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# A Scalable Synthesis of CE-157119 HCl Salt, an SRI/5-$HT_{2A}$ Antagonist

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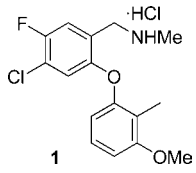
**ABSTRACT:** A scalable synthesis of CE-157119 HCl salt (**1**), an SRI/5-$HT_{2A}$ antagonist, was developed via the regioselective $S_NAr$ etherification between a phenol and an *N*-methylamide. This early development route shortened the original 5-step synthesis to three steps, eliminated all chromatography and increased the overall yield from 15% to 34%. The process was implemented for API manufacture from 100-g scale to multikilogram scale.

## INTRODUCTION

In our continuous effort to find new antidepressants that combine potent 5-$HT_{2A}$ receptor blocking activity with the established efficacy and safety of a serotonin reuptake inhibitor (SRI), CE-157119 HCl salt (**1**, Figure 1) was identified as a promising lead compound.[1] On the basis of its good *in vitro/in vivo* neuropharmacological activities and preclinical pharmacokinetics, **1** was predicted to offer greater efficacy for a broad range of patients, as well increased safety and tolerability over the current selective serotonin reuptake inhibitors (SSRI), such as sertraline (Zoloft).[2] Thus, we prepared **1** on 100-g scale for a dose-range finding toxicity study, followed by multikilogram manufacture to support regulatory toxicity and early clinical studies.




**1**

**Figure 1.** Structure of **1**.

Inhibitor **1** was originally synthesized in 15% overall yield by medicinal chemists using the route shown in Scheme 1. Aldehyde **5** was prepared from acid **2** in three steps via esterification, reduction, and oxidation. Phenol **7** was obtained through monomethylation of 2-methylresorcinol (**6**).[3] Coupling of **5** and **7** via nucleophilic aromatic substitution ($S_NAr$) formed a 4:1 mixture of desired ether **8** and 4-substituted side product **9**, which required chromatographic separation. Reductive amination of **8** with methylamine gave free amine **1a**, which was then converted to the target HCl salt (**1**). While this route was suitable for analogue synthesis with various amino side chains, poor regioselectivity in the $S_NAr$ reaction was the major obstacle for our scale-up efforts. In addition, the three-step preparation of aldehyde **5** was not practical with use of the toxic oxidant PCC; intermediates **5**, **7**, **8**, and **1a** were all purified by chromatography; and the final HCl salt formation offered poor recovery, as a significant amount of **1** remained in the mother liquor.

## RESULTS AND DISCUSSION

Improving the regioselectivity of the $S_NAr$ etherification was critical for development of a scalable synthesis. It was hypothesized that the coordination of the carbonyl oxygen with the potassium cation of the phenolate facilitates the regioselectivity at C-2 position over C-4 as depicted in Figure 2. We anticipated that replacing the aldehyde function at C-1 position with a weaker electron-withdrawing group, such as methyl amide **10** or ethyl ester **3**, would enrich the electronic density at carbonyl oxygen to benefit such interaction and therefore to improve the regioselectivity. Methyl amide **10** was selected for development[4] as the route would provide a straightforward three-step synthesis as shown in Scheme 2.

Amide **10** was easily accessed from either commercially available acid **2**[5] or ester **3** (Scheme 3). Activation of **2** with CDI in THF followed by reaction with aqueous methylamine afforded **10** cleanly. A similar result was obtained through ester aminolysis of **3** with aqueous methylamine in THF at ambient temperature. The isolation of **10** from either approach was straightforward. Concentration of the reaction mixture followed by addition of water precipitated **10** as a white crystalline powder in ~90% yield. The approach employing acid **2** was chosen for scale-up as the starting material itself is an easy-to-handle solid. In finding that the bulk lot of **2** contained 5% water, azeotropic distillation was performed at the outset to remove water before CDI activation. Two batches of **10** (6.33 and 6.40 kg) with >98% purity were obtained in 85% and 86% yields respectively.

