Organic Process Research & Development **2008,** *12,* 666–673

Development and Manufacture of the Inosine Monophosphate Dehydrogenase Inhibitor Merimepodib, VX-497

Adam R. Looker,[†,*] Benjamin J. Littler,[‡] Todd A. Blythe,[†] John R. Snoonian,[⊥] Graham K. Ansell,[§] Andrew D. Jones,[¶] Phil Nyce,[†] Minzhang Chen,[†] and Bobbianna J. Neubert[†]

Chemical Development, Vertex Pharmaceuticals Incorporated, 130 Waverly Street, Cambridge, Massachusetts 02139, U.S.A. and 11010 Torreyana Road, San Diego, California 92121, U.S.A.

Abstract:

A process for the manufacture of merimepodib (VX-497), an inosine monophosphate dehydrogenase (IMPDH) inhibitor, has been developed and efficiently scaled to produce clinical supply. The process comprises five steps, incorporating simple and robust chemistry that ultimately yielded 96.5 kg with a purity of 100% (by HPLC analysis) and 99.7% w/w assay. Highlights of the process are the effective use of production-scale phosgene, manipulation of Schotten−Baumann reaction conditions to give a low pH procedure that avoids a critical impurity, and the use of online tools to better identify parameters of the API purification.

1. Introduction

Merimepodib (VX-497)[1] **8** is an inhibitor of the inosine monophosphate dehydrogenase (IMPDH) enzyme, providing for the basis of its immunosuppressive activity.[2]

At Vertex Pharmaceutical's Chemical Development Department, the strategy for approaching incoming development projects is two-fold: (a) advancing the medicinal chemistry route towards a streamlined, scalable process enabling early-phase programs, (b) preparing for later-phase work, including registration, validation, and commercialization. The initial route (often referred to as the supply route) is characterized by quick delivery and scalability, while later-phase work is focused on making the process as robust and efficient as possible.

After early VX-497 development work, our supply route of synthesis (Scheme 1)[1,3] involved the coupling of (*S*)-3-hydroxytetrahydrofuran (**1**) with 3-aminobenzylamine (**3**), using carbonyl diimidazole (CDI) to furnish the intermediate aniline **4** by way of the acyl imidazole **2**. This intermediate was not isolated; instead it carried forward into the coupling with phenyl chloroformate to provide carbamate **5**. Nitroaromatic **6** was reduced by catalytic hydrogenation to yield the left-hand portion of VX-497, aniline **7**. The final stage involved the coupling of **5** and **7** under base-mediated conditions to form the urea functionality, as well as purification by slurry via the trisolvent mixture EtOH/acetone/H_2O.

However, the analysis of the route revealed several undesirable features in preparation for commercial route selection. These included: (a) capricious yield and purity obtained during previous production of carbamate **5**, (b) excess CDI which led to largely insoluble and difficult to remove ureas, most notably **9** (Scheme 2), (c) compound **3** having physical properties uncharacteristic of a robust raw material (semisolid at ambient temperature and prone to decomposition), (d) need for high catalyst loading in the reduction of **6**, and (e) purification of the API by slurry instead of a controlled crystallization.

This report shows the development of VX-497 chemistry into a commercial process. The first section of this paper will detail work that identified a strong raw material supply chain, along with more robust chemistry. Next, the reaction parameter screening process for the nitro reduction of **6** will be discussed. To conclude, the work that went into the identification of a reliable coupling and purification procedure, which proved a highly robust process amenable to commercial-scale production, will be presented.

2. Results and Discussion

2.1. Making Use of Key Advantages of Phosgene. The basis of a new development strategy was finding a more robust starting material to replace the diamine **3**. Several 3-nitrobenzyl adducts were most appealing because they were commercially available, offered stability, and were crystalline at ambient temperature. Although using such a starting material would require adding a reduction step to our synthetic sequence for the nitro group, it afforded greater control over chemoselectivity and introduced a stronger supply chain.

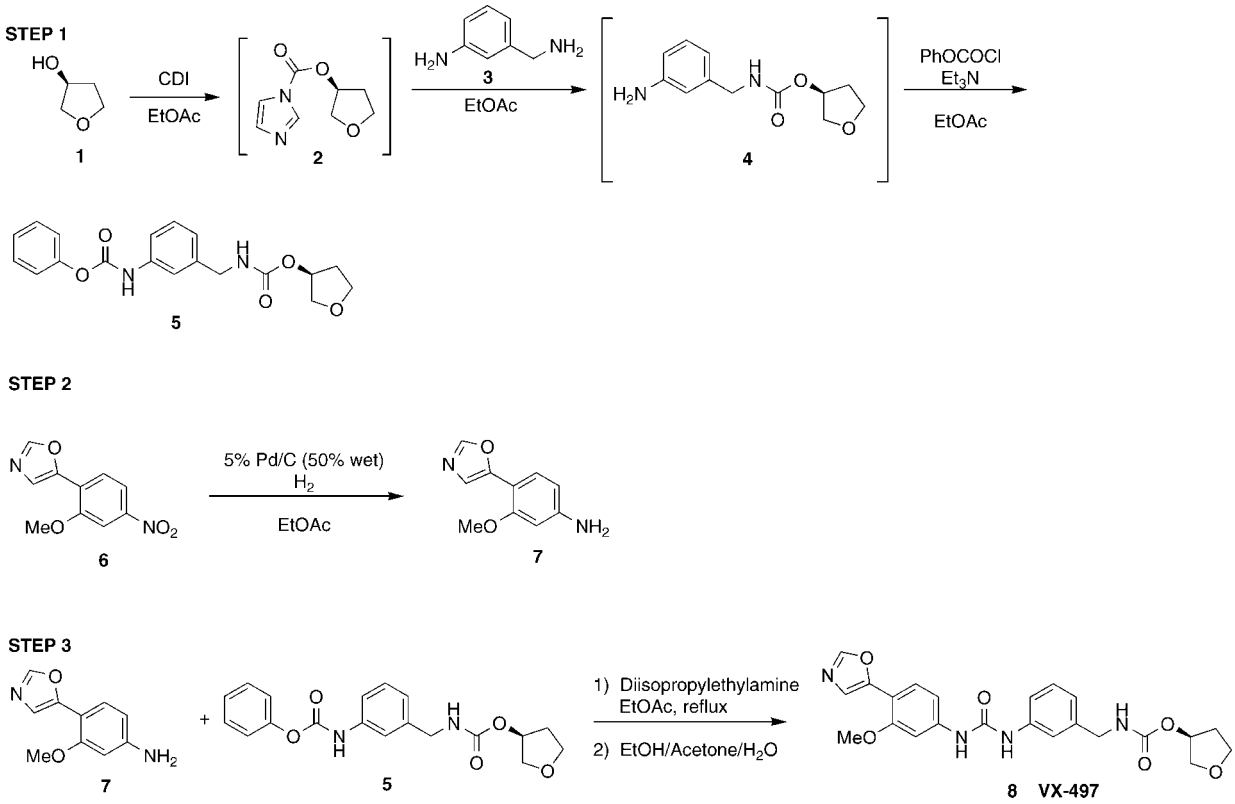
Several possible routes using 3-nitrobenzyl adducts were explored, including two utilizing isocyanate **11** (Scheme 3). Starting with 3-nitrobenzylchloride **10**, treatment with KOCN at elevated temperatures in polar aprotic solvents such as DMF could generate the intermediate isocyanate. Alcohol **1** was added to the reaction mixture, trapping the intermediate to form nitrocarbamate **12**. The carbamate formed in relatively good conversion, but there was significant difficulty in isolating clean product due to the typically poor purity profile of these reactions.

