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Streamlined Processes for the Synthesis of a Farnesyl Transferase Inhibitor Drug Candidate

Brian M. Andresen, Michel Couturier,* Brian Cronin, Michael D'Occhio, Marcus D. Ewing, Mark Guinn, Joel M. Hawkins, V. John Jasys, Susan D. LaGreca, Joseph P. Lyssikatos, Garrett Moraski, Karl Ng, Jeffrey W. Raggon, A. Morgan Stewart, Derek L. Tickner, John L. Tucker, Frank J. Urban, Enrique Vazquez, and Lulin Wei

Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340, U.S.A.

Abstract:

As part of a fast-paced oncology program, quinolinone 1 was discovered and developed as a potent inhibitor of farnesyl transferase for the treatment of cancer. The initial synthesis, which suffered from a lengthy linear sequence and a late-stage chromatographic resolution, was deemed not amenable to large-scale production. While investigating alternate routes to address these issues, the original synthesis was successively improved and streamlined. This enabled route supplied the timely production of drug substance required to support early toxicological and clinical studies. Several iterations of the process were made, and as a result of these improvements, an efficient four-step sequence was developed for the synthesis of quinolinone D-tartrate 2 starting from readily available outsourced intermediate 5 in 26% overall yield, including a classical resolution. The key features of the synthesis include a Castro–Stevens coupling, an imidazole Grignard addition, and a concomitant classical resolution/final salt formation with D-(−)-tartaric acid.

Introduction

Farnesyl transferase (FTase) inhibitors (FTIs) represent a new class of anticancer agents specifically targeting abnormal biological processes involved with cellular transformation and malignancy.[1] Ras mutations are a common genetic event in human cancers, and inhibition of Ras protein farnesylation is a new cancer treatment strategy that led to the discovery of the oncology drug candidate quinolinone **1**.[2] A fast-paced development program typical of oncology drug candidates was initiated, and to ensure that availability of drug substance was not rate-limiting, we committed to the synthesis of bulk material to support toxicology assessment and early clinical trials. Herein, we describe our approaches to streamline the original synthesis of quinolinone D-tartrate **2** to enable drug substance production in a timely fashion.

Initial Bulk Campaign

The original discovery route (Scheme 1) served to deliver initial bulk supplies for exploratory toxicology studies. The synthesis involves a lengthy and linear 11-step sequence from *p*-nitrobenzoyl chloride (**3**), with a late-stage chiral HPLC resolution of the penultimate intermediate **4**. While other routes were investigated to address these issues, we used this enabling route to support the fast-paced oncology program.

Analysis of this original route revealed that the transformations leading to ketone **5** were rather straightforward, relatively efficient, and scalable.[2,3] Moreover, compound **5** had an acceptable stability profile. Thus, our strategy was to outsource this advanced intermediate so that we could focus our attention on the late-stage process. The process-related issues with regard to the remaining transformations included a low-yielding lithiated silylimidazole addition, chromatographic resolution of the penultimate intermediate **4**, and the capricious alkyne deprotection.

In view of the fact that nucleophilic addition of the imidazole moiety to ketone **7** leads to deprotected propargylic alcohol **8**, we considered using the corresponding propargylic alcohol **9** directly since an equivalent of organolithium or Grignard reagent of **6** (Scheme 1) is consumed either way (vide infra). An added benefit is that the 4-pentyn-1-ol (**10**) is readily available and provides some cost savings relative to the corresponding TMS ether **11**. The requisite ketone **9** could be prepared directly from Sonogashira coupling with pentynol **10** (Scheme 2). The reaction was initially performed in acetonitrile, using 6 mol % of palladium chloride bis-(triphenylphosphine), 6 mol % of copper iodide and triethylamine as base to give 93% yield on laboratory scale. However, the cross-coupling gave a lower 76% yield when performed on multikilogram scale. This was attributed to the limited solubility of the product in the ethyl acetate utilized to displace the acetonitrile prior to crystallization in hexanes. This caused emulsions and difficult phase separations that led to the loss of product in the process. It was later found that by displacing the acetonitrile with 1,2-dichloroethane, a solvent that has a better ability to dissolve the product than ethyl acetate, the process showed a vast improvement with an isolated yield of 99%. In this process however, 68 volumes of dichoroethane was required to ensure that no trace of acetonitrile remained prior to the displacement of the former solvent with 75 volumes of hexanes required to precipitate the product. A superior alternative was obtained by performing the reaction in the lower-boiling THF, which required a reduced amount of dichloroethane (17 volumes) to displace the reaction solvent. Likewise, the use of the higher-boiling

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(2) Lyssikatos, J. P.; LaGreca, S. D. U.S. Patent 6,150,377, 2000.

