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Synthesis of Selective Estrogen Receptor Degrader GDC-0810 via Stereocontrolled Assembly of a Tetrasubstituted All-Carbon Olefin

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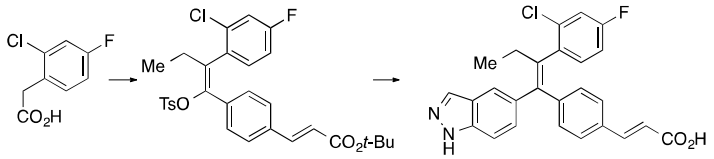
Supporting Information Placeholder

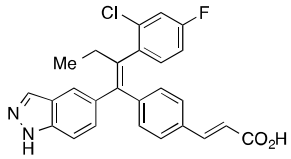


8 (*E*)-10 GDC-0810 (1)

ABSTRACT: We report an efficient synthesis of GDC-0810 based on a sequence involving a highly stereoselective lithium *tert*-butoxide mediated enolization–tosylation (≥95:5 *E*:*Z*) and a Pd-catalyzed Suzuki–Miyaura cross-coupling as key steps. Global deprotection, pyrrolidine salt formation, and final active pharmaceutical ingredient (API) form control / isolation produced GDC-0810 free acid in a 40% overall yield with >99.0% purity as ascertained by HPLC analysis.

INTRODUCTION

Estrogen receptor positive (ER+) breast cancer accounts for 70–80% of disease cases reported globally. Antihormonal therapies based on selective estrogen receptor modulators (SERMs) such as tamoxifen and aromatase inhibitors (AIs) including anastrozole and letrozole have emerged as the standard of care for treating ER+ metastatic breast cancer.[1] The appearance of mutations in the ligand-binding domain of ER-α has led to the emergence of resistance mechanisms and stimulated interest in developing selective estrogen receptor degraders (SERDs). This novel class of ER ligands can potentially overcome resistance mechanisms by utilizing a pathway that involves ER-antagonism and removal from the signaling pathway.[2]

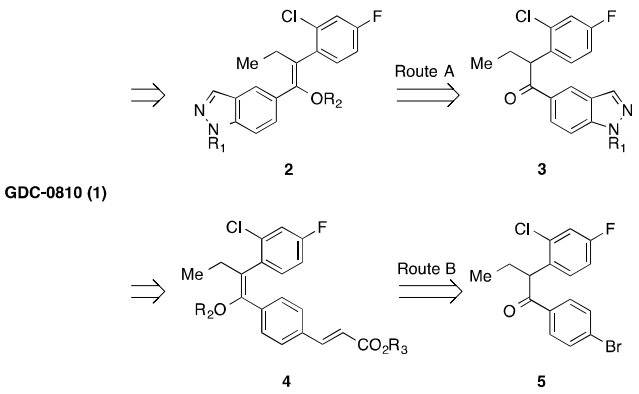


GDC-0810 (1)

Figure 1. Structure of SERD GDC-0810 (1).

GDC-0810 (**1**, Figure 1), is an orally bioavailable small molecule SERD under evaluation in clinical trials for the treatment of metastatic ER-α positive breast cancer tumors. We describe herein our efforts to develop a practical and highly stereoselective synthesis of this acyclic tetrasubstituted all-carbon olefin to support pharmaceutical and clinical development of this drug candidate, suitable for manufacturing kilogram amounts of active pharmaceutical ingredient (API).

Scheme 1. Retrosynthetic Analysis of GDC-0810



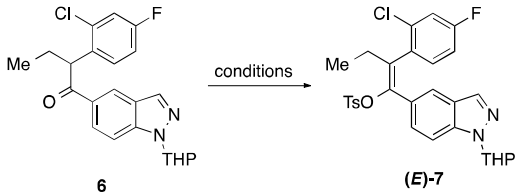
Although efficient and suitable to prepare small amounts of material for structure–activity relationship (SAR) purposes, the discovery synthesis of GDC-0810 was plagued with several drawbacks to establish the tetrasubstituted all-carbon olefin including poor regiochemistry, lack of isolation points and inconsistent performance on kilogram scale.[3,4] We sought to find a route that would provide improved stereo- and regiocontrol towards accessing the most challenging structural feature of GDC-0810, its stereodefined tetrasubstituted acyclic all-carbon olefin.[5,6,7] We also aimed to insert additional isolation points in the process to provide better control over API quality. As described in Scheme 1, a retrosynthetic analysis guided us towards approaches that would rely on a Suzuki–

Miyaura cross-coupling of enol electrophiles **2** or **4**. These compounds were envisioned to be accessed via a stereoselective enolization of complementary hindered aryl ketones **3** (route A) or **5** (route B).

