

# Synthesis of the Quinolone ABT-492: Crystallizations for Optimal Processing

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## Abstract:

ABT-492 has been under development at Abbott Laboratories as a quinolone antibiotic. A convergent syntheses was utilized to prepare the compound on a multi-kilogram scale. Difficulties in isolation of intermediates were overcome by developing control of the physical forms. Examples of controlling the agglomeration, crystal habit, and polymorphism of intermediates and the API are described.

## Introduction

While crystallization from solution is an established technique for the separation and purification of organic compounds, challenges due to complex interactions of variables including polymorphism, crystal nucleation and growth, and impurity profile are common. For drug substances, understanding and controlling the polymorphism, particle size, morphology, and crystal habit have become a fundamental steps in pharmaceutical development programs.<sup>1</sup> Less interest, however, has been focused on the manipulation of the properties of pharmaceutical intermediates to improve ease of handling or purification.<sup>2</sup> This is surprising in view of the impact physical forms have on purification and mechanical isolation.

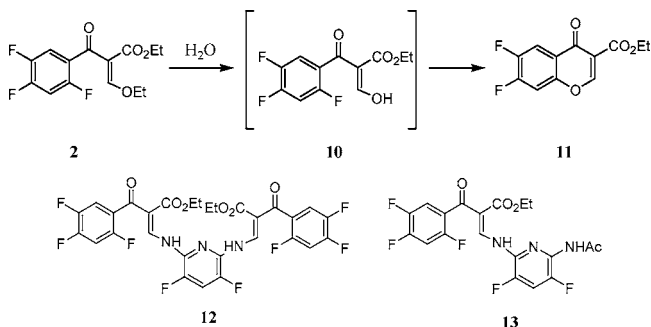
In conjunction with a clinical program,<sup>3</sup> we required kilogram quantities of the quinolone antibiotic ABT-492. For this, we developed a scaleable synthetic approach highlighted by a selective chlorination methodology.<sup>4</sup> The synthetic approach to ABT-492 entails condensation of triethylorthoformate with ketoester **1**, to give, after coupling with 2,6-diamino-3,5-difluoropyridine **3**, the vinylamide **4** in >95% isolated yield (Scheme 1). Cyclization to intermediate **6** was accomplished by treating a LiCl complex of **4** with DBU. In situ coupling of **6** with azetidinol **5** in the presence of additional DBU yielded, after esterification, the isobutyrate ester **7b** in 93% isolated yield.

Following chlorination of **7b**, the ester groups were hydrolyzed and the free acid **9** was isolated in 91% yield over the two steps (Scheme 2). To improve the solubility and bioavailability of the quinolone, a *N*-methyl-*D*-glucamine salt of **9** was prepared.<sup>5</sup> The efficiency and brevity of this sequence encouraged us to utilize this approach to provide kilogram quantities of ABT-492 for clinical development. To improve the scaleability, we focused our attention on controlling the physical properties of the intermediates for handling purposes.

## Vinyl Amide, 4

Vinyl amide **4** was chosen as the first isolated intermediate since the subsequent base induced cyclization necessitated removal of acetic acid, a byproduct of the vinyl amide formation. Additionally, residual diaminopyridine was shown to act as a competitive nucleophile with **6**, further supporting the decision to isolate **4**.<sup>4</sup>

Ketoester **1** was condensed with triethylorthoformate (TEOF) in the presence of acetic anhydride. The resulting ethoxymethylene ester, **2**, was not isolated but was instead diluted with an acetonitrile/NMP mixture and treated with sufficient water to consume residual TEOF.<sup>6</sup> Excess water led to partial hydrolysis of **2** resulting in formation of 4-oxo-benzopyran **11** under the cyclization conditions (eq 1). The



