Development of a Practical Synthesis of the 8-FDC Fragment of OPC-167832

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Abstract: A concise and practical synthesis has been developed to provide the 8-fluoro-5-hydroxy-3,4-diiodocarbostyril (8-FDC) fragment of OPC-167832 in 41 % yield and in > 99 % purity over 4 steps from 3-amino-4-fluorophenol. The key feature of this process is the development of a telescoped one pot synthesis of the quinolone via a chemoselective amidation and easier product isolation without the need for a column chromatography.

Tuberculosis (TB) is a contagious bacterium infection caused by Mycobacterium tuberculosis (mtb) and is the leading cause of death worldwide. In 2017, 10 million people were infected by TB and 1.6 million deaths by TB occurred including 230,000 children.1 Treatments for TB are available; however, drug resistance to these treatments is an ongoing problem. First-line treatments were discovered as early as 1952. Drug resistant strains of TB include multidrug resistant (MDR-TB) and extensively drug-resistant (XDR-TB). The only current compounds available to treat MDR-TB are delamanid, pretomanid, and bedaquiline in combination with other TB drugs.2 However, identification of novel compounds with unique mechanisms of action are needed to combat drug-resistance and develop shorter less toxic treatment regimens. In this regard, OPC-1678321 (1, Figure 1) is as a promising compound for the treatment of MDR-TB strains in combination therapy developed by Otsuka Pharmaceuticals Co., Ltd. and has received fast track status for development by the US FDA.4
Figure 1. OPC-167832.

Due to the biological significance of 1, efficient synthetic access to this compound is important to enable supply. The current reported synthesis of 1\textsuperscript{3b, c} utilizes a final coupling of two fragments (2 and 8-FDC, Figure 1). In collaboration with Otsuka Pharmaceuticals Co., Ltd., our group became interested in investigating improved synthetic routes to one of the key coupling fragments, 8-FDC. Access to 8-FDC suffers from a long synthetic sequence (9 chemical steps, 8 “reaction pots”) starting from fluorinated nitrobenzene 3 (Scheme 1).\textsuperscript{3b} This approach mainly suffers from multiple functional group interconversion steps, including replacement of the 5-fluoro group of 3 with the requisite OH-group of 8-FDC. This F to O swap leads to the incorporation of several additional steps in the synthetic route. As a result, we decided to investigate an alternative synthetic design from aniline 4 with the requisite 5-OH group already present in reaction with methyl 3,3-dimethoxypropionate (5) to access the desired pyridone scaffold of 8-FDC. Importantly, both 4 and 5 are commercially available, and synthetic procedures to access 4 on up to 5 kg scale have been reported.\textsuperscript{5} Herein, we describe the successful synthesis of 8-FDC utilizing this approach.

Scheme 1. Proposed Synthetic Strategy to 8-FDC.
Results and Discussion

Scheme 2. Planned Forward Synthesis of 8-FDC.

To realize our proposed synthesis plan in Scheme 1, the envisioned forward synthesis is given in Scheme 2. Chemoselective amide formation between 4 and 5 was envisioned to provide 6 that may be converted to quinolone 7 by a Friedel-Crafts type process. Recently, this approach for the synthesis of quinolones was reported. However, we were unsuccessful in identifying chemoselective conditions for formation of amide 6 over the ester formed from reaction of 5 with the phenol-group of 4. As a result, we next investigated the synthesis of amide 6 from the coupling of acid 8 prepared from the hydrolysis of 5 with aqueous NaOH (Table 1). Of the various carboxylic acid activating agents studied, MsCl and PivCl appeared to be the most promising for formation of the product 6 (entries 1 – 4). A subsequent survey of bases and solvents utilizing PivCl as the activating agent was then carried out (entries 4 – 15). Amongst the bases analyzed, DBU and Hunig’s base afforded the highest amounts of the desired amide 6 (entries 8 and 9), but the latter was preferred for its lower cost. In regards to reaction solvent, toluene provided the maximum conversion to 6 and also accounted for the highest yield (entry 13).

Table 1. Optimization of Chemoselective Amidation of 8 with Aniline 4a
With the intent to telescope the overall synthesis, a solvent study for the cyclization of amide 6 to the quinolone 7 was next performed. A comparative analysis of the efficiency of the reaction in various solvents was made on the basis of the amount of the product isolated post precipitation from the reaction mixture by pouring into ice cold water, and the results are as captured in Figure 2.