* Author for correspondence. E-mail: adam_looker@vrtx.com.
† Vertex Pharmaceuticals, Inc. Cambridge, MA.
‡ Vertex Pharmaceuticals, Inc. San Diego, CA.
⊥ Sepracor, Inc. Marlborough, MA.
§ Abbott Laboratories, Worcester, MA.
¶ Concert Pharmaceuticals, Inc. Lexington, MA.

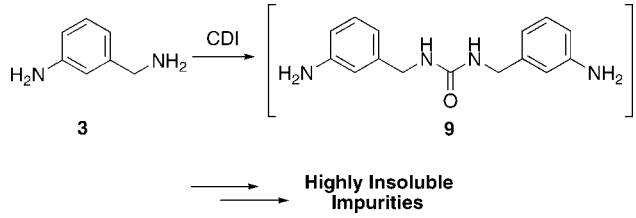
(1) (a) Armistead, D. M.; Badia, M. C.; Bemis, G. W.; Bethiel, R. S.; Frank, C. A.; Novak, P. M.; Ronkin, S. M.; Saunders, J. O. (Vertex Pharmaceuticals, Inc.). U.S. Patent 6,344,465, 2002; *Chem. Abstr.* **2002**, *136*, 151157. (b) Armistead, D. M.; Badia, M. C.; Bemis, G. W.; Bethiel, R. S.; Frank, C. A.; Novak, P. M.; Ronkin, S. M.; Saunders, J. O. (Vertex Pharmaceuticals, Inc.). U.S. Patent 6,054,472, 2000; *Chem. Abstr.* **2000**, *132*, 28897. (c) Armistead, D. M.; Badia, M. C.; Bemis, G. W.; Bethiel, R. S.; Frank, C. A.; Novak, P. M.; Ronkin, S. M.; Saunders, J. O. (Vertex Pharmaceuticals, Inc.). U.S. Patent 5,807,876; *Chem. Abstr.* **2002**, *136*, 151157.
(2) (a) Sorbera, L. A.; Silvestre, J. S.; Castañer, L. M. *Drugs Future* **2000**, *25*, 809. (b) Jain, J.; Almquist, S. J.; Shlyakhter, D.; Harding, M. W. *J. Pharm. Sci.* **2001**, *90*, 625.
(3) Herr, R. J.; Fairfax, D. J.; Meckler, H.; Wilson, J. D. *Org. Process Res. Dev.* **2002**, *6*, 677.

10.1021/op800060h CCC: $40.75
Published on Web 07/18/2008

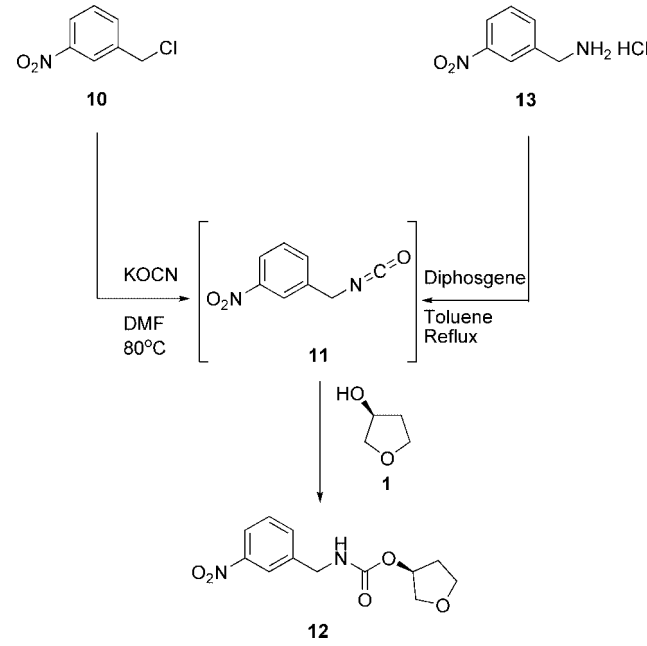
Scheme 1. **Original supply route**



Scheme 2. **Dimer from excess CDI**



Scheme 3. **Use of isocyanate intermediate**



In addition, the thermal stability of **10** at elevated temperature was of concern.[4] Alternatively, attempts to prepare **11** through a phosgenation reaction with commercially available 3-nitrobenzylamine HCl (**13**) using diphosgene at reflux in toluene led to decomposition.

