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The Process Development of Ravuconazole: An Efficient Multikilogram Scale Preparation of an Antifungal Agent[1]

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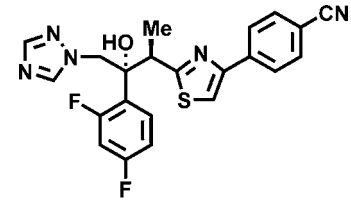
Abstract:

The development of a safe, robust process for the preparation of ravuconazole (1), an antifungal agent, is described. The discovery and development of procedures enabling the efficient synthesis of multikilogram quantities of 1 and the process demonstration through plant scale preparations are presented. A controlled means to prepare a Grignard reagent and utilization of Fourier Transform Infrared spectroscopy (FTIR) monitoring to safely conduct the reaction is featured.

Introduction

Ravuconazole (**1**) is a potent and orally active broad spectrum antifungal agent formerly in development at Bristol-Myers Squibb.[2] This novel thiazole-containing antifungal has the longest half-life of all of the known azole antifungals, and its activity against *Cryptococcus neoformans*, *Candida albicans*, and *Aspergillus* species is particularly well suited to combat opportunistic fungal infections in immunocompromised patients. The continued emergence of resistance against existing antimycotic drugs requires that our industry continue to discover new remedies for these diseases.

This report describes the development of a process for the large-scale preparation of **1** from commercially available methyl-(*R*)-lactate, bromo-difluorobenzene, triazole, and 2-bromo-4′-cyanoacetophenone in a safe, robust, and cost-effective manner. The evolution of the process encompasses three campaigns of increasing sophistication and scale. Although there are several citations regarding the gram-scale preparations of **1** and/or its precursors,[3−5] to our knowledge there are no published accounts of the large-scale preparation of ravuconazole or its intermediates. Our work presents one method for the multikilogram preparation of **1**.



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In addition to communicating an informative description of the scale-up of **1** from the laboratory to the plant, intermediates **8**, **10**, and **14** are precursors of other antifungal agents.[3,4,6−13] This description of their large-scale preparations should facilitate future syntheses of these antimycotic agents and their related analogues.[14] We also describe the use of FTIR spectroscopy for the control of the initiation, preparation, and reaction of a reactive Grignard reagent at pilot-plant scale.[15]

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(1) Aspects of this work were also carried out at Bristol-Myers Squibb's facilities in Princeton, NJ; Candiac, Canada; and Syracuse, NY.

(2) Ravuconazole was licensed from Eisai Co. Ltd. References to earlier studies include: (a) Hata, K.; Kimura, J.; Mike, H.; Toyosawa, T.; Nakamura, T.; Katsu, K. *Antimicrob. Agents Chemother.* **1996**, *40*, 2237–2242. (b) Arikan, S.; Rex, J. H. *Curr. Opin. Invest. Drugs* **2002**, *3*, 555–561. (c) Fung-Tomc, J. C.; Huczko, E.; Minassian, B.; Bonner, D. *Antimicrob. Agents Chemother.* **1998**, *42*, 313–318, and references within. (d) Naito, T.; Hata, K.; Tsuruoka, A. *Drugs Future* **1996**, *21*, 20. (e) Hoffman, H. L.; Ernst, E. J.; Klepser, M. E. *Expert Opin. Invest. Drugs* **2000**, *9*, 593–605.

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(4) Tsuruoka, A.; Kaku, Y.; Kakinuma, H.; Tsukada, I.; Yanagisawa, M.; Nara, K.; Naito, T. *Chem. Pharm. Bull.* **1998**, *46*, 623–630.

(5) (a) Soukup, M. Patent WO 03/002498 A1, *Intermediate halophenyl derivatives and their use in a process for preparing azole derivatives*, Jan 9, 2003; *Chem. Abstr.* **2003**, *138*, 89814. (b) Xu, L.; Muller, M. R.; Yu, X.; Zhu, B.-Q. *Synth. Commun.* **2009**, *39*, 1611–1625.

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(9) (a) Tasaka, A.; Tamura, N.; Matsushita, Y.; Kitazaki, T.; Hayashi, R.; Okonogi, K.; Itoh, K. *Chem. Pharm. Bull.* **1995**, *43*, 432–440. (b) Tasaka, A.; Tsuchimori, N.; Kitazaki, T.; Hiroe, K.; Hayashi, R.; Okonogi, K.; Itoh, K. *Chem. Pharm. Bull.* **1995**, *43*, 441–449. (c) Oida, S.; Tajima, Y.; Konosu, T.; Nakamura, Y.; Somada, A.; Tanaka, T.; Habuki, S.; Harasaki, T.; Kamai, Y.; Fukuoka, T.; Ohya, S.; Yasuda, H. *Chem. Pharm. Bull.* **2000**, *48*, 694–707. (d) Kitazaki, T.; Ichikawa, T.; Tasaka, A.; Hosono, H.; Matsushita, Y.; Hayashi, R.; Okonogi, K.; Itoh, K. *Chem. Pharm. Bull.* **2000**, *48*, 1935–1946.

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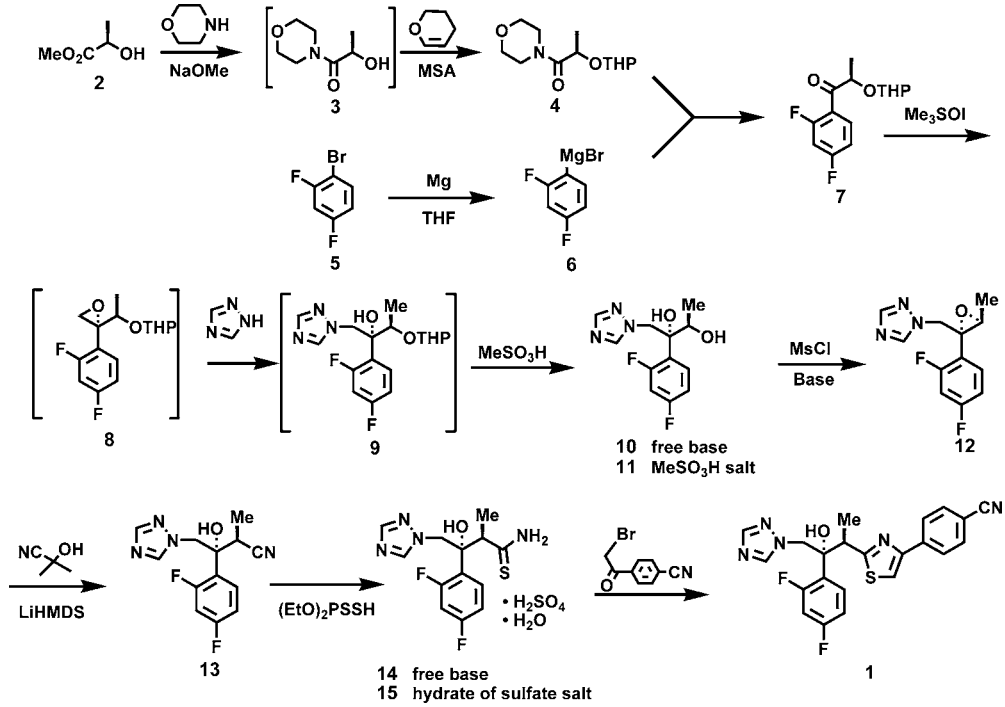
Scheme 1. **Process R&D synthesis of ravuconazole**



Results and Discussion

The optimized multikilogram route for the preparation of **1** is shown in Scheme 1. The existing preparative route was first evaluated to provide a basis for a synthetic development plan.[16] As such, the sequence of intermediates in Scheme 1 was determined to be an expeditious starting point for small scale preparative work and process development. While this established chemistry satisfied API (active pharmaceutical ingredients) material demands for early development activities, alternate approaches to **1** were explored to select the most advantageous and scalable process. While the tertiary alcohol of **1** allows installation of the three branches of the nascent drug in differing sequential order,[17] all of the alternative routes to **1** investigated proved inferior to the established approach. Consequently, instead of focusing on these unsatisfactory synthetic approaches, this report will discuss the process development of the route described in Scheme 1.

Upon evaluation of the initial route, some elements required for large-scale preparations were already in place, including readily available starting materials and reagents. Some of the challenges included the following: recurring column chromatography, lack of crystalline intermediates, the preparation of a reactive Grignard reagent, malodorous reagents and side products (diethyl dithiophosphate and hydrogen sulfide), and the use of dangerous reagents and solvents (lithium hydride, sodium hydride, diisopropyl ether, diethyl ether, and acetone cyanohydrin). The early goals of the developmental program were to circumvent the most undesirable operations and reagents, develop means to safely conduct others, and consider alternative protecting groups or salt forms to facilitate processing. The path taken to address these issues is described below.

Early Process Development Leading to the First Ravuconazole Campaign. *Preparation of the Arylpropanone 7.* At the initiation of process development, the immediate goal was the rapid production of 1−2 kg of **1** for toxicology studies and a phase I clinical trial. The focus of the development team was to quickly enable the current synthesis to satisfy API material demands.

The morpholine amide **4**, or a close analogue, was targeted as the first isolated intermediate. Flexibility in the choice of the intermediate existed, as neither the amide functionality nor the alcohol protecting group would be retained in the final product. The amide functionality would only need to serve as a good electrophile for the Grignard coupling to prepare **7**. Methyl (*R*)-lactate (**2**) was inexpensive ($12/kg) and, thus, was a clear choice as starting material. Early experiments focused on finding a crystalline analogue of the oil **4** by varying the alcohol's protecting group. We believed that the diastereomeric nature of **4** led to the noncrystallinity[18] and substitution of a nonchiral protecting group would remedy this. This expectation was realized as trityl, adamantane carboxylic ester, and *tert*-butyldiphenylsilane provided crystalline intermediates; however

(15) For other examples, see: (a) am Ende, D. J.; Clifford, P. J.; DeAntonis, D. M.; SantaMaria, C.; Brenek, S. J. *Org. Process Res. Dev.* **1999**, *3*, 319–329. (b) Stares, K. E.; am Ende, D. *Pilot Plants and Scale-up of Chemical Processes II*; The safe scale-up of a Grignard reaction using an in-situ reaction monitoring technique; Hoyle, W., Ed.; Special Publication - Royal Society of Chemistry: 1999; pp 62−80; *Chem. Abstr.* **130**, 313820. (c) Wiss, J.; Lanzlinger, M.; Wermuth, M. *Org. Process Res. Dev.* **2005**, *9*, 365–371.

(16) Privileged technology transfer documentation from Eisai Co., Ltd.; Sept 26, 1996.

(17) For example, flutriafol has been prepared by different sequences of appending the various pieces: Worthington, P. A. *Recent Developments in the Chemistry of Azole Fungicides*; Proceedings of 1984 British Crop Protection Conference, Pests and Diseases; BCPC Publications: Croydon, U.K., 1984; Vol. 3, pp 955−962.