(3) Blackwell, J.; Hickinbottom, W. J. *J. Chem Soc.* **1963**, 366.

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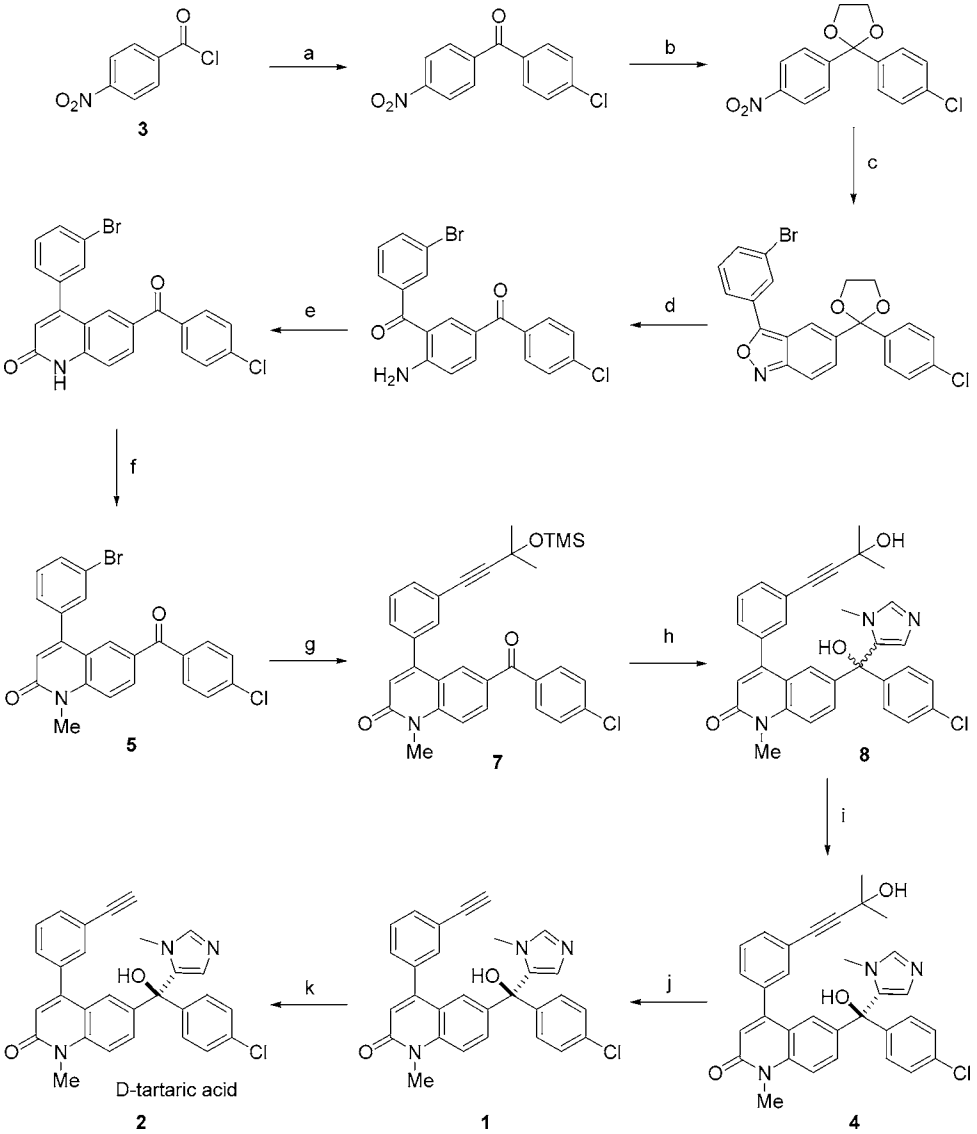
Scheme 1. **Original Discovery Synthesis**[a]