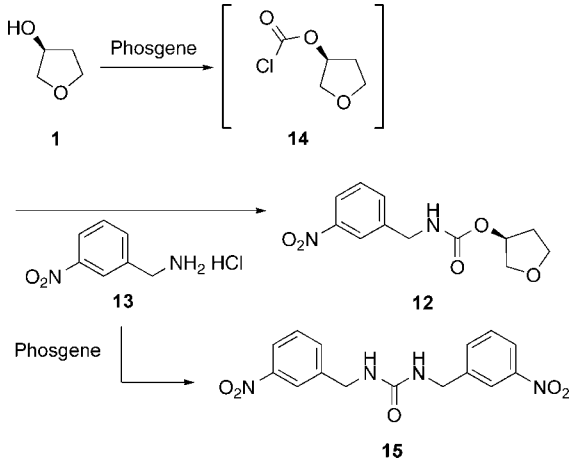
The use of a strategy similar to that of the supply route, but using phosgene in the place of CDI to produce chloroformate **14**, ultimately led to a plant-scale synthesis (Scheme 4). That phosgene could be detected down to low ppm levels by GC analysis using a diethylamine derivitization procedure was a definite advantage to the synthesis.[5] Additionally, excess phosgene could be removed by vacuum distillation if needed, an excellent way to control the byproduct urea dimer **15**. The best conditions for the phosgenation of **1** required the use of 10 mol % pyridine. Adding a stochiometric amount of base to the reaction mixture allowed for the conversion requirement to be met, but it decreased purity. Analytical results indicated that the solution yield of **14** was >98%. The yield dropped to ~95% with a distillation cycle to remove unreacted phosgene; when repeated to meet the phosgene specification of ≤20 ppm, the yield further dropped to ~92%. The major impurity was the easily rejected carbonate **16** (Figure 1). Chloroformate **14** could also be synthesized using the convenient phosgene substitute triphosgene, as this had also been scaled up effectively.[6]

For the coupling of **14** with 3-nitrobenzylamine HCl (**13**), initial investigations made use of nonaqueous conditions: Et_3N in EtOAc, using distilled chloroformate. These conditions afforded a good yield of the product, but required initial free-

(4) Pitt, M. J.; Battle, L. A. *Bretherick's Handbook of Reactive Chemical Hazards*; Urben, P. G., Ed.; Butterworth-Heinemann: Woburn, MA, 1995; *Vol. 1*, p 878.

(5) Steger, J. L.; Coppedge, E. A.; Johnson, L. D. Proceedings of the EPA/A&WMA International Symposium: Measurement of Toxic and Related Air Pollutants; Research Triangle Park, NC, May, 1996.

Scheme 4. **Phosgene as CDI replacement**



basing to achieve a clean purity profile. The main impurity formed was urea dimer **15**.[7] To avoid the need for distillation of **14**, telescoping was investigated. Overall purity of carbamate **12** when using the crude chloroformate **14** was excellent, generating only minor amounts of **15**. For precautionary reasons, a rework was explored in case this critical impurity could not be removed to sufficient levels. A recrystallization from isopropanol effectively removed the dimer below the limit of detection of the analytical method and provided for good recovery.

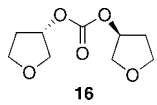


Figure 1. **Major phosgenation impurity.**

Hoping to avoid the extra process of desalting **13**, the Schotten−Baumann[8] reaction was explored. Initial focus was placed on acetate solvents, with isopropyl acetate (IPAc) having emerged as the most promising candidate, providing for **12** in good yield and purity using aqueous Na_2CO_3. The next step was to determine if the conversion of **1** to **14** could be performed in IPAc, thus allowing for an easy transition in the telescoped process. Unfortunately, it was found that IPAc was not stable under the highly acidic conditions: in situ, it formed isopropyl chloroformate leading to newly observed impurity **17** upon coupling (Figure 2).

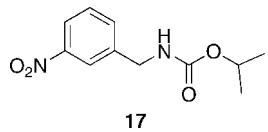
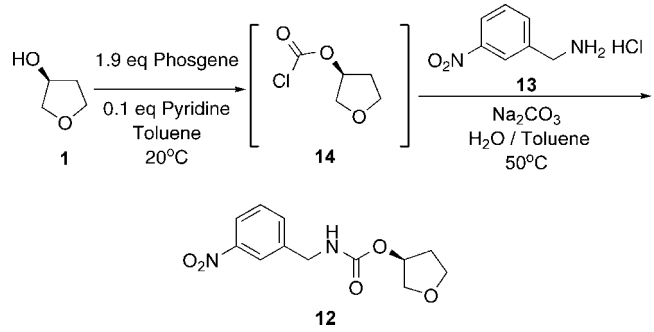


Figure 2. **Isopropyl chloroformate adduct.**

Returning to toluene for both the phosgenation chemistry and the Schotten−Baumann coupling, initial reactions gauging feasibility found this solvent to be highly successful in producing

Scheme 5. **Final conditions for 12**



12 by the telescoped process in 87% yield (96% solution yield) with a purity of 99.80%. The major impurity, as before, was identified as **15**. With these positive results in hand, we focused efforts on the crystallization process. To this end, the parameters of temperature, concentration, and hold times yielded the following results: longer hold times and varied temperatures showed no major effect; more dilute concentrations led to higher rejection levels of **15**. Encouraged by the success of the recrystallization procedure mentioned earlier using isopropanol to reduce **15** to very low levels, it was tried as a cosolvent. Fortuitously, using low concentrations of isopropanol in toluene gave excellent rejection while not sacrificing a significant amount of product to the mother liquor. There were now two ways to control the content of the critical impurity **15** in our process (a) by removing unreacted phosgene through vacuum distillation prior to the coupling and (b) by rejection to the mother liquor in the crystallization process. Process robustness was ensured by stress testing at every major operation. Temperature of the aqueous washes post coupling was the only factor found that needed to be controlled to a strict level: due to the lower solubility of **12** in toluene, product crystallized during the workup if a reaction temperature of 50 °C ± 10 °C was not kept. Production efforts[9] of this optimized step (Scheme 5) were realized in three batches with a total yield of 120.6 kg (84%), and an average purity of 99.89% and 100.0% w/w assay meeting all required specifications. Interestingly, the key impurity **15** was not detected in any batch.

2.2. Preparation of Mixed Bis-carbamate 5. The goal for the plant production of **5** was to telescope the solution of intermediate **4** produced after catalytic hydrogenation directly into the coupling with phenyl chloroformate. A solubility screen showed that **5** had relatively low solubility in IPAc, so the coupling in EtOAc was swapped to IPAc in order to isolate **5**. Development of the catalytic hydrogenation of **12** proved simple, and it was rapidly found that **4** could be reliably formed under standard Pd/C-catalyzed conditions.

Both aqueous and nonaqueous reactions were evaluated for the coupling reaction of **4** with phenyl chloroformate. Compound **5** was obtained in ~70% yield and >99.0% purity using Et_3N in EtOAc, but these anhydrous conditions were not preferred because the reaction mixture was a thick slurry due to the formation of Et_3N HCl.

(6) Greater than 150 kg of **14** was outsourced as the raw material for later campaigns, prepared by the use of triphosgene.

(7) It has been shown in laboratory studies that **14** reacts with HCl to give **1** and phosgene to a minor extent, which goes on to react in situ to form **15**. Thus, free-basing conditions were required to remove the HCl.