RESULTS AND DISCUSSION

As part of our investigation of Route A, we prepared the requisite ketone **6** according to procedures described in our recent reports.[7,8] Treatment of **6** with potassium *tert*-butoxide (KO*t*-Bu) at 23 ºC and quenching with *p*-toluenesulfonic anhydride afforded the undesired enol tosylate isomer **(*E*)-7** as the major product in a variety of solvents with the highest *E*/*Z* ratio being 90:10 in DMA (Table 1, entries 1–5). Evaluation of other bases such as LiO*t*-Bu and temperature effects (entries 6–7) or quenching with other electrophiles (methanesulfonic anhydrideor diphenyl phosphoryl chloride failed to significantly improve the *Z*/*E* ratios and additional efforts to reverse the stereoselectivity were unfortunately met with little success. The olefin *E*/*Z* configuration was examined by NMR spectroscopy. Due to ^{1}H NMR signal overlap in the aromatic region of **(*E*)-7**, step-NOESY was applied to access E/Z-indicative NOE responses (Figure 2). First, the step function incorporated selective 1D TOCSY of H-6 to transfer magnetization to its scalar coupled partner, H-5. Second, selective 1D NOE irradiation of H-5 resulted in enhancement of H-8, H-9, and H-12, consistent with the **(*E*)-7** isomer.[9]

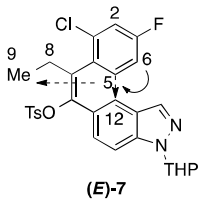
Table 1. Indazole Ketone Enol Tosylate Formation[a]



6 **(*E*)-7**

entry	base	solvent	conv[b] (%)	*Z*/*E* ratio[b]
1	KO*t*-Bu	THF	87	22:78
2	KO*t*-Bu	THF[c]	61	17:83
3	KO*t*-Bu	DMA	95	10:90
4	KO*t*-Bu	toluene	92	22:78
5	KO*t*-Bu	MTBE	99	29:71
6	LiO*t*-Bu	THF	67	7:93
7	LiO*t*-Bu	THF[c]	6	29:71

[a]Conditions: (a) **6** (500 mg, 1.25 mmol) in solvent (2.5 mL) was added base (1.75 mmol, 140 mol %) at 23 ºC, then Ts_2O (570 mg, 1.75 mmol, 140 mol %) in THF (2.5 mL). [b]Determined by HPLC analysis of crude reaction mixture. [c]Reaction performed at –20 ºC.

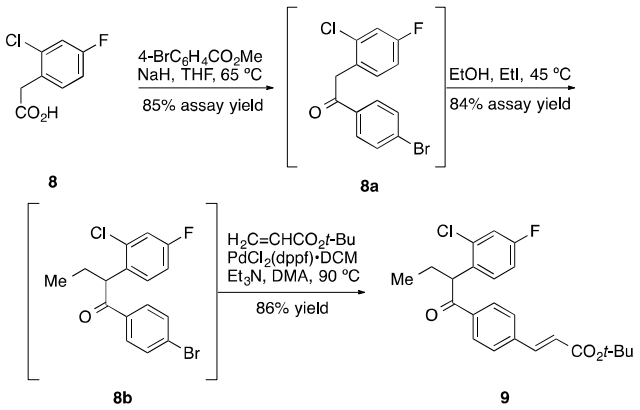


(*E*)-7

Figure 2. NMR spectroscopic analysis of (*E*)-7: Step-NOESY correlations. The solid arrow indicates a TOCSY response from H-6 to H-5 and dashed arrows indicate NOE responses from H-5 to H-8, H-9 and H-12.

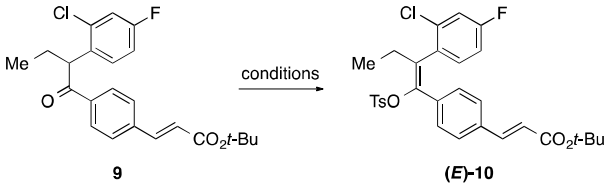
Based on these results, we investigated the alternative route B involving cinnamate ketone **9** (Scheme 2). Claisen condensation of substituted phenylacetic acid **8** and methyl 4-bromobenzoate initially used NaHMDS as the base, but we found that switching to NaH eliminated the need for cryogenic conditions and proved more economical.[10] Aqueous quench of the mixture led to extensive retro-Claisen reaction. Thus, addition of anhydrous EtOH into the reaction mixture quenched excess NaH and generated NaOEt *in situ*. Subsequent addition of iodoethane afforded the ethyl ketone intermediate that was telescoped into a palladium-catalyzed Heck cross-coupling[11] with *tert*-butyl acrylate (120 mol %). The Heck reaction proceeded smoothly under catalysis of 1 mol % $PdCl_2$(dppf)•DCM / Et_3N in DMA at 90 ºC. The crude ketone product **9** was crystallized directly from the reaction mixture by addition of aqueous EtOH. Recrystallization and charcoal treatment provided ketone **9** in 61% yield over 3 steps with >99 A % HPLC purity.

Scheme 2. Synthesis of Cinnamate Ketone 9



8 **8a** **8b** **9**

Table 2. Optimization of Stereocontrolled Enol Tosylate Formation[a]



9 **(*E*)-10**

entry	base	electrophile	conv[b] (%)	*E*/*Z* ratio[b]
1	NaO*t*-Bu	Ts_2O	99	89:11
2	KO*t*-Bu	Ts_2O	99	82:18
3	LiO*t*-Bu	Ts_2O	95	95:5
4	LiO*t*-Bu	Ts_2O	82	91:9[c]
5	LiO*t*-Bu	Ms_2O	95	89:11
6	LiO*t*-Bu	$(PhO)_2POCl$	95	90:10
7	LiO*t*-Bu	Tf_2O	95	83:17
8	LiHMDS	Ts_2O	99	64:36
9	NaHMDS	Ts_2O	99	52:48
10	KHMDS	Ts_2O	99	83:17

[a]Conditions: (a) **9** (500 mg, 1.24 mmol) in THF (2.5 mL) was added base (1.74 mol, 140 mol %) at 23 ºC, then Ts_2O (567 mg, 1.74 mmol, 140 mol %) in THF (2.5 mL). [b]Determined by HPLC analysis of crude reaction mixture. [c]Reaction performed at 0 ºC.