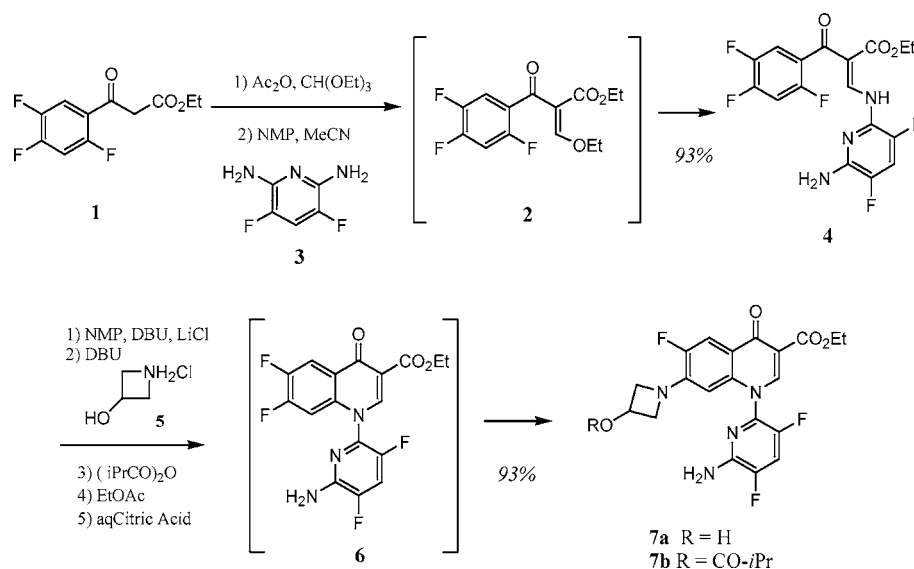
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- (1) (a) Baskin, R. J.; Bowker, M. J.; Slater, B. J. *Org. Process Res. Dev.* **2000**, *4*, 427. Myerson, A. S., Ed. *Handbook of Industrial Crystallization*; Butterworth-Heinemann: Woburn, MA, 1992. (b) Desikan, S.; Anderson, S. R.; Meenan, P. A.; Toma, P. H. *Curr. Opin. Drug Discovery Dev.* **2000**, *3*, 723.
- (2) Mueller, M.; Schneeberger, R.; Wieckhusen, D.; Cooper, M. *Org. Process Res. Dev.* **2004**, *8*, 376.
- (3) (a) Harnett, S. J.; Fraise, A. P.; Andrews, J. M.; Jevons, G.; Brenwald, N. P.; Wise, R. *Journal of Antimicrobial Chemotherapy* **2004**, *53*, 783–792. (b) Da Silva, A. D.; de Almeida, M. V.; de Souza, M. V. N.; Couri, M. R. *Current Medicinal Chemistry* **2003**, *10*, 21–39.
- (4) Barnes, D. M.; Christensen, A.; Engstrom, K. M.; Haight, A. R.; Hsu, M. C.; Lee, E. C.; Peterson, M.; Plata, D. J.; Raje, P.; Stoner, E. J.; Tedrow, J. S.; Wagaw, S. H. *Org. Process Res. Dev.* **2006**, submitted.

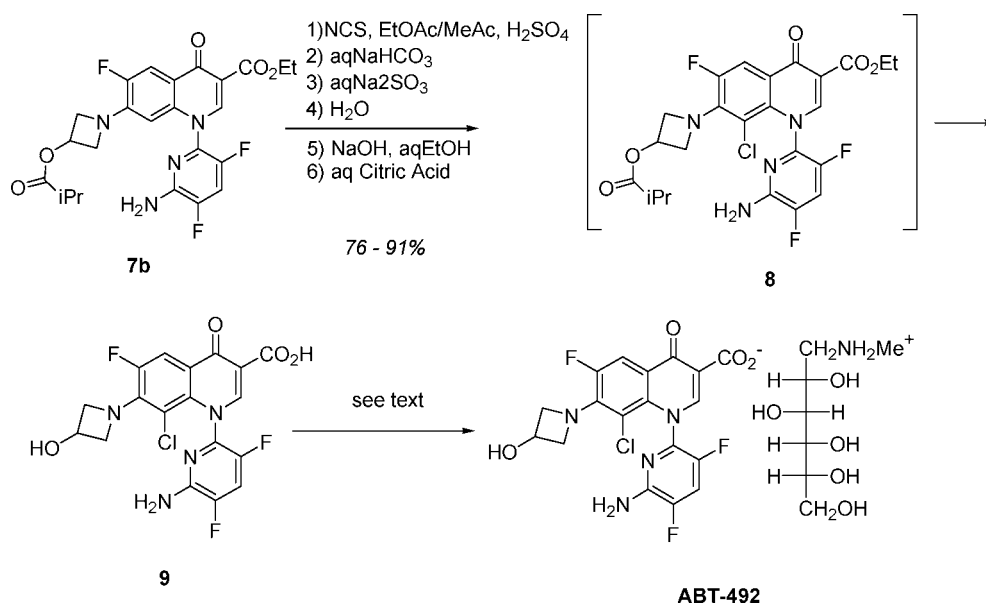
ethoxymethylene ester was added to a solution of 2,6-diamino-3,5-difluoropyridine **3** in NMP/acetonitrile giving a yellow solution of the desired amide **4**. Slow addition of water gave bright yellow needles of **4** (Figure 1a) in >93% isolated yield. Unfortunately, these crystals filtered exceptionally poorly leading to difficulties in removing both reaction byproducts and residual solvents. The product

- (5) Berge, S. M.; Bighley, L. D.; Monkhouse, D. C. *J. Pharm. Sci.* **1977**, *66*, 1.
- (6) If the excess TEOF was not hydrolyzed, *N*-formylation impurities of **3** and **4** were observed in the reaction mixture.

**Scheme 1. Synthesis of ABT-492 intermediate**



**Scheme 2. Synthesis of ABT-492**



obtained from a 40 kg run after drying under a vacuum to remove residual moisture contained approximately 5 mol % NMP and had a weight percent assay of 98.1% versus a chromatographically prepared standard

Modulating the morphology by crystallizing from alternative solvents or mixed solvents proved unsuccessful. Ostwald ripening (60 °C/12 h) did increase the needle size; however, no improvement was observed in the cake resistivity.<sup>7</sup> Additionally, Ostwald digestion resulted in higher levels of impurities including bis-amide **12** (<4% to 5–15%) and *N*-acetamide **13** (<1% to >5%). *N*-Acylation of **4** from residual  $\text{Ac}_2\text{O}$  results in acetamide **13**, while **12** is the product of metathesis of **4** under the digestion conditions.