(8) (a) Schotten, C. *Ber.* **1884**, *17*, 2544. (b) Baumann, E. *Ber.* **1886**, *19*, 3218.

(9) A phosgene generator utilizing carbon monoxide and chlorine was used to supply scale-up requirements. The phosgene stream was pumped directly into a 630 L glass-lined reactor used for the phosgenation chemistry.

Scheme 6. **Optimized Procedure to 5**

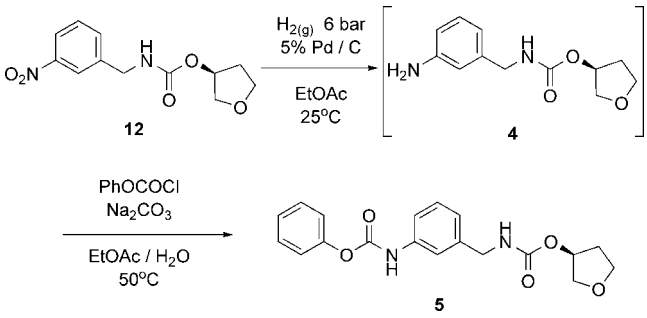


Table 1. **Effect of $NaHCO_3$, Chloroformate and Dosing Time on the Formation of 18**

entry	$NaHCO_3$ (equiv)	PhOCOCl (equiv)	dosing time	time after end of dosing (h)	**18** (%)
1	0.95	1.10	10 min	1	not detected
				24	not detected
2	1.10	0.95	10 min	1	0.11
				24	9.08
3	1.05	1.05	6 h	0	0.14
				14	0.15
4	0	1.05	10 min	1	not detected
				16[a]	not detected
5	1.20	1.10	10 min	1	not detected
				4	not detected
				6	0.04
				20	0.23
6	1.05	1.10	10 min	2	not detected
				18	not detected
7	1.05	1.15	10 min	1.5	not detected
				18[a]	not detected

[a] Homogeneous reaction mixture.

Schotten−Baumann conditions using a biphasic mixture of EtOAc and aqueous Na_2CO_3 were superior to the anhydrous conditions due to complete dissolution of the solids throughout the process and simpler workup procedures. Scheme 6 shows the initial set of reaction conditions from **12** to **5** that produced a >90% yield on a 70 g scale.

Stress testing of the reaction mixture, performed as a prelude to running the reaction in the plant, showed that prolonged exposure of the product mixture to these basic conditions formed urea **18**: a byproduct known from the initial supply route to be difficult to remove (Figure 3).

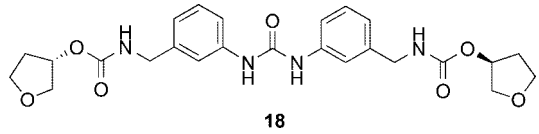


Figure 3. **Dimeric by-product.**

A comparison of aqueous sodium carbonate and sodium bicarbonate in the Schotten−Baumann reaction clearly showed the sodium carbonate system did not allow for enough of a time window following complete conversion with respect to the formation of impurity **18**. This result prompted replacement of sodium carbonate with sodium bicarbonate.

An investigation with the purpose of ensuring a robust process by examining the effect of adding different amounts of base and chloroformate is summarized in Table 1. Of these data, entry 3, where the phenyl chloroformate was added very slowly, was of particular concern because slow addition would be needed in the plant to control the reaction exotherm and the rate of carbon dioxide off-gassing. The data indicated that **18** forms only under basic conditions when excess bicarbonate is present (entries 2 and 5), but not under acidic conditions when excess chloroformate is used (entries 4 and 7).

Entry 5 demonstrates the importance of performing stress testing prior to going to the plant and fully understanding the reaction mechanism of byproduct formation. Urea **18** did not form for the first 4 h after the addition of phenyl chloroformate but then formed at a steady rate. An investigation showed that this window of stability correlated to excess unreacted phenyl chloroformate initially preventing the formation of **18** by reacting rapidly with any **4** liberated by basic hydrolysis (Scheme 7).

The production of relatively high levels of **18** under the 6 h dosing of Table 1, entry 3, was due to the fact that the phenyl chloroformate was added dropwise with a significant time interval between individual drops. During the time between the drops of reagent there was no phenyl chloroformate present to convert **4** back to **5**, and so **18** was formed. Sodium bicarbonate could therefore not be used because any interruption in dosing would lead to unacceptable levels of urea **18** and loss of the batch.

The only viable solution was to perform the reaction under acidic conditions at all times but to avoid the strongly acidic conditions at the end of the reaction that hydrolyzed the ethyl acetate and formed a single phase that could not be worked up. After many buffer systems were considered, it was realized that aqueous sodium sulfate (pH 6.5) should be ideal since the reaction would be acidic throughout and the formation of $NaHSO_4$ would buffer the acidity at the end of the reaction. An additional advantage was that sodium sulfate would not produce any off-gassing, and thus pressure build-up in the reactor would be avoided. In fact, impurity **18** was not produced with an addition time up to 2 h. At the end of each reaction, the pH of the aqueous phases was 0−1, but the phases separated readily even after stirring for 18 h.

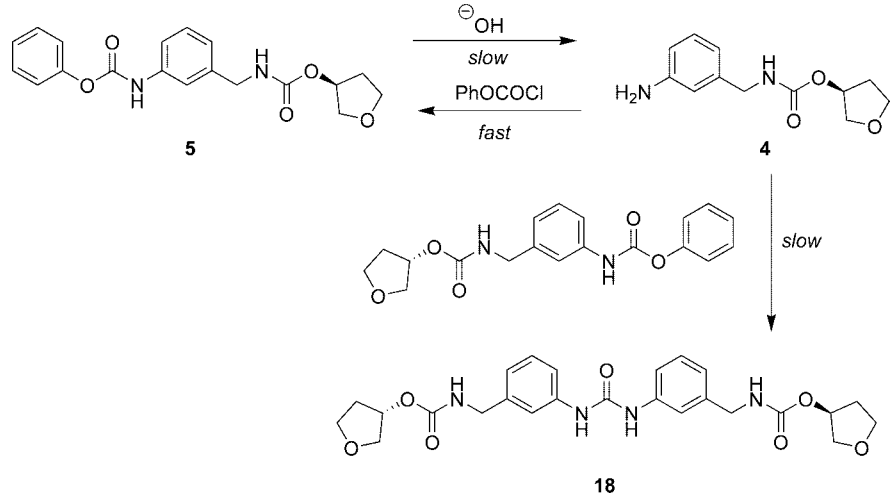
Confident the process was ready for the pilot plant, production of **5** led to a total of 111.4 kg in three batches, corresponding to a yield of 89.8% with an average purity of 100.0% and 99.8% w/w assay meeting all required specifications.