[a] Conditions: (a) PhCl, $AlCl_3$, 80 °C, 1.5 h, 77%. (b) Ethylene glycol, TsOH, toluene, reflux, 56 h, 90%. (c) 3-Br−benzyl cyanide, NaOH, MeOH, 1 h, rt, 65%. (d) $TiCl_3$, HCl (aq), THF, CH_2Cl_2, 0 °C, 1 h, 90%. (e) Ac_2O, DMAP, TEA, toluene, 3 h, rt, 64%. (f) MeI, $BnNEt_3Cl$, NaOH (aq), THF, 1 h, rt, 87%. (g) HC≡$CCMe_2OTMS$ (**11**), $Pd(PPh_3)_2Cl_2$, CuI, TEA, MeCN, 24 h, 60 °C, 75%. (h) (i) *N*-Me-2-TBS-imidazole (**6**), s-BuLi, THF, −78 °C, (ii) TBAF, THF, 1 h, rt, 83%. (i) Chiracell AD HPLC. (j) NaOH, *i*-PrOH, 80 °C, 20 h, 98%. (k) D-Tartaric acid, EtOH, 80 °C to rt 53%.

toluene also allowed complete displacement of the dichoroethane with only 12 volumes. With these modifications in place, the scale-up on 50 kg provided the ketone **9** in 87% yield.

In the original discovery route, the introduction of the imidazole moiety required a cryogenic, nonrobust lithiation with *s*-BuLi followed by a discrete desilylation step. Moreover, we found that the requisite 2-TBS-*N*-methylimidazole **6** has a limited shelf life at room temperature. Instead, we envisioned using the corresponding Grignard reagent **12** made from the 5-bromo-*N*-methylimidazole (**13**) to install the imidazole moiety. While Breslow showed that the metalation of 5-bromo-*N*-methylimidazoles was problematic,[4] more recent reports suggested that isomerization to the 2-metallo species could be avoided by Grignard halogen−metal exchange in nonpolar solvents.[5] Indeed, Ley's conditions using ethylmagnesium bromide in dichloromethane worked well in delivering the TMS deprotected adduct **8**.[6] It is noteworthy that the reaction profile was cleaner for ketone **9** with an unprotected alcohol than the trimethylsilylated alcohol **7**.

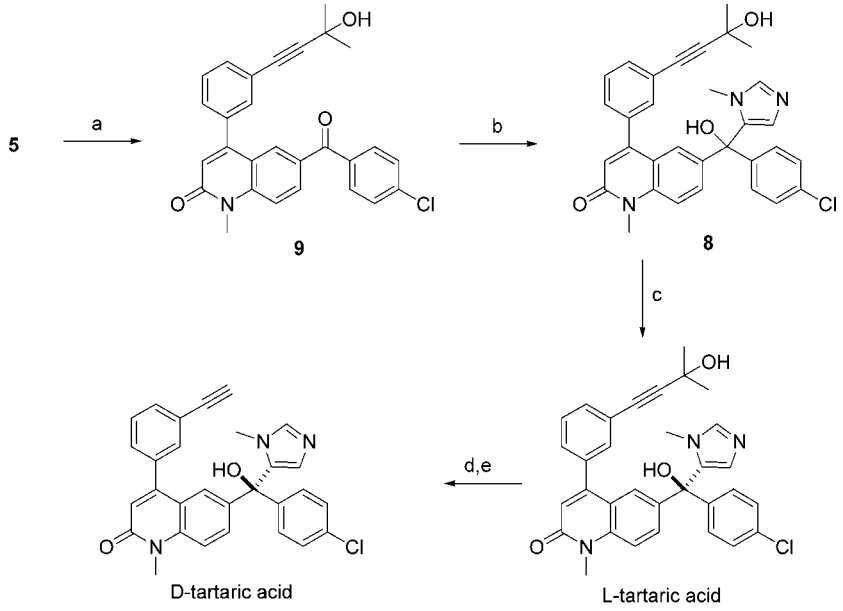
The imdazole Grignard reagent formation via halogen−metal exchange and subsequent addition to ketone **9** was studied in detail. Several parameters were examined in the optimization of this reaction and include various solvents (dichloromethane, THF, toluene, ethyl ether, 2-methyl-THF, MTBE), alkylmagnesium halides (methyl, ethyl, and isopropylmagnesium chlorides and bromides), additives (TMEDA, TEA, or DME), temperatures, and stoichiometry. In general, the reactions were gelatinous and gave incomplete conversions, even when using 4 equiv of reagent. This was

(4) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918.