By inverting the order of addition and adding the reaction mixture to water, soft agglomerates of fine needles (100–800 μm agglomerates) (Figure 1b) were observed. Presum-

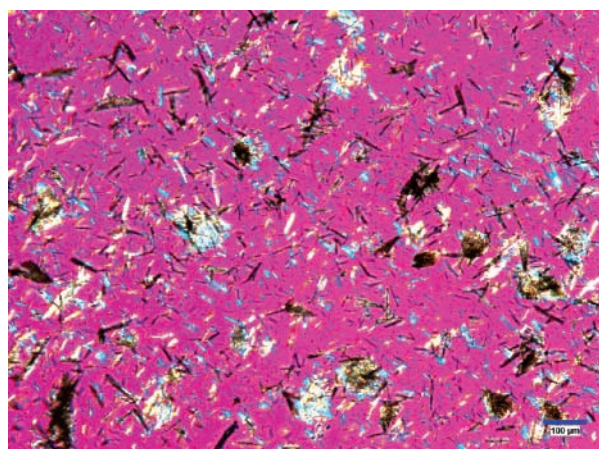
ably the rapid decrease in solubility caused by the inverse quench crystallization induces agglomeration during the dispersion of the organic phase into the water.<sup>8</sup> X-ray diffraction patterns of the agglomerated crystals indicated no form changes between the needles and the agglomerates, nor were the impurity profiles of the solids significantly different between the methods of precipitation, 95.4–96.9% versus 96.9–98.1%.

In practice, the inverse addition precipitation on a multi-kilogram scale using a retreating blade agitator produced acceptable agglomerates. Yet during the mixing prior to filtration of the solids (~1 h), the agglomerates were observed to undergo significant degradation to fine needles leading again to poor filtration and cake washing.<sup>9</sup>

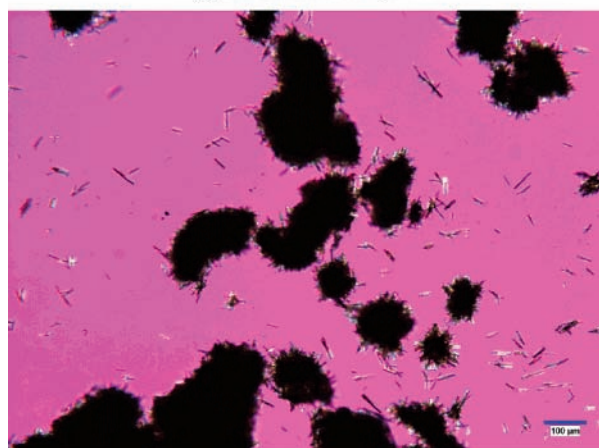
(8) Kawashima, Y.; Okumura, M.; Takenaka, H. *Science* **1982**, 216 (4550), 1127.

(9) Laser diffraction analysis of a 200 gallon reactor equipped with a pitched blade agitator with a tip speed of 14.4 m/min showed an attrition in the  $d_{90}$  of the chord length from 95 μm to 70 μm over 3 h.

(7) Particle size was measured by microscopy, as laser diffraction techniques proved unsuccessful in differentiating particles.



(a) Normal Addition Quench



(b) Inverse Addition Quench

**Figure 1.** Vinyl amide 4 quench morphologies.

Comparison of filtration rates and permeabilities demonstrated that agitation during the inverse quench was a fundamental parameter in influencing the filtration rate (Table 1, entries 2–4).<sup>10</sup> However, the resulting agglomerates underwent competitive destruction with a prolonged mix time (Table 1, entries 4–7). This encouraged us to minimize the time for completing the addition and the holding of the slurry prior to isolation.<sup>11</sup>

Although no difference was observed between a pitched blade agitator and a retreat curve design in the particle formation, the pitched blade agitator did reduce the rate of

attrition relative to the retreat curve.<sup>12</sup> On a 10 kg scale, we observed little to no attrition of the agglomerates employing a pitched blade agitator. Scaling the precipitation based on the power density (W/L),<sup>13</sup> agglomerates of **4** were produced on greater than a 50 kg scale with minimal attrition resulting in reproducible filtration rates (0.8 to 1.0 g/s) and permeabilities ( $(1.3 \text{ to } 2.6) \times 10^{-14} \text{ m}^2$ ) to provide a more preferred isolation process. Filtration times on this scale decreased from 24 h to 90 min, and the product was isolated in 91–95% isolated yield and greater than 95% purity on a 50–125 kg scale (8 runs).