We evaluated a number of bases in preliminary experiments studying the stereocontrolled enolization of ketone **9** (Table 2). NaO*t*-Bu improved enolization stereoselectivity (entry 4) relative to its HMDS counterpart (entry 9). We were gratified to identify LiO*t*-Bu (entry 3) as the base of choice to afford a 95:5 ratio of *E*/*Z* enol tosylates after quenching with *p*-toluenesulfonic anhydride, as ascertained by HPLC analysis of the crude reaction mixture.[12,13] Trapping the lithium enolate as the corresponding methanesulfonate, diphenylphosphate and trifluoromethanesulfonate (entries 5–7) failed to improve the *E*/*Z* quench selectivity, had poor physical properties or did not provide improved performance in the downstream Suzuki–Miyaura cross-coupling.[14] In comparison, use of amide bases such as Li, Na or KHMDS resulted in high levels of the undesired (*Z*)-enol tosylate isomer (entries 8–10). Performing the entire enolization / tosylation sequence at room temperature allowed for >99% conversion and under the optimized conditions, we obtained **(*E*)-10** contaminated with 5 A % HPLC of undesired enol tosylate isomer **(*Z*)-10** but simple crystallization from *n*-PrOH / H_2O purged the minor **(*Z*)-10** and resulted in isolation of **(*E*)-10** in 78% yield and ≥99.6 A % HPLC purity. The structure of enol tosylate **(*E*)-10** was unambiguously confirmed through single crystal X-ray analysis (Figure 3).

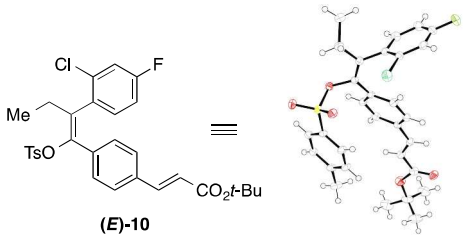


Figure 3. X-ray crystallographic analysis of (*E*)-**10**.

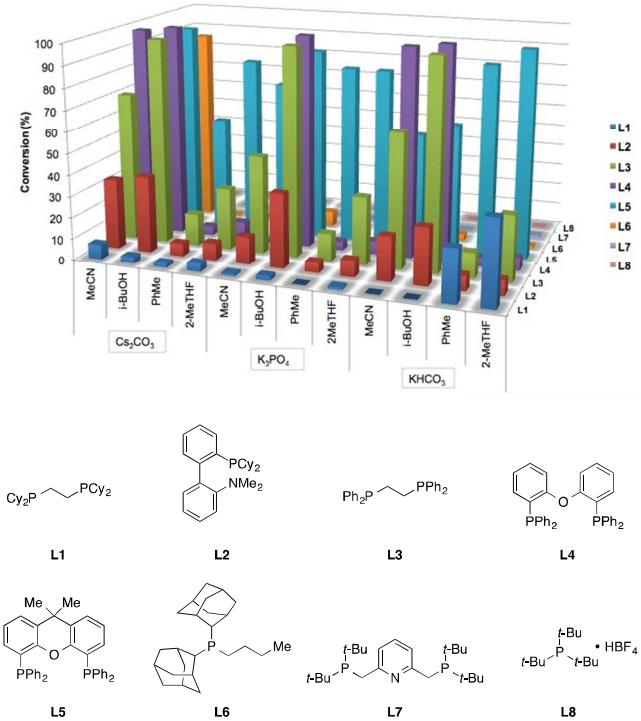
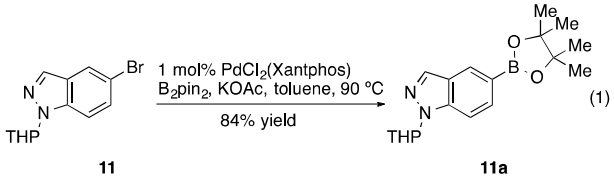


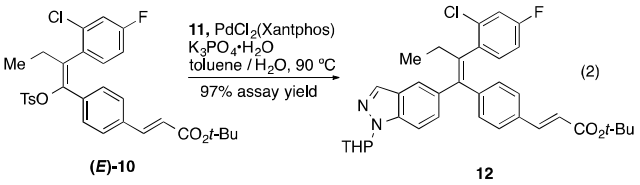
Figure 4. A subset of HTE screening results.

Using a microscale, high-throughput experimentation approach, we evaluated a broad range of ligands and reaction conditions using $Pd(OAc)_2$ (10 mol %) as the precatalyst for the key bond-forming Suzuki–Miyaura cross-coupling between enol tosylate **(*E*)-10** and *N*-THP-indazoleboronic acid pinacol ester **11a**.[14,15] A subset of the screening results is shown in Figure 4.

Indazole **11a** was prepared by palladium-catalyzed Miyaura borylation[15] of the corresponding *N*-THP-5-bromoindazole in toluene in 84% yield (eq 1).