(5) El Boria, M.; Moustafa, A. H.; Anwar, M.; Ghatts, A. G. *Croatia Chem. Acta* **1981**, *54*, 211.

(6) Turner, R. M.; Lindell, S. D.; Ley, S. V. *J. Org. Chem.* **1991**, *56*, 5739.

Scheme 2[a]



[a] Conditions: (a) HC≡CCMe$_2$OH (**10**), Pd(PPh$_3$)$_2$Cl$_2$, CuI, TEA, THF, 18 h, 87%. (b) *N*-Me-5-Br-imidazole (**13**), EtMgBr, MTBE, CH$_2$Cl$_2$, THF, 88%. (c) L-Tartaric acid, *i*-PrOH, water, 40%. (d) (i) NaOH, water, THF; (ii) *t*-BuOK, THF, 77%. (e) D-Tartaric acid, THF, water, 88%.

not the case when using a solution of ethylmagnesium bromide in MTBE and performing the reaction in dichloromethane in the presence of precisely 2 equiv of THF relative to the Grignard reagent. This latter additive was critical for obtaining a homogeneous reaction mixture and high efficiency (95% yield on laboratory scale). This procedure was exemplified on multikilogram scale to provide the racemic alcohol **8** as a white crystalline solid in 88% yield.

Initial bulk lots of racemic alcohol were resolved by chiral simulated moving bed (SMB) chromatography. The resolution was performed with a ChiralPak AD resin and 70% 2B ethanol and 30% methanol as the mobile phase. To utilize a 30-kg scale as an example, 141 L of the desired enantiomer **4** were obtained as the mobile phase solution. Isolation of the resolved material was accomplished by concentrating the solution to a minimum followed by a slurry in isopropyl ether to provide 12.7 kg of **4**.

While SMB resolution could be applied on scale, we also explored nonchromatographic alternatives. With the goal of discovering a classical resolution method, several acid salts were screened, and a promising lead was obtained with L-(+)-tartaric acid (1 equiv, 46 volumes 2-propanol, 2% water) providing an enantiomeric ratio of 9:1 in 34% yield. With this initial lead, several experiments were undertaken to optimize to yield and optical purity. By using 1 equiv of acid, 23 volumes of 2-propanol, 1% water, followed by a repulp of the filter cake in 10 volumes of 2-propanol at 50 °C, the resolution yielded the diastereomeric salts in a 99.6:0.4 ratio with an overall yield of 40% (80% of theory). A later experiment showed that using 20 volumes of 2-propanol, 1% water and a repulp of the filter cake in 10 volumes of 2-propanol produced material of slightly lower purity (98.6% er) but higher yield of 44%. Carrying this material into the deprotection step yielded material with optical purity over 99.9%. This result indicates that perhaps the resolution only needs to be taken to a 98:2 er, thus eliminating the need for the repulp procedure.

With the resolved material in hand, the final-step deprotection of penultimate intermediate **4** is carried on by base-catalyzed elimination of acetone. This was originally performed using sodium hydroxide in 2-propanol, which led to some unreacted starting material. The incomplete conversion was likely due to an equilibrium with the acetone produced. We reasoned that this issue could be resolved by distilling off the acetone to ensure reaction completion. Of several solvent and base combinations examined, the use of 2-methyl-THF and 0.2 equiv of potassium *tert*-butoxide allowed the reaction to be driven to completion. Compared to THF, the methyl analogue offers the advantages of a higher reaction temperature and a direct extractive workup with water. To improve the texture of the slurry in the reaction mixture, DMF was used as additive. Reaction completion was accomplished through successive solvent displacements, that is, with each solvent reduction, an equal amount of fresh methyl THF was added. Upon completion, the reaction was quenched with 0.2 equiv of acetic acid and the organic solution washed with water. Some ethyl acetate is required to keep the product in solution, as the DMF is extracted into the aqueous phase. After a Darco treatment, the product was displaced and granulated in IPE. Although high yielding, this procedure provided impure free-base **1** of 97.2% by HPLC.[7]

In a subsequent campaign, the deprotection was revisited to reduce the number and amount of impurities generated in the process. The next approach was to perform the reaction as in the previous campaign, but instead of reducing the reaction volume to remove acetone in discrete steps and

(7) Purification through the hydrate tartaric acid salt form brings finished goods within specifications but results in a 30% attrition of the drug substance.

replacing fresh solvent to the original volume, the solvent was displaced with continuous distillation and addition of fresh solvent, keeping the reaction volume constant. In this case, the use of THF led to a cleaner reaction profile than that seen with methyl-THF. Once the level of starting material was below 0.2% by HPLC, the THF was reduced and replaced with methylene chloride for the water washes and Darco treatment, then the methylene chloride was displaced by ethyl acetate which resulted in the isolation of 99.5% HPLC purity material (68% yield).