### Isobutyrate Ester, 7b

Complexation of vinyl amide **4** with LiCl in NMP followed by treatment with 1 equiv of DBU initiated an anionic cyclization to the quinolone core, **6**. The 3-hydroxyazetidiny functionality was prepared in situ following incremental addition of 3-hydroxyazetidine HCl and 2 equiv of DBU to the mixture. We found it advantageous to esterify the resulting alcohol **7a** to improve the solubility characteristics for the subsequent chlorination step.<sup>4</sup>

By following the three-step sequence of cyclization, coupling, and protection, quinolone ester **7b** was precipitated by addition of aqueous citric acid. Isolation at this point was necessary to remove NMP and residual azetidinol prior to chlorination.

Three distinct crystalline forms of the isobutyrate ester **7b** were characterized (Figure 2). The first characterized material was isolated following chromatographic purification. XPRD analysis of this lot (vide infra) showed Form I contaminated with Form II (Figure 2). Form I has not been observed since. Forms II and III have been observed repeatedly in essentially pure states during crystallization of the reaction mixture (Figure 2).

Form II is usually associated with a “starburst” crystal habit (Figure 3a) and was initially isolated by a slow addition of water in a drowning crystallization. While Form II particles filter well immediately after completion of the water addition, the starburst habit did not prove robust to agitation necessary to suspend the solids prior to isolation. As a result, a significant amount of attrition occurred during agitation resulting in a poor separation of the solid and liquid phases as evidenced by variable levels of lithium (0.1–2.0%),

**Table 1.** Vinyl amide 4 isolation

entry	addition time (h)	agitator blade	agitation (W/L)	hold time (h)	filtration rate (g/s)	permeability <sup>a</sup> ( $\text{m}^2 \times 10^{-14}$ )
1 <sup>b</sup>		retreat	$1.64 \times 10^{-3}$	2	0.21	Nm
2	1	retreat	$2.1 \times 10^{-4}$	0	0.54	0.52
3	1	pitched	$4.1 \times 10^{-4}$	0	0.91	2.12
4	1	pitched	$3.26 \times 10^{-3}$	0	1.27	4.34
5	1	pitched	$3.26 \times 10^{-3}$	0.5	0.86	2.99
6	3 <sup>c</sup>	pitched	$3.26 \times 10^{-3}$	0	1.54	1.42
7	6	pitched	$3.26 \times 10^{-3}$	0	0.53	0.88
8	3.1	pitched	$3.19 \times 10^{-3}$	0	1.07	2.61
9	3.1	pitched	$3.19 \times 10^{-3}$	7.5 <sup>d</sup>	0.83	1.30

<sup>a</sup> Calculated using Darcy's equation:  $(Q/A) = K * (\Delta P/L) * (g_c/\mu)$ , where  $Q$  = volumetric flow rate ( $\text{m}^3/\text{s}$ );  $A$  = filter surface ( $\text{m}^2$ );  $K$  = permeability constant ( $\text{m}^2$ );  $\Delta P$  = pressure drop across filter (Pa);  $L$  = depth of filtercake (m);  $g_c$  = gravitational constant;  $\mu$  = liquid viscosity ( $\text{Pa} \cdot \text{s}$ ). <sup>b</sup> Water added to reaction. <sup>c</sup> 4 kg of  $\text{H}_2\text{O}/\text{mol}$  of **1** versus nominal (2 kg of  $\text{H}_2\text{O}/\text{mol}$  of **1**). <sup>d</sup> Power density held at  $2.1 \times 10^{-4}$  W/L during hold time.



