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Improved Synthesis of the Nav1.7 Inhibitor GDC-0276 via a Highly Regioselective S_NAr Reaction

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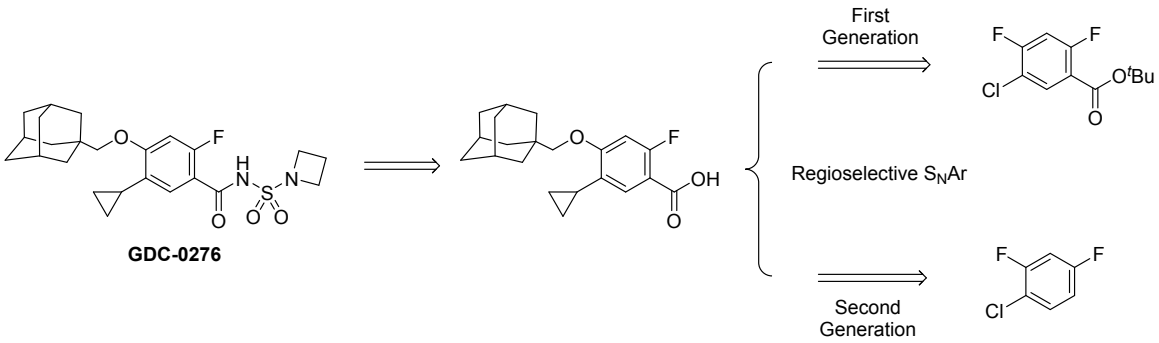
TOC


GDC-0276
First Generation
Regioselective S_NAr
Second Generation

ABSTRACT

The development of a redesigned and improved second generation synthesis of the Nav1.7 inhibitor GDC-0276 based on experience gained from a fit-for-purpose first generation synthesis will be described. The first generation synthesis proceeded via a regioselective S_NAr reaction on the advanced starting material *t*-butyl 5-chloro-2,4-difluorobenzoate with 1-adamantanemethanol. In the newly developed second generation synthesis, the much improved regioselective S_NAr reaction was performed on the readily available starting material 1-chloro-2,4-difluorobenzene, followed by installation of the carboxylate group by electrophilic aromatic bromination and a palladium-catalyzed alkoxycarbonylation. A subsequent Suzuki-Miyaura cross-coupling reaction was then telescoped directly into a phase transfer catalyzed (PTC) ester hydrolysis. Amidation of the resulting acid intermediate with 1-azetidine sulfamide in turn provided GDC-0276 in high overall yield and purity on 100 kilogram scale.

KEYWORDS. Nav1.7 inhibitor, S_NAr, Suzuki-Miyaura cross-coupling, palladium-catalyzed alkoxycarbonylation, phase transfer catalysis (PTC)

Introduction

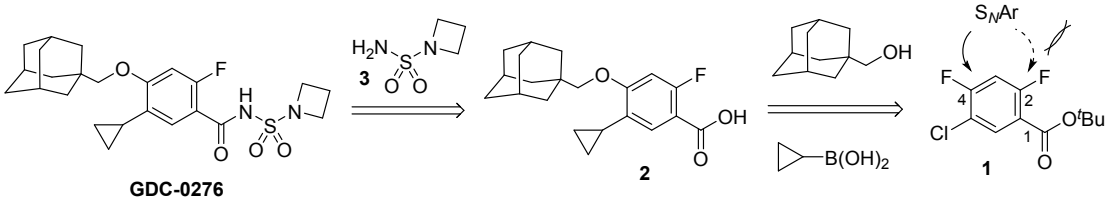
Nav1.7 is a voltage gated sodium channel expressed in pain sensing nerve C-fibers and plays an essential role in the generation of action potentials and the sensation of pain. The Nav1.7 protein complex has been validated through human genetics, and become a valuable small molecule drug discovery target for the treatment of pain.[1] GDC-0276 was developed in our laboratories[2] as a selective small molecule Nav1.7 inhibitor to provide novel and improved treatment options for pain, and to address shortcomings of existing pain medications, such as addiction and off-target side effects.

Results and Discussion

First Generation Process

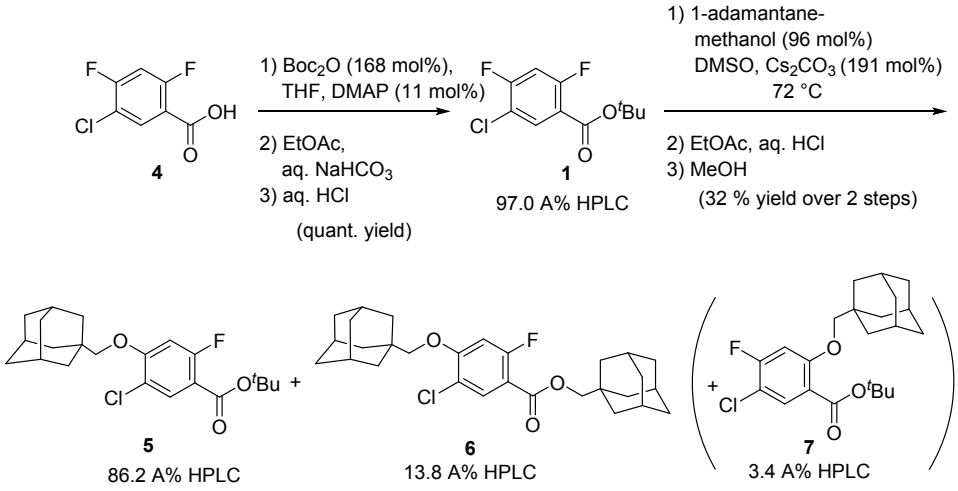
In order to quickly deliver the first kilogram amounts of active pharmaceutical ingredient (API) to initiate clinical trials, we set out to develop a first generation process for GDC-0276 based on the retrosynthetic analysis illustrated in Figure 1. We envisioned that GDC-0276 could be synthesized by amidation of benzoic acid **2** with sulfamide **3**. Suzuki-Miayura cross-coupling with cyclopropylboronic acid (CPBA), and subsequent hydrolysis of the *t*-butyl ester would then furnish penultimate intermediate **2**. S_NAr reaction of **1** with 1-adamantanemethanol would regioselectively deliver the C-4 substituted ether because of steric hindrance at C-2 caused by the *t*-butyl ester.

Figure 1. Retrosynthesis of GDC-0276



We started with esterification of 5-chloro-2,4-difluorobenzoic acid with Boc_2O in THF and a catalytic amount of DMAP to give the corresponding *t*-butyl ester **1** (Scheme 1) as oil in quantitative yield and 97.0 A% HPLC purity after workup. Next, ester **1** was subjected to a regioselective S_NAr reaction with 1-adamantanemethanol in DMSO in the presence of Cs_2CO_3 to give the expected intermediate **5** from fluoride displacement at C-4.

Scheme 1. Synthesis of Intermediate **5**

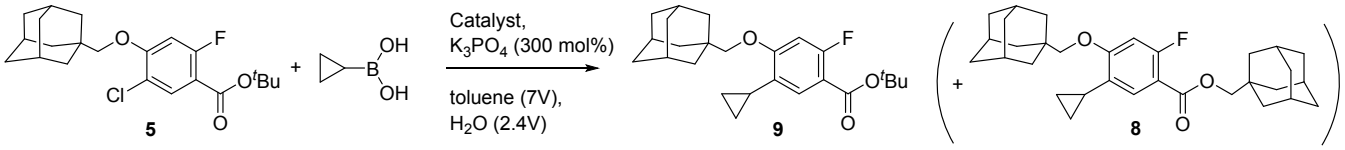


However, under these conditions, significant amounts of adamantyl ester **6** (10─15 A% HPLC) and regioisomer **7** (3─5 A% HPLC), resulting from substitution of fluoride at C-2, were also generated as major side products.[3]

We evaluated a number of bases (Cs_2CO_3, K_2CO_3, *t*-BuOK, LiHMDS) and solvents (DMF, DMSO, THF, THF / DMF, THF / DMSO), but this did not result in any improved overall reaction profile. We therefore proceeded to run the reaction with Cs_2CO_3 in DMSO;[4] crude **5** could be isolated as a solid in 32% corrected yield and 86.2 A% HPLC purity after work up with EtOAc and aqueous HCl followed by concentration of the organic layer. Although undesired regioisomer **7** could be easily removed by trituration with MeOH down to <0.2 A% HPLC, adamantyl ester **6** could not be purged (13.6 A% HPLC) at this stage.

We next investigated the Suzuki-Miyaura cross-coupling of **5** with cyclopropylboronic acid (CPBA), in toluene / water with K_3PO_4 as a base, and initiated a catalyst screen (Table 1). A Buchwald second generation palladium precatalyst G2-PdXPhos[5] was identified as the best catalyst from this screen (Table 1, entries 3─5), and the ratio of G2-PdXPhos / XPhos could be reduced from 1:2 (Table 1, entry 3) to 1:1 without compromising reaction conversion (Table 1, entry 4) at 80 °C. However, the stability of CPBA was subsequently examined using differential scanning calorimetry (DSC) and it was found to decompose at 169 °C (see the Supporting Information). Thus, for safety reasons, the Suzuki reaction was run at <70 °C. The catalyst loading was further optimized down to 0.5 mol% from 2 mol%, but required an excess of CPBA (140 mol%) for the reaction to go to completion at 65 °C (Table 1, entry 6).