Phenol **7** was prepared by either monomethylation of 2-methylresorcinol (**6**) or monodemethylation of 2,6-dimethoxytoluene (**11**) as shown in Scheme 4. Neither method was sufficiently chemoselective, as methylation provided **11** and demethylation provided **6** as byproducts. Instead, conventional purification methods were developed to isolate **7**. By modifying the reported monodemethylation method,[3] **7** was first prepared on 100-g scale for the dose-range finding study. Thus, treatment of **6** with dimethyl sulfate (1.1 equiv.) and aq NaOH (2.4 equiv) at reflux afforded a 3:1:1 mixture of **7**:**6**:**11**. The overmethylated byproduct **11** was removed from the basic aqueous reaction mixture by extraction into MTBE. The

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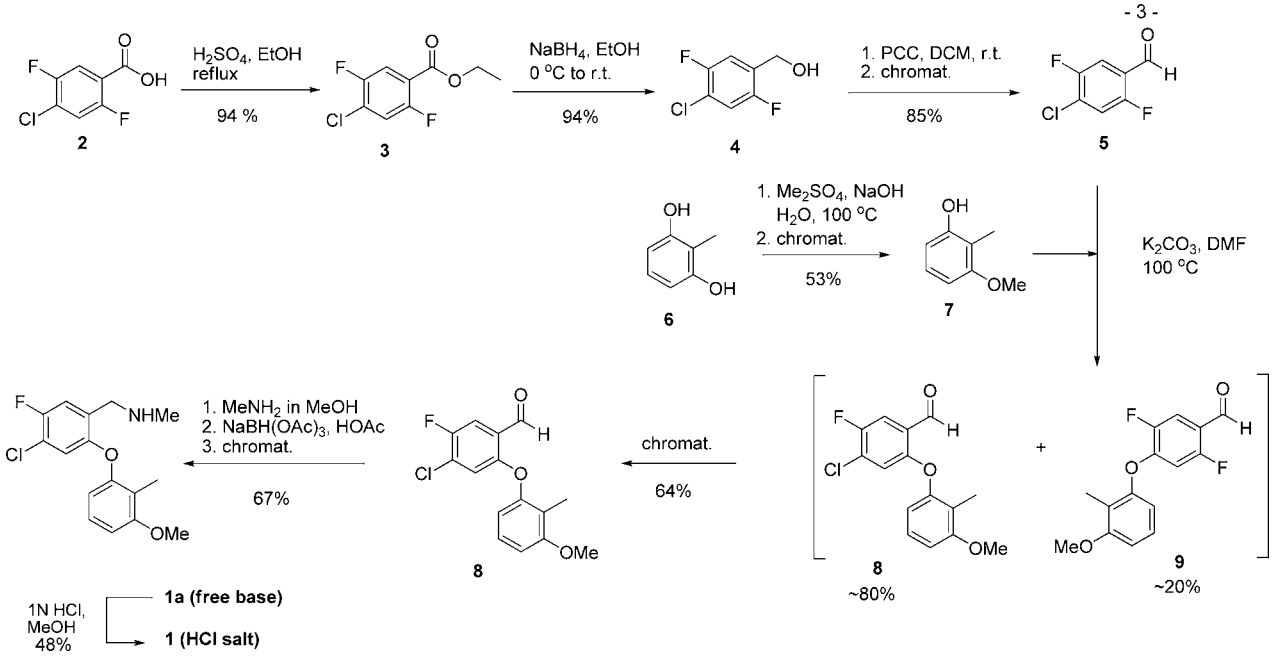
**Scheme 1. Original synthesis of 1**



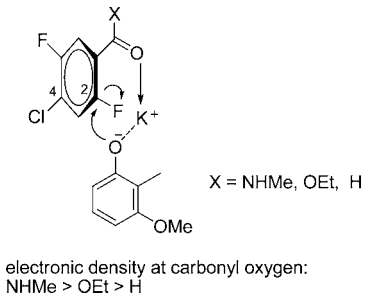



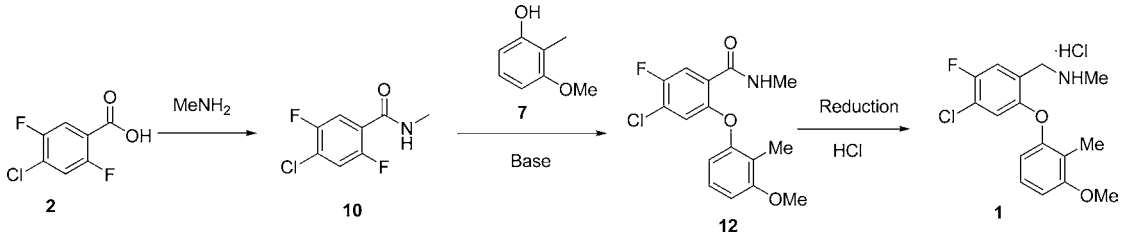

**Figure 2.** Proposed coordination state between the carbonyl oxygen and $K^+$.

aqueous layer was then acidified with HCl and extracted with DCM. The organic extracts were concentrated and passed through a pad of silica gel with a wash of 1:1 (v/v) DCM/hexanes. This purification provided **7** as a 95% pure waxy solid, which was adequate for the subsequent etherification, in 53% yield.