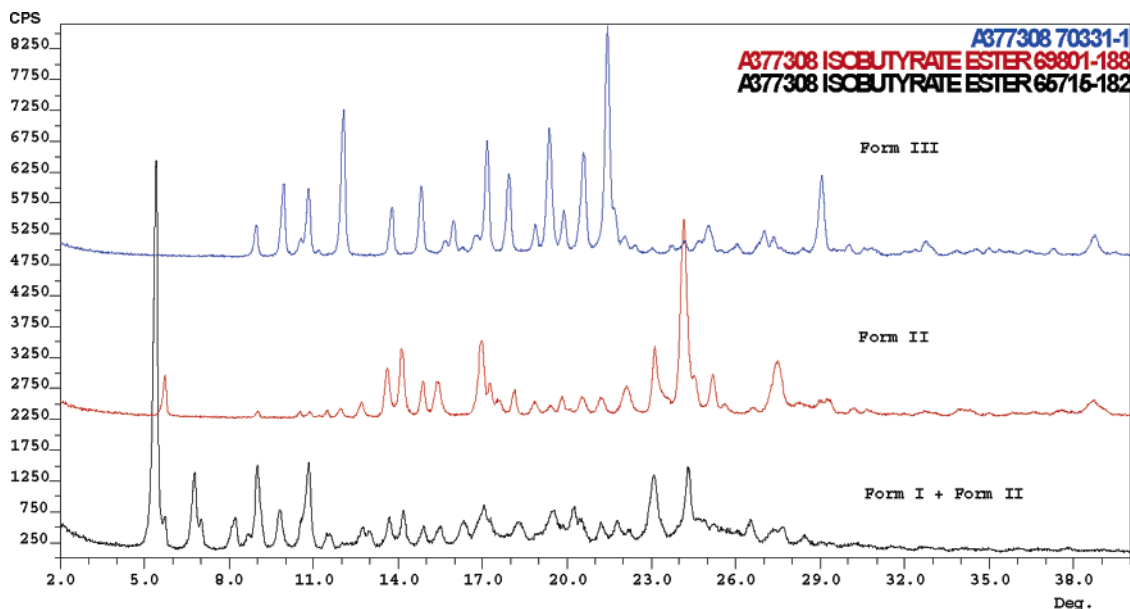
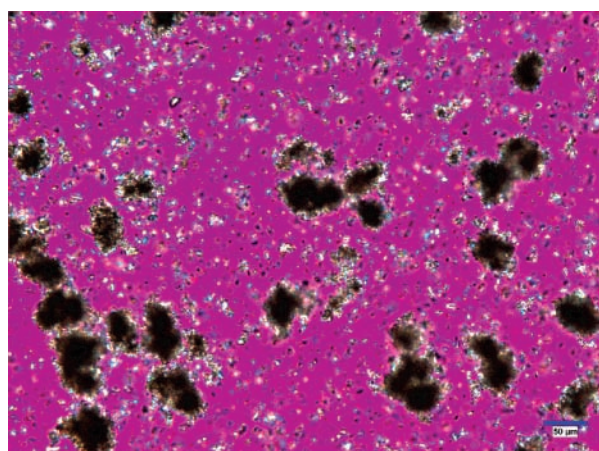
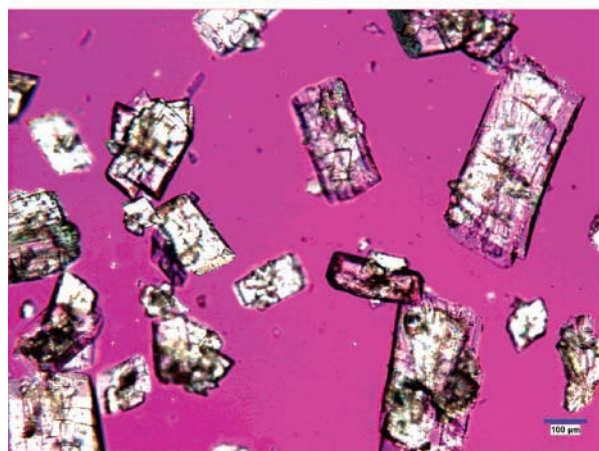


Figure 2. XRPD of isobutyrate 7b isomers.



(a) Form II



(b) Form III

Figure 3. Isobutyrate 7b polymorph habits.

chloride (0.1–2.6%), and fluoride (0.1–0.5%) in the isolated solids. Presumably the high cake resistivity inhibits effective removal of the liquors (vide infra).

Form III is typically isolated as plates by addition of 10% aqueous citric acid to the reaction mixture (Figure 3b). These plates proved more mechanically stable to prolonged agita-

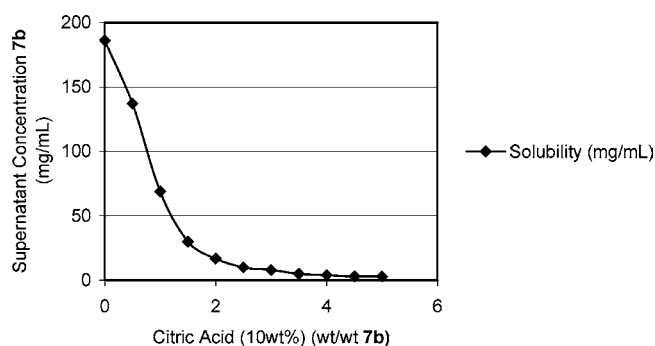


Figure 4. Isobutyrate 7b quench.

tion. In addition, the individual levels of lithium, chloride, and fluoride in the isolated solids are typically less than 200 ppm.<sup>14</sup> The filterability and washing of the Form III particles encouraged us to assess reproducible generation of this morphology.

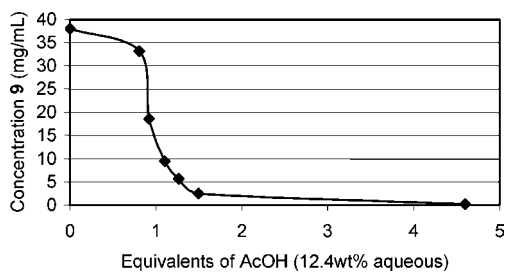
Conversion to Form III was observed in mixtures of Forms II and III in a variety of solvents including partially quenched reaction mixtures. If the partially quenched reactions had supernatant levels greater than 50 mg of 7b/mL of supernatant, the conversion was observed to occur in less than 1 h.<sup>15</sup>

Thus, the reaction mixture was diluted sequentially with ethyl acetate (1 mL/g of 3)<sup>16</sup> and 10 wt % aqueous citric acid (1 g/g of 3) to generate a solution with an approximate solution concentration of 70 mg of 7b/mL of solution. Form III seeds (1 wt %) were added as a slurry in NMP/aqueous citric acid,<sup>17</sup> and the resulting mixture was allowed to desaturate until the supernatant levels reached equilibrium (approximately 65–69 mg/mL; Figure 4). Additional aqueous citric acid was then added slowly.<sup>18</sup>

(10) Agitation was increased by increasing the rpm of the agitator blade in a vessel. Scaling up based on the power density (W/L) appeared to give comparable agglomerates on several scales.