(18) As support for this hypothesis, note that all of the THP-protected intermediates in a penem synthesis are noncrystalline while the remaining molecules are all crystalline. The authors thank a referee for this reference: Gala, D.; Steinman, M.; Jaret, R. S. *J. Org. Chem.* **1986**, *51*, 4488–4490.

they were poor substrates for the subsequent Grignard reaction. The triethylsilane, benzyl, 4-bromobenzyl, 4-nitrobenzyl, MOM, and MOP protecting analogues were not crystalline and were also inferior to **4** in regards to yield. The diastereomeric mixture of morpholine amide **4**, in spite of its lack of crystallinity, was retained for further development.

The initial preparations of **3** were adapted without notable deviation from the published process and consisted of the reaction of excess morpholine with methyl lactate at 85 °C for 30−60 h.[7] Workup and concentration yielded the amide **3** in 79−82% yields at up to 750 g scale. The product contained up to 17 wt % of morpholine by weight, which tended to be difficult to remove by further distillation. However its presence was inconsequential for further processing. The subsequent use of excess dihydropyran with catalytic toluenesulfonic acid or methanesulfonic acid in methylene chloride produced a diastereomeric mixture of **4** in 92−100% unpurified yields at up to 1140 g scale.

Several approaches to the preparation of intermediate **7** (or closely related structures) are known, including the Friedel−Crafts acylation of 1,3-difluorobenzene,[19,20] enzymatic resolution of a racemic acetate ester,[21,22] the opening of a chiral aryl epoxide,[23] lyase-catalyzed carboligation of difluorobenzaldehyde,[24] and α-hydroxylation using camphorsulfonyl oxaziridine,[25] but the organomagnesium route to **7** illustrated in Scheme 1 had been most thoroughly established.[26] It proceeded from the preparation of the Grignard reagent of bromo-2,4-difluorobenzene (**6**) and its subsequent coupling with **4**.[7,27,28] In our laboratories, the formation of the Grignard reagent initiated reproducibly, and the generation of **6** only required 1 h at 40−45 °C. Subsequently, the solution was cooled to −20 °C and **4** was added. A workup hydrolyzed any remaining Grignard reagent and converted the tetrahedral Grignard intermediate[29] to the ketone **7** in >95% crude yield as a light brown oil. The oil could be purified by distillation, but this led to significant losses (62−67%) and was not retained. This procedure performed adequately in the laboratory at up to 870 g scale; however significant changes in operational procedure were required before multikilogram scale could be considered.

*Preparation of the Diol **10***. The second phase of the synthesis of **1** required the introduction of the triazole with concomitant formation of the tertiary chiral alcohol and subsequent deprotection of the secondary alcohol. This strategy utilized epoxidation of **7**[3,4,7,19,21,30] as a convenient means to introduce the methylene fragment of **1** and to provide a substrate for the nucleophilic attack by the triazole ring. This sequence also sets the second chiral center, effectively originating all stereogenic centers from methyl (*R*)-lactate.

The epoxide **8** was formed from ketone **7** via treatment with the Corey−Chaykovsky reagent.[31] Trimethylsulfoxonium iodide was added in portions to a suspension of sodium hydride (NaH) in DMSO and THF to form the sulfur ylide, followed by the addition of the substrate **7**.[7] The adjacent chiral center induced an ∼4:1 stereoselectivity for the formation of the oxirane. The diastereomeric ratio was improved later by crystallization in the downstream chemistry. Upon reaction completion, the mixture was quenched into water and extracted with ethyl acetate. The triazole anion formed by reaction with NaH in DMF was introduced, opening the epoxide to yield the monoprotected diol **9**. After the THP group was cleaved by pyridinium *p*-toluenesulfonate, the diol **10** was obtained as a orange solid.[7,8,19b,21,23,27] Recrystallization from diethyl ether reduced impurities and increased the de to >99%.[7] The purging of impurities and diastereomers which had accumulated over six telescoped steps largely accounted for the low overall yields (38−41%). Following this protocol, five batches totaling 1125 g of **10** were completed in a rapid and reproducible manner. This completed the construction of the western half of ravuconazole and left only introduction of the cyanobenzene substituted thiazole side chain to complete the synthesis.

Preparation of Ravuconazole. Appending the side chain required sequential epoxide formation, ring opening with cyanide, conversion to the thioamide, and ultimately condensation with a bromo-cyano-acetophenone to form the thiazole ring. This sequence commenced with formation of the mesylate **16**, itself the final intermediate to another antifungal: SM 8668/Sch 42427.[19b] As an alternative to isolation, the mesylation reaction mixture could be immediately treated with sodium hydroxide to form the epoxide **12** in good yield and purity. This synthetic sequence was demonstrated to be superior to previous routes to **12**, which required chromatographic purification.[6,7,10,19a,32]

This reaction sequence continued with epoxide ring opening with a choice between lithium cyanide (LiCN)[33,34] or diethy-

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(24) Demir, A. S.; Şeşenoglu, Ö.; Eren, E.; Hosrik, B.; Pohl, M.; Janzen, E.; Kolter, D.; Feldmann, R.; Dünkelmann, P.; Müller, M. *Adv. Synth. Catal.* **2002**, *344*, 96–103.

(25) Gala, D.; DiBenedetto, D. J.; Mergelsberg, I.; Kugelman, M. *Tetrahedron Lett.* **1996**, *37*, 8117–8120.

(26) Also, the trityl analogue of **7** has been made by Grignard addition to 2-pyridylthioester; see ref 30.

(27) Singh, I. P.; Sidhu, I.; Palak, B.; Micetich, R. G. U.S. Patent 6133485, *Asymmetric synthesis of 2-aryl-1-substituted butane-2,3-diols*, Oct 17, 2000; *Chem. Abstr.* **1999**, *131*, 286254.

(28) The analogous reaction but using benzyl as a protecting group: Crosby, J.; Bailey, K. D.; Monteith, M. J. U.S. Patent 6362376; *Process for the preparation of 2-hydroxyalkyl halophenones*; March 26, 2002; *Chem. Abstr.* **1999**, *131*, 310447.

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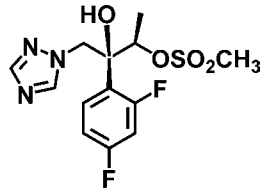
(30) Kaku, Y.; Tsuruoka, A.; Kakinuma, H.; Tsukada, I.; Yanagisawa, M.; Naito, T. *Chem. Pharm. Bull.* **1998**, *46*, 1125–1129.

(31) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.

(32) For a different route to **12** via a Payne rearrangement, see: Konosu, T.; Miyaoka, T.; Tajima, Y.; Oida, S. *Chem. Pharm. Bull.* **1992**, *40*, 562–564.

(33) Tsuruoka, A.; Negi, S.; Yanagisawa, M.; Nara, K.; Naito, T.; Minami, N. *Synth. Commun.* **1997**, *27*, 3547–3557.

(34) Naito, T.; Hata, K.; Kaku, Y.; Tsuruoka, A.; Tsukada, I.; Yanagisawa, M.; Toyosawa, T.; Nara, K. U.S. Patent 5648372, *Antifungal Agents, and Compositions*, July 15, 1997; *Chem. Abstr.* **1995**, *123*, 340144.



16

laluminum cyanide.[3,4,34,35] In consideration of a future pilot plant campaign, the handling of LiCN was considered a less hazardous operation of the two;[33] however it would still require *in situ* generation, as LiCN was not commercially available. The optimized reaction conditions required the reaction of 3 equiv of LiH with a slight excess of acetone cyanohydrin. After the *in situ* generation of LiCN, the epoxide was charged and the reaction was held at 65 °C until the generation of cyano alcohol **13** was complete (~17 h). White crystals of high purity **13** (>99 HPLC area %) in 87−89% yield were obtained after water quench, extraction, and recrystallization from isopropanol. While this procedure provided pure material in good yield, it was apparent that significant development would be required for safe production on multikilogram scale.

The conversion of a nitrile group into a thioamide appeared to be straightforward,[36] but the majority of literature procedures necessitated the use of hydrogen sulfide (H_2S). The preparative synthesis of **14** required treatment of **13** in refluxing aqueous isopropanol with diethyl dithiophosphate, followed by a workup and finally a recrystallization from diisopropyl ether.[4] A similar preparation had also been reported in which water was the only solvent.[3] Our first preparations of **14** were made in aqueous isopropanol, and two lots totaling 570 g were produced in >99% HPLC area % purity in 76−77% yield. This process was adequate for the production of moderate amounts of material, in spite of the inherent safety limitations to this route.

Reflux of the thioamide **14** with 2-bromo-4′-cyanoacetophenone in ethanol rapidly formed the thiazole ring to produce ravuconazole **1**.[3,4] Workup involved the addition of saturated sodium bicarbonate solution followed by collection of crystalline **1** by filtration. To achieve high API purity and the desired polymorph, recrystallizaion of **1** from aqueous ethanol was required. Yields of 78−81% were obtained over four batches, the largest producing 440 g (99 HPLC area %).

This completed the first ravuconazole campaign. The material satisfied clinical requirements and allowed development of analytical methods for future preparations. Perhaps most importantly, the first campaign provided familiarity with the chemistry and identified critical areas which required improvement for further scale-up. Subsequent work would address concerns related to safety, cost, equipment limitations, and elimination of impractical operations (i.e., stripping to dryness) with the objective of transforming an expedient laboratory process into a practical one for plant operation.

Second Campaign, First Pilot Plant Experience. The first campaign made extensive use of kilolab facilities, which would not suffice for the 10−100 kg batches anticipated in the next campaign. The new goal was to translate this 5−12 L reactor experience into a pilot plant campaign to satisfy larger requirements for additional clinical studies and pharmaceutical development.

Improvement of the Preparation of Amide 3. The kilolab preparation of **3** utilized the reaction of excess morpholine (3 equiv) with methyl lactate at 85 °C for 30−60 h to produce ~90% yields of product which still contained morpholine.[7] A purer product and a reduction of the morpholine charge would be desirable improvements to the process. The addition of 15 mol % of sodium methoxide catalyst[37] permitted the morpholine charge to be reduced nearly 3-fold to 1.03 equiv. Under these modified conditions, the reaction proceeded to completion at ambient temperature in only 4−6 h instead of 30−60 h. After dilution with THF, the bases were directly sequestered by a slurry of Amberlyst-15 sulfonic acid resin. After the resin was filtered, the filtrate was concentrated to remove most of the methanol. The typical yield range was 89−92% of the amide solution at up to 2 kg scale.

This modified procedure and all other process knowledge up to diol **10** were transferred to a vendor who used this information to prepare 30 kg of diol **10**. By contracting with a vendor the project team was able to focus its resources exclusively on the more challenging chemistry involved in handling cyanide, forming the thiazole ring, and controlling the purity and particle size of the API.