2.3. Synthesis of Penultimate Aniline 7. Development work on the hydrogenation of nitrooxazole **6** focused on a general parameter screening and investigation of the process. Attention was first directed at exploring the solvent and Pd/C catalyst loading, while keeping other variables constant (3 bar H_2, 40 °C).

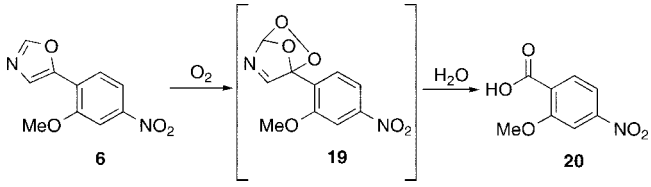
EtOAc and IPAc proved to be excellent solvents for conversion, but neither was acceptable for isolation due to relatively high solubility. Even with a low temperature isolation (−10 °C), the yield of **7** from IPAc was still only ∼60%. This could be increased, though, to >90% upon solvent exchange to heptane, making sure that the final solvent ratio did not exceed 10% IPAc.

Of significant interest was the need for a suspiciously high catalyst loading to achieve good purity. At very high loading (20% w/w Pd/C, dry basis), the reaction performs admirably.

Scheme 7. **Proposed pathway to the formation of 18**



Scheme 8. **Proposed pathway of 6 to 20**



Yet, at <6% there is significant purity reduction. The impurities consisted of the hydroxylamine, nitroso, azobenzene dimer, and to a large extent, the azoxybenzene dimer.[10] However, when the reference standard of **6** was hydrogenated using only 3% catalyst, the reaction performed to give much higher quality material. Extensive experimentation did not identify the cause of this difference between the reference standard and other lots, but it was found that pretreatment with activated charcoal allowed for acceptable processing of **6**. In addition, it was noted that **6** decomposed in solution while in the presence of light (an 80% conversion of **6** to **20** occurred in merely 24 h (Scheme 8)). Literature precedence was found for this oxidative fragmentation.[11] It was proposed that a net 4 + 2 addition of oxygen, followed by rearrangement and then hydrolysis was the likely pathway, similar to what Scarpati and co-workers described. Also noted was a significant rate difference in this oxidative fragmentation between the reference standard (significantly slower) and batches known to reduce poorly under the hydrogenation conditions. Although no direct evidence was found, the unknown impurity that likely poisoned the catalyst could also play a role in promoting such decomposition as well. This charcoal treatment was instituted into the campaign and the future raw material suppliers were notified of these results in an effort to have lots of **6** delivered that met a use test specification. This allowed for a convenient Pd/C loading of 4.5% w/w (dry basis). Finally, after a screening of pressure and temperature was performed, suitable conditions were found that used EtOAc as solvent, 4.5% w/w (dry basis) of 5% Pd/C, 7 bar H_2 pressure, at 40 °C.

(10) For excellent in-depth reading into nitroaromatic hydrogenation chemistry, please see: Augustine, R. L. *Heterogeneous Catalysis for the Synthetic Organic Chemist*; Marcel Dekker, Inc.: New York, 1996; p 473.

(11) Lesce, R. M.; Graziano, L. M.; Cimminiello, G.; Cermola, F.; Parrilli, M.; Scarpati, R. *J. Chem. Soc., Perkin Trans. 2* **1991**, *7*, 1085.

The manufacture of **7** was performed over two stages. The first stage utilized nitrooxazole **6** that was already available and required the need for pretreatment with activated charcoal. The first batch of this stage ran into immediate problems due to the in-line filtration setup for the charcoal. The filtration ran from the bottom of the vessel, through a filter bag, and back into the top of the vessel. Because of the inefficiency of this filtration, not all the charcoal was removed from the batch. When the hydrogenation was performed, the reaction time exceeded the laboratory protocol considerably (the in-process control (IPC) specification was met, but was out of trend with respect to purity). After a laboratory investigation, isolation with one less solvent exchange was undertaken to increase the amount of IPAc during crystallization and therefore give the best chance for impurity removal. In fact, adequate quality material was obtained in 97.9% and 98.3% w/w assay. The yield though was lower due to the higher IPAc content in the liquor (81.5% yield). For the next three batches, the in-line filtration was performed into a receiving tank, thus ensuring that the filtrate was free of charcoal. These batches ran smoother while providing quality material in >99.5% purity and 89% yield. Upon the receipt of newer lots of **6** that had been pretreated by our suppliers, this material processed exceptionally in four further batches to give high quality product in excellent yield (100% purity and 87.6% yield). All future campaigns will use material pretreated with charcoal at the vendor, allowing for smoother cGMP processing. A further understanding of this reduction using React-IR and other online techniques has led to a more robust and cost-effective process. Such work will be reported in due course.

2.4. Coupling and Recrystallization to Provide Merimepodib. The final bond-forming step in the merimepodib (VX-497) process did not require significant changes from the supply route, as a robust procedure with simple heating of **7** and **5** in the presence of base and EtOAc provided for title compound **8** in >90% yield, albeit with the purity lower than specification (>98%). The process itself was straightforward. During heating, all materials went into solution and as the reaction progressed, product crystallized. Cooling and filtration afforded the product in excellent yield. Purification, however, proved problematic. Knowing that API solubility is poor in nearly all common organic solvents, a slurry method originally utilized three

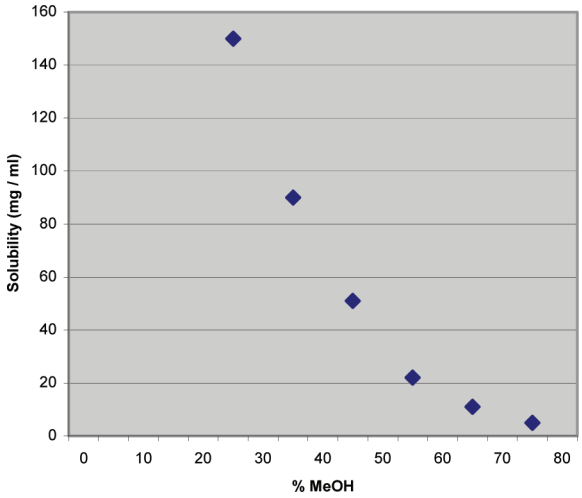


Figure 4. **VX-497 solubility in NMP/MeOH.**

solvents (EtOH, acetone, H_2O) as a quick way to obtain acceptable purity. Most of the development work was focused on the purification (as described in detail below), but some work did aim at identifying the optimal conditions for the coupling procedure.