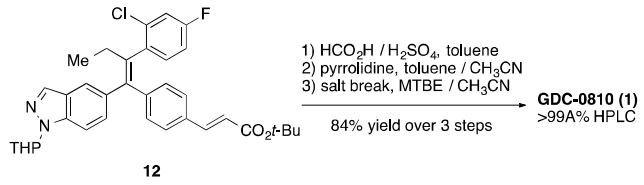


Top conditions rapidly emerged with Xantphos as the ligand of choice to provide tetrasubstituted all-carbon olefin **12**. Optimization of the reaction conditions involved the use of $PdCl_2$(Xantphos) as the precatalyst, reduction of catalyst loading to 1 mol % and increasing reaction concentration to 5.5 mL/g in toluene at 90 ºC and afforded olefin **12** in 97% assay yield (eq 2). Although the cross-coupling worked well in a variety of solvents, we found that performing the reaction in toluene allowed telescoping into the downstream global deprotection step. Gratifyingly, and unlike previous observations made on related systems in our laboratories, we did not observe olefin isomerization during the cross–coupling through what we presume to be a zwitterionic palladium carbenoid mechanistic manifold.[6a]



We next focused our attention on improving the global deprotection and inserting an additional isolation point in the process (Scheme 3). The original conditions relied on HCl in MeOH / H_2O to concomitantly remove the *N*-THP and *tert*-butyl ester groups. These conditions resulted in transesterification of the cinnamate side-chain and incomplete deprotection of *N*-THP aminal, presumably due to equilibrium between reactive pyran byproducts and **1**. These issues were circumvented by the use of HCO_2H / H_2SO_4 in toluene. Treatment of the crude cross-coupling reaction mixture with the acid mixture resulted in rapid THP cleavage and ester hydrolysis. Ultimately, this afforded crude GDC-0810 free acid as a crude solution in toluene. After aqueous workup of the reaction, addition of pyrrolidine directly to the toluene / CH_3CN process stream afforded crystalline GDC-0810 pyrrolidine salt in a 92% isolated yield and a 98.9 A % HPLC purity. The purity of GDC-0810 was further upgraded with a salt break and final crystallization from MTBE / CH_3CN produced the corresponding API free acid in 97% yield and >99 A % HPLC purity.

Scheme 3. Final Deprotection and API Crystallization



12

CONCLUSIONS

In conclusion, we have developed an efficient and practical kilogram scale synthesis of GDC-0810 based on a sequence involving a highly stereocontrolled enolization of ketone **9** mediated by LiO*t*-Bu and cross-coupling of resulting enol tosylate **(*E*)-10** with *N*-THP-indazoleboronate **11a** using $PdCl_2$(Xantphos) as the pre-catalyst. The endgame chemistry relied on global deprotection using HCO_2H / H_2SO_4, pyrrolidine salt formation and salt break. The process provided crystalline GDC-0810 API in 40% overall yield from 2-chloro-4-fluorophenylacetic acid (**8**) and >99 A % HPLC purity.

EXPERIMENTAL SECTION

General. All materials were purchased from commercial suppliers unless otherwise noted. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker 500 MHz spectrometer, collected at 296K in the solvents indicated. HPLC analysis was performed on an Agilent 1100 or 1200 series instruments. HRMS data was acquired on a Thermo Scientific Discovery Orbitrap mass spectrometer.

(*E*)-2-(2-chloro-4-fluorophenyl)-1-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazol-5-yl)but-1-en-1-yl 4-methylbenzenesulfonate ((*E*)-7). A solution of ketone 6 (500 mg, 1.25 mmol) in THF (2.5 mL) was added to KO*t*-Bu (1.75 mmol, 140 mol%, weighed in an inert glovebox) in THF (1.25 mL) and stirred for 30 min at 23 ºC. Ts_2O (570 mg, 1.75 mmol, 140 mol%) in THF (2.5 mL) was added and the mixture was stirred for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (4 mL) and extracted with MTBE (2 × 4 mL). The residue was chromatographed on SiO_2 using iPrOAc:heptane as eluent. The collected fractions were concentrated to afford (*E*)-7 as a white foam (440 mg, 64% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (1H, bs, H14), 7.46 (2H, dd, *J* = 8.3, 1.3 Hz, H26), 7.28 (1H, m, H12), 7.16 (1H, m, H23), 7.03 (1H, dt, *J* = 8.5, 2.5 Hz, H2), 7.01-6.94 (5H, m, H5, H24 and H27), 6.79 (1H, td, *J* = 8.3, 2.6 Hz, H6), 5.58 (1H, dd, *J* = 9.7, 2.6 Hz, H17), 4.04 (1H, m, H21'), 3.71 (1H, m, H21"), 2.77 (1H, dtd, *J* = 15.1, 7.5, 2.6 Hz, H8'), 2.52 (2H, m, H8" and H18'), 2.25 (3H, s, H29), 2.14 (1H, td, *J* = 5.7, 2.8 Hz, H19'), 2.02 (1H, m, H18"), 1.75 (2H, m, H19" and H20'), 1.65 (1H, m, H20"), 0.93 (3H, t, *J* = 7.6 Hz, H9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 160.6 (s, C1), 144.5 (s, C10 and C28), 138.6 (s, C22), 134.5 134.4 (s, C3), 134.2 (d, C14), 134.0 133.9 (s, C25), 133.2 (s, C4), 133.2 (s, C7), 132.6 (d, C5), 129.1 (d, C27), 128.0 (d, C26), 127.6 (d, C24), 126.8 (s, C11), 123.8 (s, C13), 122.4 (d, C12), 117.1 116.9 (d, C2), 114.1 113.9 (d, C6), 109.2 (d, C23), 85.4 85.3 (d C17), 67.7 (t, C21), 29.5 (t, C18), 25.1 (t, C8 and C20), 22.7 (t, C19), 21.4 (q, C29), 11.6 (q, C9). Peak assignments were confirmed through COSY, HSQC and HMBC 2D NMR methods. HRMS (ESI) m/z: calcd. for $C_{29}H_{29}ClFN_2O_4S$ $[M+H]^+$: 555.1515; found: 555.1510 (Δ 0.9 ppm).