Preparation of Thioamide. During the early phases of development for the conversion of the diol **10** into epoxide **12**, either THF or MTBE was used as solvent for the mesylation and epoxide ring formation. Both solvents were effective, but MTBE systems produced thick slurries and THF systems required repeated extractions during the aqueous workup to achieve high recoveries. Mixing the two solvents 1:1 retained the advantages of each without incorporating the disadvantages. The product **12** could be precipitated from solution upon addition of hydrocarbon antisolvents; however the yield never exceeded 75%. A higher yielding approach used an aqueous ethanol crystallization. The optimized recovery of **12** consisted of a solvent exchange of the worked-up reaction mixture to ethanol followed by the addition of three volumes of water. This process was transferred into the plant with no further modifications and produced 78−86% yields of **12** in 98 HPLC area % (99.8−99.9% ee) in batches ranging from 55 to 71 kg.

For the purposes of preparing **13** during the first campaign, lithium cyanide (LiCN) was generated *in situ* from lithium hydride (LiH) and acetone cyanohydrin.[38] Unfortunately, sodium or potassium cyanide, whether in organic solvents (slow reaction rates) or with phase transfer catalysis in biphasic systems (emulsions during workup), did not perform effectively when substituted for LiCN. However, lithium hexamethyldisilazane (LiHMDS) may be purchased in solution, and this more convenient and safer base was substituted for LiH. A minimum

(35) The cyano-alcohol **13** may also be prepared *via* treatment of the corresponding aldehyde with hydroxylamine-*O*-sulfonic acid.[3,30]

(36) Walter, W.; Bode, K.-D. *Angew. Chem., Int. Ed. Engl.* **1966**, *5* (5), 447–461.

(37) (a) Baltzly, R. B.; Berger, I. M.; Rothstein, A. A. *J. Am. Chem. Soc.* **1950**, *72*, 4149–4152. (b) For a similar but noncatalytic ester to morpholine conversion: Al-Masoudi, N. A.; Al-Soud, Y. A. *Nucleosides, Nucleotides Nucleic Acids* **2002**, *21* (4−5), 361–375.

(38) (a) Livinghouse, T. *Org. Syntheses*, Coll. Vol. 7, **1990**, 517−522; Vol. 60, **1981**, 126−131. (b) For a recent and convenient means to prepare LiCN, see: Ciaccio, J. A.; Smrtka, M.; Maio, W. A.; Rucando, D. *Tetrahedron Lett.* **2004**, *45*, 7201–7204.

of 2 equiv of base was required to avoid formation of unsaturated nitrile impurities.

The concentration of the reaction mixture was a critical parameter for reaction rate and completion. Commercially available 1.65 M LiHMDS solutions required further concentration to ~2.5 M to attain reaction completion once all the components were combined. Following the addition of acetone cyanohydrin, the epoxide **12** was charged as a 1 g/mL THF solution and the reaction was complete after 16 h at reflux. The reaction could be completed in only 5−6 h by further concentration of this reaction mixture, but the resulting thick slurry presented problems for efficient scale-up. Once the reaction was complete, the mixture was cooled to 0 °C and the pH was adjusted to 9−10 by the subsurface addition of HCl over 3 h, during which time the product crystallized. We assume any hydrogen cyanide (HCN) within the reactor headspace thus had time to redissolve during the slow addition of acid and subsequently reform the lithium salt. Attempts to directly precipitate the product by the addition of water led to the appearance of a second phase. If aqueous isopropanol was charged instead, the reaction mixture was homogenized but losses to the mother liquor did not appreciably increase. The yield was further optimized to 88−92% by removal of THF by distillation and cooling the mixture to −15 °C for at least 1 h.

While this chemistry functioned well in the laboratory, a reconsideration and review of safe techniques for the large-scale handling of cyanide was essential, as extractions, washes, solvent exchanges, and other operations allowed numerous opportunities for exposure to cyanide-containing streams. In addition to personal protective equipment and the design of operations that sequestered the mixtures within reactors as much as possible, the HCl charge was preweighed to eliminate the possibility of an excessive charge that would raise HCN to dangerous levels. Further control of HCN was accomplished by monitoring the pH for all reaction streams to maintain basicity (pH >8) at all times. These safety precautions ensured the safe execution of this step in the plant. Upon isolation, the purity of **13** was typically high (>99 HPLC area %). This process scaled up well, and 44 kg were made in 90% yield and 99.6 HPLC wt %.

This modified workup, consisting of pH adjustment with HCl, isopropanol addition, solvent exchange, and cooling, replaced the potentially hazardous extractions, washes, and drying operations of the original process and reduced the hazardous waste produced by at least 75%. The revised protocol also provided safe handling procedures for acetone cyanohydrin and cyanide-containing reaction streams on a multikilogram scale.

Examination of alternative methods for transforming nitriles to thioamides, such as those utilizing sodium sulfide or $P_{10}S_4$, showed them to be low yielding and impurity-laden for the preparation of thioamide **14**. So while diethyl dithiophosphate was unpleasant and difficult to handle, the existing chemistry was clearly the best choice among several unattractive options.[36] The use of diethyl dithiophosphate also produced H_2S, which was flammable, toxic, and even more malodorous. H_2S originated from the reaction of water with the side-product $(EtO)_2POSH$, as no gas was produced if the reaction was conducted in neat isopropanol. Unfortunately, isopropanol was not a viable reaction solvent, since the rate of reaction became much slower and the formation of side products interfered with the subsequent crystallization of **14**. To address the H_2S associated safety issues, its rate of formation was measured to better understand and control this reaction. It was determined that if diethyl dithiophosphate was added to an aqueous isopropanol slurry of **13** preheated to 80 °C, as compared to heating the reaction mixture subsequent to the addition of diethyl dithiophosphate, the maximum rate of H_2S off-gassing dropped by ~70%. The rate further decreased as the reaction proceeded to completion.[39] Both reactions had similar profiles and required 7−8 h to reach completion. One additional advantage to maintaining a high addition temperature was that the production of H_2S was addition controlled. By modulating the diethyl dithiophosphate charge, a greater level of control over potential spikes in off-gassing was instituted. This offered a safer operation with the same overall reaction time as the existing process.

Upon reaction completion, the cooled mixture was diluted with water and ethyl acetate before it was rendered basic. If the organic phase was concentrated to an oil and triturated with diisopropyl ether, crystalline free base gradually formed. As diisopropyl ether could not be used on scale and no other useful solvent combinations were discovered, salts of **14** were considered for the purpose of ease of isolation. Sulfuric acid cleanly formed either the sulfate or hydrogen sulfate salt, depending upon the number of equivalents charged. The partial hydrate of the latter salt (**15**) was selected for scale-up.

Once 1 equiv of sulfuric acid had been charged, workup proceeded by concentration of the slurry by azeotropic distillation. Isolation was concluded by the addition of an antisolvent, MTBE, and cooling to 5 °C to crystallize **15**. While the initially isolated crystal was a hydrate, the drying conditions ultimately determined the final water content. Water content typically was reduced to <1 wt % if active drying protocols were present (i.e., azeotropic distillation, oven drying); however exposure to atmospheric moisture for more than 2 h would allow **15** to recapture sufficient water to form a monohydrate. In general, the oven-dried solids were analyzed for weight percent and then shielded from moisture to avoid further hydration. The varying quantity of water would not be a critical process parameter, as the next step was conducted in aqueous ethanol.

At multikilogram scale, the lab procedures scaled up as predicted. A nitrogen sweep above the reactor contents was adjusted to carry the H_2S headspace contents directly to scrubbers charged with bleach and then to a thermal oxidizer. No H_2S was detected by the monitors in the processing area except momentarily during sampling operations (15 ppm). The yields were 87−91% (≥99.9 HPLC area %) at up to 58 kg of **15** scale.

(39) If diethyl dithiophosphate and 100 g of **13** in aqueous isopropanol were heated to 85 °C over 25 min, off-gassing of H_2S reached a peak level of 550 mL/min (6 L total H_2S off-gassing), after which the rate decreased as the reaction proceeded to completion. If diethyl dithiophosphate was added instead at 2.6 g/min over 2 h to an aqueous isopropanol slurry of **13** heated to 80 °C, the rate of off-gassing was reduced, peaking at only 180 mL/min after ~60% had been added.

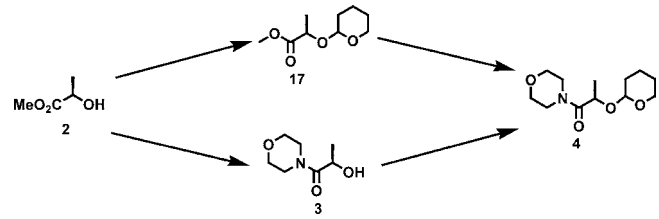
The last step was conducted in the same manner as that for the previous campaign: thioamide **15** and bromocyanoacetophenone were heated in 95% ethanol for 2 h to complete the cyclization. The use of hydroxide and bicarbonate bases for the removal of the acids in the mixture produced insoluble hydrogen sulfate salts and contaminated the isolated product. However, if triethylamine (TEA) was used to adjust the pH to 4, the TEA salts remained soluble and no further purification was required. The pH adjustment required the solution temperature to remain at >55 °C to maintain **1** in solution. A cooling ramp to 20 °C allowed **1** to crystallize smoothly to afford a 86−90% yield (>99.5 HPLC area %). In this manner, satisfactory potency, purity, and impurity benchmarks were realized, but particle size range control derived from either traditional crystallization approaches or milling failed to attain the requirements for formulation: $D_{90} = \leq 10\ \mu$m. This motivated the development of sonic impinging jet crystallization,[40] now an established technique for small particle formation.[41]

The ability of two impinging liquid jets of solution to produce high intensity micromixing and supersaturation leads to rapid crystallization within the small mixing volume at the intersection of the jets.[42] Since new nuclei are continuously forming in this area, small particle sizes are achieved. When solutions of **1** were so treated, the majority of the crystals formed by the impinging jet process were in the 3−20 μm range, still above the desired range. This crystallization method was further refined by placing a sonicator probe in the same plane as the impinging jets. After experimentation with factors such as sonication intensity, the angle between the jets, temperature, and solution concentration, the method was successfully tuned to produce particles in the 2−5 μm D_{90} range in 97−98% recovery. The impinging jet crystallization also improved the purity of **1**. For instance, multihundred gram batches of 99.4 HPLC area % material were raised to 99.7−100.0%.

Effective control of the particle size was demonstrated reproducibly in the plant. Typically **1** was redissolved into hot aqueous ethanol. While a single operation was possible by charging the solution derived from the workup directly into the sonication apparatus, it was still beneficial from an impurity perspective to proceed in a stepwise fashion and conduct a traditional crystallization prior to impinging jet recrystallization. Ultimately, a total of seven 20−41 kg batches of **1** were made in 85−91% yields with high quality (2−8 μm particle size, 99.75−99.80 HPLC area %, 99.9% de, and 99.97% ee).

Development of a Commercial Process; The Third Campaign. Promising clinical results at this stage of pharmaceutical development mandated a third campaign with much higher supply needs. This plant campaign was approached with the goal of developing a robust and durable[43] commercial process to enable phase III operations and so that multiple vendors could be utilized for future campaigns.