(11) Addition rates between 1 and 3 h were reproducibly obtained on scale with hold times of 2–5 hours

(12) Impellers such as the A-310 used here are designed to improve axial flow and mixing with reduced power input.



**Figure 5.** Neutralization of hydrolysis reaction.

Following washing with water to remove residual inorganics, isobutyric acid, DBU, and NMP, the isobutyrate ester **7b** was isolated as large plates in 96% yield and >99% purity with less than 50 ppm of Li, Cl, and F.

### Free Acid Isolation

With the isobutyrate ester **7b** prepared, introduction of the chlorine atom and hydrolysis of the protecting groups were all that remained. To a solution of NCS in methyl acetate is added an ethyl acetate solution of **7b** containing 6.5 mol %  $\text{H}_2\text{SO}_4$ . The MeOAc/EtOAc mixed solvent system was developed to ensure the starting ester **7b**, and the resulting chlorinated quinolone **8** stayed in solution throughout the chlorination sequence.<sup>4</sup> The resulting reaction is washed sequentially with aqueous sodium bicarbonate followed by aqueous sodium bisulfite. After solvent exchange into 2-propanol and addition of excess aqueous NaOH, the reaction mixture is heated to 50 °C to complete the hydrolysis of the esters. The isobutyrate cleaves rapidly, while the ethyl ester requires the elevated temperature to ensure a rapid rate of hydrolysis. The product is isolated by a reactive crystallization in which 12.4 wt % acetic acid is slowly added to the reaction mixture. A large excess of acetic acid is added at this point to drive the pH of the reaction mixture to less than 5.0 and precipitate the product. The solubility of ABT-492 increases significantly between pH 8.5 and 10.0, and thus, the rate of addition of the acid was controlled in this range (Figure 5).<sup>19</sup>

The first equivalent of acetic acid is added over a 5–15 min period. The contents of the reactor are then stirred at low agitation<sup>20</sup> for 1 h during which time the solution becomes opaque with the initial crystals. The agitation is kept only high enough to suspend the solids forming in the vessel and to maintain a homogeneous mixture. The second equivalent of the 12.4 wt % acetic acid is added over 1 h followed by an additional 3 equiv of acid over another hour.

(13) Bates, R. *Mixing Theory and Practice*; Academic: New York; Vol. 1, Chapter 3, p 111.

(14) This proved critical for the following NCS chlorination step which appeared to be catalyzed by Li and conversely inhibited by fluoride.

(15) The solution concentration of **7b** is the critical in the rate of interconversion between Forms II and III. Solution concentrations <20 mg/mL can require days for complete conversion.

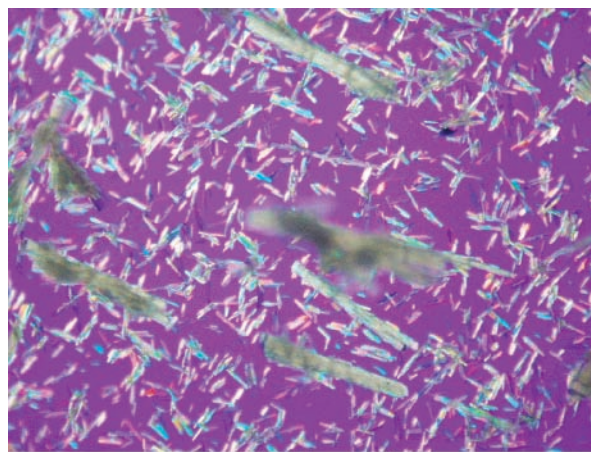
(16) EtOAc was added to decrease the viscosity of the mixture to improve the crystal growth.

(17) For ease of operation, the seeds were added in a slurry. Lab experiments with dry seeding also was successful.

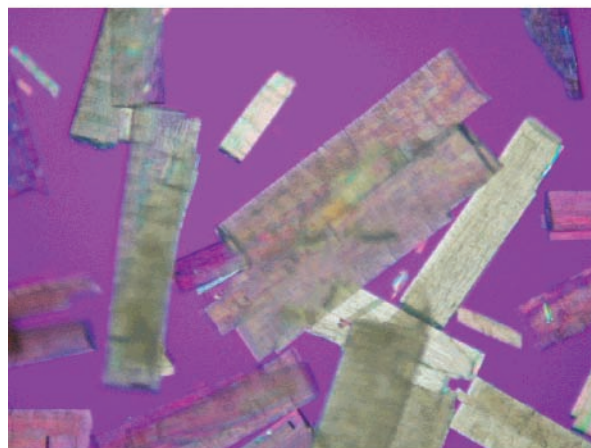
(18) Slow addition was critical to avoid formation of Form II which does not convert in an acceptable time frame to Form III after the quench.