The D-tartrate salt formation of quinolinone **1** was initially performed in ethanol using 1.5 equiv of the corresponding acid. A high-energy crystalline form was discovered and characterized as a hydrate. Gratifyingly, this polymorph was better able to purge impurities as compared to the anhydrous salt. By isolating the hydrate form and then converting it to the lower-energy anhydrous form, the purity of the material greatly increased, and this procedure allowed purification of initial lots of drug substance (**2**) to specifications.

Meanwhile, an alternative salt-formation procedure was sought, and after screening several reaction conditions, we found that the hydrate could be produced in 9 volumes of THF and 1 volume of water using 1.1 equiv of D-(−)-tartaric acid. The final conversion to the anhydrous form could be accomplished by azeotropic removal of water by ethyl acetate. With the process improvements made on the deprotection step (vide supra), we later demonstrated that isolation of the hydrate salt was unnecessary and the material could be converted directly to the anhydrous form with purities within specification. This procedure was demonstrated on pilot-plant scale and provided 8.8 kg of drug substance **2** in 88% yield.

Second Iteration of the Process

At this stage, the process still necessitated 4 equiv of Grignard reagent, employed a resolution with the antipode of tartaric acid found in the drug substance, and required a separate free-basing. The acetylene deprotection generated several impurities and required a tricky continuous removal of acetone. Although the initial process allowed for the preparation of adequate quantity of drug substance, the process required further development.

The Grignard reaction to produce **8** required 4 equiv of organomagnesium reagent and was performed under high dilution. Since these factors translate to a low and inefficient reactor throughput, a larger campaign of drug substance would have required several weeks of manufacturing in the pilot plant to process this step alone. In an effort to address this capacity issue, several options were investigated to reduce the volumes and increase throughput to a satisfactory level. Numerous efforts to reduce the 4.0 equiv of Grignard required to fully convert **9** to **8** were in vain. Actually, the tertiary alcohol protecting group does not fully serve its purpose since it consumes one full equivalent of imidazole Grignard **12** in the process. We therefore explored the use of alternate protecting groups for the acetylene functionality, not only because of the aforementioned reason but also because its deprotection was complicated from a practical standpoint. We found that the TMS-protected acetylene underwent coupling quite efficiently using essentially the same procedure that was used for the acetone-protected acetylene. The best process was exemplified on a 100-g scale using 2% $Pd(PPh_3)_2Cl_2$, 2% CuI, in EtOAc; crystallization from EtOAc/hexanes gave high-quality crystalline material of **14** in 88% yield.

Changing the acetylene protecting group from tertiary alcohol **9** to TMS−acetylene **14** reduced the palladium catalyst load from 6 to 2%. The reaction was run in EtOAc rather than THF, thus avoiding two solvent displacements (first into dichloroethane to perform aqueous workup and second into toluene to perform crystallization) with concomitant reduction in organic solvents by 51% and aqueous solvent volumes by 73%.