Table 1. Optimization of Suzuki Cross-Coupling of **5** with CPBA



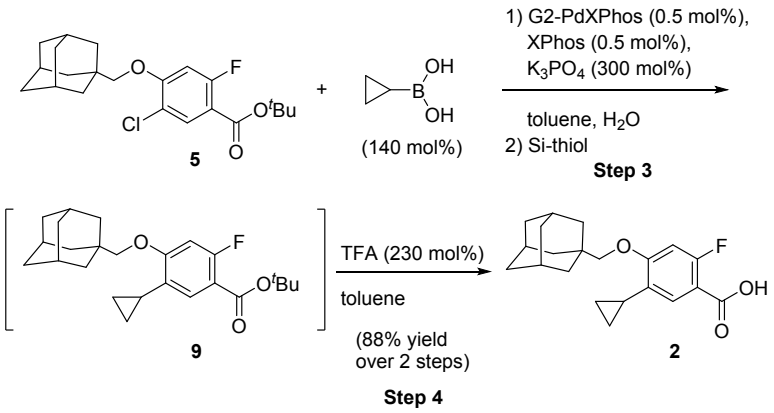
Entry[a]	**5** (mmol)	CPBA (mol%)	Catalyst (2 mol%)	XPhos (mol%)	Conversion (A%)[b]
1	0.50	140	$PdCl_2(PPh_3)_2$	N/A	0
2	1.00	140	$Pd(OAc)_2$	4	95
3	1.00	140	G2-PdXPhos[c]	4	100
4	5.00	140	G2-PdXPhos	2	100
5	5.00	120	G2-PdXPhos	4	98
6[d]	253.00	140	G2-PdXPhos[f]	0.5	100

[a]Reactions conducted by mixing **5** and CPBA in toluene (7V), and adding K_3PO_4 (300 mol%) in water (2.4V), catalyst and ligand at rt, evacuating and backfilling with N_2, and then heating to 80ºC for 14 h. [b]Conversion was

determined by HPLC analysis. [c]Chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II). [d]Heated to 65 ºC for 16 h. [f]G2-PdXPhos (0.5 mol%)

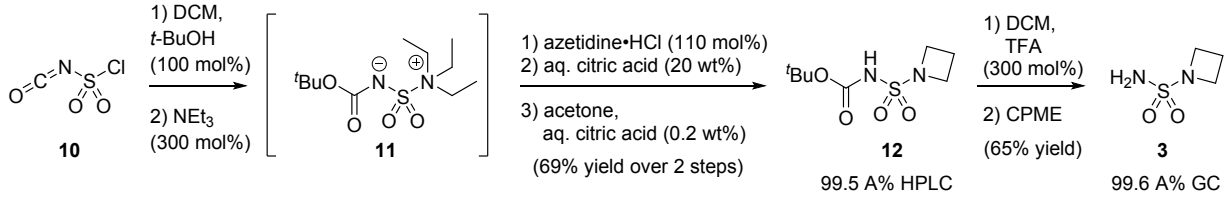
In order to remove residual Pd after aqueous workup, the crude solution of **9** in toluene was treated with Si-thiol®[6] and palladium content was reduced from 504 ppm to <10 ppm in the solution after filtration of the resin scavenger. All attempts to isolate intermediate **9** as a solid were unsuccessful, and therefore the resulting solution of **9** was directly subjected to trifluoroacetic acid at 65 °C for 12 h to cleave the *t*-butyl ester.

Scheme 2. Optimized Suzuki Cross-Coupling and Cleavage of Ester **9**



After distillation of solvent and addition of heptane, the resulting acid **2** was isolated by filtration. Gratifyingly, adamantyl ester **8** (Table 1), originating from side product **6**, was completely purged (<0.1 A% HPLC) and **2** was obtained in 88% yield over 2 steps and 99.8 A% HPLC purity (Scheme 2).

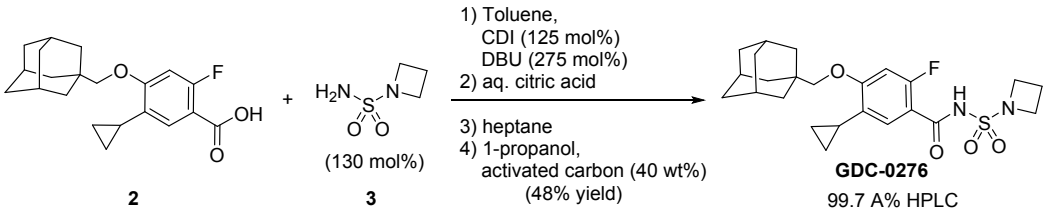
Scheme 3. Synthesis of Sulfamide **3**



The synthesis of a sulfamoylating agent derived from chlorosulfonyl isocyanate (CSI, **10**) had been described previously in the literature.[7] Using similar conditions, **10** was reacted with *t*-BuOH in DCM[8] in the presence of NEt_3 to provide zwitterion **11**, which was directly quenched with azetidine•HCl[9] to give *N*-Boc-protected sulfamide **12** **(**Scheme 3). Crude solid **12** (>81.0 A% HPLC purity) was recrystallized from acetone and dilute aqueous citric acid

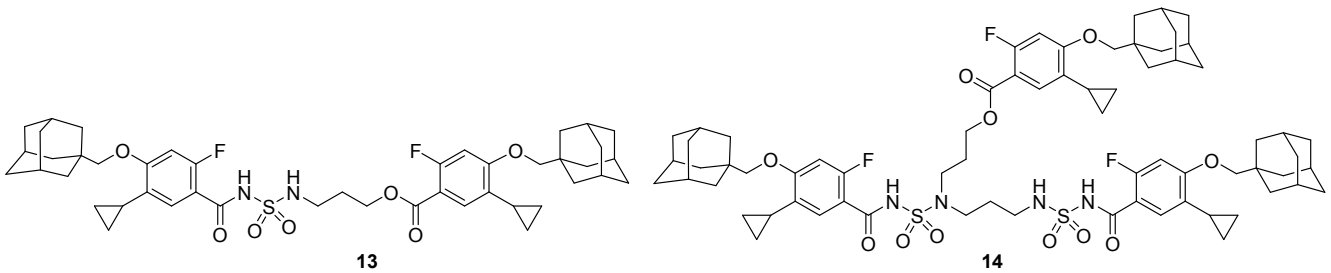
(0.2 wt%) to furnish **12** with 99.5 A% purity by HPLC. Deprotection of **12** was then accomplished by treatment with TFA in DCM at 25 °C, and sulfamide **3** was directly isolated in 65% yield as a white solid from the concentrated reaction mixture after addition of CPME.

Scheme 4. Amidation to GDC-0276



For the final amidation to GDC-0276, acid **2** was first activated with CDI in toluene and DBU, and then reacted with sulfamide **3** to afford GDC-0276 (Scheme 4). Imidazole byproduct was removed from the reaction mixture by aqueous acidic washes. After investigating a small subset of acids (including HCl and acetic acid), citric acid was selected to adjust the pH from 9 to 4, since it offered clean phase separation. Crude GDC-0276 was directly isolated as a solid from the reaction mixture after addition of heptane, in ~98 A% HPLC purity. Unexpectedly, two major side products were detected in the API in 0.57 A% and 0.20 A% HPLC, and were later identified by NMR spectroscopy / LCMS analyses as side products **13** and **14**, respectively (Figure 2, see also the Supporting Information). These impurities were most likely formed from the corresponding azetidine ring-opened precursors generated during the Boc deprotection of **12** with TFA, and carried through the amidation reaction.[10] Furthermore, GDC-0276 crystallized from toluene was obtained as an undesired solvate[11] Treatment with activated carbon (40 wt%) and recrystallization from 1-propanol was thus necessary to further upgrade the purity of the API to >99 A% HPLC.[12] In order to obtain the API with the desired polymorphic form I,[13] GDC-0276 seed crystals (1 wt%) were added to a supersaturated solution of GDC-0276 in 1-propanol at 70 °C, followed by slow cooling to 25 °C.

Figure 2. Side products **13** and **14**

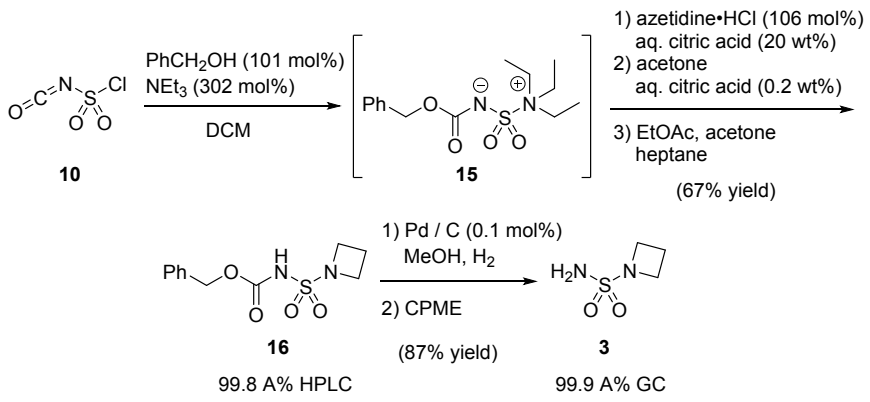


Following this route, the first scale-up synthesis of GDC-0276 quickly provided 3.4 kg of API for early clinical trials, but a number of shortcomings were identified that needed to be addressed before a further pilot plant campaign could be run: 1) S_NAr reaction with 1-adamantanemethanol on the *t*-butyl ester **1** generated significant amounts of undesired regioisomer **7** and adamantyl ester **6** that contributed an important overall loss of material; 2) The high level of downstream oligomeric impurities in the API originating from the sulfamide **3** required a carbon treatment as a penultimate operation; 3) The isolation of an undesired crystal solvate from toluene necessitated recrystallization in a separate additional step.

