activation by prostanoids.

A medicinal chemistry campaign directed at identifying a potent, selective antagonist of the EP_3 receptor yielded DG-041 (see Scheme 1) as a clinical candidate. DG-041 demonstrated an IC_{50} of 5 nM against the EP_3 receptor, with greater than 1000-fold selectivity over the EP_1, EP_2, EP_4, and IP receptors. The compound showed no significant binding to any other GPCR and demonstrated excellent profiles in preclinical safety studies. An Investigational New Drug (IND) application was filed with the Food and Drug Administration (FDA) in January 2005, and human clinical trials were initiated during the following months.

Scheme 1. **Retrosynthesis of DG-041**



Following selection of DG-041 as a clinical candidate, we focused on development of a safe, economical, scalable synthetic route for DG-041 that would be amenable to large-scale production. Originally a six-step synthesis requiring chromatography, our research efforts reduced the synthesis to a four-step process that required no chromatography, which has been used to manufacture DG-041 on a scale of 45 kg. We herein report the results of our research.

Chemistry

A retrosynthetic analysis of DG-041 is illustrated in Scheme 1. As illustrated, the key central scaffold for DG-041 is 5-fluoro-3-methylindol-7-yl-acrylic acid (**1**). Once **1** is in hand, one could conceptually proceed to DG-041 through stepwise incorporation of the 2,4-dichlorobenzyl moiety and the 2,3-dichlorothiophene-5-sulfonamide moiety, in either order.

Intermediate **1** was efficiently prepared via Heck coupling of 7-bromo-5-fluoro-3-methylindole (**3**) with methyl acrylate, followed by base-catalyzed saponification of the resulting

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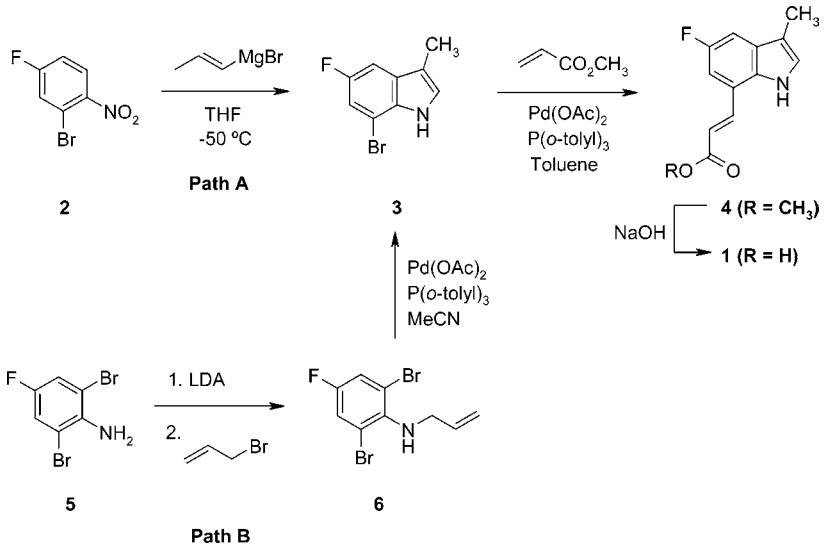
Scheme 2. **Original sequential synthetic routes to intermediate 1**



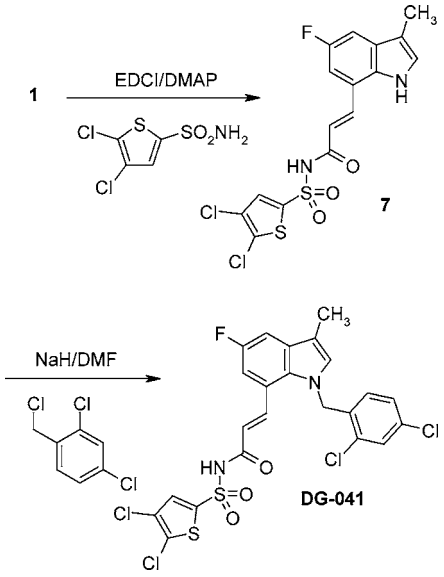
methyl ester (see Scheme 2). The required indole **3** was initially synthesized using the Bartoli indole synthesis,[6] starting from 2-bromo-4-fluoronitrobenzene (**2**, Path A). Treatment of **2** with 3 equiv of 1-allylmagnesium bromide in THF at −50 °C provided the indole **3** in 42% yield. Heck coupling of **3** with methyl acrylate, catalyzed with palladium(II) acetate/tri-(*o*-tolyl)phosphine in toluene afforded intermediate **4**, which was hydrolyzed to the key intermediate **1** using NaOH in THF/MeOH.

Though the Bartoli procedure effectively provided **3** for early production campaigns, the reaction presented several challenges for future scale-up. First, the requirement for low temperature (−50 °C) was cumbersome. Second, purification of **3** required silica gel chromatography, which was necessary for removal of the substantial byproducts generated using the Bartoli procedure. Third, the reaction afforded the product **3** in consistently modest yields. Finally, reagent **2** presented challenges for long-term, economical large-scale supply.