Alternatively, the monodemethylation of **11** was developed for further scale-up as this process allowed for more control over the reaction end point and afforded pure **7** as a crystalline solid. Dimethyl ether **11** was treated with $BBr_3$ in DCM at −10 °C for 24 h, at which point >70% of **11** was consumed, and the typical reaction profile was 6:1:2 to 6:1:1 of **7**:**6**:**11**. An aqueous ethanolamine scrubber was applied to trap methyl bromide, a toxic and a volatile side product.[6] The reaction was quenched with water, and the DCM layer was isolated. Extraction of the DCM phase with aq NaOH separated **7** and **6** from the side products, **11** and methyl bromide.[7] Acidification of the aqueous layer to pH 2−3 with aq citric acid followed by DCM extraction further upgraded **7** to ~95% purity while leaving most of **6** in the acidic aqueous layer. Crystallization from hexanes/DCM isolated **7** (>98% purity) as a white powder. Two batches of **7** (3.1 and 3.3 kg) were manufactured in 57% and 61% yields, respectively.

With both **7** and **10** in hand, we set out to screen the base and solvent effects on regioselectivity for the key $S_NAr$ reaction (Scheme 5). Unlike aldehyde **5**, methyl amide **10** generated almost exclusively the desired C-2 substituted product (**12**) under all conditions tested (Table 1). With equimolar ratio of **7** and **10**, the reaction reached completion in 18 h at 120 °C in the presence of $K_2CO_3$ in DMF or NMP but required several days for high conversion with *t*-BuOK at reflux in 2-methyl THF, THF or toluene. The $K_2CO_3$/DMF conditions (entry 1) were selected for scale-up, and two slightly different isolation procedures were developed. On 100-g scale, we diluted the mixture with 4 volumes of water and 1 volume of isopropyl ether (both relative to DMF) to precipitate **12** as a 97% pure tan granular solid in 63% yield. For multikilogram-scale manufacture, adding 1 volume of water (relative to DMF) resulted in precipitation of crude **12** in 78% yield. This isolated crude contained 94.3% of **12** with two ~1% unidentified

**Scheme 2. Proposed process route**





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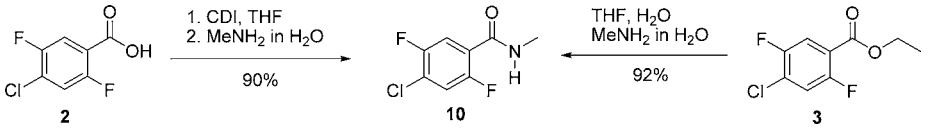
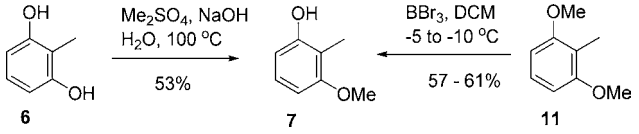
**Scheme 3. Two approaches to amide 10**




**Scheme 4. Two approaches to phenol 7**




**Scheme 5. Regioselective $S_NAr$ etherification to 12**

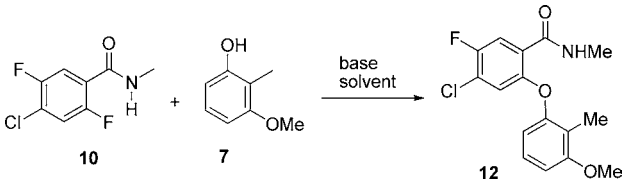



**Table 1. Base and solvent screen for the regioselective $S_NAr$ etherification**

| entry | base (equiv) | solvent, temp | reaction time | conversion (%) (HPLC) | isolated yield of **12** (%) |
|---|---|---|---|---|---|
| 1 | $K_2CO_3$ (2.2) | DMF, 120 °C | 12 h | 96 | 63 |
| 2 | $K_2CO_3$ (2.2) | NMP, 120 °C | 18 h | 88 | NA |
| 3 | $K_2CO_3$ (2.2) | DME, 85 °C | 24 h | 40 | NA |
| 4 | *t*BuOK (1.1) | THF, 65 °C | 6 d | 82 | NA |
| 5 | *t*BuOK (1.1) | 2-MeTHF, 78 °C | 5 d | 92 | 62 |
| 6 | *t*BuOK (1.1) | toluene, 110 °C | 4 d | 93 | NA |

impurities, which could be carried over to the API. A brief solvent screen unfortunately indicated that isopropyl ether was the solvent providing the best purging efficiency with good recovery. In order to minimize the potential safety hazard caused by peroxides, freshly made isopropyl ether (with BHT as stabilizer) was purchased and used quickly upon receipt. This additional reslurry operation in isopropyl ether integrated the purity of **12** over 98% with 87% recovery. Two batches of **12** (5.5 and 5.8 kg) were therefore obtained in 63% and 67% yields.