Optimization of the coupling conditions made use of DoE and screening tools, through which a slight excess of **7** (1.07 equiv with respect to **5**) was recognized as most advantageous. EtOAc was selected as the best solvent for the coupling, but with a higher dilution of 15 vol (with respect to the original conditions of 8 vol) that alleviated stirring problems and gave more consistent reaction times. In a similar manner, diisopropylethylamine was chosen as base.

A true recrystallization procedure was sought to ensure that the isolated API consistently met specification and allowed the batch to be polish filtered in the final step of the process, removing any accumulated inorganic material. An initial solvent screen of merimepodib **8** showed that only highly polar aprotic solvents (such as NMP, DMF, and DMSO) would be suitable for a polish filtration. A screen of solvents and antisolvents indicated that mixtures of NMP (solvent) and methanol (antisolvent) were best able to reject the main impurity, urea **18**. This system also provided for an effective filtration, whereas other systems with NMP showed very poor filtration characteristics.

A solubility curve was determined for the NMP/MeOH system (Figure 4), and a ratio of ~70% MeOH was chosen as the target final concentration for further optimization based on potential recovery. The initial recrystallization procedure charged an NMP solution of **8** into a reactor containing MeOH heated to 65 °C, but this approach led to an uncontrolled crystallization event, as well as being operationally difficult to safely control. An improved procedure dissolved **8** in NMP (5.6 vol) and polish filtered at room temperature, then heated the filtrate to 50 °C. Methanol (8.4 vol) was added and the mixture seeded with **8**. At this point, the mixture was a thin, turbid slurry, but no defined solids could be observed. The mixture was cooled to 20 °C over 6 h, and additional MeOH (2 vol) was added. The mixture was then cooled to 0 °C over 4 h and filtered. This provided excellent purity API (typically 99.9%) in >85% yield, but the level of residual NMP remaining was variable (typically 800−2000 ppm) and higher than ideal: the ICH option 1 limit for NMP is 530 ppm.[12,13] In spite of RC1 recrystallization studies and extensive evaluation of washing conditions and drying temperature, the NMP level could not be reduced below 700 ppm.

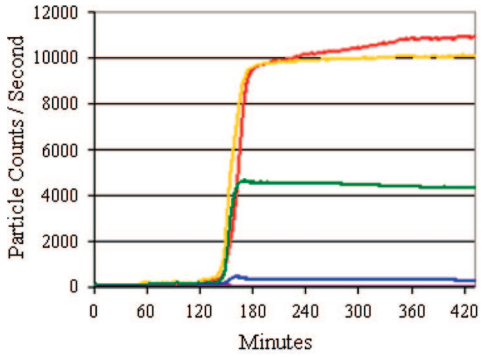
Microscope photos of the solids produced by this procedure showed areas of crystal agglomeration that were thought to trap NMP so that it could not be removed by washing or prolonged drying under vacuum. Agglomerates were thought to form because the solution was highly supersaturated at the time of the primary nucleation event. A more controlled and gradual crystallization was thus developed to favor crystal growth over nucleation during the primary crystallization and to prevent entrapment of NMP. An experiment was performed that reduced the initial methanol charge at 50 °C from 8.4 vol to 4.05 vol in order to reach the cloud point with the minimum volume of antisolvent. Seeds of **8** were added, and the mixture was stirred for 1 h before the remaining 4.35 vol of methanol was added. The mixture was cooled and filtered to afford API with 380 ppm NMP. Microscope images revealed well-defined needles with no agglomeration. Washing was again revisited with this procedure in an attempt to lower the NMP levels even more, but once again, the washing proved to have little or no effect. This study confirmed that low levels of NMP would be produced by a carefully controlled crystallization.

At this stage in the studies, a focused beam reflectance measurement (FBRM available from Mettler Toledo) particle size monitor became available, allowing for key variations of the NMP/MeOH recrystallization to be re-examined. The FBRM data is presented in Figure 5. The *x*-axis is shown in minutes (a scan was recorded every 15 s). The *y*-axis is the number of particle counts per second. The graphs show four groupings of crystal size based on particle chord length: 1−5 μm (red); 10−23 μm (yellow); 29−86 μm (green); 100−251 μm (blue); 292−1000 μm (violet). Since the crystals of **8** are needles, the measured chord length is highly dependent on the crystal orientation, so the data are semiquantitative.

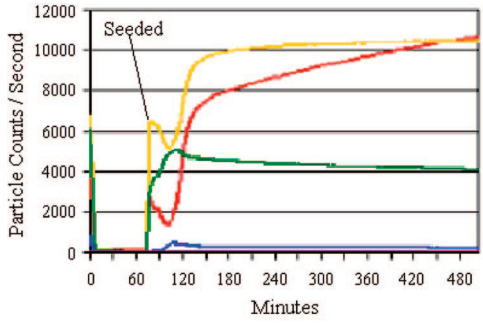
The data presented show that the initial procedure where 8.4 vol of methanol is added in a single portion leads to a single nucleation-controlled crystallization event (Figure 5a). The data in b and c of Figure 5 show that adding either crude API (Figure 5b) or recrystallized API (Figure 5c) as seeds to a mixture with 4.05 vol MeOH leads to slow crystal growth with only a minor difference in the final crystal size distribution. Crude seeds were preferred for the initial plant campaign because recrystallized seeds would have to be prepared in a separate operation, whereas crude material will be directly available from the coupling. The crystal growth phase is particularly well illustrated in Figure 5b where the number of counts for the fine particles (red and yellow lines) decreases in the immediate period after seeding, while the number of counts for the larger particles increases in this same time frame. The API was obtained with NMP levels (200−250 ppm) well within the ICH limit for the two crystallizations performed at low supersaturation.

(12) ICH Harmonized Tripartite Guideline Q3C (R3), revised November 2005, available at http://www.ich.org.