We next evaluated a synthetic approach that utilized sequential Heck reactions (Path B). Alkylation of 2,6-dibromo-4-fluoroaniline (**5**) with allyl bromide using lithium diisopropylamide (LDA) in THF afforded the key intermediate **6** in near quantitative yield. Intramolecular Heck reaction with catalytic palladium(II) acetate/tri-(*o*-tolyl)phosphine, using acetonitrile as reaction solvent, provided the indole **3** in excellent yield.[7] The indole **3** was then subjected to a second, intermolecular Heck reaction with methyl acrylate using palladium(II) acetate/tri-(*o*-tolyl)phosphine in toluene, affording intermediate **4** as described for Path A.[8] Finally, saponification of **4** provided the desired key intermediate **1**.

With intermediate **1** in hand, we evaluated the installation of the two final pieces of the molecule. Amidation of **1** with 2,3-dichlorothiophene-5-sulfonamide was found to proceed most efficiently using EDCI as the dehydrating reagent. Addition of an activating reagent such as 4-(dimethylamino)-

Scheme 3. **Original route to DG-041 from intermediate 1**



pyridine (DMAP) was necessary for the reaction to proceed to completion in a reasonable time period. Using the EDCI/DMAP combination with dichloromethane as solvent, conversion of **1** to **7** proceeded in good yield (Scheme 3). Upon reaction completion, washing of the dichloromethane phase with 2 M aqueous HCl induced precipitation of the desired **7** with excellent purity. Deprotonation of the indole nitrogen of **7** with sodium hydride in DMF followed by quenching with 2,4-dichlorobenzyl chloride provided the desired compound, **DG-041**. A single recrystallization from 90 volumes of absolute ethanol afforded material that was consistently greater than 99.5% pure.

During the early chemical development phases of DG-041, several lots of material were prepared using the route described in Scheme 2 (Path B) and Scheme 3, with excellent reproducibility and impurity profiles. However, we recognized that significant improvements could be realized, particularly in the conversion of **6** to **1**. Additionally, we wanted to evaluate the possibility of reversing the order of the two steps described in Scheme 3. The underlying objective of this latter goal was to move the use of

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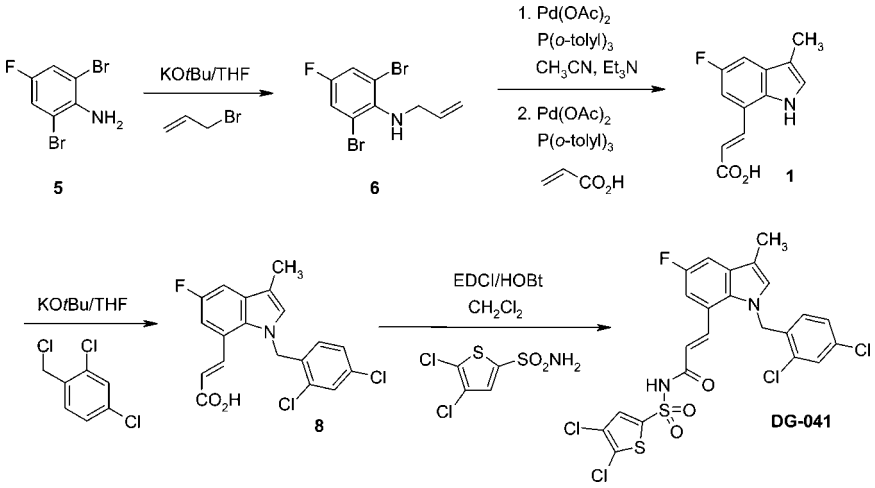
Scheme 4. **Final optimized four-step route to DG-041**



2,4-dichlorobenzyl chloride as early in the synthesis as possible, to minimize the quantity of residual reagent in the final product. An additional benefit to this reversal in sequence would be the use of the most expensive raw material, 2,3-dichlorothiophene-5-sulfonamide, at the final step of the synthesis.

In planning for future large-scale campaigns, we sought to improve every step of the process. For the first step, involving the alkylation of **5** with allyl bromide, we found that a solution of potassium *tert*-butoxide in THF at room temperature allowed the reaction to proceed efficiently and cleanly to completion, in essentially quantitative yield without the need for cryogenic conditions. The use of potassium *tert*-butoxide was also more desirable than LDA from a reagent preparation perspective and tended to yield product that was a light amber color, rather than the dark brown material isolated from the LDA reactions.

For the conversion of compound **6** to key intermediate **1**, we evaluated the possibility of conducting the two Heck reactions in one pot, to minimize the processing time and number of unit operations. Treatment of **6** with the palladium acetate/(tri-*o*-tolyl)phosphine system in acetonitrile, in the presence of triethylamine, catalyzed the transformation to intermediate **3**, typically within 3 h at reflux (monitored by HPLC). Upon completion of conversion, the reaction mixture was recharged with additional palladium acetate/(tri-*o*-tolyl)-phosphine followed by methyl acrylate, and the reactor was then reheated to reflux until HPLC analysis again indicated reaction completion. This tandem reaction sequence proved to be extremely efficient and yielded intermediate **4** in excellent yield and purity. Saponification of **4** using KOH or NaOH in THF/MeOH/H_2O as before afforded **1**.