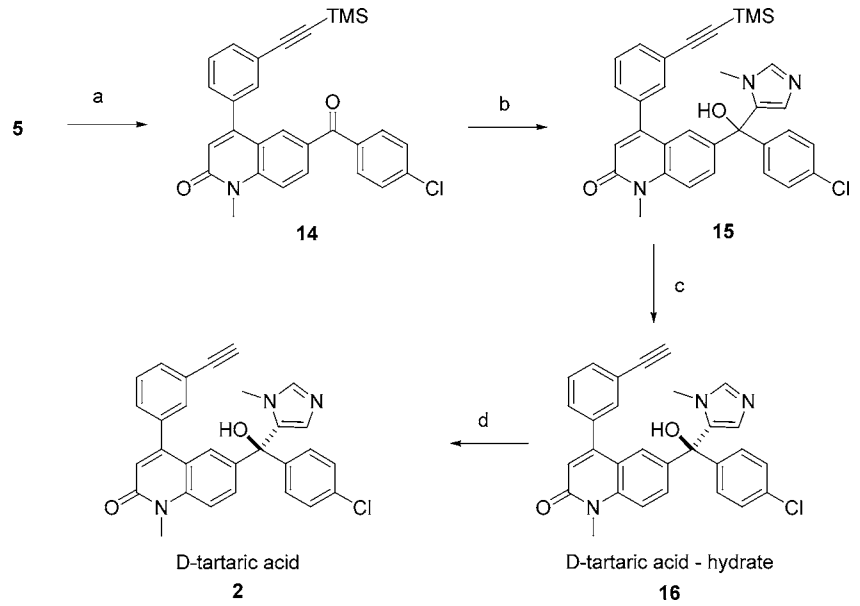
An issue typical of Grignard chemistry includes gelatinous textures upon reagent formation. In the previous process, this texture created a need for extremely large solvent volumes and required a precise amount of three solvents (THF, methylene chloride, and MTBE) to ensure soluble reagent. Upon higher concentrations, ethylmagnesium bromide tended to produce a gummy texture. However, we later found that ethylmagnesium chloride produced a thin slurry and that the reagent needs not be completely soluble to ensure complete conversion. Unlike ethylmagnesium bromide (1 M in MTBE), ethylmagnesium chloride (2 M in THF) is a common stock item, offers a more concentrated source, and does not crystallize at room temperature, eliminating the requirement that the reagent be shipped and stored warm. Gratifyingly, Grignard addition to the ketone **14** led to promising results, as the reaction works very efficiently with less than 2 equiv of Grignard. Furthermore, the product could be crystallized from acetonitrile, which gave crystalline solids in 80−90% yield on laboratory scale. Thus, the new procedure using 2 equiv of EtMgCl (2 M/THF) was performed on 40-g scale and yielded 86% of the desired crystalline product. The highest volume for this procedure is 29 L/kg. On 100-g scale, using only 1.5 equiv of the Grignard reagent, a 75% yield of pure, crystalline material (**15**) was obtained.

By changing the solvent system, the Grignard counterion, and most importantly, the acetylene protecting group, we were able to vastly decrease the solvent volumes as well as the equivalents of the imidazole reagent. These changes reduced the total organic solvent by 38% and the total aqueous waste by 94%. By the same token, the amount of bromo-imidazole and Grignard reagent was reduced by 70%.

The next reaction entails a TMS deprotection of **15**, and we found that 1 equiv of K_2CO_3 in 10 volumes of MeOH is a mild method, giving high-purity product in quantitative yield on 85-g scale. This procedure does not seem to generate significant amounts of impurities. This finding is significant, considering how difficult it was to cleave the tertiary alcohol **4** with the acetone-derived protecting group.

Since the former resolution procedure cannot be applied on the current route, an alternative resolution procedure was sought. It is noteworthy that the former resolution procedure, which is performed one step prior to the drug substance, utilizes the antipode of the tartaric acid found in the final form. We were pleased to find that D-tartaric acid, which is

Scheme 3. **Second Process Iteration**[a]



[a] Conditions: (a) TMSC≡CH (**14**), Et_3N, $Pd(Ph_3)_2Cl_2$, CuI, EtOAc, 87%. (b) **13**, EtMgCl, THF, CH_2Cl_2, 75%. (c) (i) K_2CO_3, MeOH; (ii) D-Tartaric acid, H_2O, THF, 41%, 97.2 er. (d) EtOAc, azeotropic removal of H_2O, 96%, 99.9 er.

the actual drug substance counterion, was also an effective resolving agent. An optimized procedure was performed on 74-g scale using 7% water in THF, and yielded 41% of the hydrate **16** with a chiral purity of 98.6% er for the desired enantiomer. Subsequent polymorph conversion, by azeotropic distillation with EtOAc, provided the desired anhydrous polymorph **2** in 96% yield with a chiral purity greater than 99.9% er (see Scheme 3). Thus, by resolving the racemic drug substance through the use of the actual counterion found in the drug substance, we achieved the following improvements: we eliminated the two-step salt-break/salt-formation sequence and the use of L-tartaric acid, and we also decreased the organic solvent volumes by 27% and the aqueous solvent volumes by 93%.