Scheme 2. **Competing routes from methyl lactate to 4**



Improved Workup and Isolation of Functionalized Lactate. Amide **4** had been prepared[7,27] from methyl (*R*)-lactate over two steps: amide formation and THP protection, with flexibility in the order of the steps[44] (Scheme 2). Both sequences were re-examined for comparison of process attributes such as yield, quality (both chemical and chiral), and crystallinity. When the amide formation was completed first, **3** was converted to **4** by reaction with dihydropyran *via* methanesulfonic acid (MSA) catalysis in an 80% overall yield. In comparison, the THP ester **17** was the intermediate if the steps were reversed but forming **4** in an identical 80% overall yield. However, the amidation rate of **17** was slow, and the use of sodium methoxide as an amidation catalyst led to a slow epimerization of **17**. Once the amidation was complete, the product failed to meet the acceptance criterion of ≥98% ee. In comparison, since intermediate **3** was stable (loss of only 1.3% ee on scale compared to the ee of the methyl lactate charge) under the optimized reaction conditions, this pathway was selected.

A reconsideration of the acid quench workup eliminated the use of the ion-exchange resin as a base scavenger. While the resin had simplified the large-scale processing, it also presented several disadvantages, including swelling of the resin, a vigorous exotherm, and difficulty in removing the exhausted resin beads from the reactor. An improved process resulted when the reaction was instead quenched with methanolic hydrogen chloride, generated *in situ* from acetyl chloride and methanol. Following this quench, the volatiles were exchanged for THF by distillation, and the resulting solution of alcohol **3** was directly converted to **4**. The MSA-catalyzed ketalization with dihydropyran was ≥95% complete within 12−24 h. Unfortunately **4** was exceedingly water-soluble, and it partitioned into both wet THF and the aqueous phase during workup. This issue could be minimized by the use of a wash solution which contained sufficient sodium bicarbonate to simultaneously quench the MSA and form salts, leading to an increase in polarity and pH that allowed an acceptable partition without requiring a cosolvent. The THF was subsequently exchanged for MTBE to dry the solution (water content <0.1%), and then dry THF was recharged for improved reactivity in the subsequent coupling to **7**. If desired, 70−80% of **4** that remained in the aqueous phase could be recovered by methylene chloride extraction. This optimized process was transferred to the plant and proceeded as expected producing 187 kg of **4** in 78% overall yield from methyl lactate in 98% ee.

(40) Lindrud, M. D.; Kim, S.; Wei, C. U.S. Patent 6302958; *Sonic impinging jet crystallization apparatus and process*, Oct 16, 2001; *Chem. Abstr.* **2000**, *133*, 140214.

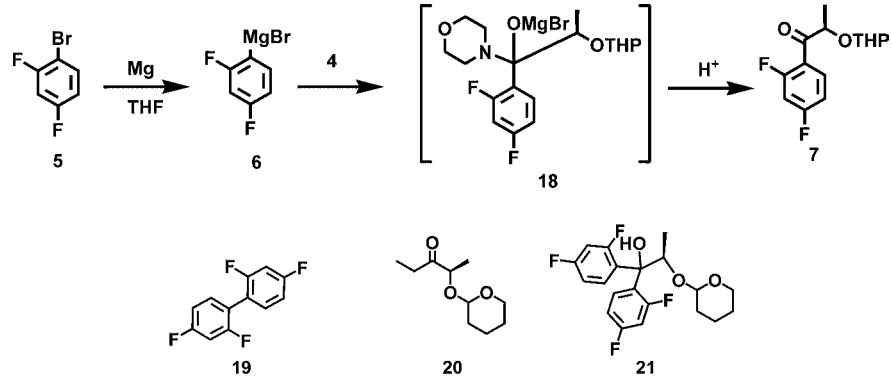
(41) Gleeson, M.; Kim, S.; Kientzler, D. Kiang, S. WO Patent 041970 A1, *Process for making sterile aripiprazole of desired mean particle size*, May 12, 2005; *Chem. Abstr.* **2005**, *142*, 451843.

(42) Midler, M.; Paul, E. L.; Whittington, E. F.; Futran, M.; Liu, P. D.; Hsu, J.; Pan, S.-H. U.S. Patent 5314506, *Crystallization method to improve crystal structure and size*, Nov 18, 1991; *Chem. Abstr.* **1994**, *121*, 117827.

(43) Zhang, T. Y. *Chem. Rev.* **2006**, *106*, 2583–2595.

(44) Mizuno, Y.; Yamane, T.; Ikeuchi, M. WO Patent 98/39305, *Crystalline form of a bis 1,2,4-triazole compound*, Sept 11, 1998; *Chem. Abstr.* **1999**, *129*, 230729.

Scheme 3. **Synthesis of 6**



These modifications removed the need to isolate two noncrystalline intermediates, avoided a problematic workup, and retained the advantages established in the earlier process work generating a safe, convenient, and scalable process to **4**.

Grignard Preparation at Plant Scale Facilitated by Use of FTIR Monitoring. Although the use of Grignard reagents are a well-known synthetic methodology,[45−47] problems in large-scale preparation, such as irreproducible or difficult to detect initiations, difficulty in monitoring the rate of its formation,[48] limitations in cooling highly exothermic reactions, and the dangers of handling pyrophoric metals pose limitations. All these challenges were successfully managed in the plant-scale preparation of arylpropanone **7**.

Laboratory examination established that when the solvent was dry (<800 ppm water) the formation of the Grignard reagent could be initiated quickly at 10−15% concentrations of the aryl bromide. However the temperature window for this reaction was narrow. If the formation was conducted at >40 °C or if the resulting solution was stored for extended periods at >0 °C, the impurity content would become unacceptable with the main constituent being the tetrafluorobiphenyl **19**.[49,50] In consideration of the inherent exothermicity of the metal insertion (380 kJ/mol Mg), the difficulty in charging the aryl bromide safely, and the need to utilize the unstable solution of **6** immediately, we decided to explore alternatives to the classical Grignard reaction.

A promising approach appeared to be the infrequently utilized Barbier modification, in which the Grignard reagent **6** is prepared in the presence of the electrophile **4**.[51] This would effectively circumvent the stability issues of **6** as its existence would be transitory. Magnesium metal and **4** were mixed, and the solution was dried via a charge of 1.05 equiv (relative to residual water) of ethyl magnesium bromide.[52] Azeotropic distillation had been ineffective as a drying protocol. The subsequent addition of 10−15% of **5** at 30 °C led to inconsistent initiation of the metal insertion,[53] and the subsequent reactions to form **7** were typically incomplete and unsatisfactory. This route was abandoned.

Instead, the traditional two-step process was re-examined. Once 0.9 equiv of magnesium turnings (relative to **5**) were slurried in THF and the water content was ascertained, the ethyl Grignard drying protocol described above was conducted. If 10% of the total aryl bromide charge was now added at 30 °C, the insertion reaction reproducibly initiated in <15 min. Trace ethyl Grignard remaining from the water quench step may be responsible for the dependable initiations. The Process Safety and Evaluation group determined that the aryl bromide level should not exceed 15% of the total charge at any point of the addition period to limit the potential adiabatic temperature rise to 33 °C. This still allowed a reasonable charging period and fully met our requirements for a safe reaction.

The excess of aryl bromide led to more consistent reactions and ensured the consumption of all of the metal, minimizing the risk of residual highly pyrophoric magnesium remaining in the workup. These reaction conditions led to a reproducible 90% conversion (>99% theoretical yield) of aryl bromide into Grignard reagent **6**. Unreacted aryl bromide **5** was innocuous during the subsequent chemistry and was removed during the solvent exchange to DMF.

Real-time monitoring[54] of the reactions (initiation, reaction of **6**, and formation of the coupled intermediate **18**) comprising this step would be critical to process safety. Sampling and external analysis is quantitative but can be slow. We were pleased to find that the aryl bromide **5**, Grignard reagent **6**, starting material **4**, and the unquenched intermediate **18** could all be quantified by FTIR,[15,55] allowing real time data collection and process control for initiation of Grignard formation, Grignard formation rate, and the coupling reaction with the amide. In particular, initiation would be difficult to ascertain in

(45) *Grignard Reagents, New Developments*; Richey, H. G., Jr., Ed.; J. Wiley & Sons: Chichester, 2000.
(46) *Handbook of Grignard Reagents*; Silverman, G. S., Ed.; Marcel Dekker: New York, 1996.
(47) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995.
(48) Pesti, J. A.; Downard, J. A.; Lauritsen, M. D.; Kauffman, G. S.; Bryant, W. M., III; Huhn, G. F.; Arnett, J. F.; Yule, R. E.; Segretario, J.; Nelson, K. A.; Gorko, E. F.; Page, G.; Lloyd, L. M.; Olson, R. E.; Barnum, C. S.; Mrowca, J. J. *Heterocycl. Chem.* **1998**, *35*, 249–255.
(49) Stability studies in THF indicated a loss of 2.l wt % of Grignard intermediate per day at 0 °C and 11.1 wt %/day at ambient temperatures. This may be partially due to elimination of the ortho fluorine and magnesium halide to lead to reactive benzyne species.[63]
(50) Dickerson, D. R.; Finger, G. C.; Shiley, R. H. *J. Fluorine Chem.* **1973/1974**, *3*, 113–116.
(51) (a) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18–30, and ref 32 therein for an example of an amide as electrophile. (b) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; pp 921−922. (c) A Pfizer group has employed a similar Barbier modification to prepare plant-scale quantities of an aspartyl protease inhibitor precursor: Urban, F. J.; Jasy, V. J. *Org. Process Res. Dev.* **2004**, *8*, 169–175.
(52) The amide insertion side product **20** arising from ethyl Grignard addition to **4** was not significant under these conditions.
(53) There are other established means to accomplish plant-scale initiations of Grignard reagent preparations: Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 906–910.