After successfully developing the optimal conditions for the one-pot conversion of **6** to **4**, we evaluated a direct one-pot conversion of **6** to **1** by simply replacing methyl acrylate with acrylic acid. To our delight, this reaction sequence proceeded beautifully. Additionally, isolation of the product **1** was facilitated by the discovery that it crystallized readily from the reaction mixture upon dilution with MTBE, as its triethylamine salt, along with quantities of triethylamine hydrobromide. The desired product was readily isolated with high purity by collection of the salt mixture, dissolution in water, and acidification, which induced precipitation of **1** with excellent purity.

As mentioned earlier, we wished to reverse the order of the final two steps illustrated in Scheme 3, to minimize the levels of residual 2,4-dichlorobenzyl chloride in the final material. We first evaluated the *N*-alkylation of methyl ester **4** with 2,4-dichlorobenzyl chloride, using a variety of base−solvent combinations. However, this approach was not promising, resulting in either poor reaction progression or significant levels of ester cleavage during the reaction, which gave complex mixtures of products. One point that was noted, though, was that even though some experiments resulted in significant methyl ester cleavage, we did not observe formation of 2,4-dichlorobenzyl esters from the liberated carboxylic acid. We thus decided to investigate direct *N*-benzylation of the carboxylic acid **1**.

Deprotonation of **1** using 2.2 equiv of potassium *tert*-butoxide in THF followed by quenching with 2,4-dichlorobenzyl chloride was found to efficiently give the desired penultimate compound **8** in excellent yield (Scheme 4). For the final step to produce DG-041, we repeated the conditions used to form the same bond in intermediate **7** (Scheme 3), using EDCI/DMAP, which proceeded well. After an examination of multiple combinations of dehydrating and activating agents, we found that EDCI and HOBt represented the optimal pair, and thus proceeded into larger scale productions with that combination. Thus, coupling of **8** with 2,3-dichlorothiophene-5-sulfonamide catalyzed with EDCI/HOBt afforded DG-041 in good yield, with purity similar to that of the material produced using the original route.

For the final recrystallization, we wished to avoid the need for large volumes of recrystallization solvent. In our initial production campaigns, DG-041 was recrystallized from 90 volumes of absolute ethanol, which required a very large reactor capacity to purify even modest quantities of material. We found that recrystallization of DG-041 from 40 volumes of acetone/water (1:1) effectively provided material of identical purity, while requiring only one-third of the volume of solvent. The crystal habits of the compounds obtained from the two solvent systems were visually different, but all physical properties and the polymorphic forms of material purified from the two systems were identical.

Discussion

The goal of chemical development in the pharmaceutical industry is to develop efficient synthetic routes that could be used for economical large-scale production of a target molecule. Oftentimes, the original synthetic route developed by the medicinal chemistry team can serve as the basis for the eventual production route, but this usually requires significant modification. Thus was the case with DG-041.

As described in this paper, the original medicinal chemistry route involved synthesis of the indole **3**, which subsequently underwent a Heck coupling with methyl acrylate to incorporate the necessary propenoic acid moiety at the indole 7-position. Originally, the indole **3** was prepared using the Bartoli method, which proved to be tedious and difficult to scale. Indole **3** was eventually prepared via an intramolecular Heck reaction of the substituted aniline **6**, which was readily prepared on a large scale from inexpensive raw materials. As process research progressed, we were eventually able to convert aniline **6** directly to the key intermediate **1** in a one-pot sequence, by conducting the intramolecular and intermolecular Heck reactions in a tandem fashion, and by using acrylic acid in the latter step. The use of acrylic acid allowed us to eliminate the original saponification step that was required when using methyl acrylate, and to our pleasure, isolation and purification of **1** were facilitated by its propensity to crystallize from the workup solution as its triethylamine salt.

Once intermediate **1** was in hand, from two straightforward steps, we focused on the optimal order for incorporation of the 2,3-dichlorothiophene-5-sulfonamide fragment and the 2,4-dichlorobenzyl fragment. Our desire to use the potent alkylating agent (2,4-dichlorobenzyl chloride) as early in the sequence as possible led us to develop the conversion of **1** to **8**, which was achieved without requiring protection of the carboxylic acid moiety of **1**. Once penultimate intermediate **8** was in hand, incorporation of the 2,3-dichlorothiophene-5-sulfonamide moiety was achieved with the use of standard coupling/activating reagents, the most efficient of which proved to be EDCI/HOBt.