Conclusions

This work demonstrates a streamlined and practical large-scale synthesis of quinolinone **2**. As we were seeking alternate routes, a bulk-demanding drug development program required us to use a less than perfect route to produce bulk drug substance in a timely manner to support development activities. While initial campaigns served to deliver the necessary drug substance, we recognized that subsequent bulk material demands would monopolize our pilot-plant facilities if the synthesis were not improved. As a result of the process changes described herein, the overall yield was modestly increased from 20.8% to 25.7%, but more importantly, the total solvent volumes were reduced (organics by 47%, and aqueous by 78%), thereby increasing throughput. Changing the protecting group resulted in a much more efficient use of activated Grignard reagent where the equivalents were reduced from 4.0 to 1.5. Utilization of the actual enantiomer of tartaric acid found in the drug substance for the resolution eliminated a salt-formation and free-basing step, and recourse to TMS−acetylene instead of the acetone adduct simplified the process as well. Such improvements achieved our initial goal of streamlining the current synthesis and relieved pressure on our manufacturing facilities.

Experimental Section

General Procedures. Unless otherwise noted, all the operations were performed in Clean-By-Test nitrogen purged vessels. All charges and transfers are performed using isolated vacuum whenever possible.

6-(4-Chlorobenzoyl)-4-(3-(3-hydroxy-3-methylbutyn-1-yl)-phenyl)-1-methyl-1H-quinolin-2-one (9). To a dry vessel under nitrogen were successively charged 6-(4-chlorobenzoyl)-4-(3-bromo-phenyl)-1-methyl-1H-quinolin-2-one (**5**) (50 kg, 110 mol), triethylamine (210 L, 1492 mol), THF (415 L), 2-methyl-3-butyn-2-ol (16.1 L, 165 mol), $Pd(PPh_3)_2Cl_2$ (9.3 kg, 2.8 mol), and CuI (1.26 kg, 2.8 mol). The reaction mixture was heated to reflux for 18 h and then allowed to cool to room temperature. Darco (16.5 kg) and filter aid (16.5 kg) were added, and the resulting mixture was stirred for 2 h. The solid material was removed by filtration and rinsed with THF (210 L). The filtrate was concentrated by distillation under vacuum to a final volume of 490 L. 1,2-Dichloroethane (1250 L) was added to the residual material, and the solution was further concentrated by distillation under vacuum to a final volume of 490 L. Additional 1,2-dichloroethane (210 L) was added, and the organic solution was successively washed with NH_4Cl (50 kg in 400 L of water), then twice with sodium bicarbonate (20 kg in 400 L of water), then water (400 L), and then brine (50 kg sodium chloride in 400 L water). The organic solution was distilled under vacuum to 245 L, then toluene (625 L) was added, and the resulting solution was further concentrated to 245 L. The solution was cooled to ambient temperature; the resulting slurry was stirred for 6 h. The crystalline material was isolated by filtration, rinsed with toluene (57 L) and then hexanes (57 L), and dried in a vacuum oven at 40−45 °C to yield the title compound (43.7

kg, 86.7%) as a colorless crystalline solid, mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.5 Hz, 1H), 7.92 (s, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.52−7.43(m, 4H), 7.38 (t, J = 7.5 Hz, 1H), 7.31−7.22 (m, 2H), 6.71 (s, 1H), 3.80 (s, 3H), 2.34 (2, 1H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.52, 161.93, 150.47, 143.21, 139.12, 136.33, 135.54, 132.48, 132.29, 131.77, 131.47, 130.59, 130.57, 129.21, 129.19, 128.90, 128.49, 125.47, 123.91, 122.10, 119.66, 115.12, 95.99, 81.08, 65.36, 31.73, 30.11.