Second Generation Synthesis

We hypothesized that deprotection of Boc sulfamide **12** with TFA resulted in opening of the azetidine ring and subsequent formation of side products which carried through the amidation reaction. To overcome this issue, we sought to swap the Boc-protecting group in **12** for a Cbz group, which would allow mild deprotection by hydrogenolysis. Thus, simply replacing *t*-butanol with benzyl alcohol during the synthesis of sulfamide **3** provided the corresponding Cbz-protected sulfamide **16** (Scheme 5). The reaction was performed in DCM[8] at 5 °C, and intermediate **15** was not isolated but telescoped into the next step with Et_3N and azetidine•HCl to achieve conversion to **16**. Filtering off the precipitated Et_3N•HCl from the reaction mixture was found to be problematic at pilot plant scale (~100 kg) due to long filtration times (>10 h). We therefore implemented an extractive aqueous acidic workup using citric acid,[14] and the resulting solution of **16** was swapped to acetone–H_2O, followed by addition of dilute aqueous citric acid as antisolvent. Crude **16** (97.4 A% HPLC purity) was recrystallized from acetone and dilute aqueous citric acid (0.2 wt%) to furnish **16** with high purity in 67% overall yield over the 2 steps.

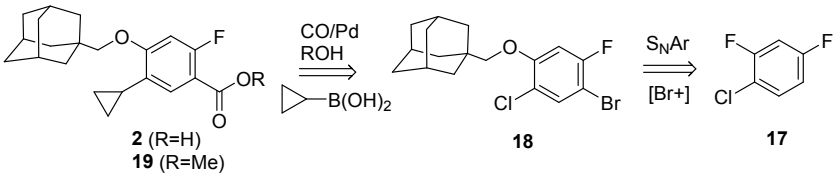
Scheme 5. New Synthesis of **3**



We next investigated the Cbz deprotection of **16** by hydrogenolysis on 3 g scale at 20 ºC using Pd / C as catalyst (~0.8 mol% Pd) and H_2 (80 psi) in various solvents (2-propanol, EtOH, *i*PrOAc, MeOH, 2-MeTHF and acetone, 10V). Most reactions went to completion after 4 h, however, product **3** precipitated from the reaction mixtures, which rendered the removal of the catalyst problematic, unless MeOH or acetone were employed.[15]

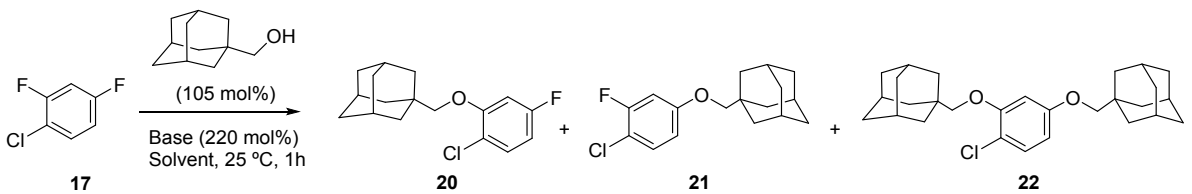
Optimizing the Pd / C loading and temperature, we found that the conversion of **16** in MeOH (10V) to **3** was complete after 18 h at 20 ºC when using 0.1 mol% Pd / C at 80 psi H_2. The catalyst was then filtered off and **3** was isolated by filtration after addition of CPME antisolvent. This new optimized process was successfully demonstrated on plant scale and delivered 48 kg of azetidine-1-sulfonamide (**3**) in 58% overall yield and 99.9 A% purity by GC. More importantly, a sample from this material was taken forward into the crude API amidation step, and this time oligomer impurities **13** and **14** could not be detected by HPLC, confirming our hypothesis that they originated from the original acidic Boc-deprotection.

Figure 3. Retrosynthetic Analysis of **2**



In order to increase the regioselectivity of the S_NAr transformation and to alleviate the reactivity of the *t*-butyl ester **1** towards transesterification, a new approach to acid **2** was devised, as illustrated with the retrosynthesis shown in Figure 3. Installation of the carboxylate group of **18** was set to follow regioselective bromination, which would occur after a selective S_NAr[16] reaction of 1-chloro-2,4-difluorobenzene (**17)**, a commercially and readily available starting material.[17] We first investigated the nucleophilic aromatic substitution of **17** with 1-adamantanemethanol to give **20** (Table 2), using different bases[18] and solvents at 25 ºC.[19]

Table 2. S_NAr of **17** with 1-adamantanemethanol



Entry[a]	Solvent	Base	Conversion (A%)[b]	**20** (A%)	**21**[c] (A%)	**22**[c] (A%)

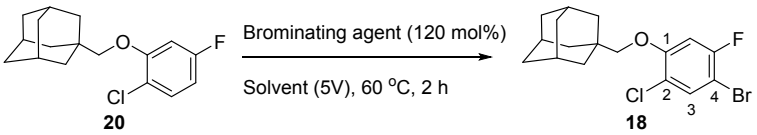
1	THF	*t*-BuONa	6.4	6.0	0.4	NA
2	THF	NaH	5.8	4.2	>0.01	NA
3	THF	*t*-BuOK	98	84.7	6.1	3.7
4	CH_3CN	*t*-BuOK	49	NA	NA	NA
5	MTBE	*t*-BuOK	29	NA	NA	NA
6	DMF	*t*-BuOK	>99	82.1	12.1	0.5
7	DMA	*t*-BuOK	>99	81.6	10.9	0.8
8[d]	THF	*t*-BuOK	>99	94.5	3.0	NA

[a]Reactions conducted in closed vials with stir bars at 25 ºC by mixing **17** (3.4 mmol) and 1-adamantanemethanol in solvent (10V), adding bases (220 mol%) as solids. [b]HPLC A% after 1 h reaction time. [c]Proposed structure based on EI-MS analysis (see SI). [d]**17** (135 mmol), 1-adamantanemethanol, solvent (2.6V), base added as solution in solvent (7.4V) at 25 ºC.

Among the various bases screened, *t*-BuOK gave the highest conversion (>98 A% HPLC) to **20** (Table 2, entry 3), but significant amounts of regioisomer **21** (6.1 A%) and bis-addition impurity **22** (3.7 A%) were also formed. THF was selected over DMF and DMA[20] which exhibited similar reaction rates, but resulted in significantly larger amounts of regioisomer **21** (Table 2, entries 3, 6 and 7). Adding *t*-BuOK as a 20 wt% solution in THF[21,22] instead of as a solid further improved the reaction profile (Table 2, entry 8). Next, the isolation and purification of **20** by direct crystallization from the reaction mixture was optimized. The reaction mixture was quenched into water, followed by distillation to remove excess THF[23], and then a mixture of H_2O / MeOH was dosed in to initiate crystallization of the product. **20** was thus obtained as a white solid in 91% yield and >97.7 A% purity by HPLC with acceptable levels of **22** (<0.07 A%) and **21** (<1.9 A%), which was further purged down to <0.2 A% in the next step.

Based on literature precedence[24], we expected bromination of **20** to occur at the C-4 position of the aromatic ring, and when **20** was reacted with Br_2 (120 mol%) in DCE (10V) at 50 ºC for 5 h, **18** was isolated in 93% yield and >99 A% HPLC as a single isomer after aqueous $Na_2S_2O_3$ workup. With proof of concept in hand, we focussed on investigating various less hazardous brominating agents like *N*-bromosuccinimide (NBS) and *N,N*-dibromo-dimethylhydantoin (DBDMH) in various solvent combinations with regards to selectivity and impurity profile (Table 3).

Table 3. Bromination of **20**



20 **18**

Entry[a]	Solvent	Reagent	Conversion (A%)[b]	Conversion With HBr / HOAc[c] (A%)[b]
1	DMF	NBS	84.0	91.0
2	THF	NBS	4.6	4.6
3	CH_3CN	NBS	0.5	84.0
4	DMF	DBDMH	93.0	93.0
5	THF	DBDMH	2.7	2.7
6	CH_3CN	DBDMH	3.6	76.0
7[d]	CH_3CN	NBS	N/A	99.2

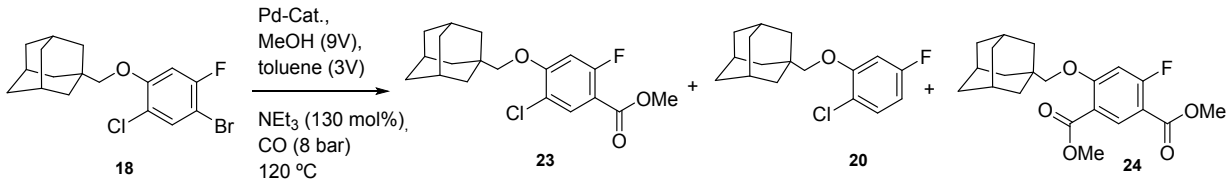
[a]Reactions conducted by mixing **20** (3.4 mmol) with solvent (5 mL) and brominating agent (120 mol%) in closed vials with stir bars, and heating at 60 ºC for 2 h. [b]Determined by HPLC analysis. [c]Addition of HBr as a solution in HOAc (10 mol%, 33 wt % solution). [d]Reaction conducted by mixing **20** (17.0 mmol) with solvent (50 mL) and brominating agent (120 mol%) and heating at 80 ºC for 1 h.

Both NBS and DBDMH provided good conversion (>84 A% HPLC) to **18** in DMF at 60 ºC (Table 3, entry 1 and 4),[25] but only <4 A% in CH_3CN (Table 3, entry 3 and 6). The poor reactivity in CH_3CN was improved by adding catalytic HBr (10 mol% in HOAc), decreasing the concentration, and increasing the temperature from 60 ºC to 80 ºC, which combined to boost conversion up to >99 A% (Table 3, entry 7). On kilogram scale, NBS needed to be charged to the reactor below the boiling point of the reaction mixture (~85 ºC), which correlated with the addition of NBS in 10 portions over 1 h at 70 ºC, followed by further heating at reflux until **20** was reduced to <1 A% as ascertained by HPLC analysis. Furthermore, **18** crystallized from the reaction mixture in CH_3CN, which presented a path forward to purify and isolate this intermediate. The crystallization was optimized by seeding of the reaction mixture at 75 ºC, followed by slow cooling to avoid encrustation. In order to safely quench excess brominating agent, a 5 wt% aqueous $NaHSO_3$ was added to the reaction mixture at 5 ºC, which was then warmed to 20 ºC.[26] The

optimized process was eventually demonstrated at 93 kg scale, delivering 170 kg of **18** as a white solid in 98% yield and >99.0 A% by HPLC analysis.