Over the course of our process development work, significant efficiencies were achieved. First, the number of discrete synthetic steps was reduced from five (Scheme 2 Path A, and Scheme 3) to four (Scheme 4). Second, all chromatography was eliminated. Third, all base-mediated reactions originally utilizing LDA or NaH were developed to run with potassium *tert*-butoxide solution. Fourth, the use of 2,4-dichlorobenzyl chloride was moved forward one step in the sequence. And finally, the recrystallization of DG-041, which originally required 90 volumes of ethanol, was replaced with 40 volumes of acetone/water, substantially reducing the required reactor capacity and volume of waste.

Experimental Section

General Experimental. All reagents were purchased from commercial vendors and used without further purification unless otherwise noted. Large-scale supplies of 2,3-dichlorothiophene-5-sulfonamide were obtained from commercial vendors. ^{1}H NMR spectra were recorded on a Varian Oxford 400 MHz spectrometer. Chemical shifts are reported in ppm relative to internal tetramethylsilane. APCI-MS were recorded with an Agilent 1100 LC/MS system in either positive or negative ionization mode. Melting points were measured using digital scanning calorimetry.

7-Bromo-5-fluoro-3-methy-1*H*-lindole (3) via Path A. Into a 2 L three-neck round-bottom flask equipped with a mechanical stirrer, temperature probe, and nitrogen inlet were charged 710 mL of THF followed by 39.1 g (0.61 mol) of Mg turnings and several mg of I_2, under a nitrogen atmosphere. Using an addition funnel, 3-bromo-1-propene (194.5 g, 0.61 mol) was added in the following manner: approximately 25% of the reagent was added dropwise over a 30 min period, at which point the reaction initiated. The remaining reagent was added dropwise over a period of about 20 min, while maintaining the internal reaction temperature below 45 °C by adjusting the addition rate. After mixture stirred for an additional 1 h, most of the Mg had been consumed. The resulting Grignard reagent solution was cooled to −60 °C, and a solution of 2-bromo-4-fluoronitrobenzene (**2**, 71.0 g, 0.12 mol) in 355 mL of THF was added at such a rate to maintain the internal reaction temperature below −50 °C. Upon completion of addition, the reaction was stirred at −50 °C for 1 h, at which point TLC analysis indicated complete consumption of the reagent **2**. The solution was allowed to warm to −10 °C, transferred to a 12 L reaction flask, quenched by the careful addition of saturated aqueous ammonium chloride (4 L), and then stirred at ambient temperature overnight. The aqueous phase was separated and extracted with 2 L of diethylether, which was added to the original organic phase. The combined organic phases were washed sequentially with saturated aqueous ammonium chloride, water, and brine and then dried over sodium sulfate. Filtration and concentration *in vacuo* provided a dark oil (88 g). The oil was extracted with warm (45 °C, 3 × 1 L) hexanes. The hexane extracts were cooled and then filtered through a 50 g plug of silica gel topped with 20 g Celite. The combined filtrates were concentrated in vacuo to provide the desired product as an amber-colored semisolid (30.9 g, 42%); ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3 H), 7.06 (br s, 1 H), 7.13 (d, 1 H, J = 2.4 Hz), 7.15 (dd, 1 H, J = 8.8, 2.4 Hz); 7.18 (dd, 1 H, J = 9.2, 2.4 Hz), 8.01 (br s, 1 H); APCI-MS m/z 229 (M + 1), 148. Anal. Calcd for C_9H_7BrFN: C, 47.40; H, 3.09; N, 6.14. Found: C, 47.52; H, 3.19; N, 6.01.

7-Bromo-5-fluoro-3-methyl-1*H*-indole (3) Via Path B. *Step 1. 1-N-Allyl-2,6-dibromo-4-fluoroaniline (**6**).* To a 72 L three-neck round-bottom flask equipped with a mechanical stirrer, nitrogen purge, temperature probe, addition funnel, and external cooling bath were charged 2,6-dibromo-4-fluoroaniline (**5**, 5.00 kg, 18.6 mol) and 2.5 L of anhydrous THF. The mixture was stirred to achieve dissolution, and then a solution of potassium *tert*-butoxide (1 M in THF, 22.5 L, 22.5 mol) was added. The resulting mixture was stirred for approximately 15 min at ambient temperature and then cooled to 15 °C. Allyl bromide (2.70 kg, 22.3 mol) was added via an addition funnel over approximately 45 min, maintaining the internal reaction temperature between 10 and 20 °C by adjusting the addition rate as needed. The resulting

mixture was allowed to stir for 1 h at 10 to 20 °C at which point TLC analysis indicated reaction completion. The mixture was quenched with the careful addition of water (15 L), then diluted with EtOAc (15 L), and stirred for 15 min. The aqueous phase was separated, and the upper organic phase was washed successively with water (10 L) and saturated brine solution (10 L). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to afford the desired product as an amber-colored oil (5.90 kg, >100% yield). The material was sufficiently pure to be used in the subsequent step without any further processing. A pure sample was readily obtained via chromatography through silica gel; ^{1}H NMR ($CDCl_3$) δ 3.79 (d, 2 H, J = 6.4 Hz), 5.13 (dd, 1 H, J = 10.0, 0.8 Hz), 5.26 (dd, 1 H, J = 17.2, 0.8 Hz), 5.97 (ddd, 1 H, J = 17.2, 10.0, 6.4 Hz), 7.28 (s, 2 H); APCI-MS *m*/*z* 309.8 (M + 1), 229, 148. Anal. Calcd for $C_9H_8Br_2FN$: C, 34.99; H, 2.61; N, 4.53. Found: C, 35.38; H, 2.71; N, 4.37.