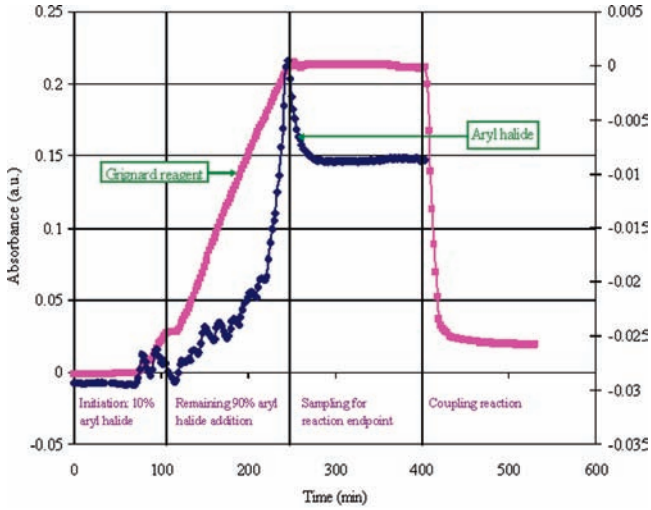


Figure 1. **FTIR results for conversion of 5 into 6.**

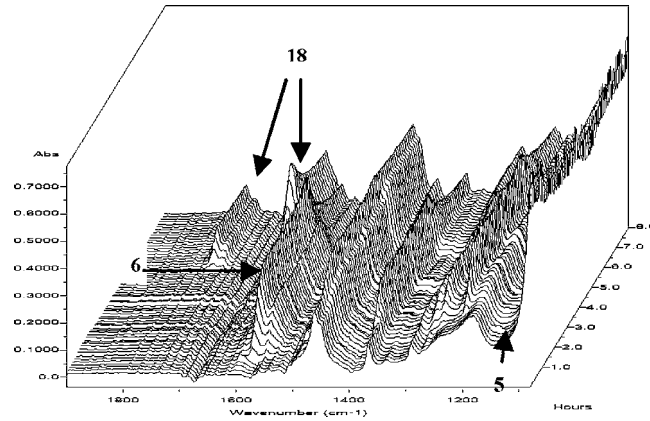


Figure 2. **Waterfall plot of 6 preparation and reaction with 4 to form 18.**

the plant by other means. Similarly, the level of aryl bromide **5** could be monitored and thus maintained at nonhazardous levels by prior calibration of the signal generated by the presence of 10% of the aryl bromide charge, the preagreed safety limit to minimize chances for a runaway reaction. FTIR utilization scaled up exactly as expected in the plant. Once the addition of **5** began, the 1582 cm^{-1} signal which had been correlated to the Grignard intermediate grew within 5 min, concomitantly with a slow rise in temperature. The aryl bromide was then metered in while the IR frequencies representing **5** and **6** were monitored. The aryl bromide addition rate was decreased whenever **5** approached the 10% threshold or if the temperature approached 50 °C. In practice, no batch ever exceeded 45 °C if the addition was metered over 2−2.5 h. The use of FTIR monitoring permitted the safe and efficient completion of five batches of Grignard reagent formation and subsequent coupling (Figures 1 and 2).

Once the Grignard reagent formation was complete, amide **4** was charged directly into the Grignard solution to form the putative aminol intermediate **18**. As calorimetry had established the heat of reaction as 47 kJ/mol with a adiabatic temperature rise of only 20 °C, the reaction temperature was easily controlled at <35 °C over the 15 min charging period. The conversion of amide **4** into **18** was completed during an aging period at 40 °C. FTIR also effectively detected the reaction end point by marking when the Grignard signal no longer decreased. For a quantitative confirmation, a GC sample demonstrated that the product/starting material ratio was >40:1.

The quench of the aminol alkoxide **18** to form **7** was accomplished by the transfer of the reaction mixture into cold aqueous acetic acid (<25 °C) which permitted both control of a very exothermic quench (adiabatic temperature rise of 67 °C) and the assurance of rapid hydrolysis of any remaining Grignard reagent or magnesium metal. The quench was addition controlled. Not surprisingly, 2−7% of the product consisted of the double-addition impurity **21**, which is known to be a traditional problem for Grignard reactions with carboxylic acid derivatives.[56] However, this was still preferable to charging the quench solution into the reaction mixture as the content of **21** then rose to 10−15%. This is explained as any unreacted Grignard reagent would have had a higher probability of reacting further with any freshly formed ketone **7** under those conditions.

The workup required the presence of ethyl acetate to produce an adequate phase separation. Sufficient acetic acid was present in the quench solution to produce a final pH of 5−6, sufficiently low to both minimize base-catalyzed epimerization and avoid the precipitation of voluminous magnesium salts, but high enough to retain the THP group. The subsequent water wash required the addition of heptane for efficient phase separation since the magnesium salts, which had assisted the separation of the first phase separation from the THF-rich organic phase, were no longer present. The resulting solution was azeotropically dried by distillation with ethyl acetate to lower the water content from 3−4% to ≤0.1%.

Once the solution was dry, a final solvent exchange to DMF permitted the formation of a 28−56 wt % solution of **7**, optimal for the subsequent epoxidation reaction. The preparations were carried out reproducibly and safely in the plant on a 390 mol scale to produce 355 kg of **7** in 79% overall yield and 98.0−98.5% ee over five batches. The consideration of safety factors and use of FTIR allowed an efficient implementation of a potentially dangerous reaction into the plant.

Optimization of Reaction Conditions To Allow Plant Production of Diol ***11.*** The use of sodium hydride in DMSO and a poor 4:1 diastereomeric selectivity during the epoxide formation of **8** required remediation before it could be considered an efficient process.[57] To avoid hydride bases, oxirane formation using phase transfer catalysts was explored first, as milder bases are usually used in combination with such catalysts.[58] Modestly higher diastereomeric selectivity (up to 7:1) was achieved at

(54) (a) *Guidance for industry PAT - A framework for innovative pharmaceutical development, manufacturing and quality assurance:* US Food and Drug Administration, Rockville, MD, USA (2004), http://www.fda.gov/cder/guidance/6419fnl.pdf. (b) *Process Analytical Technology (PAT) Initiative*: U.S. Food and Drug Administration, Rockville, MD, USA (2005). http://www.fda.gov/cder/OPS/PAT.htm. (c) Tummala, S.; Shabaker, J. W.; Leung, S. S. W. *Curr. Opin. Drug Discovery* **2005**, *8*, 789–797.

(55) A detailed description of this use of PAT will appear separately: Leung, S. Manuscript in preparation. For additional discussion of Grignard reaction safety using real time monitoring, see ref 62.

(56) Huston, R. C.; Bailey, D. L. *J. Am. Chem. Soc.* **1946**, *68*, 1382–1383.

(57) Although others report higher (>7:1) ratios of the desired threo to erythro isomers; see ref 21.

(58) *Phase-Transfer Catalysis* ; Halpern, M. E., Ed.; ACS Symposium Series 659; American Chemical Society: Washington, DC, 1996.

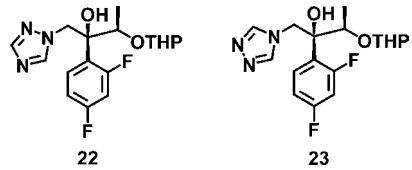


Figure 3. **Impurities produced during triazole opening of 8.**

the cost of reaction rate (~24 h for completion) and difficult workups. A variety of other bases (alkali HMDS, sodium *tert*-butoxide and *n*-butyl lithium) and solvents were screened. The best combination of diastereoselectivity and yield resulted from the use of sodium *tert*-butoxide (NaO*t*Bu) in DMF, producing an improved yield (88%) and diastereomeric ratio (8.6:1).

The original conditions for the conversion of **8** to the monoprotected diol **9** required triazole and sodium hydride.[7,21] As in the previous step, less hazardous bases (potassium carbonate, lithium hydroxide, NaO*t*Bu, and sodium triazole) were screened in DMF.[59] All provided yields of >88% if heated at 80−90 °C for 6−8 h but still created the impurity **22** (arising from the undesired epoxide diastereomer of **8**) and the symmetrical triazole regioisomer impurity (**23**), both identified by independent synthesis. The symmetrical triazole regioisomer **23** is an ubiquitous impurity to this class of reactions due to the well-known propensity of triazole to produce regioisomeric products when employed as nucleophiles.[48] All efforts to limit the formation of **23** to <4% were unsuccessful, but this level still compared favorably with triazole openings of similar epoxides.[60] Presumably an impurity incorporating both of these undesired moieties also formed during this reaction but at undetectable levels. The majority of these impurities were removed by the subsequent workup.

Since the epoxide opening with 1,2,4-triazole could also be carried out in DMF using a NaO*t*Bu solution in THF, it appeared that telescoping the epoxidation and triazole opening into a single process operation would be possible. It was possible to combine all reagents for both steps and select the desired transformation by varying the temperature. Once 1.9 equiv of a solution of 30 wt % NaO*t*Bu in THF were added to trimethylsulfoxonium iodide and triazole in DMF, the ylide formed within 30 min and the subsequent addition of **7** led to a clean conversion to **8**. Once the epoxidation was complete, heating the reaction mixture to 80−90 °C now activated the triazole to regioselectively attack the oxirane to form alcohol **9**. Following workup, the overall isolated yields for these two steps were 80−85%.

Removal of the THP protecting group by the standard means of pyridinium *p*-toluenesulfonate yielded a hydrophilic brown oil that was difficult to isolate upon aqueous workup. Purification required trituration in diethyl ether and usually silica gel chromatography to obtain acceptable product quality. We found that hydrochloric acid, methanesulfonic acid, sulfuric acid, or *p*-toluenesulfonic acid would also cleave the protecting group cleanly, but isolations remained inefficient and impurities remained entrained. A salt was sought to improve purity and to streamline the workup and isolation.

The hydrochloride salt was prepared by adding 6 N HCl in isopropanol to a dried and concentrated toluene solution of **9**; however the crystalline salt was problematic to isolate and unstable to drying. In comparison, the MSA salt **11** could be easily crystallized in high recovery from isopropyl acetate, isopropanol, or a mixture of the two solvents and was a stable salt after isolation. When MSA was charged slowly to a isopropyl acetate/isopropanol solution of **9**, the precipitation of the crystalline salt signaled that the deprotection was complete. If further purification was required following workup, isopropanol/heptane recrystallization would raise the purity from 96 to 99.7+ HPLC area % in 86−88% recovery while retaining only 0.2% of the symmetrical triazole regioisomer corresponding to **23**. Although the properties of both the HCl and the MSA salts were comparable in terms of overall yield and purity, the ready isolation and robustness of the MSA salt led to its further development.

In the plant, trimethylsulfoxonium iodide, 1,2,4-triazole, DMF, and NaO*t*Bu were stirred for 30 min, and a solution of **7** in DMF was charged. The epoxidation reaction was complete within 30 min, and reaction mixture was heated to 90 °C to initiate triazole addition to the epoxide. Complete conversion to **9** required 9−12 h and typically formed 11−12% of **22** and 6−7% of regioisomer **23**, among additional smaller impurities. Following workup, the subsequent addition of MSA cleaved the THP group. The resulting slurry was cooled, and filtration yielded 254.3 kg of **11** over five batches. The overall yield was 49%[61] (95 HPLC area % and 98.5% ee). The salt formation was not only an effective means for isolation of **11** but also efficient in rejecting the high levels of diastereomeric and regioisomeric impurities formed in this process, as well as those impurities that had been carried along during the several steps telescoped into this reaction.

The campaign and further project development was terminated upon the completion of this step. While it was disappointing to interrupt a successful and interesting campaign, the remaining steps had been adequately demonstrated at pilot plant scale in the previous campaign; thus a completed preparation of ravuconazole at multikilo scale had been established.