For installation of the carbonyl moiety contained in **23**, two general pathways were considered: (1) Mg-halogen exchange, followed by quench of the resulting Grignard with a suitable carbonate and (2) metal-catalyzed alkoxycarbonylation, both of which have been described extensively in the literature.[27] Although proof of concept could be obtained using the Mg-halogen exchange route on gram scale, our efforts focused on the Pd-catalyzed alkoxycarbonylation of **18**, because it avoided a subsequent tedious workup to remove the stoichiometric Mg salts. Based on literature precedent,[27e] we selected the $Pd(BINAP)Cl_2$, $PdCl_2(dppf)•CH_2Cl_2$ and $Pd(Xantphos)Cl_2$ catalysts for evaluation (1 mol%, entries 1─3, Table 4), and performed a series of reactions in an autoclave under pressure of CO[28] (8 bar) at 120 ºC, with MeOH as reaction solvent (~9V), toluene (~3V) as co-solvent,[29] and NEt_3 as base. From this screen, $PdCl_2(dppf)•CH_2Cl_2$ emerged as the catalyst with the fastest conversion (Table 4, entry 3), although a similar reaction profile was observed across other ligands. The catalyst loading for $PdCl_2(dppf)•CH_2Cl_2$ could be further reduced from 1 mol% down to 0.05 mol% (Table 4, entry 3─5) while maintaining conversion >99%. Subsequently, $PdCl_2(dppf)•CH_2Cl_2$ was exchanged for the similarly effective $PdCl_2(dppf)$[30] at 0.1 mol% (entry 8).

Table 4. Pd Catalyzed Carbonylation of **18**



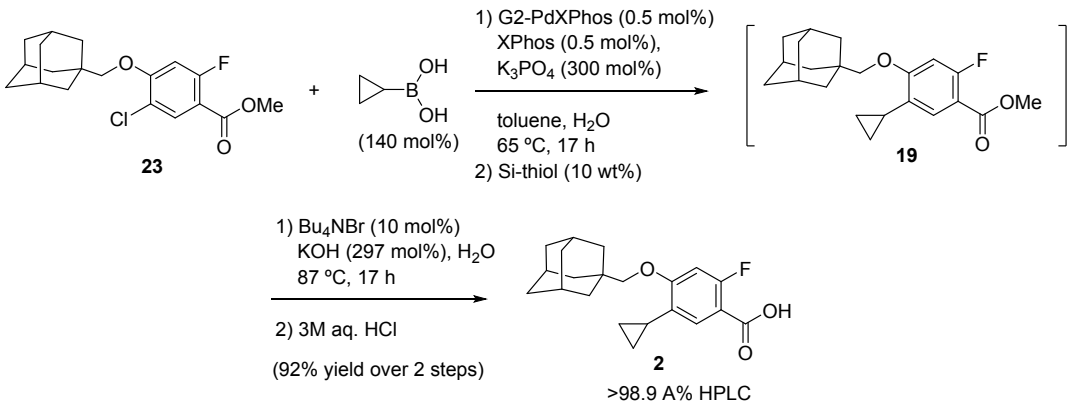
Entry[a]	Time (h)	Cat (mol%)	Conv (A%)[e]	**23** (A%)	**20** (A%)	**24**[d] (A%)
1	16	$Pd(BINAP)Cl_2$ (1)	>99	89	0.56	6.5
2	1.45	$Pd(Xantphos)Cl_2$ (1)	>99	93	0.60	-
3	1.2	$PdCl_2(dppf)•CH_2Cl_2$ (1)	>99	92	0.47	-
4	3.4	$PdCl_2(dppf)•CH_2Cl_2$ (0.2)	>99	94	1.71	-
5	6.4	$PdCl_2(dppf)•CH_2Cl_2$ (0.05)	>99	93	1.01	-
6[b]	5.4	$PdCl_2(dppf)•CH_2Cl_2$ (0.2)	4	2	0.11	-

7[c]	5.5	$PdCl_2(dppf)•CH_2Cl_2$ (0.2)	>99	91	1.29	1.36
8[c]	8	$PdCl_2(dppf)$ (0.1)	>99	96.6	0.46	0.69

[a]Reactions conducted by mixing **18** (31.6 mmol) in MeOH (9.3V), toluene (3.4V) and Et_3N (130 mol%) at ambient temperature, evacuating and backfilling with nitrogen 3 times, and then pressurizing with CO (8 bar). The reaction was then stirred (1000 rpm) at 120 ºC for 15 min. [b]MeOH (0.7V), toluene (12V). [c]MeOH (7.6V), toluene (3.4V). [d]Proposed structure based on ESI-MS analysis (see SI). [e]Determined by HPLC analysis.

Because of the high solubility of **23** and the low solubility of Et_3N•HBr in toluene, we thought to precipitate and filter off salts from the reaction mixture by increasing the amount of toluene relative to MeOH (Table 4, entry 6), but the reaction itself resulted in a very poor conversion (4%).[31] With respect to a safe pilot plant operation, the filtration for removal of the catalyst[32] needed to be performed at least 20 ºC below the boiling point of the azeotropic mixture (63 ºC). This required the dilution of the reaction mixture (Table 4, entry 7) with toluene to avoid crystallization of the product in the transfer lines, and subsequent concentration by azeotropic distillation,[33] followed by addition of MeOH / water at 60 ºC to further increase the solubility of Et_3N•HBr and allow it to be removed in the supernatant. No seeding was necessary to initiate crystallization of **23**, and the reaction mixture was thereafter cooled to 5 ºC and aged to improve recovery. The optimized process delivered 141 kg of **23** as a white solid in 90 % yield and with an excellent purity profile of >99.7 A% by HPLC.

Scheme 6. Suzuki-Miyaura Cross-Coupling of **23** with CPBA and PTC Hydrolysis of **19**

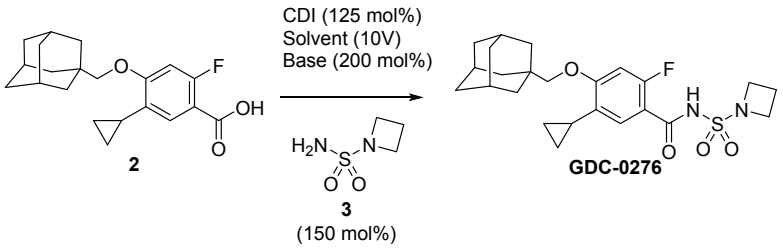


Because the new route replaced *t*-butyl ester **5** with methyl ester **23**, we needed to reinvestigate the Suzuki-Miyaura cross-coupling coupling of **23** with CPBA (Scheme 6). Fortunately, the previously established reaction and work-up conditions could be applied almost exactly as before, and the resulting solution of crude **19** was directly

telescoped to the hydrolysis. We quickly developed a new protocol for a phase transfer catalyzed (PTC) hydrolysis of **19** in toluene in the presence of H_2O (2.4V), KOH and Bu_4NBr. After phase separation and addition of aqueous HCl to adjust to pH <1, intermediate **2** crystallized and was isolated by filtration to give 92 kg of a white solid in 92% yield and purity >98.9 A% by HPLC.

Finally, we set out to optimize the CDI activated amidation of **2** with sulfamide **3**, and directly isolate the API from the reaction mixture as the desired polymorph. Towards this end, toluene needed to be replaced with another solvent, because it resulted in an undesired solvate (*vide supra*). EtOAc and *i*PrOAc were identified to give the desired Form I. A base screen was then performed, activating **2** in EtOAc with CDI, and reacting with sulfamide **3** (Table 5). From this screen it was found that organic bases such as DBU and DIPEA, as well as $NaHCO_3$, resulted in low purity reaction profiles (Table 5, entries 1, 2 and 6). K_3PO_4 was identified as the best base in terms of conversion to GDC-0276 (Table 5, entry 5) (>98 A% HPLC), and *i*PrOAc as the best solvent (>99 A% HPLC) (Table 5, entry 7).

Table 5. Base Screen of Amidation of **2** with **3** in EtOAc

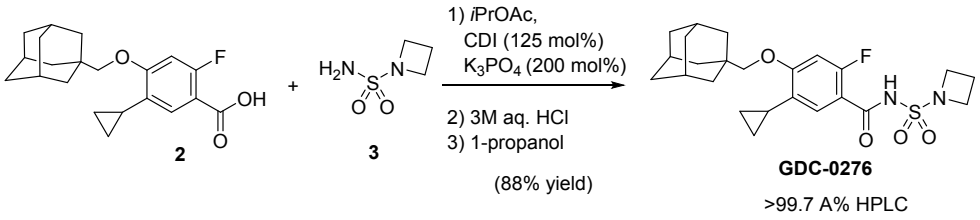


Entry[a]	Base	Solvent	**2** (A%)[c]	GDC-0276 (A%)[c]
1	DBU	EtOAc	6.7	9
2	DIPEA	EtOAc	4.2	24
3	K_2CO_3	EtOAc	2	97.4
4	Cs_2CO_3	EtOAc	5.6	92.6
5	K_3PO_4	EtOAc	1	98.4
6	$NaHCO_3$	EtOAc	2.7	5.3
7[b]	K_3PO_4	*i*PrOAc	<1	99.8

[a]Reactions conducted by mixing **2** (3 mmol) with solvent (10V) and CDI (125 mol%) in closed vials with stir bars, heating at 70 ºC for 1 h, adding base (200 mol%), **3** (150 mol%) and heating at 70 ºC for 18 h. [b] **2** (145 mmol), solvent (7V), CDI (130 mol%), base (200 mol%) at 70 ºC for 18 h. [c]Determined by HPLC analysis.