*Step 2. 7-Bromo-5-fluoro-3-methyl-1H-indole (**3**).* To a 22 L three-neck round-bottom flask equipped with a mechanical stirrer, nitrogen purge, and a condenser were charged 8 L of MeCN and **6** (2.40 kg, 7.8 mol). With stirring the following reagents were added in the following order: palladium(II) acetate (17.4 g, 0.078 mol), tris-(*o*-tolyl)-phosphine (94.5 g, 0.31 mol), and triethylamine (1.6 L, 11.7 mol). Following addition, the reaction mixture was heated to reflux with stirring for 5 h, at which point TLC analysis indicated complete consumption of the reagent **6**. The heating source was removed, and the solution was allowed to naturally cool to ambient temperature. The solution was diluted with water (4 L) and MTBE (4 L), and the solution was stirred and then allowed to settle. The aqueous layer was separated, and the organic layer was washed sequentially with water (4 L, then 2 × 3 L) and brine (4 L; note that, at this stage, an emulsion sometimes formed that required filtering the entire two-phase solution through Celite to achieve a reasonable phase separation). The organic phase was dried over sodium sulfate, filtered, and concentrated to provide the crude product as a dark oil (1.8 kg). The oil was dissolved into 1 L of hexanes and applied onto a silica gel column (7.2 kg), which was eluted with hexanes. Collection, combination, and concentration of the appropriate fractions afforded the desired product as a pale yellow oil (1.145 kg, 65%), which was sufficiently pure for use in the next step. An analytically pure sample could be obtained as described in the previous example.

Methyl (2*E*)-3-(5-Fluoro-3-methyl-1*H*-indol-7-yl)acrylate (4), from 3. To a 22 L three-neck round-bottom flask equipped with a mechanical stirrer, condenser, and nitrogen purge were charged compound **3** (1.145 kg, 5.02 mol) and 6.9 L MeCN. With stirring the following reagents were added in the following order: palladium(II) acetate (56.3 g, 0.25 mol), tris-(*o*-tolyl)-phosphine (229 g, 0.75 mol), and triethylamine (4.2 L, 30 mol). Following addition, the reaction mixture was heated to reflux with stirring overnight, at which point TLC analysis indicated complete consumption of reagent **3**. The solution was cooled to ambient temperature and diluted with water (5.5 L) and MTBE (4.5 L), stirred, and allowed to settle. The aqueous layer was separated and the organic layer was washed sequentially with water (2 × 4 L) and brine (2 L). The organic layer was dried over sodium sulfate, filtered through 500 g Celite, and concentrated in vacuo to provide the product as an orange solid (1.6 kg). The crude product was slurried with 3 L hexanes for 3 h, then collected on a filter pad, rinsed with hexanes (3 × 250 mL) and air-dried to afford the desired product as a yellow solid (1.4 kg, >100% yield), which was of sufficient quality for use in the next step. An analytically pure sample was obtained via silica gel column chromatography; mp 156 °C; ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 3,84 (s, 3 H), 6.49 (d, 1 H, J = 16.0 Hz), 7.07 (br s, 1 H), 7.15 (dd, 1 H, J = 10.0, 2.2 Hz), 7.27 (dd, 1 H, J = 11.2, 2.2 Hz), 7.95 (d, 1 H, J = 16.0 Hz), 8.32 (br s, 1 H); APCI-MS *m*/*z* 232 (M-1), 202, 146. Anal. calcd. for $C_{13}H_{12}FNO_2$: C, 66.94; H, 5.19; N, 6.01. Found: C, 67.29; H, 5.55; N, 5.97.

Methyl (2*E*)-3-(5-fluoro-3-methyl-1*H*-indol-7-yl)acrylate (4), via tandem Heck reactions from 6. To a nitrogen purged 500 mL magnetically stirred round-bottom flask were added intermediate **6** (11.37 g, 36.8 mmol), MeCN (50 mL), palladium(II) acetate (83.4 mg, 0.36 mmol), tris-(*o*-tolyl)-phosphine (340 mg, 1.1 mmol) and additional acetonitrile (36 mL) with stirring. Triethylamine (20.4 mL, 146 mmol) was added via syringe, and then the clear, dark orange mixture was heated to reflux for 3.25 h, at which point TLC (9:1 hexane/EtOAc) showed complete consumption of **6**. The solution was cooled and methyl acrylate (3.82 g, 43.9 mmol) was added via syringe. The mixture was further heated to reflux with stirring for 18.5 h, at which point TLC showed disappearance of intermediate **3** and formation of a new spot for the product **4**. The reaction mixture was cooled and partitioned with water (100 mL) and MTBE (100 mL), and the organic layer was collected. The aqueous layer was re-extracted with MTBE (25 mL). The combined organic extracts were washed with water (4 × 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to a brown solid. The solid was refluxed for 1.5 h with 80 mL hexane, then cooled to ambient temperature. The resulting suspension was filtered with suction through a fritted glass funnel, washing the solids with more hexanes to complete the transfer. The cake was vacuum-dried (30 mmHg, 48 °C) for 15 h providing the product as a dark yellow powder (7.45 g, 86.8%). An analytically pure sample could be obtained as described in the previous example.