1-(4-Bromophenyl)-2-(2-chloro-4-fluorophenyl)butan-1-one (8b). To a reactor under N_2 was charged NaH (0.90 kg, 22.5 mol, 310 mol %, 60% dispersion in mineral oil) and THF (1.25 kg), then heated to 66 ˚C. A solution of 2-(2-chloro-4-fluoro-phenyl)acetic acid **(8)** (1.36 kg, 7.21 mol, 100 mol%), methyl 4-bromobenzoate (1.71 kg, 7.95 mol, 110 mol%), and THF (1.70 kg) was then charged to the reactor over 3 h (*caution*: gas evolution!). Once the addition was complete, the reaction mixture was aged for 3.5 h, cooled to 40-50 ˚C and EtOH (2.13 kg) was slowly charged to the reactor (*caution*: gas evolution!). Iodoethane (2.6 kg, 16.7 mol, 230 mol %) was then added over 1.5 h at 40–50 ˚C and aged for 12 h. Aqueous NaOH (1.36 kg, 15% w/w solution) was charged to the reactor and the reaction mixture was cooled to 15–25 ˚C and aged for 2 h. Aqueous HCl (4.28 kg, 12.3% w/w) was charged to obtain pH 1–2. MTBE (3.52 kg) was added, the layers were cut and the bottom aqueous layer was removed. Aqueous Na_2CO_3 (2 × 7.48 kg, 17% w/w) was charged over 30 min and aged for an additional 30 min. The layers were cut and the bottom aqueous layer was removed. The organic layer was distilled to a minimum stir volume under vacuum at 40 ˚C. DMA (6.3 kg) was charged, providing a crude DMA solution of **8b** (82% yield, 93 A % HPLC purity), which was used directly in the next step: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.47 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.24 (dd, *J* = 8.8, 6.2 Hz, 1H), 7.17 (td, *J* = 8.5, 2.7 Hz, 1H), 4.97 (dd, *J* = 7.8, 6.4 Hz, 1H), 2.05 (sep, *J* = 14.1, 7.2 Hz, 1H), 1.74 (dt, *J* = 13.6, 7.4 Hz, 1H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.5, 161.7, 159.8, 135.1, 133.7, 133.1, 133.1, 132.0, 130.6, 130.5, 130.1, 127.5, 117.1, 116.9, 115.2, 115.0, 49.7, 25.4, 11.6; HRMS (APCI) m/z: calcd for $C_{16}H_{14}BrClFO$ $[M+H]^+$: 354.9901; found: 354.9888 (Δ 2.0 ppm).

***tert*-Butyl (*E*)-3-(4-(2-(2-chloro-4-fluorophenyl)butanoyl)phenyl)acrylate (9).** To an inerted reactor was charged a solution of **8b** (2.4 kg @ 25 wt % in DMA, 0.60 kg, 1.69 mol, 100 mol %). The solution was heated to 50–60 ˚C and *tert*-butyl acrylate (0.259 kg, 2.02 mol, 120 mol%) and Pd(dppf)Cl_2•DCM (13.5 g, 0.017 mol, 1.0 mol%) were charged. The reaction mixture was degassed with 3 vacuum / nitrogen purge cycles. Triethylamine (205 g, 2.02 mol, 120 mol %) was charged and the reaction mixture was heated to 110–130 ˚C and aged for ≥2 h. The reaction mixture was cooled to 40–50 ˚C and EtOH (6.15 kg) was added. Water (15.0 kg) was charged slowly over 2 h and aged for an additional 1 h after the addition was complete. The reaction mixture was seeded with **9** (6.0 g) and cooled to 20–30 ˚C over 1 h and aged for an additional 1 h. The crude solids were filtered and dried at 45 ˚C to afford crude **9** (0.48 kg (corrected), 87.9 A % HPLC purity). To an inerted 20 L reactor was charged crude **9** (3.62 kg (corrected)) and heptane (34.4 kg). The batch was heated to 50–60 ˚C and stirred until all solids were dissolved. The reaction mixture was treated with activated carbon (0.37 kg) at 50–60 ˚C, and then filtered. The reaction mixture was cooled to 25 ˚C over 2 h, then cooled further to 5 ˚C and aged for an additional 2 h. The solids were filtered and washed with pre-cooled heptane (2.0 L, 0–5 ˚C). The solids were dried under vacuum at 55 ˚C for at least 18 h to give **9** (3.39 kg, 64% overall yield and 99.0A% HPLC purity): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (bd, *J* = 8.5 Hz, 2H), 7.76 (bd, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 16.0 Hz, 1H), 7.44 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.24 (dd, *J* = 8.8, 6.2 Hz, 1H), 7.16 (td, *J* = 8.8, 2.7 Hz, 1H), 6.58 (d, *J* = 16.1 Hz, 1H), 4.98 (dd, *J* = 7.8, 6.5 Hz, 1H),