For workup, K_3PO_4 was filtered off and the resulting solution washed with aqueous HCl. Unfortunately, the recovery of API after addition of heptane anti-solvent was only moderate because of high solubility in the iPrOAc / heptane mixture (~85% yield).[34] Therefore, the solvent was swapped to 1-propanol, GDC-0276 seed crystals (1 wt%) were added to the supersaturated solution at 70 °C, and this was followed by slow cooling to ~10 °C. The optimized amidation (Scheme 7) was then implemented at 92 kg scale, delivering 108 kg of GDC-0276 as a white solid in 88% yield and >99.7 A% by HPLC (no single impurity >0.05 A%).

Scheme 7. Optimized Second-Generation Synthesis of GDC-0276



Conclusion

We have developed an improved large-scale synthesis of GDC-0276 via a newly designed six-step synthetic sequence from readily available 1-chloro-2,4-difluorobenzene. A key step of the revised route was the highly regioselective S_NAr fluoride displacement of 1-chloro-2,4-difluorobenzene with 1-adamantanemethanol (regioselectivity >98:2), followed by regioselective bromination and an efficient subsequent palladium-catalyzed methoxycarbonylation of aryl bromide **18** to give methyl ester **23**. This intermediate was then subjected to a Suzuki-Miyaura cross-coupling with CPBA to give **19**, and telescoped into the PTC ester hydrolysis to furnish **2**. The optimized CDI-activated amidation of **2** with sulfamide **3** delivered GDC-0276 as the desired crystal form from 1-propanol in >99.7 A% HPLC purity. This second generation manufacturing process represented a significant improvement in term of costs and efficiency over the first generation route: 1) the difluorochlorobenzene starting material was about four times less expensive (in molar ratio) than the original more functionalized starting material **4**; 2) overall yield was improved to 64% from 12% over the 6-step sequence; 3) Most of the intermediates were

isolated via direct crystallization which considerably reduced the number of unit operations by eliminating extractive workups.

Experimental Section

General. Unless otherwise noted all reactions were run under a nitrogen atmosphere, solvents and reagents were used without further purification. ^{1}H NMR (300 MHz, 500 MHz, 600 MHz), ^{13}C NMR (125 MHz) were recorded on a Bruker Avance 3 spectrometer. Chemical shifts are reported in ppm (δ units) downfield of internal tetramethylsilane [$(CH_3)_4Si$] or residual $CHCl_3$; coupling constants are reported in hertz (Hz). Multiplicities are as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet. Melting points were measured by differential scanning calorimetry (DSC, Büchi B-540). Compound **1** (CAS No. 1354961-13-9), **4** (CAS No. 130025-33-1) and **17** (CAS No. 1435-44-5) are commercially available. In process method for analysis of **2**, **3**, **5**, **7**, **9**, **19**, **23** and GDC-276. Diluent: acetonitrile. Mobile phase A: 0.05% TFA / water. Mobile phase B: 0.05% TFA / acetonitrile. Column: Ace 3 C18 HL column, 3x50 mm 3.0 µm. Column temperature: 35 °C. Detector wavelength: 220 nm. Signal 220 nm Bandwidth 4 nm, Reference off. Injection volume: 2 µL. Flow rate: 1.5 mL/min. Sample Concentration: 0.5─1.0 mg/mL in 50% acetonitrile / water. Program: 0.0 min 30.0% B, 0.3 min 30.0% B, 5.0 min 90.0% B, 6.5 min 5%. Typical retention times: **2** (RT 2.6 min), **3** (RT 5.4 min), **5** (RT 4.0 min), **7** (RT 5.3 min), **9** (RT 5.2 min), **19** (RT 2.8 min), **23** (RT 3.6 min), GDC-0276 (RT 4.2 min).

Method for analysis of **17**, **18**, **20**, **21**, **22**, **23**, **24**. Diluent: acetonitrile. Mobile phase A: 0.05% TFA / water. Mobile phase B: 0.05% TFA / acetonitrile. Column: XBridge C18, 150 x 4.6 mm. Column temperature: 40 °C. Detector wavelength: 220 nm. Signal 220 nm Bandwidth 4 nm, Reference off. Injection volume: 5 µL. Flow rate: 1.5 mL/min. Sample Concentration: 0.5─1.0 mg/mL in 50% acetonitrile / water. Program: 0.0 min 60.0% B, 5.0 min 85.0% B, 14.0 min 92.5% B, 16.0 min 100%, 16.5 min 60%, 22.0 min 60%. Typical retention times: **17** (RT 10.7 min), **18** (RT 9.1 min), **20** (RT 14.2 min), **21** (RT 14.5 min), **22** (RT 17.6 min), **23** (RT 15.1 min), **24** (RT 9.5 min). Injection volume 5 µl.

First Generation Synthesis

***tert*-Butyl-5-chloro-2,4-difluorobenzoate (1)**

A reactor was charged with 5-chloro-2,4-difluorobenzoic acid (10.5 kg, 54.5 mol, 100 mol%), 4-dimethylaminopyridine (0.73 kg, 6.0 mol, 11 mol%) and THF (60 kg) at 20 ºC, and to the solution was added $(Boc)_2O$ (20 kg, 91.6 mol, 170 mol%) as solids in portions over 1 h. The resulting mixture was heated to 35 ºC for

18 h. HPLC analysis indicated that 5-chloro-2,4-difluorobenzoic acid **4** <2 A%. The mixture was concentrated to 35 L, diluted with EtOAc (40 kg), washed with saturated $NaHCO_3$ (3 x 25 L), 10% aqueous HCl (3 x 6 L) and brine (3 x 25 L), dried over Na_2SO_4 (5 kg) and concentrated under vacuum at 40 ºC to give 14.0 kg of **1** as a light-brown oil (100% uncorrected yield, 97.0 A% HPLC), which was used in the next step without any further purification.

***tert*-Butyl 4-((-adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate (5)**

A reactor was charged with **1** (14.0 kg, 56.3 mol, 100 mol%), DMSO (77 kg, 5V), 1-adamantanemethanol (9.0 kg, 54.1 mol, 96 mol%) and Cs_2CO_3 (35 kg, 107.4 mol, 191 mol%). The resulting mixture was heated to 72 ºC for 20 h, cooled to 25 ºC and filtered through a pad of Celite® (4 kg). The filtered cake was washed with EtOAc (140 kg). The combined filtrates were washed with 1M aqueous HCl (170 kg) and brine (170 kg), dried over Na_2SO_4 (10 kg) and concentrated to ~30 L, which was triturated with MeOH (30 kg). The solid was collected and dried at 45 ºC under vacuum overnight to give crude **5**, which was triturated with MeOH (11 kg) for 2 h at 20 ºC. The white solid was collected, washed with MeOH (11 kg) and dried under vacuum to give 8.3 kg of **5** (32% corrected yield, 86.2 A% HPLC purity; by-product **17**: 13.6 A% HPLC): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, 1H), 7.61 (d, 1H), 3.55 (s, 2H), 2.01─2.15 (m, 3H), 1.65─1.81 (m, 12H), 1.55 (s, 9H); ^{13}C NMR (105 MHz, $CDCl_3$) δ 161.5 (d, 260 Hz)[a], 162.e (d, 150 Hz)[a], 158.94 (d, 105 Hz)[a], 132.5, 117.9, 112.4, 101.5, 89.8,.77.2, 39.3, 37.0, 33.9, 33.4, 28.2, 28.2, 28.1, 28.1, 28.1, 28.1. [a] Splitting due to ^{13}C─^{19}F coupling. HRMS $[M+H]^+$ calcd for $C_{22}H_{28}ClFO_3$ 339.1158; found 339.1145.

***tert*-Butyl (azetidin-1-ylsulfonyl)carbamate (12)**[35]

A reactor was charged with *t*-butanol (4.77 kg, 64.4 mol, 100 mol%), anhydrous dichloromethane (190 kg) and cooled to 0 ºC. Chlorosulfonyl isocyanate (9.16 kg, 64.4 mol, 100 mol%) was added slowly. The resulting mixture was stirred at 0 ºC for 1 h. Et_3N (19.55 kg, 193.2 mol, 300 mol%) was added drop-wise to the mixture at 5─10 ºC, followed by azetidine hydrochloride (6.65 kg, 71.0 mol, 110 mol%) in four portions. The resulting mixture was stirred for 15 h at 20 ºC. Et_3N•HBr was filtered off and the filtrate was washed with 20 wt% aqueous citric acid (102 kg, 106 mol, 160 mol%) (pH = 4─5) below 5 ºC, brine (2 x 135 kg) and dried over anhydrous sodium sulfate. The solid was filtered and the organic fraction was concentrated under vacuum to afford 13.3 kg of crude **12** as a pale pink solid. The crude product was dissolved in acetone (10.8 kg), and the mixture was treated with 0.2 wt% aqueous citric acid (106 kg, 1 mol, 2 mol%) at 0─5 ºC for 1 h. The product was filtered and washed with water (2 x 25 kg). The cake was collected and dried under vacuum to afford 10.5 kg of **12** as a solid (69% yield, 99.5 A% HPLC): mp

= 83 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (br s, 1H), 3.94 (t, J = 7.7 Hz, 4H), 2.15 (p, J = 7.8 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.30, 82.15; 51.86, 28.13, 15.11. HRMS $[M+H]^+$ calcd for $C_8H_{16}N_2O_4S$ 237.0904; found 237.0905.