(2*E*)-3-(5-Fluoro-3-methyl-1*H*-indol-7-yl)acrylic acid (1) via saponification of 4. To a 72 L three-neck round-bottom flask equipped with a mechanical stirrer and nitrogen purge was charged reagent **4** (2.50 kg, 10.7 mol) and 36 L of THF/MeOH (1:1). With stirring, a solution of 2 M aqueous NaOH (21 L, 42.0 mol) was added in one portion, and the solution was allowed to stir at ambient temperature overnight, at which point TLC analysis indicated complete consumption of reagent **4**. The solution was concentrated in vacuo (≤45 °C) to remove the volatile organics, then diluted with 15 L water. The aqueous solution was extracted with CH_2Cl_2 (5 × 6 L), then acidified to pH 1−2 (litmus paper) with 15%

aqueous HCl. The desired product precipitated as a yellow solid, which was collected on a filter pad, rinsed with water (3 × 1.5 L), then dried in a vacuum oven at 55 °C. The dry product (2.012 kg, 85%) was used without purification in the next step; mp 224 °C; ^{1}H NMR (DMSO-d_6) δ 2.24 (s, 3 H), 6.67 (d, 1 H, J = 16.0 Hz), 7.24 (br s, 1 H), 7.34 (dd, 1 H, J = 9.2, 2.4 Hz), 7.42 (dd, 1 H, J = 10.8, 2.4 Hz), 8.08 (dd, 1 H, J = 16.0, 1.2 Hz), 11.35 (s, 1 H), 12.45 (br s, 1 H); APCI-MS m/z 218 (M-1), 200, 174, 148. Anal. calcd. for $C_{12}H_{10}FNO_2 \cdot 1/2\ H_2O$: C, 63.16; H, 4.86; N, 6.14. Found: C, 63.33; H, 4.58; N, 6.01.

(2*E*)-3-(5-Fluoro-3-methyl-1*H*-indol-7-yl)acrylic acid (1) via tandem Heck reactions from 6. To a nitrogen purged 200 L reactor were charged acetonitrile (34 L), compound **6** (5.0 kg, 16.18 mol), triethylamine (6.55 kg, 64.7 mol), tris-(*o*-tolyl)phosphine (29.6 g, 0.097 mol), and palladium(II) acetate (7.3 g, 0.033 mol) with continuous stirring. The reaction mixture was brought to a gentle reflux (75 °C) for ~4 h under nitrogen at which point TLC analysis showed the reaction to be complete. The reaction mixture was cooled to 50−60 °C followed by addition of tris-(*o*-tolyl)phosphine (118 g, 0.39 mol) and palladium(II) acetate (29.1 g, 0.13 mol) as a slurry in 500 mL of acetonitrile. Acrylic acid (1.40 kg, 19.4 mol) was then added [note: a mild (ca. 4 °C) exotherm occurred upon the acrylic acid addition]. The resulting mixture was brought to reflux and allowed to remain at reflux for ~17 h at which point TLC analysis indicated ~30% of unreacted **3**. The reaction mixture was again cooled to 50−60 °C, additional catalyst (7.3 g, 0.033 mol) and tris-(*o*-tolyl)phosphine ligand (29.6 g, 0.097 mol) were added, and the mixture was allowed to reflux for an additional 21 h at which point TLC analysis showed complete reaction. The reaction mixture was cooled to ambient temperature, and 40 L of 1:1 (v/v) MTBE:heptanes were added. After 1 h of stirring at ambient temperature, the resulting precipitate was filtered through a 50 cm stainless steel funnel fitted with a filter cloth. The solids were washed on the filter with 2 × 10 L of 1:1 (v/v) MTBE/heptanes and suction dried to afford 8.13 kg of crude product, consisting of a mixture of the triethylammonium salt of **1** and triethylammonium hydrogen bromide. These solids were transferred to a 200 L reactor and dissolved in 152 L of water. The resulting solution was acidified with 2 M aqueous HCl to pH 1−2. The stirring was continued for 30 min at ambient temperature, after which the resulting solids were collected by filtration and washed on the funnel with water (4 × 15 L). The collected solids were vacuum-dried at 60 °C to constant weight, affording 2.17 kg (67%) of **1** as a bright yellow solid, of sufficient purity for use without further processing. An analytically pure sample could be obtained as previously described, giving identical analytical characteristics.