(19) Solubilities: pH 8.5 = 4 mg/mL; 9.0 = 16 mg/mL; 9.5 = 55 mg/mL; 10.0 = 194 mg/mL

(20) A retreating bar agitator was used with a tip speed of 9.6 m/min.



**(a)** 20% aq iPrOH



**(b)** 100%  $\text{H}_2\text{O}$

**Figure 6.** ABT-492 crystal habits (micrographs same scale).

The driving force for the precipitation is so great between the addition of the first and second equivalents of acid (35 mg/mL to <5 mg/mL) that the pH increases, from 7.4 to 7.7, during the crystallization.

After completion of the crystallization, the slurry is stirred at 40 °C for at least 30 min to ensure that entrained potassium salt in the solid has sufficient time to equilibrate. The slurry is then cooled to 20 °C and filtered.

Washing of the cake is critical to removing both potassium acetate and acetic acid. To ensure removal of the acetic acid, the pH of the filtrate is monitored until the eluent stream matches the pH of the water used for the wash. After drying, the ivory solid, **9**, is obtained in 90% assay adjusted yield with an assay purity of >95%.

Unfortunately, the poor solubility characteristics of the acid **9** precluded evaluation of this compound in a clinical setting. A salt screen of pharmaceutically relevant counterions<sup>6</sup> identified the *N*-methyl-*d*-glucamine salt, ABT-492, as a viable candidate capable of providing bioavailability. Initial quantities of ABT-492 were acquired by crystallization from 10 to 30% aqueous 2-propanol to yield large needles of the trihydrate of the desired salt in >98% purity (Figure 6a). The anhydrous form of the compound could then be obtained via dehydration under a vacuum.

This needle morphology, while acceptable for early clinical evaluation of the compound, proved challenging to formulate due to the poor flow characteristics of the solid.



Bravais–Friedel–Donnay–Harker modeling<sup>21</sup> of the trihydrate crystal structure suggested an oblong hexagonal lathe should be the preferred habit. Surveying of crystallization solvents and methods determined that crystallization directly from water generated a comparable plate habit (Figure 6b) presumably due to the increased water concentration inhibiting growth of the other faces.<sup>22</sup>

In practice, seeding an aqueous mixture of **9** and 1.2 equiv of *N*-methyl-*d*-glucamine at 38 °C, followed by slow cooling yielded, after filtration at 0 °C, 80% of ABT-492 in >99% purity.

Thus, we have described examples of successful applications of crystallization techniques to improve both isolations and purifications in the development of a pharmaceutical process. The utilization of crystal form and habit to improve solid/liquid separation and thus enhance purity should be generally considered when confronted with scaling of pharmaceutical processes.

## Experimental Section

**3-(2,4,5-Trifluorophenyl)-2-(*N*-[6'-amino-3',5'-difluoro]-aminopyridine)methylene-3-oxopropionic Acid, Ethyl Ester, **4**.** Ketoester **1** (83.2 kg, 337.9 mol) and triethylorthoformate (80.1 kg, 540.7 mol) are heated to reflux (~140 °C) and stirred for 30 min. Acetic anhydride (103.5 kg, 1014 mol) is then added, and heating continued for about 12 h, and then the mixture was cooled and diluted with NMP (210 kg) and acetonitrile (161 kg) and stirred. Water (3.0 kg, 169 mol) is added, and the mixture was held for 10 min.

The resulting solution is added to a suspension of 2,6-diamino-3,5-difluoropyridine, **3** (57.4 kg, 395.4 mol), NMP (210 kg), and acetonitrile (161 kg). The resulting homogeneous solution is added to water (662 kg) over 2 h, precipitating the yellow product. The product is filtered and washed with a solution of acetonitrile (161 kg) and water (102 kg). The wetcake is washed with water (600 kg) and dried at 60 °C to provide 120 kg (93%) of the vinyl amide **4**, as a mixture of *E* and *Z* isomers. Mp 157–160 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) (*E*-isomer) δ 1.15 (t, 3H), 4.16 (q, 2H), 4.64 (br s, 2H), 6.90 (m, 1H), 7.22 (t, 1H), 7.32 (m, 1H), 9.03 (d, 1H), 12.44 (bd, 1H); (*Z*-isomer) δ 1.03 (t, 3H), 4.11 (q, 2H), 4.60 (br s, 2H), 6.90 (m, 1H), 7.20 (t, 1H), 7.48 (m, 1H), 8.90 (d, 1H), 11.17 (bd, 1H). Anal. Calcd for C<sub>17</sub>H<sub>12</sub>F<sub>5</sub>N<sub>3</sub>O<sub>3</sub>: C, 50.88; H, 3.01; N, 10.47. Found: C, 50.83, H, 2.70, N, 10.32.