Azetidine-1-sulfonamide (3)[34]

A reactor was charged with dichloromethane (96.73 kg), **12** (7.30 kg, 30.9 mol, 100 mol%), TFA (10.57 kg, 92.7 mol, 300 mol%) and the mixture was held at 25 ºC for >14 h. HPLC analysis showed **12** to be <3 mg/mL. The contents of the reactor were distilled under vacuum until a volume of 45 L was obtained while maintaining the internal batch temperature at less than 25 ºC. Cyclopentyl methyl ether (CPME, 31.39 kg) was charged to the reactor and the mixture was aged for a minimum of 30 min at 25 ºC. The contents of the reactor were filtered through an Aurora filter and washed twice with CPME (5.18 kg each time). After no more filtrate could be collected from the filter, the cake was dried on the filter at 50 ºC (jacket temperature) under vacuum with a nitrogen purge for ≥24 h. The process gave 2.72 kg of **3** (65% yield; 99.6 A% by GC) as an off white solid: mp = 129 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.84 (s, 2H), 3.67 (t, 4H), 2.07 (p, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 50.38, 14.92; HRMS calcd for $C_3H_8N_2O_2S$ $[M+H]^+$ 137.0379, found *m/z* 137.0380.

***t*-Butyl 4-((adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate (9)**

A reactor was charged with water (19.44 kg), K_3PO_4 (13.06 kg, 61.5 mol, 300 mol%), toluene (49.09 kg), **5** (8.10 kg, 20.5 mol uncorrected, 100 mol%), cyclopropylboronic acid (2.47 kg, 28.7 mol, 140 mol%) and XPhos (49 g, 103 mmol, 0.5 mol%). The reactor was inerted with nitrogen by cycling from full vacuum to nitrogen three times and then sparged with nitrogen for minimum 10 min. Chloro(2-dicylcophexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (81 g, 103 mmol, 0.5 mol%) was then charged and sparged for another 20 min with nitrogen. The mixture was heated to 65 ºC and held at that temperature for >14 h. HPLC analysis showed **5** to be <1.0 A%. The contents of the reactor were cooled to 40 ºC. Water (16.20 kg) was charged to the reactor at 40 ºC and the contents were stirred for a minimum of 5 min. Agitation was stopped and the bottom aqueous layer was drained to waste. A brine solution was prepared from NaCl (4.86 kg) and water (32.40 kg), added to the reactor and the contents stirred for a minimum of 5 min. Agitation was stopped and the bottom aqueous layer was drained to waste. Silica-thiol (0.81 kg) was charged to the reactor and the mixture heated to 65 ºC and held at that temperature for >14 h. ICP MS analysis showed Pd to be <10 ppm. The contents of the reactor were cooled to 40 ºC and filtered through a Nutsche filter. The reactor and Nutsche filter were rinsed with toluene (21.06 kg) and

combined with the filtrate in another reactor and the crude solution of **9** (100% corrected yield, 7.1 kg, 17.7 mol, 11.7 wt% in toluene) and telescoped to the subsequent *t*-butyl ester cleavage. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 1H), 6.47 (d, *J* = 12.9 Hz, 1H), 3.49 (s, 2H), 2.05─1.95 (m, 4H), 1.78─1.61 (m, 12H), 1.55 (s, 9H), 0.91─0.84 (m, 2H), 0.64─0.58 (m, 2H).

4-((Adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid (2)

TFA (4.68 kg, 41 mol, 232 mol%) was charged to the toluene solution from the previous Suzuki-Miyaura coupling (7.1 kg of **9**, 17.7 mol, 11.3 wt%) in the reactor, the mixture was heated to 65 ºC and then held at that temperature for ≥12 h. HPLC analysis showed **9** to be ≤2.0 A%. The contents of the reactor were distilled at 65 ºC under vacuum until a volume of 65 L was obtained (35 L distillate removed). Heptane (11.10 kg) was charged to the reactor and the mixture was heated to 65 ºC and held at that temperature for ≥30 min. The mixture was cooled over 5 h to 20 ºC and aged at that temperature for a minimum of 4 h. The mixture was filtered through a filter dryer and the cake was washed twice with heptane (11.10 kg each). After no more filtrate could be collected from the filter, the cake was dried on the filter at 60 ºC (jacket temperature) under vacuum with a nitrogen purge. Drying was continued for ≥24 h. The process gave 5.36 kg of **2** (88% yield; 99.8 A% HPLC purity) as an off-white solid: mp = 298 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.79 (br s, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 13.2 Hz, 1H), 3.64 (s, 2H), 2.03 (dt, 1H), 2.00 (t, 3H), 1.72 (m, 6H), 1.66 (s, 6H), 0.91 (m, 2H), 0.60 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.38, 162.62 (d, 255 Hz)[a], 160.50, 128.46, 127.77, 110.19, 100.71, 78.70, 39.30, 37.04, 33.95, 27.97, 9.62, 7.52. [a] Splitting due to ^{13}C─^{19}F coupling. HRMS $[M+H]^+$ calcd for $C_{21}H_{25}FO_3$ 345.1861; found 345.1863.

4-(Adamantan-1-ylmethoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluorobenzamide, GDC-0276

A reactor was charged with toluene (31.90 kg), acid **2** (5.27 kg, 15.3 mol, 100 mol%), 1,1-carbonyldiimidazole (3.10 kg, 19.1 mol, 125 mol%) and the mixture was heated to 50 ºC and held at that temperature for >2 h. HPLC analysis showed **2** to be ≤2.0 A%. DBU (2.33 kg, 15.3 mol, 100 mol%) was charged to the reactor at 50 ºC. A second reactor was charged with toluene (13.68 kg), sulfonamide **3** (2.71 kg, 19.9 mol, 130 mol%), DBU (3.49 kg, 22.9 mol, 150 mol%) and the mixture was transferred at 25 ºC during 5 min into the first reactor. The second reactor was rinsed with toluene (5.00 kg) into the first reactor. The contents of the reactor were heated to 50 ºC and held at that temperature for a minimum of 2 h, then cooled to 20 ºC. A solution of citric acid (8.23 kg, 42.8 mol, 280 mol%) in water (30.00 kg) was added and agitated for a minimum of 5 min. The bottom aqueous layer was drained to waste and the reactor contents were filtered through a Nutsche filter with a subsequent toluene rinse (5.00 kg) into another

reactor in order to remove any unreacted acid. The contents were distilled under vacuum until a volume of 30 L was obtained while maintaining the internal batch temperature of less than 65 ºC. Heptane (21.63 kg) was charged to the reactor at 50 ºC and the mixture was aged for a minimum of 30 min at 50 ºC. The contents of the reactor were cooled to 20 ºC and aged at that temperature for a minimum of 8 h. The content was filtered through an Aurora filter followed by a rinse with heptane (8.66 kg). The cake was washed three times with heptane (7.21 kg each) and after no more filtrate could be collected from the filter, the cake was dried on the filter at 60 ºC (jacket temperature) under vacuum with a nitrogen purge. Drying was continued under vacuum for ≥24 h. The process gave 7.26 kg of crude GDC-0276 (100% uncorrected yield, 98.20 A% HPLC purity) as an off-white solid.

Recrystallization of GDC-0276

A reactor was charged with 1-propanol (32.58 kg), GDC-0276 (4.50 kg, 15.3 mol, 100 mol%), activated carbon (Darco™ G-60, 1.80 kg, 40 wt%) and the contents were heated to 95 ºC and held at that temperature for >1 h. HPLC analysis showed **13** ≤0.45 A% and **14** ≤0.15 A%. The reactor contents were transferred through a Nutsche (pre-rinsed with 1-propanol at 90 ºC, 16.07 kg) followed by a 1μm polish filter into a clean reactor. The equipment was rinsed with 1-propanol (3.60 kg) and combined with the mother liquors. The reactor content was heated to 85 ºC until a clear solution was obtained, and then cooled to 70 ºC. A suspension of GDC-0276 seed crystals (45.0 g, 1 mol%) in 1-propanol (0.36 kg) was transferred to the reactor and aged for >0.5 h at 70 ºC. The reactor contents were cooled over a minimum of 1 h to 60 ºC and held at that temperature for a minimum of 1 h, then cooled to 25 ºC during a minimum of 2 h and held at that temperature for ≥2 h. The content was filtered through a filter dryer followed by a rinse with 1-propanol (7.20 kg). The cake was washed two times with 1-propanol (7.20 kg each) and after no more filtrate could be collected from the filter, the cake was dried on the filter at 75 ºC (jacket temperature) under vacuum with a nitrogen purge. Drying was continued for ≥24 h. Head-Space GC showed 1-propanol ≤0.4 wt%. The process gave 3.43 kg of GDC-0276 (48% yield, 99.7 A% HPLC purity) as an off-white solid: mp = 151 ºC; 1H NMR (600 MHz, benzene-d6) δ 8.85 (s, NH), 7.84 (d, J = 8.96 Hz, 1H), 6.12 (d, J = 14.23 Hz, 1H), 3.98 (t, J = 7.75 Hz, 4H), 3.06 (s, 2H), 1.94 (m, 3H), 1.92 (m, 1H) 1.69 (m, 12.36 Hz, 3H), 1.62 (m, 11.46 Hz, 3H), 1.54 (m, 2.58 Hz, 6H), 1.42 (m, 7.73 Hz, 2H) 0.66 (m, 2.74 Hz, 2H), 0.52 (m, 3.22 Hz, 2H); 13C NMR (150 MHz, benzene-d6) δ 163.54 (d, 120 Hz)[a], 161.52─159.89 (245 Hz)[a], 161.21─161.19 (30 Hz)[a], 129.85 (d, 30 Hz)[a], 129.10 (d, 165 Hz)[a], 128.04, 110.20 (d, 105 Hz)[a], 99.10 (d, 285 Hz)[a], 78.79, 51.43, 39.58, 37.24, 33.97, 28.49, 15.01, 9.87, 7.29. [a] Splitting due to 13C─19F coupling. HRMS [M+H]+ calcd for $C_{24}H_{31}FN_2O_4S$ 462.5773; found 463.2045.