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*Conditions: 0.93-1.55 mmol 8, base (1.25 eq), PivCl (1.25 eq) 0°C to rt for 3 h then 0.93-1.55 mmol 4, rt, 16 h. *Value represents the area % at 210 nm by reverse phase HPLC analysis after 16 h. *Value in parantheses represents assay yield determined by quantitative 1H NMR analysis of the unpurified reaction mixture using mesitylene as the analytical standard. *PivCl replaced by MsCl. *PivCl replaced by p-TsCl. *PivCl replaced by ClCO2-i-Pr.
Although CPME and Toluene gave excellent mass recovery, toluene was preferred for telescoping the reaction due to its better performance than CPME in the amidation step. In toluene, 67% assay yield of the quinolone was obtained in 75 wt% purity by quantitative $^1$HNMR analysis after direct precipitation from the reaction mixture using water (normal quench). Telescoping the process into a one-pot synthesis of quinolone 7 was found to be successful (Scheme 3), and the quinolone was isolated in 65 wt% purity (quantitative $^1$HNMR analysis) after precipitation. Due to the significant exotherm observed during the normal quenching procedure, a reverse-quench by transferring the reaction mixture to ice cold water was next tested in an effort to increase the reaction yield. Gratifyingly, this led to an improved yield of 75% on a 10 g scale.

Scheme 3. Telescopened one-pot quinolone synthesis
The stages of this one-pot sequence are shown in Figure 3. The initial reaction solution of acid 8 in toluene was homogeneous, however, upon addition of the pivaloyl chloride, the reaction becomes biphasic. After addition of DIPEA, the reaction remained biphasic and resulted in the formation of precipitated DIPEA-HCL and amide 6 (solubility of 6 in toluene is ~0.3 mg/mL) after overnight agitation. H₂SO₄ was then slowly added by addition funnel at 0 °C to control the exotherm leading to the formation of a triphasic reaction mixture. Final reverse-quenching into water induces the precipitation of the quinolone 7 that was isolated by filtration. Losses of 7 to the filtrate were determined to be 348 mg in 390 mL (~3 %) when using a normal quench mode and 656 mg in 448 mL (~6 %) when a reverse quench was employed as determined by quantitative reverse phase HPLC analysis.

**Figure 3. Reaction progress at different stages utilizing reverse-quenching**

Purification of the resultant quinolone obtained from direct precipitation with water can be achieved using either recrystallization from 80:20 MeOH:H₂O or by treatment with 10 V aqueous sodium bicarbonate solution. Using these procedures, 7 could be obtained in 100 wt% purity with
78% recovery after recrystallization with MeOH/H2O or in 93 wt% purity in 88% recovery if treated with aqueous NaHCO3. As a result, the overall yield of 7 from acid 8 was 59% when recrystallization was employed or 62% when utilizing a NaHCO3 reslurry.

Since an increased overall yield of 7 was obtained when purifying the material from aqueous NaHCO3, this quality material was attempted to be converted to 8-FDC by the established literature procedure3b,c to ascertain if 93 wt% material was acceptable (Scheme 4). Gratifyingly, 7 was smoothly converted to 8-FDC in comparable yields without issue.

Scheme 4. Conversion of quinolone 7 to 8-FDC

In conclusion, we have developed a concise process using cheap reagents and starting materials accessible on a bulk scale for the preparation of the key dihydroquinolone (8-FDC) fragment of OPC-167832. The novel process described herein features a telescoped one-pot operation for the preparation of quinolone 7 from 3-amino-4-fluorophenol and 3,3-dimethoxy propionic acid without the need for isolation of any of the intermediates. The method described herein should in principle be broadly applicable for selective acylation of a wide variety of aminophenols, and would therefore be significant for efficient synthesis of various biologically active molecules.

EXPERIMENTAL SECTION
General. All reactions were carried out under nitrogen atmosphere unless otherwise indicated. Glassware was pre-dried in an oven prior to use. 3-Amino-4-fluorophenol was purchased from Oakwood, Methyl 3,3-dimethoxy propionate was purchased from TCI chemicals, acetic anhydride from Chem Impex, trimethylacetyl chloride, 10 % Pd/C and N,N-Diisopropylethylamine from Sigma Aldrich. Toluene and Methanol reagent grade were purchased from J T Baker whereas MTBE, NaOH (pellets), dimethyl fumarate, mesitylene, Hydrochloric acid, sulfuric acid, Acetic acid were purchased from Sigma Aldrich.