Conclusions

At the onset of this work, there existed numerous challenges to a large-scale preparation of ravuconazole. Practical solutions, such as identifying salts to permit isolation of crystalline intermediates, eliminating numerous purifications/isolations by telescoping steps, developing safe means to handle potentially hazardous chemicals or operations, and utilizing a novel crystallization technology to produce small particles of bulk drug, were put in place to provide a viable process. In particular, the use of in-line FTIR monitoring allowed the safe formation of a Grignard reagent and its subsequent reaction. This body

(59) The hazards of combining DMF and NaH are well established: *Handbook of Reactive Chemical Hazards*; Bretherick, L., Ed.; Butterworths: London, 1985; p 1133.

(60) See ref 48 and refs 17−19 therein.

(61) The last batch is not included in the yield range reported, as an incomplete epoxidation lowered the purity.

(62) (a) Kryk, H.; Hessel, G.; Schmitt, W. *Org. Process Res. Dev.* **2007**, *11*, 1135–1140. (b) Wiss, J.; Ermini, G. *Org. Process Res. Dev.* **2006**, *10*, 1282–1286.

(63) (a) Mazza, D. D.; Reinecke, M. G. *J. Org. Chem.* **1988**, *53*, 5799–5806. (b) Newman, M. S.; Dali, H. M.; Hung, W. M. *J. Org. Chem.* **1975**, *40*, 262–264. (c) Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. *J. Org. Chem.* **1984**, *49*, 4518–4523.

of work has created a means to prepare multikilogram batches of ravuconazole and advanced intermediates for related compounds with a potential for further scale-up to commercial quantities

Experimental Section

(*R*)-1-Morpholino-2-(tetrahydro-2*H*-pyran-2-yloxy)propan-1-one (3). Methyl (*R*)-lactate (100 kg, 961 mol) and MTBE (300 kg) were heated to 60 °C and distilled until all of the MTBE had been removed (final volume ~109 L). The solution was cooled to 10 °C and treated with morpholine (86.2 kg, 1000 mol) at 10−20 °C. The batch was cooled to 5 °C, and a 25 wt % solution of sodium methoxide in methanol (31.2 kg, 149 mol) was added at <5 °C. The mixture was warmed to 20 °C and sampled for reaction completion by GC after 16 h (residual lactate: 1.18 HPLC area %). The batch was titrated to a pH of 6.8 using a solution of methanolic hydrogen chloride which had been previously prepared by mixing methanol (84.7 kg) at 5 °C with acetyl chloride (14.6 kg, 186 mol). The neutralized reaction mixture was stirred 30 min and filtered through a 10 μ polypropylene cloth bag to remove salts. The reactor was rinsed with THF (50 kg) to facilitate removal of the solids and charged to the reaction mixture. The filtrate was heated to 60−65 °C, and the methanol was exchanged for THF (total of 880 kg of THF added) while maintaining a constant volume (residual methanol relative to **3** was 3.9 GC A%). This solution was carried into the next step without further isolation. An analytical sample of **3** was purified by chromatography on silica gel (20→50% ethyl acetate/heptane) to yield a colorless oil: HRMS calcd M − H: 158.0832; obsd. M − H: 158.0824. IR (neat, thin film) 3419 (broad), 1644, 1114 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) 4.43−4.48 (m, 1H), 3.61−3.83 (m, 7H), 3.42−3.44 (m, 2H), 1.33 (d, 3H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 175.1, 67.5, 67.1, 64.8, 46.0, 43.3, 21.8. See ref 7 for a laboratory scale preparation and further spectral data.

(2*R*)-1-Morpholino-2-(tetrahydro-2*H*-pyran-2-yloxy)propan-1-one (4). A mixture of the solution containing **3** prepared above and 3,4-dihydro-2*H*-pyran (122 kg, 1450 mol) at 5 °C was treated with MSA (4.6 kg, 48 mol) in two portions while maintaining the temperature at <10 °C. The reaction mixture was warmed to 20−25 °C and held for 12 h. GC at this point indicated 4.5 A% of **3** remaining. The reaction was washed sequentially with the following solutions: 4% aqueous sodium bicarbonate solution (150 kg), water (75 kg), and twice with 17% aqueous sodium chloride solution (220 kg, 440 kg). The aqueous streams were held for later rework. The organic phase was diluted with MTBE (400 kg), and water as a distilled mixture of MTBE, THF, and water was removed at 65 °C. This protocol was repeated until a total of 1000 kg of MTBE had been charged (water content at end <0.1%). THF (400 kg) was added, and the distillation continued until the MTBE was removed as noted by the attainment of a batch temperature of 65−70 °C. The reaction mixture was sampled for wt % **4** (75 GC wt %), THF (170 kg) was charged, and the solution was sent through a 5 μ filter to produce 407.2 kg (78.4% yield) of a 45 wt % solution. The purity of **4** relative to the non-THF components was 82.5 HPLC A % (ee = 98%). Additional **4** was recovered by extraction of the aqueous washes. Two batches were individually extracted with methylene chloride (750 kg). The combined organic phases were distilled down to ~250 L at 50−55 °C jacket temperature to reduce the water level to ≤0.5%. THF (400 kg) was added and distilled at 55−65 °C until the water level was ≤0.05%. THF was added to produce a total of 274.8 kg of a 35 wt % solution of **4** for a 77% recovery of **4** from the aqueous washes. No detectable methylene chloride remained. An analytical sample was purified by silica gel chromatography (10→50% ethyl acetate/heptane) to yield a colorless oil (>98% ee, >99 GC area %). HRMS calcd M + H: 244.1524; obsd. M + H: 244.1544. IR (neat, thin film) 2941, 1655, 1116, 1032 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) mixture of diastereomers, 4.51−4.69 (m, 2H), 3.86−3.88 (m, 1H), 3.61−3.73 (m, 8H), 3.47−3.50 (m, 1H), 1.70−1.84 (m, 3H), 1.52−1.56 (m, 3H), 1.41 (dd, J = 7.0, 18.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) mixture of diastereomers, 171.5, 171.1, 99.0, 97.7, 72.3, 70.4, 67.4, 67.3, 67.2, 64.2, 63.0, 46.3, 46.2, 42.9, 42.8, 31.3, 31.0, 25.7, 25.6, 20.7, 19.7, 19.0, 17.6. See ref 7 for a laboratory scale preparation and further spectral data.

2*R*-1-(2,4-Difluorophenyl)-2-(tetrahydro-pyran-2-yloxy)-propan-1-one (7). A stainless steel reactor with a recirculation loop was assembled. The loop inlet was equipped with a protective 40 mesh screen, and a Mettler FTIR instrument with a 1" diameter flowcell equipped with a DeComp IR sensor installed on a recirculation loop and running on ProcessIR was installed.[55] THF (303 kg) was charged followed by magnesium turnings (9.30 kg, 383 mol) *via* a solids addition funnel. A 1 M solution of ethyl magnesium bromide (2.25 kg, 1.16 eq versus water in solution) was charged followed by a THF rinse (10 kg) of the line. After 1 h, bromo-2,4-difluorobenzene (9.15 kg, 47.4 mol) was charged at 29−32 °C over 5 min, followed by a THF rinse (1 kg). Initiation was observed by FTIR before the entire charge was complete. Additional bromo-2,4-difluorobenzene (69.7 kg, 361.2 mol) was charged at <32 °C over 2.5 h, so that the FTIR-monitored aryl bromide levels never exceeded 10% of the total aryl bromide charge. After a THF rinse (1 kg) of the charging container, the reaction mixture was aged at 25−27 °C until the Grignard level was no longer increasing as monitored by FTIR (30 min). A solution of **4** (30.0 wt %, 257.3 kg, 317.3 mol) was charged over 20 min at <35 °C, and the reaction aged at 35 °C for 18 min. FTIR monitoring indicated no further decrease of the Grignard content at this point, and a quenched sample analyzed by HPLC displayed 1.0 area % of **4** relative to **7**. The reaction mixture was transferred over 40 min into a glass-lined reactor containing acetic acid (41.5 kg, 691 mol) in water (207 kg) while maintaining the temperature at <18 °C. The lines were rinsed with THF (35 kg), and the hydrolysis was completed by warming the mixture to 25 °C over 30 min. Ethyl acetate (207 kg) was charged, and the mixture was agitated and allowed to settle for 30 min. The phases were separated, the organic phase was diluted with heptane (85 kg), and the solution was washed with water (206 kg). The solution was vacuum distillated at 0.1 bar and 15−20 °C to dry the solution to <0.1% by KFT. Additional ethyl acetate (398 kg) was charged, and the mixture was distilled down to a volume of ~125 L (final water content = 0.08%). Dimethylformamide (90 kg) was charged, and volatiles were removed by distillation at 22−50 °C at 0.5 bar

to attain the following levels of volatiles: ethyl acetate (<5 A %), heptane (<1 A %), THF (<1 A %), bromodifluorobenzene (<2 A %), and KF < 0.5%. After 4 h, the final ethyl acetate content by GC was 0.004%. This produced 122.7 kg of solution (56.7 wt % **7**, 81.1% yield, 98.0% ee). An analytical sample was prepared by silica gel chromatography using ethyl acetate/heptane. HRMS calcd M + H: 271.1146; obsd. M + H: 271.1145. ^{1}H NMR ($CDCl_3$, 500 MHz) mixture of diastereomers, 7.85−7.92 (m, 1H), 6.96 (dd, J = 8.6, 7.8 Hz; 1H), 6.79−6.90 (m, 1H), 5.08 (q, J = 7.1, 2.4 Hz; *S* diast. of THP), 4.86 (qd, J = 6.8, 1.2 Hz; *R* diast; 1H if combined with previous signal), 4.75 (t, J = 3.6 Hz; *R* diast.), 4.65 (t, J = 3.6 Hz; *S* diast.; 1H if combined with previous signal), 3.82−3.91 (m), 3.66−3.75 (m, 1H if combined with previous signal), 3.45−3.54 (m), 3.28−3.36 (m, 1H if combined with precious signal), 1.30−1.90 (m, 6H), 1.47 (dd, J = 6.8, 1.2 Hz; *S* diast.), 1.42 (dd, J = 6.8, 1.2 Hz; *R* diast.; 3H if combined with previous signal). ^{13}C NMR ($CDCl_3$, 100 MHz) mixture of diastereomers, 198.2 (*S* diast.), 197.9 (*R* diast.), 165.9 (dd, J = 258, 12 Hz; *S* diast.), 165.7 (dd, J = 257, 12 Hz; *R* diast.), 163.0 (dd, J = 257, 13 Hz; *S* diast.), 162.0 (dd, J = 257, 13 Hz; *R* diast.), 133.1 (dd, J = 11, 10.8 Hz; *S* diast.), 133.0 (dd, J = 11, 10.8 Hz; *R* diast.), 121.4 (dd, J = 42.1, 14.0 Hz; *R* diast.), 121.2 (dd, J = 42.1, 14 Hz; *S* diast.), 112.5 (dd, J = 21.6, 3.4 Hz; *R* diast.), 112.3 (dd, J = 21.6, 3.4 Hz; *S* diast.), 104.8 (dd, J = 27.8, 25.4 Hz; *R* diast.), 104.7 (dd, J = 27.8, 25.4 Hz; *S* diast.), 98.7 (*R* diast.), 98.3 (*S* diast.), 77.4 (*R* diast.), 76.7 (*S* diast.), 62.8 (*S* diast.), 62.6 (*R* diast.), 30.7 (assign. uncer.), 30.6 (assign. uncer.), 25.6 (*R* diast.), 25.4 (*S* diast.), 19.5, 18.4 (*S* diast.), 17.5 (*R* diast.). Anal. Calcd for $C_{14}H_{16}F_2O_3$: C, 62.21; H, 5.96. Found: C, 62.37; H, 5.81. See ref 7 for a laboratory scale preparation and further spectral data.