Second Generation Synthesis

1-((2-Chloro-5-fluorophenoxy)methyl)adamantane (20)

A reactor was charged with 1-adamantanemethanol (29.4 kg, 177 mol, 105 mol%), **17** (25.0 kg, 168 mol, 100 mol%) and THF (71.2 kg). To the reaction mixture was added a 20% solution of *t*-BuOK in THF (208 kg, 371 mol, 221 mol%) at 20 °C during 1 h. After 1 h stirring, HPLC analysis showed **17** to be ≤1.0%. The reaction mixture was added onto purified water (286 kg) at 20 °C during 30 min. The biphasic solution was distilled under vacuum (250─500 mbar, 40─60°C) down to 8.4V. Then a mixture of purified water (375 kg) and MeOH (59 kg) was charged at 53°C during 30 min. The reaction mixture was cooled to 20 °C during 2 h, stirred for 1 h, filtered, and the cake washed successively with a 1:1 mixture of water and MeOH (44 L), and twice with purified water (2 x 150 L). The cake was dried in vacuum at 53 °C to give 45.0 kg of **20** as a white solid (91% yield, 97.7 A% HPLC purity, **21** = 1.85 A% HPLC): mp = 119 ºC; ^{1}H NMR (500 MHz, DCM-d_2) δ 7.33 (dd, 1H), 6.71 (dd, 1H), 6.64 (td, 1H), 3.57 (s, 3H), 2.06 (m, 3H), 1.79 (m, 6H), 1.74 (d, 6H). ^{13}C NMR (125 MHz, DCM-d_2) δ 162.02 (d, 244 Hz)[a], 155.92, 130.19, 117.92, 107.08, 101.27, 79.36, 39.28, 37.01, 33.90, 28.31. [a] Splitting due to ^{13}C─^{19}F coupling. HRMS $[M+H]^+$ calcd for $C_{17}H_{20}ClFO$ 294.1187; found 294.1190.

1-((4-Bromo-2-chloro-5-fluorophenoxy)methyl)adamantane (18)

In a reactor **20** (45.0 kg, 153 mol, 100 mol%) was dissolved in acetonitrile (540 kg) and heated to 75 °C. A solution of 33 wt% HBr in acetic acid (3.7 kg, 15 mol, 10 mol%) was added, followed by NBS (32.6 kg, 183 mol, 120 mol%) in 10 portions over 1 h. Subsequently, the mixture was heated to 85 °C (reflux) and stirred for 1 h until deemed complete by HPLC (**20** ≤1.0 A%). The contents of the reactor were cooled to 77 °C, seeded, further cooled to 53 °C during 1 h, aged for 1 h, and then cooled to 3 °C during 2 h. The reaction mixture was quenched with a 5 wt% aqueous sodium bisulfite solution (22.0 kg, 11 mol, 7 mol%) and heated to 20 °C during 30 min. The suspension was filtered at 20 °C, washed with a 3:1 mixture of water and acetonitrile (270 kg), and the cake dried under vacuum at 48 °C to give 56.3 kg of **18** as a white solid (98% yield, 99.9 A% HPLC purity): mp = 116 ºC; ^{1}H NMR (500 MHz, DCM-d_2) δ 7.56 (d, 1H), 6.79 (d, 1H), 3.56 (s, 2H), 2.06 (m, 3H), 1.79 (m, 6H), 1.73 (m, 6H). ^{13}C NMR (125 MHz, DCM-d_2) δ 158.20 (d, 246 Hz)[a], 155.43, 132.85, 118.89, 102.02, 98.02, 79.71, 39.97, 33.92, 28.27. [a] Splitting due to ^{13}C─^{19}F coupling. HRMS $[M+H]^+$ calcd for $C_{17}H_{19}BrClFO$ 372.03; not observed.

Methyl 4-((adamantan-1-yl)methoxy)-5-chloro-2-fluorobenzoate (23)

In a reactor **18** (42.2 kg, 113 mol, 100 mol%) was dissolved in toluene (210 kg), heated to 55 °C and Et_3N (15.0 kg, 148 mol, 131 mol%) was charged. The solution was diluted with MeOH (311 kg) and then transferred to an autoclave. A solution of $Pd(dppf)Cl_2$ (84 g, 0.11 mol, 0.1 mol%) in MeOH (19 kg) was added to the reaction mixture followed by a rinse with MeOH (24 kg). The reactor was inerted with nitrogen by cycling from vacuum to nitrogen three times, pressurized with carbon monoxide (98%) to 7.80 bar, heated to 120 °C and stirred for 8 h. The reaction mixture was then cooled to 57 °C and the autoclave was vented. The reactor was inerted with nitrogen by cycling from vacuum to nitrogen three times. The contents of the reactor were filtered through a polish filter, followed by a rinse with toluene (129 kg). The solution was concentrated at 70 °C under atmospheric pressure (removal of 527 L distillate). Afterwards MeOH (34 kg) was added and another 1.0V of solvent (42 L) was removed. Then MeOH (269 kg) was charged to the reactor, followed by a 5:1 mixture of MeOH and water (104 kg). The suspension was cooled to 60 °C during 30 min, cooled to 5 °C during 3 h, then aged for 90 min at this temperature. The suspension was filtered and the cake washed with a 5:1 mixture of MeOH and water (90 kg), followed by MeOH (43 kg). The cake was dried under vacuum (21 mbar) at 50 °C to give 36.6 kg of **23** as a white solid (92% yield, 99.8 A% HPLC purity): mp = 128 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.00 (s, 1H), 7.87 (d, 1H), 7.22 (d, 1H), 3.82 (s, 3H), 3.73 (s, 2H), 1.99 (m, 3H), 1.70 (m, 6H), 1.64 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.23, 160.70 (d, 259 Hz)[a], 159.44, 132.14, 117.50, 110.65, 103.39, 79.68, 52.74, 39.07, 36.98, 33.94, 27.89. [a] Splitting due to ^{13}C—^{19}F coupling. HRMS $[M+H]^+$ calcd for $C_{19}H_{22}ClFO_3$ 353.1315; found 353.1300.

Benzyl (azetidin-1-ylsulfonyl)carbamate (16)

A reactor was charged with DCM (1378.0 kg), benzyl alcohol (66.2 kg, 612 mol, 101 mol%), and the content of the reactor was cooled to -5 °C. Chlorosulfonyl isocyanate (85.3 kg, 603 mol, 100 mol%) was added at -5 °C, and the mixture was stirred for 3 h at this temperature until deemed complete by HPLC analysis (derivatization with dibenzylamine, chlorosulfonyl isocyanate <0.3 A%, see SI). Et_3N (184.6 kg, 1824 mol, 302 mol%) and azetidine hydrochloride (60.0 kg, 641 mol, 106 mol%) was added to the reaction mixture at -5 °C, and stirred for 3 h at -5 °C until the reaction was deemed complete by HPLC (derivatization with dibenzylamine, **15** <1 A%, see SI). Aqueous 20% citric acid (328 kg) was added to adjust to pH=4.5. The DCM layer was drained into another reactor and the aqueous layer was extracted with DCM (671.0 kg) followed by addition of water (170 kg). The DCM layer was drained into the reactor containing the first DCM extract, and the mixture was washed with water (520 kg), then acetone (680.9 kg, 686.7 kg, 681.8 kg, 100 kg) was added to the reactor in four portions while continuously

distilling off DCM (residual DCM of final solution = 0.2 wt% by head-space GC). Aqueous 0.2% citric acid (1038 kg) and seed crystals of **16** (40 g) were added to the reactor to initiate crystallization. The mixture was stirred for 30 min at 10 °C and cooled to 0 °C during 4 h. The suspension was centrifuged and the cake washed with aqueous 0.2% citric acid in acetone (72.0 kg, 75.8 kg, 76.0 kg) to give after drying at 40 °C, 133.90 kg of crude **16**. The crude **16** was dissolved in EtOAc (489.8 kg), acetone (7.0 kg), and heptane (916.8 kg) was added followed by seed crystals of **16** (40.0 g). The mixture was stirred for 30 min at 25 °C, cooled to 0 °C during 3 h and stirred for 2 h at 0 °C. The suspension was centrifuged and the cake washed with EtOAc–heptane (92.0 kg : 88 kg), and then dried for 16 h at 40 °C in vacuum to give 110 kg of **16** (67% yield, 99.8 A% HPLC purity) as a white solid: mp = 110 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.43 (s, 1H), 7.39 (m, 5H), 5.18 (m, 2H), 3.95 (t, 4H), 2.12 (p, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.40, 136.12, 128.97, 128.76, 128.56, 67.57, 51.91, 15.03; HRMS calcd for $C_{11}H_{14}N_2NaO_4S$ $[M+H]^+$ 293.0572, found *m/z* 293.0568.