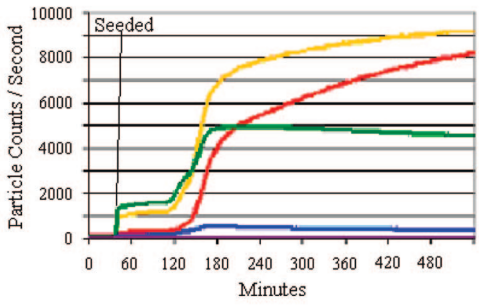
(13) Option #1 (530 ppm for NMP) of the ICH Q3C guideline on residual solvents is based on the assumption of a 10 g daily dose. Option #2 (see section 3.3) allows for the calculation based on actual daily dose.



(a) 8.4 vol MeOH added in single portion



(b) 4.05 vol MeOH with crude API seeds



(c) 4.05 vol MeOH with rxd API seeds

Figure 5. **FBRM data of the crystallization: (a) 8.4 vol MeOH added in single portion; (b) 4.05 vol MeOH with crude API seeds; (c) 4.05 vol MeOH with rxd API seeds.**

The research performed up to this point in identifying optimal recrystallization conditions made use of **8** that was of very high purity (since representative crude API was unavailable at the time). When the optimized procedure was then applied to representative crude API, excellent purity was attained, but the levels of NMP were higher than anticipated (~600 ppm). Presumably the trace impurities that were now present in the test article led to a less perfect crystal lattice resulting in more NMP becoming entrapped.[14] The decision was made to go forward into production with this procedure, as an acceptance limit of 1500 ppm was easily justified by the predicted clinical dose and using option #2 in the ICH guideline for residual solvents.[13]

The production of API performed very smoothly in the plant. A total of 96.5 kg of **8** was produced in four batches, corresponding to a yield of 78.4% over two steps with an average purity of 100.0% and 99.7% w/w assay meeting all required specifications. The average NMP level was 633 ppm.

(14) (a) Mullin, J. W. *Crystallization*, 3rd ed.; Butterworth-Heinemann Ltd.: Oxford, 1993; p 172. (b) Okamoto, M.; Hamano, M.; Igarashi, K.; Ooshima, H. *J. Chem. Eng. Jpn.* **2004**, *37*, 1224.

3. Conclusion

A five-step process was developed for the immunosuppressive drug candidate merimepodib (VX-497, **8**). Through the understanding of critical mechanistic pathways, insight into impurity formation/rejection, and the use of powerful online tools to better gauge process variables, a highly robust synthesis was devised.

4. Experimental Section

4.1. General. HPLC conditions: Analyses were performed using an Atlantis dC_{18} 100 mm × 4.6 mm, 3 μm column (Part #186001337). The mobile phase consisted of a gradient method using A: 0.025% (v/v) phosphoric acid (85%)/water and B: acetonitrile. Assays were determined using high purity reference standards. NMR spectra were collected using a Bruker 499.87 MHz spectrometer. Solvents and reagents were obtained from commercial sources and used as is without further purification, unless otherwise noted. All reactors are standard multipurpose equipment, either glass-lined or stainless steel. All reactions were carried out under an atmosphere of nitrogen.

4.2. Carbamic acid [(3-nitrophenyl)methyl]-(3*S*)-tetrahydro-3-furanyl ester (12). 1 (20.5 kg, 232.7 mol) was charged to a glass-lined reactor, followed by toluene (174 kg). Pyridine (1.82 kg, 23.3 mol) was charged to the system. Phosgene (43.2 kg, 436.8 mol) was charged to the reactor while maintaining a temperature of 20 °C ± 5.0 °C. The reaction was warmed to 25 °C ± 5.0 °C, and stirred for 6 h. 101 kg of solvent was removed by distillation (20 mbar), followed by the addition of toluene (72 kg). Distillation removed 76 kg of solvent (20 mbar). IPC confirms residual phosgene content in solution to be 4 ppm. The reaction mixture was filtered, and the reactor and cake were rinsed with toluene (68 kg). To a separate glass-lined reactor was charged Na_2CO_3 (23.4 kg, 220.8 mol), followed by water (145 kg). This was stirred at 25 °C ± 5.0 °C to attain full dissolution. Charged to this solution was **13** (34.0 kg, 180.3 mol), followed by toluene (262 L). The reaction was heated to 50 °C ± 5.0 °C. To this solution was charged the toluene solution of **14** previously produced, while maintaining a temperature of 50 °C ± 5.0 °C. The reaction was stirred at this temperature for 1 h and sampled for completion. The phases were separated at 50 °C ± 5.0 °C, and the organic phase (top layer) was washed with 1 M HCl (41.4 kg) at this same temperature. The phases were separated at 50 °C ± 5.0 °C, and the organic phase (top layer) was polish filtered into a second glass-lined reactor. The solution was distilled to remove 254 kg of solvent at <100 mbar. The reaction was cooled to 40 °C ± 5.0 °C, and isopropanol (25 L) was charged. The slurry was cooled to 0 °C ± 5.0 °C and stirred 1 h at this temperature. The product was filtered, washed with toluene/isopropanol (32 L: 8 L), and dried under reduced pressure (40 mbar) at 50 °C ± 5.0 °C. The title compound (41.39 kg, 86.7%) was isolated as a white solid (99.78% purity, 99.9% w/w assay): ^{1}H NMR (d_6-DMSO): 8.10 (m, 2H); 7.90 (m, 1H); 7.70 (d, 1H); 7.62 (t, 1H); 5.10 (br, 1H); 4.30 (d, 2H); 3.72 (m, 4H); 2.10 (m, 1H); 1.87 (m, 1H).