Methanesulfonate 1-[(2*R*,3*R*)-2-(2,4-difluoro-phenyl)-2,3-dihydroxy-butyl]-1*H*-[1,2,4]triazol-4-ium (11). A solution of 30 wt % sodium *tert*-butoxide in THF (197.3 kg, 615.9 mol) was added to a solution of trimethylsulfoxonium iodide (70.8 kg, 321.7 mol), 1,2,4-triazole (22.2 kg, 321.4 mol), and DMF (498 kg) at <35 °C. The addition line was rinsed with DMF (5 kg), and the reaction mixture was stirred at 20−25 °C for 30 min. A solution of 53.1 wt % **7** in DMF (142.4 kg, 279.8 mol) was added at <30 °C followed by a DMF (26 kg) rinse. The reaction mixture was stirred for 30 min at which point an HPLC sample determined complete reaction (<0.1 HPLC area % of **7** relative to **8**; target was <5%). The mixture was heated to 85−90 °C for 12 h at which point an HPLC sample determined a complete reaction (2.9 HPLC area % **8** relative to **9**; target was <5%). The mixture was cooled to 20 °C and quenched with water (381 kg). The solution was extracted with isopropyl acetate (2 × 393 kg), and the combined extracts were washed first with 12 wt % NaCl solution (378 kg) followed by water (2 × 378 kg). The organic solution was distilled to 150 L at 0.08 bar at 55 °C. Isopropyl acetate (298 kg) was added and again distilled to achieve the end points of <0.3% water and of isopropyl acetate at ≤15 relative GC area % versus all other solvents. The solution was concentrated to 150 L and cooled to 25 °C, and MSA (34.9 kg, 363.1 mol) was added at <35 °C. The mixture was stirred at 20−25 °C for 30 min during which time **11** started to crystallize. Sampling indicated complete reaction (1.1 HPLC area % **9** relative to **10**; target <5%). The slurry was stirred for an additional 12 h at 20−25 °C, cooled to 0−5 °C, and stirred for 3 h. The solids were collected by filtration and washed sequentially with isopropyl acetate (2 × 90 kg) and *n*-heptane (77 kg). The cake was dried under vacuum at 45−50 °C to yield **11** (52.48 kg, 143.6 mol) in 51.3% yield as an off-white crystalline solid (mp = 173.5−174.5 °C). HRMS calcd M + H for $C_{12}H_{14}F_2N_3O_2$: 270.1054; found M + H: 270.1054. ^{1}H NMR (DMSO-d_6, 400 MHz) 8.92 (s, 1H), 8.09 (s, 1H), 7.25−7.19 (m, 1H), 7.18−7.11 (m, 1H), 6.87 (td, J = 8.46, 2.53 Hz, 1H), 4.80 (d, J = 14.40 Hz, 1H), 4.72 (d, J = 14.40 Hz, 1H), 4.19 (qd, J = 6.31, 2.78 Hz, 1H), 2.40 (s, 3H), 0.80 (d, J = 6.31 Hz, 3H); exchangeable protons not detected. ^{13}C NMR (DMSO-d_6, 126 MHz) 161.70 (dd, J_{C-F} = 246.05, 12.62 Hz), 158.56 (dd, J_{C-F} = 246.83, 11.83 Hz), 146.45, 143.45, 129.79 (t, J_{C-F} = 8.68 Hz), 124.01 (dd, J_{C-F} = 12.62, 3.15 Hz), 110.94 (dm, J_{C-F} = 20.50 Hz), 103.81 (t, J_{C-F} = 27.61 Hz), 76.73 (d, J_{C-F} = 6.31 Hz), 68.14 (d, J_{C-F} = 4.73 Hz), 56.20 (d, J_{C-F} = 4.73 Hz), 39.68, 17.45. Anal. Calcd for $C_{13}H_{17}F_2N_3O_5S$: C, 42.73; H, 4.69; F, 10.40; N, 11.50; S, 8.77. Found: C, 42.63; H, 4.55; F, 10.47; N, 11.51; S, 9.16. See ref 7 for a laboratory scale preparation of the free base and spectral data.

2-((*R*)-1-((*R*)-2-(2,4-Difluorophenyl)oxiran-2-yl)ethoxy)tetrahydro-2*H*-pyran (8). An analytical sample was prepared by flash chromatography on silica gel using ethyl acetate/heptane to produce a colorless oil. HRMS calcd M + H for $C_{15}H_{19}F_2O_3$: 285.1302; found M + H: 285.1302. ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of diastereomers, 7.54−7.48 (m, 1H), 7.40−7.35 (m, 1H), 6.89−6.83 (m, 2H), 6.81−6.75 (m, 2H), 4.92−4.90 (m, 1H), 4.75−4.74 (m, 1H), 4.07−4.00 (m, 1H), 3.99−3.93 (m, 1H), 3.89−3.79 (m, 2H), 3.53−3.46 (m, 2H), 3.31 (d, J = 5.31 Hz, 1H), 3.03 (d, J = 5.06 Hz, 1H), 2.84−2.80 (m, 2H), 1.86−1.46 (m, 12H), 1.21 (dd, J = 6.82, 1.51 Hz, 3H), 1.12 (dd, J = 6.44, 1.14 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) mixture of diastereomers, 162.76 (dd, J_{C-F} = 249.20, 4.73 Hz), 162.66 (dd, J_{C-F} = 249.20, 4.73 Hz), 160.56 (dd, J_{C-F} = 249.20, 3.15 Hz), 160.46 (dd, J_{C-F} = 249.20, 3.15 Hz), 131.70 (t, J_{C-F} = 4.73 Hz), 131.58 (dd, J_{C-F} = 9.47, 6.31 Hz), 121.40 (dd, J_{C-F} = 14.99, 3.95 Hz), 120.76 (dd, J_{C-F} = 14.99, 3.95 Hz), 111.16 (dd, J_{C-F} = 20.51, 3.16 Hz), 111.11 (dd, J_{C-F} = 22.08, 3.15 Hz), 103.54 (t, J_{C-F} = 26.03 Hz), 103.41 (t, J_{C-F} = 26.03 Hz), 98.61, 94.59, 74.45, 71.08, 62.58, 61.60, 59.77, 59.73, 51.18, 50.77, 30.59, 30.49, 25.41, 19.74, 19.48, 19.00, 17.48, 14.55. Anal. Calcd for $C_{15}H_{18}F_2O_3$: C, 63.37; H, 6.25; F, 13.36. Found: C, 63.29; H, 6.25; F, 13.40. See ref 7 for a laboratory scale preparation and further spectral data.

(3*R*)-2-(2,4-Difluoro-phenyl)-3-(tetrahydro-pyran-2-yloxy)-1-[1,2,4]triazol-1-yl-butan-2-ol (9). An analytical sample was prepared by flash chromatography on silica gel using ethyl acetate/heptane to isolate **9** as a colorless oil. HRMS calcd M + H for $C_{17}H_{22}F_2N_3O_3$: 354.1629; found: 354.1629. ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of diastereomers, 7.94 (s, 1H), 7.91 (s, 1H), 7.70 (s, 1H), 7.69 (s, 1H), 7.43−7.37 (m, 2H), 6.75−6.68 (m, 4H), 4.90−4.79 (m, 3H), 4.69−4.67 (m, 1H), 4.65−4.57 (m, 2H), 4.40−4.34 (m, 1H), 4.34−4.29 (m, 1H), 3.99−3.93 (m, 1H), 3.92−3.86 (m, 1H), 3.56−3.49 (m, 2H), 1.89−1.70 (m, 4H), 1.65−1.48 (m, 8H), 1.09 (d, J = 6.32 Hz,

3H), 0.96 (d, J = 6.31 Hz, 3H); alcohol proton not detected. ^{13}C NMR ($CDCl_3$, 126 MHz) mixture of diastereomers 162.64 (dd, J_{C-F} = 249.99, 12.61 Hz, 2C), 158.54 (dd, J_{C-F} = 246.05, 12.62 Hz, 2C), 151.14, 151.11, 143.99, 143.82, 130.46−130.25 (m, 2C), 122.91 (dd, J_{C-F} = 12.62, 4.73 Hz), 122.83 (dd, J_{C-F} = 12.61, 3.15 Hz), 111.57 (dd, J_{C-F} = 15.77, 3.15 Hz), 111.40 (dd, J_{C-F} = 14.20, 3.16 Hz), 103.77 (t, J_{C-F} = 26.82 Hz, 2C), 100.41, 97.25, 78.15 (d, J_{C-F} = 4.73 Hz), 77.90 (d, J_{C-F} = 4.73 Hz), 77.72 (d, J_{C-F} = 4.73 Hz), 73.57 (d, J_{C-F} = 4.73 Hz), 64.46, 63.64, 55.97 (d, J_{C-F} = 6.31 Hz), 55.72 (d, J_{C-F} = 6.31 Hz), 31.23, 30.99, 25.18, 25.12, 20.74, 20.18, 15.61, 13.62. Anal. Calcd for $C_{17}H_{21}F_2N_3O_3$: C, 57.78; H, 5.98; N, 11.89; F, 10.75. Found: C, 56.95; H, 5.78; N, 11.58; F, 10.61. See ref 7 for a laboratory scale preparation and further spectral data.