3,3-dimethoxpropanoic acid (8). To a 100 mL round bottom flask with stir bar is charged 20 mL of water followed by 8.1 mL of 10 M NaOH (30%). The ester 5 (10 g) was charged and stirred at 55 °C for 2 h. TLC (30% EtOAc/hex) and NMR of a worked-up aliquot (obtained by quenching 20 µl of solution with a few drops of concentrated HCl until pH was acidic, extraction with MTBE (2 ml) and concentration) showed consumption of the starting ester. The reaction mixture was then cooled to rt and washed with MTBE (1x30 mL). To the aqueous layer was then added 6.7 mL of conc. HCl over ~10 min keeping the internal temperature below 18 °C using an ice bath. The batch was warmed up to room temperature and 4.5 g of sodium chloride was added. The reaction mixture was stirred for about 10 min to dissolve the salt, and the organic layer was extracted with MTBE (3x50mL). The organics were further dried with Na2SO4, filtered and concentrated in vacuo to provide 9.72 g (99%) of 8 as a near colorless oil in 91.7 wt % purity as determined by quantitative 1HNMR spectroscopic analysis using dimethyl fumarate as the analytical standard. Spectral data was identical to the literature.

8-fluoro-5-hydroxyquinolin-2(1H)-one (7). 3,3-dimethoxy propionic acid 8 (9.5 g, 63 mmol, 89 wt %) was weighed into a three neck round bottom flask having mechanical stirring and under an atmosphere of N2. Reagent grade toluene (95 ml) was added followed by N,N-diisopropyl
ethylamine (14 ml, 1.25 eq, 79 mmol) at room temperature. The reaction mixture was then cooled to 0 °C and trimethylacetyl chloride (9.7 ml, 1.25 eq, 79 mmol) was added dropwise over 5 minutes. The reaction mixture became cloudy post addition with the formation of a precipitate. The reaction was then warmed to room temperature and stirred for 4 h. 3-Amino-4-fluorophenol (4, 8.9 g, 63 mmol, 1 eq, 90 wt %) was added neatly as a solid to the reaction mixture at room temperature. The heterogeneous biphasic reaction mixture was then allowed to stir for overnight. HPLC analysis post overnight showed clean formation of 6. At this stage, the reaction was again cooled to 0 °C and H₂SO₄ (50 ml, 15 eq, 950 mmol) was added via an addition funnel dropwise over 45 minutes. Post addition, the reaction was warmed up again to room temperature and stirred for 45 minutes. At this stage, clear formation of two layers was observed. The reaction mixture was transferred carefully into cold water (~30 V, 300 ml) in a 500 ml Erlenmeyer flask kept in an ice bath. To the viscous and oily nature of the bottom sulfuric acid layer that still remained in the round bottom flask was added additional water (10 V, 100 ml) successively in portions dropwise in cold condition and the precipitate obtained was combined with the material in the Erlenmeyer flask above. After stirring the contents for 30 minutes at room temperature, the obtained precipitate was filtered and successively washed with water and toluene (5 V each). Lastly, the precipitate was washed with MTBE (5 V) and dried for 30 minutes under house vacuum. The buchner funnel was kept for drying inside a beaker in a vacuum oven at 60 °C for 15 h to provide 12.8 g (75%) of 7 as a light-yellow solid in 66 wt% purity determined by quantitative ¹HNMR spectroscopic analysis using mesitylene as the analytical standard. This crude material was added to 130 ml, 10 V of 9 % aqueous sodium bicarbonate solution and stirred at room temperature for 1 h. After gas evolution subsided (~40 min), the solid was collected by filtration and washed with water (20mLx2 times) and dried in a vacuum oven at 60 °C for 15 h under a gentle stream of N₂ to afford 7.5 g (62%
overall, 82% recovery) of 7 as a beige colored solid in 93 wt% purity determined by quantitative
$^1$HNMR spectroscopic analysis using mesitylene as the analytical standard. Spectral data was
consistent with the literature. $^{3b,c}$ $^1$H NMR (DMSO-d$_6$, 600 MHz): $\delta$ 11.6 (br s, 1H), 10.3 (br s, 1H),
8.01 (d, 1H, $J$ = 12 Hz), 7.19 (t, 1H, $J$ = 12 Hz), 6.51 (dd, $J$ = 12, 6 Hz), 6.46 (d, 1H, $J$ = 12 Hz)
$^{13}$C($^1$H) NMR (151 MHz, DMSO-d$_6$): $\delta$ 162.0, 150.4, 143.0, 141.4, 135.0, 128.2, 120.9, 116.3,
110.2, 100.6.