4.3. Carbamic Acid [[3-[(Phenoxycarbonyl)amino]phenyl]methyl]-(3*S*)-tetrahydro-3-furanyl ester (5). 12 (31.8 kg, 119.4 mol) was charged to a stainless-steel hydrogenator, followed by 5% Pd/C (50% wet, 0.5 kg, 0.75% dry basis). Inerting with nitrogen was performed to 4 bar. EtOAc (254 L) was charged, and inerting with nitrogen performed again to 4 bar. The reaction was stirred to a setpoint of 25 °C ± 5.0 °C. The reactor was pressurized to 6 bar with hydrogen gas, and stirred at 25 °C ± 5.0 °C for 7 h. After removal of hydrogen pressure, and inerting with nitrogen, the reaction slurry was filtered in-line to a receiver with the aid of an EtOAc (64 L) rinse. To a separate glass-lined reactor was charged water (223.0 kg), followed by anhydrous Na_2SO_4 (37.4 kg, 263.3 mol). This mixture was stirred at 30 °C ± 5.0 °C to attain complete dissolution. The solution of **4** previously made was charged to the solution. The temperature was increased to 50 °C ± 5.0 °C, and phenyl chloroformate (20.9 kg, 133.5 mol) was charged in a continuous fashion over 30 min while maintaining a temperature of 50 °C ± 5.0 °C. The reaction was stirred at this temperature for 4 h, and sampled for completion. The phases were separated at 50 °C ± 5.0 °C, and the organic phase (top layer) washed with water (127.5 kg) at this same temperature. The phases were separated at 50 °C ± 5.0 °C, and the organic phase (top layer) was distilled to remove 240 kg of solvent at <50 °C. Isopropyl acetate (276.2 kg) was charged to the reactor, and this mixture was distilled to remove 277 kg of solvent at <50 °C. Isopropyl acetate (276.3 kg) was charged to the reactor, and this mixture was distilled to remove 280 kg of solvent at <50 °C. The resulting suspension was cooled to 15 °C ± 5.0 °C and stirred for 30 min at this temperature. The product was filtered, washed twice with isopropyl acetate (55.1 kg, 55.3 kg), and dried under reduced pressure (20 mbar) at 45 °C ± 5.0 °C. The title compound (39.2 kg, 91.8%) was isolated as a white solid (100.0% purity, 99.8% w/w assay): ^{1}H NMR (d_6-DMSO): 10.20 (br, 1H); 7.85 (br, 1H); 7.40 (m, 4H); 7.25 (t, 2H); 7.20 (d, 1H); 6.95 (m, 1H); 6.75 (m, 1H); 5.15 (m, 1H); 4.15 (d, 2H); 3.75 (m, 2H); 3.70 (m, 2H); 2.10 (m, 1H); 1.90 (m, 1H).

4.4. Benzenamine 3-Methoxy-4-(5-oxazolyl) (7). 6 (9.98 kg, 45.3 mol) was charged to a stainless-steel hydrogenator, followed by 5% Pd/C (50% wet, 0.91 kg, 4.5% dry basis). Inerting with nitrogen was performed to 3.5 bar. IPAc (87.1 kg) was charged, and inerting with nitrogen performed again to 3.5 bar. The reaction was stirred to a setpoint of 40 °C ± 5.0 °C. The reactor was pressurized to 7 bar with hydrogen gas, and stirred at 40 °C ± 5.0 °C for 5 h. After removal of hydrogen pressure, and inerting with nitrogen, the reaction slurry was cooled to 20 °C ± 5.0 °C. The reaction slurry was filtered in-line to a receiver with the aid of an IPAc (18.2 kg) rinse. The solution was distilled to remove 90 L of solvent at <40 °C. Heptane (68.0 kg) was charged to the reactor, and this mixture was distilled to remove 94 L of solvent at <40 °C. Heptane (68.0 kg) was charged to the reactor, and this mixture was distilled to remove 94 L of solvent at <40 °C. The resulting suspension was cooled to 20 °C ± 5.0 °C and stirred for 1 h at this temperature. The product was filtered, washed with heptane (15.1 kg), and dried under reduced pressure (15 mbar) at 45 °C ± 5.0 °C. The title compound (7.27 kg, 84.4%) was isolated as a yellow solid (100.0% purity, 99.8% w/w assay): ^{1}H NMR (d_6-DMSO): 8.20 (s, 1H); 7.32 (d, 1H); 7.15 (s, 1H); 6.31 (s, 1H); 6.25 (d, 1H); 5.50 (s, 2H); 3.80 (s, 3H).

4.5. Carbamic Acid, *N*-[[3-[[[[3-Methoxy-4-(5-oxazolyl)phenyl]amino]carbonyl]amino]phenyl]methyl]-(3*S*)-tetrahydro-3-furanyl Ester (8). 5 (34.09 kg, 95.7 mol) and **7** (19.50 kg, 102.5 mol) were charged to a glass-lined reactor. EtOAc (461 L) was charged, followed by diisopropylethylamine (12.3 kg, 95.2 mol). The lines were rinsed with EtOAc (50 L). The reaction was stirred at reflux (76 °C ± 2.5 °C) for 13.5 h. The resulting suspension was cooled to 20 °C ± 5 °C and stirred for 1 h at this temperature. The product was filtered, washed with EtOAc three times (133 L each), and dried under reduced pressure (<20 mbar) at 50 °C ± 5.0 °C. The crude title compound (40.2 kg, 91.4%) was isolated as an off-white solid (98.7% purity, 98.3% w/w assay). This material was purified as follows: Crude **8** (28.00 kg, 61.9 mol) was charged to a glass-lined reactor, followed by NMP (147 L). The reaction was stirred at 20 °C ± 5.0 °C for 0.5 h to attain full dissolution. This solution was polish filtered through a 1.0 μm filter to a second glass-lined reactor. This solution was heated to 51 °C ± 5.0 °C. MeOH (99.7 kg) was charged to the solution maintaining a temperature of 51 °C ± 5.0 °C. The temperature was reduced to 48 °C ± 2.0 °C. The reaction was seeded with a slurry of crude **8** (280 g in 1300 g MeOH), followed by a rinse with MeOH (700 g). This slurry was stirred at 48 °C ± 2.0 °C for 15 min. The slurry was cooled to 45 °C ± 5.0 °C, and MeOH (130.7 kg) charged over 1.5 h. The resultant suspension was cooled linearly to 0 °C ± 5.0 °C over 5 h and held at this temperature for 1 h. The product was filtered, washed with MeOH two times (280 L each), and dried under reduced pressure (<20 mbar) at 50 °C ± 5.0 °C. The recrystallized title compound (25.6 kg, 92.2%) was isolated as a white solid (100.0% purity, 99.8% w/w assay): ^{1}H NMR (d_6-DMSO): 8.90 (br, 1H); 8.75 (br, 1H); 8.35 (s, 1H); 7.75 (t, 1H); 7.60 (d, 1H); 7.50 (d, 1H); 7.41 (s, 1H); 7.38 (m, 1H); 7.33 (m, 1H); 7.25 (t, 1H); 7.05 (d, 1H); 6.85 (d, 1H); 5.15 (m, 1H); 4.15 (d, 2H); 3.90 (s, 3H); 3.77 (m, 2H); 3.70 (m, 2H); 2.10 (m, 1H); 1.90 (m, 1H).

Acknowledgment

We acknowledge and thank Dave Turnquist, Chris Sanderson, and Amy Zhang currently, and formerly of Vertex Pharmaceuticals, Inc. for critical analytical support and guidance. We also thank Sara Dilliplane for her help in preparing the manuscript.

Received for review March 15, 2008.

OP800060H