Our initial attempts to reduce amide **12** to free base **1a** were conducted with $LiAlH_4$. Unfortunately, this reduction generated a ~4:1 mixture of desired **1a** and dechlorinated side product **13** (Scheme 6), which were difficult to separate through recrystallization, salt formation, or chromatography. Satisfactory results were obtained by reduction with two *in situ* generated reducing reagents: sodium acetoxyborohydride from $NaBH_4$ and acetic acid,[8] or diborane from $BF_3{\cdot}OEt_2$ and $NaBH_4$.[9] Both methods offered clean conversion to **1a** without formation of byproduct **13** in similar yields (~80%) on lab scales. The first method was used for the 100-g-scale preparation with replacement of 1,4-dioxane with 2-methyl THF. Thus, reaction of **12** with $NaBH_4$ (5 equiv) and acetic acid (5 equiv.) in 2-methyl THF at reflux for 20 h generated a mixture of **1a** and the corresponding boron−amine complex, which was neutralized with aq NaOH and extracted into 2-methyl THF. Treatment of the organic extracts with 2 N aq HCl at reflux broke the complex and precipitated crude **1** (~96% purity) in 83% yield.

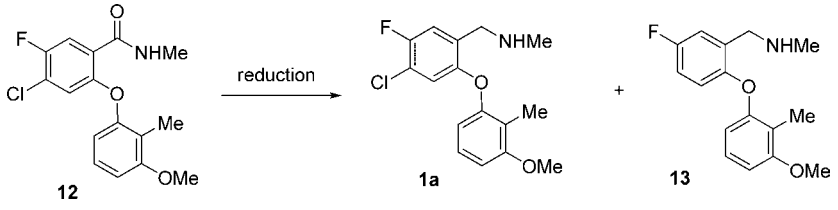
The second method was developed for kilogram-scale manufacture as it required shorter reaction time and used less reducing agent. Slow addition of a solution of **12** and $BF_3{\cdot}OEt_2$ (2.5 equiv) in THF to a 55 °C suspension of $NaBH_4$ (1.9 equiv) in THF, followed by 3 h at reflux, cleanly converted **12** to **1a** as a boron−amine complex. After an aqueous quench, the complex was extracted into 2-methyl THF from the acidic media. Breaking the complex with aq HCl at reflux offered 8.36 kg of crude **1** (96% purity) in 69% yield in the kilo lab.

Conducting a HCl salt break and reformation further enhanced the quality of **1** to meet the API delivery criteria.[10] Crude **1** was neutralized with aq NaOH and extracted into 2-methyl THF. Addition of conc HCl (1.1 equiv) and azeotropic distillation to remove water led to the recrystallization of **1** as the desired polymorph (Form A).[11] CE-157119 HCl salt (**1**, 7.36 kg) with 99.8% purity was obtained as a white powder in 88% yield.

## ■ CONCLUSIONS

An improved synthesis of CE-157119 HCl salt (**1**) was achieved through the regioselective $S_NAr$ etherification between phenol **7** and methyl amide **10**, followed by amide reduction with *in situ*-generated diborane (Scheme 7). This early development route shortened the original five-step synthesis to three steps, eliminated all chromatography, and increased the overall yield from 15% to 34%. The process was implemented for API manufacture from 100-g to multikilogram scale.