1-(((2*R*,3*S*)-2-(2,4-Difluorophenyl)-3-methyloxiran-2-yl)-methyl)-1*H*-1,2,4-triazole (12). Triethylamine (109.3 kg, 1080 mol) was charged to a solution of **11** (130 kg, 356 mol) in THF (520 kg) and MTBE (443 kg) held at −10 to −5 °C. Methanesulfonyl chloride (61.4 kg, 536 mol) was charged at <10 °C. The solution was cooled to 2 °C and held for 1 h. Sampling at this point indicated a complete reaction by HPLC. A 3.75 M solution of sodium hydroxide (394 kg) was charged at <5 °C and held until reaction completion by HPLC. Agitation was stopped, and the lower aqueous phase was discarded. The temperature was raised to 20 °C, and the organic layer was washed with a 20 wt % NaCl solution (624 kg). The solution was distilled at 0.4 bar and <55 °C to remove MTBE and THF to a volume of 50 L, and 95% ethanol (434 kg) was charged. The solution was again distilled at 0.4 bar and <60 °C until GC indicated <2 relative GC area % MTBE remained (final volume ∼275 L). Water (812 kg) was charged over 1 h. The slurry was cooled to 2 °C and held 8 h, and the product was collected by filtration. The cake was washed with 10 °C water (2 × 400 kg) and dried under vacuum at 50 °C to produce 71.4 kg of an off-white crystalline solid in 78% yield (96.9 HPLC area %, 97.8 HPLC wt %; 99.8% ee). The physical data for this compound have been published.[7]

(2*S*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)butanenitrile (13). *Safety Requirements for Handling a Process Involving Cyanide*. PPE: chemical resistant gloves, safety goggles, a supplied air respirator, and chemical resistant suit, such as Saranax, for any charging or sampling operations. All personnel were equipped with cyanide monitors set to 10 ppm, and amyl nitrate capsules were supplied near but outside the bay. The bay was barricaded with cyanide warning signs during operations. An observer outside the bay watched during all operations involving potential exposure. All reaction streams were kept caustic (pH >8) to minimize the possibility of formation of HCN. Quench solutions of 3% bleach were kept immediately available for decontamination purposes. The reactors were cleaned by filling them with a 5% bleach solution and agitating for 30 min. The risers and lines were similarly treated. The waste, such as the mother liquor and washes, contained 3−4% lithium cyanide and was *not* quenched with bleach due to the possibility of forming peroxides from the THF present. It was safer to drum up the waste, label as containing cyanide, and ship to a waste disposal facility equipped to handle cyanide. This description is meant only as a summary of the safety precautions our plant operators used, and the authors do not recommend this procedure be used at any other facility without prior evaluation by a safety officer familiar with cyanide chemistry.

Reaction Protocol. A solution of 1.65 M lithium bis(trimethylsilyl)amide in THF (190.6 kg, 352.5 mol) was distilled under vacuum at <30 °C to a volume of 140 L over 1 h and held at 0 °C for 10.5 h. Acetone cyanohydrin (37.9 kg, 441.1 mol) was charged over 45 min, raising the temperature to 22 °C. In another vessel, **12** (98.1 wt %, 44.2 kg, 173 mol) and THF (40 kg) were heated to 39 °C and held at that temperature until dissolution was complete. This solution was transferred to the reactor containing the mixture of lithium bis(trimethylsilyl)amide and acetone cyanohydrin over 10 min. The reactor and transfer line were washed over with THF (8 kg). The reaction mixture was heated to 65 °C and held at reflux for 12 h at which time the reaction was determined to be complete by HPLC (0.2% **12** remaining in relation to **13**). After 24 h (the reaction was held an extra 12 h only to accommodate a new shift; this had been established as an acceptable hold point), the reaction was cooled to 1 °C and the pH was adjusted to 9 −10 with a 13.7 wt % solution of aqueous hydrochloric acid (243 kg). During the neutralization, the temperature rose to 7 °C and the product crystallized. Water (51 kg) and isopropanol (166 kg) were charged over 0.5 h. The solution was heated to 40 °C and concentrated under vacuum to 550 L. The resulting slurry was cooled to −11 °C and held for 15 h. The product was isolated in a Hastelloy centrifuge and was washed with 25% aqueous isopropanol solution (3 × 15 kg) at 15 °C. The cake was dried at 45 °C under vacuum over 20 h to yield 43.5 kg of an off-white crystalline solid (99.6 HPLC area %, 90.2% yield). An analytical sample was recrystallized from isopropanol: mp 178−182 °C (lit.[4] 179−182 °C). HRMS calcd M + H for $C_{13}H_{13}F_2N_4O$: 279.1052; found M + H: 279.1059. ^{1}HNMR ($CDCl_3$, 300 MHz) 7.98 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.41 (m, 1H), 6.78 (m, 2H), 5.57 (s, 1H), 4.97 (d, J = 14.6 Hz, 1H), 4.84 (d, J = 14.6 Hz, 1H), 3.31 (q, J = 9.0 Hz, 1H), 1.18 (d, J = 9.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) 163.25 (dd, J = 12.7, 251.8 Hz), 157.89 (dd, J = 12.7, 256.9 Hz), 152.37, 143.98, 130.97 (d, J = 5.1 Hz), 121.28 (d, J = 12.7 Hz), 119.65, 112.20 (d, J = 17.8 Hz), 104.34 (t, J = 27 Hz), 75.83 (d, J = 5.1 Hz), 55.76 (d, J = 7.6 Hz), 33.57, 12.86. Anal. Calcd for $C_{13}H_{12}F_2N_4O$: C, 56.11; H, 4.35; F, 13.66; N, 20.13. Found: C, 56.10; H, 4.23; F, 13.35; N, 20.09. See ref 33 for a laboratory scale preparation and further spectral data.

(2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)butanethioamide Hydrate Hydrosulfate (15). *Safety Requirements for Handling a Process Involving Hydrogen Sulfide*. PPE: same as for compound **13** except that H_2S monitors were used for all operations. Cleaning and waste treatment are the same except the waste was labeled as containing hydrogen sulfide and other stench producing chemicals prior to shipment to waste disposal.

Reaction Protocol. A solution of **13** (43.0 kg, 154.5 mol), water (17.2 L), and isopropyl alcohol (54.0 kg) was heated to 78 °C over 80 min at which point a solution had occurred. Diethyl dithiophosphate (86.2 kg, 462.9 mol) was added over

1.5 h while maintaining the temperature at 75−80 °C. (**CAUTION**: diethyl dithiophosphate is highly toxic, corrosive, and combustible and produces a stench. This reaction also leads to off-gasing of hydrogen sulfide, which is highly flammable, toxic, and irritating and produces a stench. Proper precautions are required prior to conducting this reaction.) Additional isopropanol (2 kg) was used to rinse the line into the reactor. The heating was maintained for 7.5 h, until reaction completion (**13** = 0.93 HPLC area %). The mixture was cooled to 20 °C over 1 h. Ethyl acetate (194 kg) and water (215 kg) were charged to the mixture over 50 min, and the mixture cooled to 2 °C over 80 min. Sodium hydroxide solution (3N, 284 kg) was charged over 75 min while maintaining the resulting temperature at 10−20 °C. The final pH was 8.1, and the final temperature 15 °C. The phases were separated, and the organic phase was treated with 20 wt % sodium hydroxide (259 kg). The mixture was stirred for 30 min at ambient temperature (23 °C), and the layers were separated. The transfer lines were rinsed with ethyl acetate (2 kg). The combined organic phases were then treated with 98 wt % sulfuric acid (15.3 kg, 152.9 mol) over 3 min at a final temperature of 40 °C. The lines were rinsed with ethyl acetate (2 kg). The solution was concentrated to 87 L by vacuum distillation at 50−60 °C over 6 h. The slurry was cooled to 26 °C over 70 min, and MTBE (128 kg) was charged over 9 min. The slurry was further cooled to 5 °C over 1.5 h and held at 0.2−5 °C over 1 h. The crystals were collected by filtration and washed with MTBE (136 kg). The salt was dried at 60 °C under vacuum for 34 h to achieve an LOD of 0.35%. A total of 58.2 kg were isolated in 91.2% yield (99.9 HPLC area %). An analytical sample was recrystallized from ethyl acetate/MTBE. Mp = 152 °C (dec.). Anal. Calcd for $C_{13}H_{18}F_2N_4O_6S_2$: C, 36.44; H, 4.23; N, 13.08; F, 8.76; S, 14.97. Found: C, 36.41; H, 4.07; N, 13.13; F, 9.14; S, 15.02. ^{1}H NMR (DMSO-d_6, 300 MHz) (not all exchangeable protons detected) 10.19 (d, J = 46.1 Hz, 2H), 8.85 (s, 1H), 7.98 (s, 1H), 7.28 (m, 2H), 6.92 (m, 1H), 6.70 (br s, 1H), 4.84 (d, J = 14.1 Hz, 1H), 4.57 (d, J = 14.1 Hz, 1H), 3.60 (q, J = 6.6 Hz, 1H), 0.92 (d, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6, 76 MHz) 208.3, 162.7 (d, J = 250 Hz), 157.1 (d, J = 264 Hz), 146.7, 143.9, 130.7, 123.3, 111.6, 104.2, 75.2, 57.3, 49.6, 16.3. Spectral data for the free base **14** are found in ref 4.

4-(2-((2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butan-2-yl)thiazol-4-yl)benzonitrile (1). A mixture of **15** (25.8 kg, 99.4 area % purity, 60.2 mol adjusted for water content), 2-bromo-4′-cyanoacetophenone (hazard, this is a powerful lachrymator and requires PPE as described for the previous step) (13.8 kg, 61.9 mol), and 95% ethanol (104 kg) was heated to 60−70 °C and held for 2 h until the reaction was complete (0.09 HPLC area % of the aryl bromide relative to **15**). Water (122 kg) and 95% ethanol (104 kg) were charged at 55−70 °C. The pH of the solution was adjusted with triethylamine (15.6 kg, 154.2 mol) to pH 3.5−4.0. The solution was stirred at 55−65 °C for 20 min followed by cooling to 20 °C over 2 h. The slurry was stirred for 10 h at 20−25 °C, and the crystals were isolated in a Hastelloy filter dryer. The cake was washed twice with a 50 v/v% ethanol/water solution (98 kg ethanol, 123 kg water) and vacuum-dried at 50−55 °C for 8 h to yield 22.7 kg of a white, crystalline solid (99.7 HPLC area %, LOD 0.12%, 85.8% yield).

Sonic Impinging Jet Crystallization Protocol. A solution of **1** (2 kg) in 25 L of 95% ethanol at 70−79 °C was filtered through a 0.2 μm cartridge filter into a holding vessel and maintained at 70−79 °C. Water (55 L) was filtered in the same manner and transferred to another holding vessel at 0−5 °C. Seed crystals (∼0.25 g) of **1** were suspended in ∼600 mL of 1:2 v/v 95% ethanol/water in the impingment vessel. The suspension was sonicated for 1 min by a 0.5" probe with a 120 W power output. The solution containing **1** was pumped through a 0.02" diameter nozzle at 0.18 kg/min and was impinged with a water jet being pumped at 0.37 kg/min through a 0.03" diameter nozzle. The newly formed crystal slurry was sonicated in the impingment vessel which was maintained at a constant volume by continuous transfer of slurry to a receiver (Residence time of the crystal slurry in the impingment vessel was ∼1 min). After the entire solution was crystallized and transferred to the receiver, the slurry was cooled to 0−5 °C and filtered. The solid was vacuum-dried at 55 °C until the LOD was ≤1 w/w% to afford 1.95 kg (97.5% recovery) of **1** with a mean particle size of 7.5 μm. The physical and spectral data for the pure compound is in ref 4.

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Supporting Information Available

Analytical methods are fully described. This material is available free of charge via the Internet at http://pubs.acs.org.

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