2.05 (ddd, J = 13.7, 7.3, 6.5 Hz, 1H), 1.72 (dt, J = 13.7 ,7.8 Hz, 1H), 1.46 (s, 9H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.2, 163.6, 160.1 158.1, 140.4, 137.0, 135.3, 132.1, 132.1, 131.6, 131.6, 128.9, 128.8, 127.0, 126.9, 121.0, 115.4, 115.2, 113.5, 113.4, 78.9, 48.2, 26.1, 23.9, 10.0; HRMS (APCI) m/z: calcd for $C_{23}H_{25}ClFO_3$ $[M+H]^+$: 403.1471; found: 403.1461 (Δ 2.5 ppm).

***tert*-Butyl (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(tosyloxy)but-1-en-1-yl)phenyl)acrylate [(*E*)-10].** To an inerted 20 L jacketed glass reactor was charged **9** (1.20 kg, 2.98 mol, 100 mol %) and THF (3.20 kg). Lithium *tert*-butoxide (3.71 kg, 4.18 mol, 140 mol %, 1.0 M in THF) was charged at 20–30 ˚C over 30 min. The reaction mixture was stirred for 30 min and then a solution of *p*-toluenesulfonic anhydride (1.36 kg, 4.17 mol, 140 mol %) in THF (6.40 kg) was added over 30 min while maintaining the internal temperature at 20–25 ˚C. The reaction mixture was aged for 30 min. The batch was distilled under vacuum at 40–50 ˚C to obtain a total volume of 6.67 L/kg. MTBE (2.67 kg) was charged and the reaction mixture was cooled to 0–10 ˚C. Aqueous NaOH (2.40 kg, 1 M solution) was charged while maintaining the temperature < 20 ˚C. The reaction mixture was aged for 5 min, then agitation was stopped and the bottom aqueous layer removed. The organic layer was washed with aqueous NaCl (2 × 2.88 kg, 23% w/w). The bottom aqueous layer was removed and then the organic layer was distilled under vacuum to a minimum stir volume. 1-Propanol (1.93 kg) was charged and the mixture was again distilled under vacuum to a minimum stir volume. 1-Propanol (1.93 kg, 1.61 kg/kg) was charged and the mixture was distilled under vacuum to a minimum stir volume. 1-Propanol (2.89 kg, 2.41 kg/kg) was charged and check for removal of THF (< 0.6% w/w) by GC. The batch was heated at 80–90 ˚C and H_2O (1.80 kg, 1.50 kg/kg) was added. The batch was cooled to 60 ˚C and seeded with **(*E*)-10** (6.0 g) suspended in 1-propanol (25.0 g). The resulting slurry was aged for ≥ 30 min, then cooled to 15–25 ˚C over 5 h. The solids were filtered and the filter cake was washed with a mixture of 1-propanol (3.52 kg) and H_2O (1.62 kg). The solids were dried under vacuum at 55–65 ˚C to provide enol tosylate **(*E*)-10** as an off-white solid (1.30 kg, 78% yield and 99.6 A % HPLC purity): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.61 (m, 2H), 7.45-7.37 (m, 2H), 7.36 (m, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.14-7.08 (m, 2H), 6.90 (m, 2H), 6.42 (d, J = 16.0 Hz, 1H), 2.49 (dq, J = 15, 7.5, 1H), 2.36 (s, 3H), 2.25 (dq, J = 15.0, 7.6 Hz, 1H), 1.46 (s, 9H), 0.76 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.8, 162.7, 160.8, 145.9, 143.5, 143.0, 135.5, 134.4, 134.0, 133.9, 133.45, 133.4, 132.9, 132.9, 130.4, 129.3, 128.4, 127.9, 121.1, 117.4, 117.2, 115.1, 115.0, 80.5, 28.3, 25.0, 21.5, 11.5; HRMS (ESI) m/z: calcd for $C_{30}H_{30}ClFNaO_5S$ $[M+Na]^+$: 579.1384; found: 579.1385 (Δ 0.1 ppm).