**Scheme 6. Amide reduction to free base 1a**





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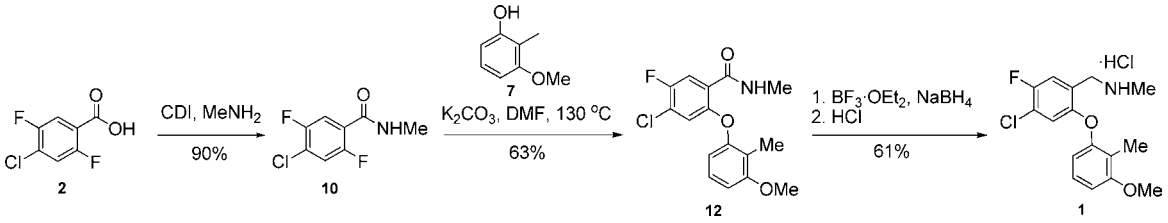
**Scheme 7. Improved three-step synthesis of 1**




## EXPERIMENTAL SECTION

Proton NMR spectra were recorded at 400 MHz, and carbon NMR spectra were recorded at 100 MHz. HPLC analyses were carried out using a Zorbax SB-CN column (4.6 mm × 150 mm, 5 $\mu$m) at 30 °C with 0.2% aq $H_3PO_4$ (A) and MeCN (B) as mobile phase in linear gradient from 95% of A to 5% of A over 15 min at 2 mL/min flow rate; HPLC purity was detected at 210 nm wavelength and reported by area %. All chemicals were of commercial quality and used as received.

***N*-Methyl 2,5-difluoro-4-chloro-benzamide (10), from 2 on Kilogram Scale.** 2,5-Difluoro-4-chloro-benzoic acid **2** (7.0 kg, 36.4 mol) was dissolved in THF (175 L), and 105 L of THF was atmospherically distilled off.[12] The residual solution was cooled to 20 °C, and CDI (6.48 kg, 40 mol) was added. The mixture was stirred at 20 °C for 2 h.[13] Methylamine (11.3 kg, 145 mol, 40 wt % in water) was added, and the mixture was stirred at 20 °C for 2 h. Forty-two liters of solvent were distilled off under vacuum (<30 °C, 0.1 bar), and water (140 L) was added. The resulting slurry was cooled to 2 °C, stirred for 2 h, and filtered. The cake was washed with water (14 L) and dried in a vacuum oven (35 °C) for 24 h to obtain **10** (6.33 kg, 30.8 mol) with 99.4% purity as a white powder in 85% yield: mp 127−128 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.92 (dd, $J$ = 9.2, 6.8 Hz, 1H), 7.24 (dd, $J$ = 10.6, 5.6 Hz, 1H), 6.73 (brs, 1H), 3.05 (d, $J$ = 4.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 161.84, 155.61 (dd, $J_{FC}$ = 246, 3 Hz), 154.85 (dd, $J_{FC}$ = 247, 2 Hz), 125.21 (dd, $J_{FC}$ = 21, 2 Hz), 121.05 (dd, $J_{FC}$ = 15, 6 Hz), 118.98 (dd, $J_{FC}$ = 26, 3 Hz), 118.31 (d, $J_{FC}$ = 31 Hz), 26.97. GC−MS: 205.0 ($M^+$). Elemental Analysis: Calcd for C, 46.74; H, 2.94; N, 6.81; Found C, 46.94; H, 2.98; N, 6.72.

***N*-Methyl 2,5-difluoro-4-chloro-benzamide (10), from 3 on lab scale.** Ethyl 2,5-difluoro-4-chloro-benzoate **3** (154 g, 0.70 mol) was dissolved in THF (250 mL). Water (250 mL) was added, followed by methylamine (303 mL, 3.5 mol, 40 wt % in water). The mixture was stirred at 20 °C for 2 h. Water (500 mL) was added, and most of THF was distilled off under vacuum (<30 °C, 0.05 bar). The resulting slurry was stirred at 20 °C for 1 h and filtered. The cake was washed with water (500 mL) and dried in a vacuum oven (40 °C) for 16 h to obtain **10** (132.6 g, 0.64 mol) as a white powder in 92% yield.