**1-(6-Amino-3,5-difluoropyridin-2-yl)-6-fluoro-7-(3-isobutyryloxyazetididin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid, Ethyl Ester, **7b**.** To a solution of vinyl amide **4** (115.5 kg, 288 mol) and LiCl (24.3 kg, 573 mol, 1.99 equiv) in NMP (769 kg) is added DBU (46.1 kg, 303 mol, 1.06 equiv) over 1 h 40 min, maintaining the internal temperature at 35 °C. The reaction temperature is then adjusted to 23 ± 5 °C, and the reaction is stirred for 2 h. When the cyclization is complete, azetidine hydrochloride,

**5** (33.9 kg, 309 mol, 1.08 equiv), is added followed by DBU (109.2 kg, 717 mol, 2.5 equiv) over 2 h. The reaction temperature is then adjusted to 23 ± 5 °C. After the addition is complete, isobutyric anhydride (99.7 kg, 630 mol, 2.2 equiv) is added, the reaction is stirred for 1 h at 35 °C and then cooled to 23 °C, and ethyl acetate (104.2 kg) is added. A 10% citric acid solution (300 kg) is added slowly. Seeds of **7b** are added. An additional 270 kg of 10% citric acid solution are then added, and the resulting slurry is filtered and washed twice with 115 kg of water. The product is dried at 50 °C to yield 136.1 Kg (93%) of the title product, **7b**. mp: 201–209 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 8.49 (s, 1H), 8.00 (dd, *J* = 9.0, 9.3 Hz, 1H), 7.75 (d, *J* = 12.8 Hz, 1H), 6.79 (br s, 2H), 5.95 (dd, *J* = 1.5, 7.6 Hz, 1H), 5.21 (m, 1H), 4.36 (t, *J* = 7.4 Hz, 2H), 4.02 (q, *J* = 7.0 Hz, 2H), 3.95 (dd, *J* = 3.7, 9.2 Hz, 2H), 2.58 (hept, *J* = 7.0 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 6H). Anal. Calcd for C<sub>24</sub>H<sub>23</sub>F<sub>3</sub>N<sub>4</sub>O<sub>5</sub>: C, 57.14; H, 4.60; N, 11.11. Found: C, 56.86; H, 4.30; N, 10.89.

**1-(6-Amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-hydroxyazetididin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid, **9**.** A solution of *N*-chlorosuccinimide (25.3 kg) in methyl acetate (419 kg) at 17 °C was treated with sulfuric acid (0.56 kg, 5.7 mol). This solution was transferred to a slurry of isobutyrate ester **7b** (92.7 kg, 184 mol) in ethyl acetate (244 kg) at 17 °C while maintaining the reaction temperature at 17 °C. The solution was stirred at 17 °C for 1–8 h and diluted with 1.5% (w/w) NaHCO<sub>3</sub> (370 kg). The layers were separated, and the organics washed with 10% (w/w) aqueous sodium sulfite (200 kg) and concentrated. The concentrate was dissolved in 2-propanol, treated with 4% (w/w) KOH (750 kg), and stirred at 50 °C until hydrolysis was complete. The reaction was passed through a filter, treated with 12% (w/w) acetic acid (410 kg), and filtered. The filtrate was washed with water and dried at 50 °C to provide 73 kg (90%) of product **9**. Mp: 238–241 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 14.63 (brs, 1H), 8.70 (d, *J* = 0.7 Hz, 1H), 7.95 (dd, *J* = 9.9, 0.7 Hz, 1H), 7.83 (d, *J* = 13.6 Hz, 1H), 6.75 (s, 2H), 5.75 (d, *J* = 5.8 Hz, 1H), 4.61 (m, 12H), 4.47 (m, 1H), 4.18 (m, 2H). Anal. Calcd for C<sub>18</sub>H<sub>12</sub>ClF<sub>3</sub>N<sub>4</sub>O<sub>4</sub>: C, 49.05; H, 2.74; N, 12.71. Found: C, 48.90; H, 2.48; N, 12.62.

***N*-Methyl-*d*-glucammonium 1-(6-Amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-hydroxyazetididin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate, ABT-492.** To a vessel containing acid **9** (29.6 kg, 67.2 mol) and *N*-methyl-*d*-glucamine (18.4 kg, 94.3 mol) was added distilled water (133 kg). This was heated to 60 °C to dissolve the solids and then cooled to 38 °C. An aqueous slurry of seeds was added to the mixture (0.64 kg, 1.5 wt %), and the solution was held at 38 °C for 24 h before cooling parabolically to 0 °C. The slurry was filtered and washed with 25% (w/w) aqueous 2-propanol. The solid was dried at 30 °C to provide 31.7 kg of product (72.9%). Mp: 168–171 °C.

(21) Docherty, R.; Clydesdale, G.; Roberts, K. J.; Bennema, P. *J. Phys. D: Appl. Phys.* **1991**, *24*, 89.

(22) Even in the presence of seeds, the desupersaturation rate requires approximately 48 h at ~38 °C to reach equilibrium in water versus <2 h in 20% aqueous 2-propanol.

Received for review March 10, 2006.

OP060054E