1-(Tetrahydro-2*H*-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazol-1-ium (11a). A round-bottom flask was charged with *N*-THP-bromoindazole **11** (10.6 g, 35.6 mmol), bis(pinacolato)diboron (10.8 g, 42.7 mmol, 120 mol%), $PdCl_2$(dppf) (260 mg, 0.36 mmol, 1 mol%), KOAc (10.5 g, 106.7 mmol, 300 mol%) and toluene (50 mL). The reaction was sparged with N_2 bubbles and then heated at 100 ºC for 20 h. The mixture was cooled to rt, filtered on SiO_2, and the filter cake was washed with toluene (150 mL). The filtrate was solvent-switched to heptane (150 mL) under vacuum and cooled to 0 ºC for 1 h. The resulting solids were filtered and washed with heptane (20 mL) and dried under vacuum to afford boronate **11a** as a white solid (9.77 g, 84% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (bs, 1H), 8.16 (s, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.67 (dd, J = 8.4, 1.0 Hz, 1H), 5.85 (dd, J = 9.8, 2.6 Hz, 1H), 3.93-3.84 (m, 1H), 3.74 (ddd, J = 11.4, 8.0, 5.8 Hz, 1H), 2.46-2.36 (m, 1H), 2.06-2.00 (m, 1H), 1.96 (dq, J = 13.0, 3.5 Hz, 1H), 1.81-1.69 (m, 1H), 1.58 (tq, J = 8.0, 3.9 Hz, 2H), 1.32 (s, 12H); ^{13}C NMR (125 MHz, DMSO) δ 141.2, 134.7, 131.9, 129.3, 124.5, 121.2, 110.3, 84.5, 84.0, 67.0, 29.4, 25.3, 25.2, 22.7; HRMS (ESI) m/z: calcd. for $C_{18}H_{25}BN_2O_3$ $[M+H]^+$: 329.2031; experimental: 329.2026 (Δ 1.5 ppm).

tert-Butyl (*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1-(tetrahydro-2*H*-pyran-2-yl)-1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylate (12). To an inerted reactor was charged (*E*)-10 (1.20 kg, 2.15 mol, 100 mol %), boronate 11a (0.794 kg, 3.21 mol, 150 mol %), $PdCl_2$(Xantphos) (17.14 g, 0.02 mol, 1.0 mol%) and toluene (3.92 kg). The batch was degassed by sparging with N_2 for ≥ 20 min. To a separate container was charged K_3PO_4•H_2O (0.783 kg) and H_2O (1.50 kg). This solution was degassed by sparging with N_2 for ≥ 20 min, then transferred into the reactor. The combined reactor contents were then further sparged with N_2 for ≥ 20 min. The reactor contents were heated to 80–100 ˚C. The reaction mixture was aged for 4 h, cooled to 20–30 ˚C, and H_2O (1.80 kg) was charged. The layers were cut and the organic layer was washed with aqueous NaCl (1.44 kg, 23% w/w), then washed with H_2O (1.20 kg). The organic layer was then treated with Darco KB-WJ (0.120 kg) under agitation for ≥ 4 h. The slurry was filtered and the filter cake was rinsed with toluene (0.836 kg). The combined filtrates were distilled under vacuum at 45–55 ˚C to a total volume of 4.0 L/kg and stored as a toluene solution of 12 for the next reaction: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14 (bs, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.69 (m, 1H), 7.41-7.33 (m, 5H), 7.28 (dd, J = 8.7, 3.5 Hz, 1H), 7.14 (td, J = 8.5, 2.7 Hz, 1H), 6.94 (m, 2H), 6.36 (d, J = 16.0 Hz, 1H), 5.86 (dd, J = 9.8, 2.5 Hz, 1H), 3.89 (m, 1H), 3.74 (ddd, J = 11.4, 8.0, 5.9 Hz, 1H), 2.43 (m, 1H), 2.37 (q, J = 7.5 Hz, 2H), 2.05 (m, 1H), 1.98 (m, 1H), 1.75 (m, 1H), 1.59 (dd, J = 8.5, 4.3 Hz, 2H), 1.44 (s, 9H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.0, 162.2, 160.2, 144.7, 143.4, 140.8, 139.0, 138.9, 136.8, 134.9, 134.2, 133.8, 133.7, 133.6, 133.5, 132.5, 130.0, 128.3, 128.0, 124.7, 121.2, 120.0, 117.0, 116.8, 114.7, 114.5, 110.9, 84.5, 80.3, 67.0, 29.4, 28.5, 28.3, 25.2, 22.7, 13.0; HRMS (ESI) m/z: calcd for $C_{35}H_{37}ClFN_2O_3$ $[M+H]^+$: 587.2471; found: 587.2470 (Δ 0.2 ppm).

(*E*)-3-(4-((*E*)-2-(2-chloro-4-fluorophenyl)-1-(1*H*-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid (GDC-0810, 1). To an inerted reactor was charged the toluene solution of **12** (1.20 kg, 4.8 L). The temperature was maintained at 10–20 ˚C while charging HCO_2H (1.46 kg), followed by H_2SO_4 (0.44 kg, 98% w/w) while maintaining the internal temperature at < 25 ˚C. The reaction mixture was stirred at 15–25 ˚C for at least 4 h, then sampled for HPLC analysis. Once complete, the reactor contents were cooled to 0–10 ˚C and 50 wt % aqueous NaOH (0.86 kg) was charged while maintaining the temperature at < 25 ˚C. Water (2.40 kg) was added and the mixture was stirred for ≥ 5 min. Agitation was stopped and the bottom aqueous layer was removed. The organics were distilled under vacuum at 40 ˚C to a total volume of 3.42 L/kg. Toluene (2.09 kg) was charged and the mixture was distilled under vacuum at 40 ˚C to a total volume of 3.42 L/kg. Toluene (1.67 kg) was charged, followed by addition of CH_3CN (2.83 kg). The reactor con-