**2-Methyl-3-methoxyphenol (7), through Monodemethylation of 11 on Kilogram Scale.** The solution of 2,6-dimethoxytoluene **11** (6.0 kg, 39 mol) in DCM (60 L) was cooled to −6 °C. A scrubber containing ethanolamine (4.34 kg, 71.1 mol) and water (17.4 L) was connected to the reaction system. 1 M $BBr_3$ in DCM (21.2 L, 21.2 mol) was added over 2 h, while the reaction temperature was maintained between −8 to −4 °C. The mixture was agitated at −6 °C for 24 h until 70% of **11** was consumed. Water (60 L) was slowly added, while the reaction temperature was maintained below 10 °C. The DCM layer was separated and then extracted with 1 N aq NaOH (42 L). The aqueous solution was adjusted to pH 2−3 with 2 N aq citric acid (30 kg, 60 mol) and extracted with DCM (30 L). The DCM layer was dried with $MgSO_4$ (3 kg) and concentrated under vacuum (30 °C, 0.1 bar) to ∼7 L of the residual volume. Hexanes (60 L) were added, and the mixture was seeded. The resulting slurry was stirred at 20 °C for 3 h and at 4 °C for 17 h and then filtered. The cake was washed with hexanes (10 L) and dried in a vacuum oven (20 °C) for 16 h to obtain **7** (3.27 kg, 23.7 mol) with 98.7% purity as a white powder in 61% yield: mp 43.9−44.5 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.06 (t, $J$ = 8.2 Hz, 1H), 6.52 (d, $J$ = 8.2 Hz, 1H), 6.48 (d, $J$ = 8.2 Hz, 1H), 4.65 (brs, 1H, exchanged with $D_2O$), 3.85 (s, 3H), 2.16 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 159.69, 154.43, 126.45, 112.15, 108.08, 103.12, 55.73, 7.98. GC−MS: 138 ($M^+$). Elemental Analysis: Calcd for C, 69.54; H, 7.30; Found C, 69.25; H, 7.65.

**2-Methyl-3-methoxyphenol (7), through Monomethylation of 6 on Lab Scale.** A mixture of 2-methylresorcinol **6** (550 g, 4.43 mol) and NaOH (212 g, 5.30 mol) in water (2.65 L) was heated to 90 °C. Dimethyl sulfate (462 mL, 4.88 mol) was added over a period of 45 min, followed by 10 wt % aq NaOH (2.2 kg, 5.5 mol) over a period of 30 min, while the reaction temperature was maintained between 90 to 100 °C. The mixture was stirred at 100 °C for additional 30 min and then cooled to 20 °C. The mixture was extracted with MTBE (2 L). Conc HCl (800 mL) was added slowly to the aqueous layer to adjust pH <2. The aqueous mixture was extracted with DCM twice (2 L each) and the combined extracts were washed with water (1 L) and dried over $MgSO_4$. The DCM layer was concentrated to ∼1 L of the residual volume, and the resulting oil was passed through a pad of silica gel (1 kg, 16 cm D × 14 cm H) with a wash of 1:1 (v/v) hexanes/DCM (6 L). The filtrates were concentrated to dryness under vacuum (<40 °C, 0.1 bar) to provide **7** (324 g, 2.35 mol) with 95.0% purity as an off-white, waxy solid in 53% yield.

**4-Chloro-5-fluoro-2-(3-methoxy-2-methyl-phenoxy)-*N*-methyl-benzamide (12), Using DMF As Solvent on Kilogram Scale.** 2-Methyl-3-methoxyphenol **7** (3.70 kg, 26.7 mol), *N*-methyl 2,5-difluoro-4-chloro-benzamide **10** (5.54 kg, 26.9 mol), and $K_2CO_3$ powder (6.23 kg, 44.6 mol) were added to DMF (46.5 L). The mixture was heated to 130 °C and stirred for 12 h. The mixture was then cooled to 20 °C, and water (46.5 L) was added slowly over 1 h. The resulting slurry was stirred at 20 °C for 2 h and at 2 °C for 2 h and then filtered. The cake was washed with water (15.5 L) and dried in a vacuum oven (40 °C) for 32 h to obtain crude **12** (6.75 kg) as a beige powder. This crude was added to isopropyl ether (26.8 L, ***CAUTION**: isopropyl ether may contain explosive peroxides.* Use appropriate safety precautions). The slurry was stirred at 50 °C for 30 min, slowly cooled to 0 °C over 1 h, further stirred at 0 °C for 2 h, and then filtered. The cake was washed with isopropyl ether (6.7 L) and dried in a vacuum oven (30 °C) for 24 h to obtain **12** (5.45 kg, 16.8 mol) with 98.8% purity as an off-white powder in 63% yield: mp 126.7−128.1 °C. $^1$H NMR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(400 MHz, $CDCl_3$): $\delta$ 8.10 (d, $J$ = 9.8 Hz, 1H), 7.81 (brs, 1H), 7.12−7.36 (m, 1H), 6.83 (d, $J$ = 8.3 Hz, 1H), 6.49−6.74 (m, 2H), 3.92 (s, 3H), 3,04 (d, $J$ = 4.8 Hz, 3H), 2.10 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 163.63, 159.37, 153.56 (d, $J_{FC}$ = 244 Hz), 152.73, 152.07 (d, $J_{FC}$ = 3 Hz), 127.54, 124.73 (d, $J_{FC}$ = 20 Hz), 122.25 (d, $J_{FC}$ = 6 Hz), 119.38 (d, $J_{FC}$ = 23 Hz), 117.72, 113.06, 107.80, 55.86, 26.87, 8.99. LC−MS: 324.4 ($ES^+$). Elemental Analysis: Calcd for C, 59.36; H, 4.67; N, 4.33; Found C, 59.62; H, 4.53; N, 4.23.