2,3-Dichlorothiophene-5-sulfonic Acid [(2*E*)-3-(5-Fluoro-3-methyl-1*H*-indol-7-yl)acryloyl]amide (7). To a 100 L reactor were charged reagent **1** (2.0 kg, 9.1 mol), CH_2Cl_2 (50 L), EDCI (3.5 kg, 18.2 mol), and DMAP (2.2 kg, 18.2 mol). The resulting slurry was stirred at ambient temperature for 20 min, and then 2,3-dichlorothiophene-5-sulfonamide (2.3 kg, 10.0 mol) was added in one portion. After stirring several minutes, the solution became homogeneous. The solution was allowed to stir overnight, at which point TLC analysis indicated complete consumption of starting reagent **1**. The reaction mixture was diluted with 41 L of 5% aqueous HCl, and the biphasic solution was stirred for 30 min, during which copious yellow solids precipitated and remained suspended in the organic layer. The solids were collected by filtering the organic layer, then rinsed with water (4 × 1 L), air-dried for 15 min, and then rinsed with CH_2Cl_2 (2 L). The product was dried in a vacuum oven (45 °C) to afford 3.0 kg (76%) of the desired product as a bright yellow solid, which was of sufficient purity for use in the next reaction. An analytically pure sample was obtained via recrystallization from methanol; ^{1}H NMR (DMSO-d_6) d 2.23 (s, 3 H), 6.72 (d, 1 H, J = 15.8 Hz), 7.22 (dd, 1 H, J = 10.4, 2,4 Hz), 7.27 (br s, 1 H), 7.39 (dd, 1 H, J = 9.2, 2.4 Hz), 7.96 (s, 1 H), 8.16 (dd, 1 H, J = 15.8, 1.2 Hz), 11.36 (s, 1 H); APCI-MS m/z 433 (M-1), 215. Anal. Calcd for $C_{16}H_{11}Cl_2FN_2O_3S_2$: C, 44.35; H, 2.56; N, 6.46. Found: C, 44.01; H, 2.66; N, 6.46.

2,3-Dichlorothiophene-5-sulfonic Acid {(2*E*)-3-[5-Fluoro-1-(2,4-dichlorobenzyl)-3-methyl-1*H*-indol-7-yl]acryloyl}-amide (DG-041): Preparation from 7. To a 72 L three-neck round-bottom flask equipped with a mechanical stirrer, temperature probe, and nitrogen purge were charged reagent **7** (2.9 kg, 6.7 mol) and anhydrous DMF (14.4 L). The solution was cooled to −10 °C, and then solid sodium hydride (60% dispersion in mineral oil, 990 g, 24.8 mol) was added in portions over 80 min, at such a rate that the internal temperature did not rise above −5 °C. The resulting dark orange solution was allowed to warm to 18 °C over a period of 3 h and then cooled back to −10 °C. 2,4-Dichlorobenzyl chloride (1.9 L, 13.4 mol) was added at a constant rate over a period of 1 h, keeping the internal temperature below −5 °C. After addition was complete, the solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the careful addition of 30 L of water and then transferred to a 100 L reactor containing CH_2Cl_2 (18 L) and 3 M aqueous HCl (16 L). The 72 L vessel was rinsed with 10 L of CH_2Cl_2 and 3 L of water, which were added to the 100 L vessel. The solution was stirred vigorously for 30 min and then allowed to settle. A thick precipitate formed in the organic layer, which was collected on a filter pad and rinsed with water (2 × 1.5 L) and EtOH (2 × 1 L). After air drying, the solid was dried in a vacuum oven at 45 °C to afford 2.32 kg of a yellow solid. The aqueous phase was extracted with 30 L of CH_2Cl_2, which was then concentrated in vacuo to afford a second crop of yellow solid. This second crop was rinsed with water and EtOH and then vacuum-dried as described for the first crop, affording an additional 0.317 kg of material. The filtrate from the first crop was concentrated to a volume of 8 L, which induced precipitation of a third crop, which was washed and dried as in the case of the first two crops, affording a third crop of yellow solid (0.530 kg). HPLC analysis of the three lots confirmed they were of similar quality. At this stage, the solids were a 1:1 solvate of DG-041 with DMF. The three crops were combined and dissolved

in 90 volumes of boiling absolute EtOH, and then the EtOH was distilled until half the volume had been removed (DG-041 begins to crystallize as the volume is reduced). The remaining solution was cooled to 0 °C, and the bright yellow crystalline solid was collected on a filter pad, rinsed with cold EtOH (2 × 1.5 L), and air-dried for 30 min. The material was further dried in a vacuum oven at 45 °C, affording 2.39 kg (73%) of DG-041 as bright yellow needles: mp 236−238 °C; ^{1}H NMR (DMSO-d_6) d 2.26 (s, 3 H), 5.52 (s, 2 H), 6.13 (d, 1 H, J = 6.8 Hz), 6.22 (d, 1 H, J = 12.0 Hz), 7.04 (dd, 1 H, J = 7.4, 2.0 Hz), 7.22 (dd, 1 H, J = 6.8, 1.6 Hz), 7.36 (br s, 1 H), 7.38 (d, 1 H, J = 1.6 Hz), 7.45 (dd, 1 H, J = 7.4, 2.0 Hz), 7.73 (d, 1 H, J = 12.0 Hz), 7.91 (s, 1 H); APCI-MS m/z 590 (M-1). Anal. Calcd for $C_{23}H_{15}Cl_4FN_2O_3S_2$: C, 46.64; H, 2.55; N, 4.73. Found: C, 46.61; H, 2.75; N, 4.75.