Azetidine-1-sulfonamide (3)

An autoclave was charged with **16** (109.0 kg, 403 mol, 100 mol%), Pd / C (Noblyst P1070, 803 g, 0.377 mol, 0.09 mol%, 10 wt% Pd / C dry basis, ~50 wt% water) and MeOH (823.9 kg) at 20 ºC. The reactor was inerted with nitrogen by cycling from vacuum (-0.8 bar) to nitrogen three times, pressurized with hydrogen to 5.4 bar and then stirred at this temperature for 18 h. HPLC analysis showed **16** to be not detected. The reactor was inerted with nitrogen by cycling from vacuum (-0.8 bar) to nitrogen two times. The contents of the reactor were filtered through a 1.2 µm polish filter, followed by a rinse with MeOH (196.2 kg). The filtrate was distilled under vacuum (200 mbar) until a volume of 100 L was obtained. The contents of the reactor were cooled to -10 ºC, CPME (215.0 kg) was charged over 20 min and the mixture was aged for 11 h at -10 ºC. The contents of the reactor were filtered over a filter dryer and washed with CPME (43.0 kg). After no more filtrate could be collected from the filter dryer, the cake was dried at 50 ºC under vacuum (20 mbar) for 14 h. The process gave 47.7 kg of **3** (87% yield, 99.9 A% GC purity) as a white solid.

4-((Adamantan-1-yl)methoxy)-5-cyclopropyl-2-fluorobenzoic acid (2)

A reactor was charged with water (84.0 kg,), K_3PO_4 (63.0 kg, 297 mol, 300 mol%), toluene (378.0 kg), **23** (35.0 kg, 99 mol, 100 mol%), cyclopropyl boronic acid (11.9 kg, 139 mol, 140 mol%) and XPhos (240 g, 0.503 mol, 0.5 mol%). The reactor was sparged with nitrogen for 15 min, chloro(2-dicylcophexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (390 g, 0.496 mol, 0.5 mol%) was added. The mixture was

heated to 65 ºC and held at that temperature for 17 h. HPLC analysis showed **23** to be not detected. The contents of the reactor were cooled to 20 ºC, agitation was stopped and the bottom aqueous layer was drained to waste. Silica-thiol (3.5 kg, 10 wt%) was charged to the reactor, the mixture heated to 70 ºC and held at that temperature for 18 h. ICP MS showed Pd to be <10 ppm. The contents of the reactor were cooled to 21 ºC and a solution Bu_4NBr (3.20 kg, 9.9 mol, 10 mol%) and KOH (19.4 kg, 294 mol, 297 mol%, pellets 85 wt%) in water (84 kg) was added, followed by toluene (34.7 kg). The contents of the reactor were heated to 87 ºC and held at that temperature for 17 h, then cooled to 70 ºC. HPLC analysis showed **19** to be <0.2 A%. Agitation was stopped and the bottom aqueous layer was drained to waste. The contents of the reactor were heated to 46 ºC, filtered over a 1μm polish filter and rinsed with toluene (26.0 kg). The combined filtrate was heated to 45 ºC, aqueous 3M HCl (50.5 kg, 144 mol, 145 mol%) was added (pH ≤1), aged for 1 h, then cooled over 2 h to 25 ºC and aged for 10 h. The content was filtered over a filter dryer followed by a rinse with toluene (65.0 kg). The cake was dried at 60 ºC for 135 h. The process gave 31.4 kg of **2** (92% yield, 99.6 A% HPLC purity) as an off white solid.

4-((Adamantan-1-yl)methoxy)-N-(azetidin-1-ylsulfonyl)-5-cyclopropyl-2-fluorobenzamide, GDC-0276

A reactor was charged with acid **2** (47.2 kg, 137 mol, 100 mol%), and *i*PrOAc (278.0 kg). The mixture was heated to 40 ºC and held at that temperature for 25 min. A suspension of CDI (27.8 kg, 171 mol, 125 mol%) in *i*PrOAc (87.0 kg) was added to the reactor in three portions and stirred for 15 min between additions. The contents of the reactor were then heated to 50 ºC and stirred for 50 min at this temperature. HPLC showed acid **2** to be not detected. K_3PO_4 (58.2 kg, 274 mol, 200 mol%) and **3** (24.3 kg, 178 mol, 130 mol%) was charged to the reactor, the mixture was heated to 70 ºC and held at this temperature for 19 h. The contents of the reactor were cooled to 12 ºC and aqueous 3M HCl (309.0 kg, 862 mol, 630 mol%) was added. The mixture was then heated to 58 ºC and agitated for 20 min. The bottom aqueous layer was drained to waste. The organic layer was washed twice with water (235.0 kg, 95.0 kg) and the aqueous layer was drained to waste. The contents of the reactor were filtered over a 1 μm polish filter at 55 ºC and rinsed with *i*PrOAc (26.0 kg). The filtrate was distilled under vacuum (280 mbar) until a volume of 140 L was obtained. 1-Propanol (144.0 kg) was added to the reactor and distilled under vacuum to a volume of 140 L. 1-Propanol (376.0 kg) was added to the reactor and distilled under vacuum to a volume of 470 L at 97 ºC. The contents of the reactor were cooled to 72 ºC over 2 h. A suspension of GDC-0276 seed crystals (0.64 kg) in 1-propanol (1.8 kg) was added to the mixture and aged at 70 ºC for 1 h, then cooled to 11 ºC over 8 h, aged for 13 h at this temperature and then filtered over a filter dryer, followed by a rinse with 1-propanol (94.0 kg). The cake was

dried under vacuum at 65 ºC for 65 h. The process gave 55.6 kg of GDC-0276 (88% yield, 99.8 A% HPLC purity) as a white solid (NMR in accordance with previous procedure).

ASSOCIATED CONTENT

Supporting Information. NMR spectra for **2**, **3**, **5**, **6**, **12**, **13**, **14**, **16**, **18**, **20**, **23**, GDC-0276, solubility data for **4** and **16**, experimental information about derivatization of *CSI* **(10)** and **15**, DSC data for cyclopropylboronic acid, and LCMS spectra of **6**, **21**, **22**, **24** are 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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[10] The precursor impurities have not been identified and characterized in isolated **4** since they were not detected by the GC method.

[11] Several polymorphic forms have been identified in a screen: Form I, Form II, and Form III, along with solvates of IPA, DMSO, DMF, dioxane, THF, DCM, toluene, and acetone. See ref 13 for further details.

[12] **13**: 0.25 A% HPLC; **14**: <0.03 A% HPLC.

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[14] Aqueous HCl was also effective in removing excess NEt_3, but citric acid gave better phase separation, and was therefore implemented.

[15] A solubility screen of **16** and **3** (see SI) confirmed that either solvent could be used at more concentrated conditions (>10 mg/mL) without **3** coming out of solution prior removal of Pd / C by filtration.

[16] Nucleophilic substitution reactions on 1-bromo-2,4-difluorobenzene with alcohols proceeded in excellent regioselectivity: Ouellet, S. G., Bernardi, A., Angelaud, R., O'Shea, P. D. Regioselective S_NAr Reactions of Substituted Difluorobenzene Derivatives: Practical Synthesis of Fluoroaryl Ethers and Substituted Resorcinols. *Tetrahedron Letters*, **2009**, *50*, 3776–3779**.**

[17] Starting material **17** is available in bulk and about 4 fold less expensive than starting material **4** based on molar ratio.

[18] Other bases screened: K_2CO_3, Cs_2CO_3 showed poor conversion (<0.01 A% HPLC), $KOCH_3$, NaHMDS, KHMDS resulted in low purity reaction profiles containing various side products (<45 A% HPLC).

[19] When the reaction was performed at 50 °C significant amounts of a byproduct, presumably the *t*-butoxide adduct, was formed.

[20] Phase transfer catalysis was also attempted with NaOH (220 mol%) in biphasic solvent mixtures (toluene / water; MTBE / water). Different catalysts (Bu_4NCl, $BnEt_3NCl$), catalyst concentrations (10–130 mol%), increased temperatures were investigated. No significant product formation occurred.

[21] Water content in THF used for the pilot plant batches was controlled (<0.05 wt% H_2O by Karl Fischer) to avoid quenching of *t*-BuOK, which impeded reaction conversion.

[22] Addition of *t*-BuOK THF solution was exothermic and was therefore dose controlled over 1 h to maintain T <25 ºC.

[23] The solvent composition of the ternary reaction mixture (*t*-butanol, H_2O and THF) impacted solubility of **20**, and needed to be controlled by headspace GC (THF <89.1 wt% of distillate) in order to achieve reproducible quality and yield.

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[25] No conversion of **20** to **18** occurred at 25 ºC.

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[29] Solubility of **18** in toluene: 209 mg/mL. Solubility of **23** (25 ºC) in toluene: 209 mg/mL; in MeOH: 3.4 mg/mL. Solubility of Et_3N•HBr (25 ºC) in MeOH: 294 mg/mL; MeOH / toluene (69:31): 238 mg/mL.

[30] $PdCl_2(dppf)$•CH_2Cl_2 was difficult to source on large quantities and had a higher cost than $PdCl_2(dppf)$.

[31] The carbonylation in MeOH (7.6V) and THF (1.7V) as an alternative co-solvent which would allow to run the reaction under more concentrated conditions due to the higher solubility of **18** in THF was also tested and performed similarly to toluene. However, all attempts to crystallize **23** from the MeOH / THF reaction mixture after concentration and addition of antisolvents (MeOH, 1-propanol, H_2O, CH_3CN) resulted in poorly filterable solids and inferior product purity compared to material isolated from the MeOH / toluene solvent system.

[32] Pd content in isolated **23** <5 ppm as measured by ICP-MS.

[33] Azeotropic solvent composition measured by Headspace GC: MeOH–toluene (69:31), bp = 63 ºC.

[34] Solubility of GDC-0276 in *i*PrOAc / heptane (1:1) at 25 ºC: 20 mg/mL.

[35] Buckman, B.; Nicholas, J. B.; Beigelman, L.; Serebryany, V.; Stoycheva, A. D.; Thrailkill, T.; Seiwert, S. D. Reparation of Macrocyclic Peptides, Especially Proline-Containing Peptides, as Inhibitors of Hepatitis C Virus Replication for Treating Hepatitis C Infection and Liver Fibrosis. PCT Int. Appl. (**2011**), WO 2011038293 A1 20110331.