**4-Chloro-5-fluoro-2-(3-methoxy-2-methyl-phenoxy)-*N*-methyl-benzamide (12), Using DMF As Solvent on Lab Scale.** 2-Methyl-3-methoxyphenol **7** (12.42 g, 89.9 mmol), *N*-methyl 2,5-difluoro-4-chloro-benzamide **10** (18.48 g, 89.9 mmol), and $K_2CO_3$ powder (27.33 g, 197.7 mmol, <325 mesh) were added to DMF (170 mL). The slurry was stirred at 120 °C for 12 h and then cooled to 20 °C. Water (680 mL) was added slowly, followed by isopropyl ether (150 mL). The resulting slurry was stirred at 20 °C for 2 h and filtered. The cake was washed with water (100 mL) and isopropyl ether (50 mL), and dried in a vacuum oven (40 °C) for 16 h to obtain **12** (18.18 g, 56.1 mmol) as a light-tan granule in 63% yield.

**4-Chloro-5-fluoro-2-(3-methoxy-2-methyl-phenoxy)-*N*-methyl-benzamide (12), Using 2-Methyl THF As Solvent.** 2-Methyl-3-methoxyphenol **7** (242 g, 1.75 mol), *N*-methyl 2,5-difluoro-4-chloro-benzamide **10** (343 g, 1.67 mol) and *t*-BuOK (196 g, 1.75 mol) were added to 2-methyl THF (3.4 L). The suspension was refluxed for 5 d. The mixture was cooled to 20 °C. Water (1.5 L), brine (1.5 L), and 1 N aq HCl (900 mL) were added. The organic layer was separated, and the aqueous layer was extracted twice with 2-methyl THF (1 L each). The combined organic extracts were washed with brine (1.5 L), dried with $MgSO_4$, and concentrated to dryness. Isopropyl ether (1.8 L) was added, and the mixture was stirred at reflux for 1 h and cooled to 5 °C slowly over 1 h. The slurry was further stirred at 5 °C for 2 h and filtered. The cake was washed with isopropyl ether (500 mL) and dried in a vacuum oven (40 °C) for 16 h to provide **12** (333.2 g, 1.03 mol) with 98% purity as an off-white powder in 62% yield.

**[4-Chloro-5-fluoro-2-(3-methoxy-2-methyl-phenoxy)-benzyl]methylamine hydrochloride (1), through Reduction with Sodium Acetoxyborohydride Generated *in Situ* on Lab Scale.** $NaBH_4$ (58.2 g, 1.54 mol) was added to a solution of 4-chloro-5-fluoro-2-(3-methoxy-2-methyl-phenoxy)-*N*-methyl-benzamide **12** (100 g, 0.31 mol) in 2-methyl THF (700 mL). The suspension was cooled to 2 °C. A solution of acetic acid (88 mL, 1.5 mol) in 2-methyl THF (300 mL) was added over a period of 1 h. The mixture was heated to reflux and stirred for 22 h. The mixture was then cooled to 10 °C and slowly poured into stirred ice/water (1.4 L); then 50 wt % aq NaOH (120 g, 1.5 mol) was slowly added. The organic layer was separated, and the aqueous layer was extracted with 2-methyl THF (1 L). The combined organic extracts were washed with brine (1 L) and concentrated to ∼300 mL of the residual volume. 2 N aq HCl (1 L) was added, and the mixture was refluxed for 2 h. The resulting slurry was cooled to 20 °C and filtered. The cake was washed with water (200 mL) and 2-methyl THF twice (200 mL each) and dried in a vacuum oven (40 °C) for 24 h to obtain **1** (88.6 g, 0.256 mol) with 95.8% purity as a white powder in 83% yield.