(2*E*)-3-[1-(2,4-Dichlorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acrylic Acid (8). To a 200 L cylindrical glass reactor vessel fitted with a cooling coil, a condenser, a temperature probe, and an overhead mechanical stirrer was charged a solution of potassium *tert*-butoxide (0.97 M in THF, 16.08 L, 15.60 mol). A solution of **1** (1.533 kg, 6.99 mol) in 3.5 L of THF was added over a period of 70 min while keeping the internal solution temperature between 17 and 23 °C, at which point the solution appeared as a milky yellow suspension. After the solution stirred for an additional 60 min, 2,4-dichlorobenzyl chloride (1.657 kg, 8.39 mol) was added neat over a period of 1 h, again maintaining the internal solution temperature between 17 and 23 °C. The solution was stirred for 18 h, at which point HPLC analysis indicated complete conversion of the starting material. Water (19 L) was added over a period of 15 min, and the solution was then filtered through a bed of Celite 521 (200 g). The filtrate was diluted with heptanes (20 L) and MTBE (20 L), and the solution was stirred for 25 min. The phases were allowed to separate, and the top organic layer was separated. The aqueous layer was acidified with 3 M aqueous HCl to a pH of 6 and then further acidified to a pH of 1 with 6 M aqueous HCl, which induced precipitation of the desired product. Heptanes (12 L) and MTBE (3.55 L) were added, and the solution was mixed for about 30 min. The triphasic mixture was filtered through a fritted glass funnel to collect the solids, and the solids were rinsed with water. After air drying, the solids were transferred to a vacuum oven and dried at 64 °C for 2 days, providing the desired product as a golden yellow powder (1.816 kg, 68.7% yield), of sufficient purity for use in the next step without additional manipulation: mp 210−212 °C; ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 3 H), 5.50 (s, 2 H), 6.20 (d, 1 H, J = 8.4 Hz), 6.24 (d, 1 H, J = 15.6 Hz), 7.22 (dd, 1 H, J = 10.4, 2.4 Hz), 7.28 (dd, 1 H, J = 8.4, 2.0 Hz), 7.34 (s, 1 H), 7.42 (dd, 1 H, J = 9.2, 2.0 Hz), 7.66 (d, 1 H, J = 15.6 Hz), 7.67 (d, 1 H, J = 2.0 Hz), 12.29 (s, 1 H); APCI-MS m/z 377 (M − 1). Anal. Calcd for $C_{19}H_{14}Cl_2FNO_2$: C, 60.34; H, 3.73; N, 3.70. Found: C, 60.70; H, 3.90; N, 3.65.

2,3-Dichlorothiophene-5-sulfonic Acid {(2*E*)-3-[5-Fluoro-1-(2,4-dichlorobenzyl)-3-methyl-1*H*-indol-7-yl]acryloyl}-amide (DG-041): Preparation from 8. To a 100 L reactor equipped with a condenser, a temperature probe, a heating controller, and an overhead mechanical stirrer were charged CH_2Cl_2 (8.0 L), compound **8** (1.772 kg, 4.68 mol), EDCI (1.352 kg, 7.05 mol), and HOBt hydrate (126.5 g, 0.936 mol). The solution was stirred until homogeneous, then diisopropylethylamine (1.88 kg, 14.55 mol) was added, and stirring was continued for about 45 min. 2,3-Dichlorothiophene-5-sulfonamide (1.14 kg, 4.91 mol) was added, and the solution was stirred at ambient temperature for 1 h and then stirred at a gentle reflux for 20 h. The reaction was cooled slowly to ambient temperature (approx 2.5 h), and then water (9 L) was added with vigorous stirring. A solution of 2 M aqueous HCl (9 L) was added over 20 min, and the solution was then stirred for 15 min. The phases were allowed to separate, and the top aqueous layer was removed. Additional 2 M aqueous HCl (18 L) was added to the organic layer, inducing precipitation of the desired product, and the mixture was stirred vigorously for 17 h, then cooled to about 10 °C, and held for 5 h. The solids were collected on a fritted glass funnel, rinsed with water (6 L), and suction dried. The product was slurried with heptanes (4 L), collected on a fritted glass funnel, and again air-dried. The solids were transferred to a vacuum oven and dried at 63 °C under vacuum for 31 h to provide crude DG-041 as a bright yellow powder (1.466 kg, 52.8%). At this point, the material had a purity of 98.8% (HPLC). Recrystallization from acetone/water (1:1 v/v, 16 L/kg) provided an average mass recovery of about 97%, with purity greater than 99.5%. The analytical data were identical with the material prepared from intermediate **7**, described above.

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