tents were heated to 55–65 ˚C and pyrrolidine (132 mL, 1.58 mol) was added. The reaction mixture was seeded (6.0 g) at 55–65 ˚C and aged for at least 10 min. Pyrrolidine (132 mL, 1.58 mol) was charged at 55–65 ˚C and the slurry was aged for at least 1 h. The reactor contents were cooled to 15–25 ˚C and aged for at least 1 h. The solids were filtered, washed with CH_3CN (2.83 kg) and dried under vacuum at 20–40 ˚C to give GDC-0810•pyrrolidine (1.01 kg, 91% yield over two steps, 98.9 A % HPLC purity): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (d, J = 1.0 Hz, 1H), 7.68 (t, J = 1.1 Hz, 1H), 7.56 (dd, J = 8.5, 1.0 Hz, 1H), 7.37–7.30 (m, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.19 (dd, J = 8.7, 1.7 Hz, 1H), 7.13 (dt, J = 2.5, 8.5 Hz, 1H), 7.09 (d, J = 15.7 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 6.29 (d, J = 15.7 Hz, 1H), 3.04–2.93 (m, 4H), 2.38 (q, J = 7.5 Hz, 2H), 1.81–1.70 (m, 4H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.6, 162.1, 160.1, 143.3, 141.4, 139.5, 138.3, 138.0, 137.1, 137.0, 134.3, 134.2, 134.1, 133.8, 133.7, 133.7, 133.6, 129.9, 128.0, 127.0, 126.9, 123.3, 120.7, 117.0, 116.8, 114.6, 114.5, 110.7, 44.7, 28.4, 24.7, 13.1; FT-IR (cm^{-1}) v: 2975, 2930, 2871, 1637, 1540, 1507, 1486, 1374, 1347, 1256, 1197, 992, 939, 896, 851, 804, 725; HRMS (ESI) m/z calcd for $C_{26}H_{21}ClFN_2O_2$ $[M + H]^+$: 447.1270, found 447.1262 (Δ 1.8 ppm). To an inerted reactor was charged GDC-0810•pyrrolidine (1.01 kg, 1.95 mol, 100 mol %), MTBE (1.48 kg), and 1N aqueous HCl (2.0 kg). The reaction mixture was stirred at 30–50 ˚C until all solids were dissolved. The layers were cut and the organic layer was washed with water (1.18 kg) and then distilled at 60–80 ˚C to a total volume of 1.2 L/kg. The batch was cooled to 40–60 ˚C and charged with CH_3CN (2.29 kg). The reaction mixture was seeded with **1** (25 g) at 40–60 ˚C. The slurry was aged for 2 h and then cooled to 15–25 ˚C over 4 h. CH_3CN (3.21 kg) was charged over 2 h and then the reaction mixture was cooled to –15 to 5 ˚C over 3 h. The resulting solids were filtered and the filter cake was washed with CH_3CN (0.70 kg) and dried under vacuum at 100–120 ˚C for 24 h to give **GDC-0810 (1)** as a white solid (0.80 kg, 92% yield and 99 A % HPLC purity): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 (1H, d, J = 1.0 Hz, H15), 7.70 (1H, t, J = 1.1 Hz, H14), 7.57 (1H, d, J = 8.5 Hz, H11), 7.46 – 7.32 (5H, m, H2, H5, H20, and H22), 7.20 (1H, dd, J = 8.5, 1.5 Hz, H10), 7.14 (1H, td, J = 8.5, 2.7 Hz, H6), 6.96 (2H, d, J = 8.4 Hz, H19), 6.39 (1H, d, J = 16.0 Hz, H23), 2.39 (2H, q, J = 7.5 Hz, H25), 0.91 (3H, t, J = 7.5 Hz, H26); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.0 (s, C24), 162.1 160.2 (s, C1), 144.9 (s, C18), 143.8 (d, C22), 141.1 (s, C8), 139.5 (s, C12), 138.7 (s, C7), 136.9 (s, C4), 134.2 (d, C15), 134.0 (s, C9) , 133.8 133.7 (d, C5), 133.6 133.5 (s, C3), 132.6 (s, C21), 130.1 (d, C19), 128.0 (d, C10), 127.9 (d, C20), 123.3 (s, C13), 120.8 (d, C14), 119.3 (d, C23), 117.0 116.8 (d, C2), 114.7 114.5 (d, C6), 110.7 (d, C11), 28.4 (t, C25), 13.1 (q, C26). 168.0 (s, C24), 162.1 160.2 (s, C1), 144.9 (s, C18), 143.8 (d, C22), 141.1 (s, C8), 139.5 (s, C12), 138.7 (s, C7), 136.9 (s, C4), 134.2 (d, C15), 134.0 (s, C9) , 133.8 133.7 (d, C5), 133.6 133.5 (s, C3), 132.6 (s, C21), 130.1 (d, C19), 128.0 (d, C10), 127.9 (d, C20), 123.3 (s, C13), 120.8 (d, C14), 119.3 (d, C23), 117.0 116.8 (d, C2), 114.7 114.5 (d, C6), 110.7 (d, C11), 28.4 (t, C25), 13.1 (q, C26). Peak assignments were confirmed through COSY, HSQC and HMBC 2D NMR methods. HRMS (ESI) m/z: calcd for $C_{26}H_{21}ClFN_2O_2$ $[M + H]^+$: 447.1270; found: 447.1263 (Δ 1.6 ppm).

ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra and single crystal X-ray data for **(*E*)-10**. The Supporting Information is available free of charge on the ACS Publications website.

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