**[4-Chloro-5-fluoro-2-(3-methoxy-2-methyl-phenoxy)-benzyl]methylamine Hydrochloride (1), through Reduction with Diborane Generated *in Situ* on Kilogram Scale.** 4-Chloro-5-fluoro-2-(3-methoxy-2-methyl-phenoxy)-*N*-methyl-benzamide **12** (11.3 kg, 34.6 mol) was dissolved in THF (33.9 L). $BF_3{\cdot}OEt_2$ (12.3 kg, 86.4 mol) was added. The solution was slowly transferred to a heated (55 °C) suspension of $NaBH_4$ (2.45 kg, 64.8 mol) in THF (28.2 L) over 3 h while the temperature of the receiving reactor was maintained between 50 to 60 °C. The mixture was stirred at 60 °C for 3 h and then cooled to 5 °C. A 10:1 (w/w) mixture of water and THF (20.6 kg) was slowly added, while the temperature of the receiving reactor was maintained between 5 to 20 °C. After the mixture stirred at 20 °C for 2 h, water (45.2 L) was slowly added over 30 min, and the mixture was extracted with 2-methyl THF (45.2 L). The organic layer was washed with water (56.5 L) and brine (65 kg). MeOH (11.3 L) and conc HCl (6.81 kg, 69.1 mol) were then added, and the mixture was slowly heated to 60 °C over 2 h and stirred for 1 h. The mixture was concentrated under vacuum (35 °C, 0.1 bar) to ∼25 L of the residual volume, and 2-methyl THF (113 L) was added. The mixture was concentrated atmospherically at 80 °C to ∼65 L of the residual volume. The resulting slurry was cooled to 10 °C, stirred for 2 h, and filtered. The cake was washed with 2-methyl THF (11 L) and blown with nitrogen for 12 h to give crude **1** (8.36 kg, 24.1 mol) with 96% purity as a white powder in 69% yield.

**Purification of [4-Chloro-5-fluoro-2-(3-methoxy-2-methyl-phenoxy)-benzyl]methylamine Hydrochloride (1).** A solution of 0.67 N aq NaOH (40 L, 26.3 mol) was added to a slurry of crude [4-chloro-5-fluoro-2-(3-methoxy-2-methyl-phenoxy)-benzyl]methylamine hydrochloride **1** (8.36 kg, 24.1 mol) in 2-methyl THF (80 L). The mixture was stirred for 30 min until all solids dissolved and the organic layer was separated. The organic layer was washed with water twice (40 L each) and filtered through a 0.5 $\mu$m filter to a speck-free reactor with a rinse of 2-methyl THF (5 L). Conc HCl (2.77 kg, 28.1 mol) was added, and the mixture was concentrated under vacuum (35 °C, 0.1 bar) to ∼18 L of the residual volume. Additional 2-methyl THF (50 L) was added, and the mixture was concentrated atmospherically at 80 °C to ∼42 L of the residual volume. The slurry was slowly cooled to 5 °C over 1 h, stirred for 2 h, and filtered. The cake was washed with 2-methyl THF (8 L) and dried in a vacuum dryer (40 °C) for 20 h to obtain **1** (7.36 kg, 21.3 mol) with 99.8% purity as a white powder (Form A) in 88% yield: mp 186.5−188.8 °C. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 7.44 (d, $J$ = 9.1 Hz, 1H), 7.23 (t, $J$ = 8.3 Hz, 1H), 6.88 (d, $J$ = 8.3 Hz, 1H), 6.49−6.73 (m, 2H), 4.32 (s, 2H), 3.86 (s, 3H), 2.77 (s, 3H), 2.03 (s, 3H). $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 160.93, 154.78, 154.67 (d, $J_{FC}$ = 3 Hz), 154.62 (d, $J_{FC}$ = 244 Hz), 128.87, 124.14 (d, $J_{FC}$ = 19 Hz), 121.84 (d, $J_{FC}$ = 7 Hz), 120.70 (d, $J_{FC}$ = 24 Hz), 120.08, 118.34, 113.94, 108.96, 56.53, 47.90, 33.87, 9.22. LC−MS: 310.4 ($ES^+$). Elemental Analysis: Calcd for C, 55.51; H, 5.24; N, 4.05; Cl, 20.48; F, 5.49; Found C, 55.49; H, 5.13; N, 3.99; Cl, 20.33; F, 5.49.

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### Notes

The authors declare no competing financial interest.

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(7) Adding ethanolamine solution in the scrubber to the organic layer converted the volatile methyl bromide to mono- or dimethylethanolamine.

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(10) At the stage of early development API should have >98% HPLC purity with no individual unidentified impurity over 0.2%.

(11) Form A is the only polymorph of CE-157119 HCl salt (**1**) obtained up to date.

(12) After azeotropic distillation, the solution contained <0.2% of water.

(13) The completion of acid activation was monitored by HPLC through derivatization with benzylamine. The reaction reached to >98% conversion.