Analytical data for 6: $^1$H NMR (MeOH-d$_4$, 600 MHz): $\delta$ 7.43 (dd, 1H, $J$ = 2.4, 6 Hz), 6.88 (t, 1H, $J$ = 10 Hz), 6.42 – 6.50 (m, 1H), 4.77 (t, 1H, $J$ = 6 Hz), 3.35 (s, 6H), 2.68 (d, 2H, $J$ = 6 Hz)
$^{13}$C($^1$H) NMR (151 MHz, MeOH-d$_4$): $\delta$ 169.0, 153.2, 148.4, 146.8, 125.9, 114.9, 111.0, 110.0,
100.2, 53.0, 40.6. HRMS (ESI) m/z calcd for C$_{11}$H$_{14}$FNNaO$_4$ [M + Na]$^+$: 266.0805; Found [M + Na]$^+$: 266.0789.

Synthesis of 8-fluoro-5-hydroxy-3,4-dihydrocarbostyril (8-Fluoro-5-hydroxy-3,4-
dihydroquinolin-2(1H)-one, 8-FDC). To a suspension of 7 (2.00 g, 10.4 mmol, 93 wt %) in a 20
ml reaction vial was added 12 ml of acetic anhydride and heated to 120 °C for 2 h. The reaction
mixture was cooled to room temperature (Upon cooling precipitation occurred) and poured into
10 V of iced water. The reaction mixture was stirred at this temperature for 1 h. The precipitate
was collected and washed with 3 V of water to afford 10 as a beige colored solid (2.1 g, 90 % yield,
98 wt %). The analytical data was identical in all respects to the literature. $^{3b,c}$

In a mini autoclave vessel, 10% Pd/C (20 mg, 10 wt % as a dry powder) was added to a
suspension of 10 (0.200 g, 0.832 mmol) in 10V of AcOH. The vessel was backfilled and vented
with nitrogen followed by H$_2$ at 60 psi (4 atm). The reaction mixture was then heated at 75 °C for
8 h. The vessel was then cooled to 40 deg. C and vented/replaced autoclave with N$_2$. The residue
was filtered through 2 wt % celite. Filtrate was evaporated to a white solid under reduced pressure
to provide 214 mg (97 % yield, 84 wt %) of acetate-protected 8-FDC as a white solid. To a suspension of this material (214 mg) in 1 ml, 5V of MeOH was added conc. HCl (5V), 1 ml. The reaction mixture was heated at 100°C for 1 h. It was then cooled to 40 °C and water (2 ml) was added (precipitation occurred) followed by stirring at 30°C for 1 h. The reaction mixture was then cooled to 0 °C and stirred an additional 1 h. The precipitate was then filtered and dried to provide 113 mg (77%, 75% over two steps) of 8-FDC as a white solid in 99.3 wt% purity by quantitative 1HNMR spectroscopic analysis using mesitylene as the analytical standard. Analytical data of 8-FDC exactly matched the original literature.3b,c

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publication website at DOI: Copies of 1H and 13C NMR spectra of all new compounds (below).
$^1$H NMR of Acid 8 in CDCl$_3$
$^{13}$C NMR of Acid 8 in CDCl$_3$
$^1$H NMR of Amide 6 in MeOH-d$_4$
$^{13}$C NMR of Amide 6 in MeOH-d$_4$
$^1$H NMR of Compound 7 in DMSO-$d_6$
$^{13}$C NMR of Compound 7 in DMSO-d$_6$
$^1$H NMR of 8-FDC in DMSO-$d_6$
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Notes

The authors declare no competing financial interest.

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$^{13}$C NMR of 8-FDC in DMSO-d$_6$
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References