(*R*,*S*)-6-[(4-Chlorophenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-(3-hydroxy-3-methylbutyn-1-yl)-phenyl)-1-methyl-1H-quinolin-2-one (8). To a stirred solution of **13**-mesylate (43.5 kg, 169 mol) in MTBE (160 L) was added water (30 L) followed by aqueous NaOH (10.5 L, 50%). The mixture was stirred for 30 min, after which the layers were separated. The aqueous phase was extracted with MTBE (83 L), and the combined organic phases were washed with water (17 L), followed by aqueous sodium chloride (5.35 kg in 15 L of water). The organic solution was dried over $MgSO_4$ (14 kg), filtered, and rinsed with MTBE (19 L). The filtrate was stirred in the presence of molecular sieves (4Å, 20 kg) for 24 h. The sieves were removed by filtration and rinsed with MTBE (19 L). The solution was concentrated under vacuum to an oil, then diluted with THF (22.7 L, 276 mol) and dichloromethane (625 L). A solution of 1 M EtMgBr/MTBE (116 kg, 138 mol) was slowly added over 1 h, and the resulting solution was stirred for an additional 7 h. A solution of **9** (15.8 kg, 35 mol) in dichloromethane (265 L) was added to the Grignard mixture over 30 min. The reaction mixture was heated to reflux for 8 h and then allowed to cool to room temperature and was quenched with aqueous NH_4Cl solution (80.2 kg in 590 L of water). The biphasic mixture was stirred for 30 min, allowed to settle, and then the layers were separated. The organic solution was washed with water (590 L) and then atmospherically distilled to 75 L. The resulting slurry was allowed to cool to ambient temperature and further stirred for 2 h. The crystalline material was isolated by filtration, rinsed with dichloromethane (38 L), and dried under vacuum at 40−45 °C to yield the title compound (16.4 kg, 88%) as a colorless crystalline solid, mp 175 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63−7.55 (m, 3H), 7.46−7.40 (m, 2H), 7.36−7.27 (m, 4H), 7.18−7.14 (m, 3H), 6.83 (s, 1H), 6.53 (s, 1H), 6.04 (s, 1H), 5.74 (s, 1H), 3.65 (s, 3H), 3.34 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.15, 149.90, 144.96, 141.27, 139.87, 139.71, 137.29, 136.02, 132.55, 132.00, 130.96, 130.30, 129.64, 129.15, 128.56, 125.38, 123.67, 121.58, 118.98, 115.87, 97.52, 80.58, 75.77, 64.30, 33.58, 32.25, 29.93.

(*R*)-6-[(4-Chlorophenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-(3-hydroxy-3-methylbutyn-1-yl)-phenyl)-1-methyl-1H-quinolin-2-one L-Tartaric Acid Salt (4). A solution of **8** (700 g, 1.3 mol) and L-tartaric acid (195 g, 1.3 mol) in *i*-PrOH (16.1 L) and water (116 mL) was heated to 80 °C, allowed to cool slowly to room temperature, and then stirred for 12 h. The crystalline material was isolated by filtration and rinsed with I *i*-PrOH (3.5 L). The wet cake was stirred in *i*-PrOH (3.8 L) at 50 °C for 1 h. The suspension was allowed to cool and stirred at room temperature for 1 h. The crystalline material was isolated by filtration, rinsed with *i*-PrOH (1.9 L), and then dried under vacuum at 40−45 °C to yield the tartrate salt **4** (358 g, 40%, 98.4% ee), mp 157 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (s, 1H), 7.63−7.55 (m, 2H), 7.46−7.40 (m, 2H), 7.36 (m, 4H), 7.18−7.14 (m, 3H), 6.85 (s, 1H), 6.53 (s, 1H), 6.07 (s, 1H), 4.28 (s, 2H), 3.65 (s, 3H), 3.32 (s, 3H), 2.49 (s, 2H), 1.47 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.05, 161.18, 149.92, 144.65, 140.99, 140.94, 139.90, 139.50, 137.25, 136.30, 132.71, 132.00, 130.69, 129.59, 129.11, 128.60, 125.43, 123.72, 121.58, 119.04, 115.85, 97.49, 80.61, 75.74, 72.89, 64.33, 33.90, 32.21.

(*R*)-6-[(4-Chlorophenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethynylphenyl)-1-methyl-1H-quinolin-2-one (1). A solution of **4** (5.8 kg, 8.4 mol) in 2-Me-THF (116 L) was stirred in the presence of aqueous sodium hydroxide (58 L, 1 M) for 30 min. The layers were separated, and the organic phase was successively washed with 1 N NaOH (58 L), water (58 L), and saturated brine (58 L). The organic solution was concentrated by distillation to 50 L, diluted with THF (46.4 L), and further distilled to 50 L. The residual material was allowed to cool to room temperature and then was diluted with THF (46.4 L). To the resulting solution was added KOtBu (208 g, 1.85 mol), and the reaction mixture was atmospherically distilled while adding fresh THF to maintain constant reaction volume until 186 L THF had been distilled. The solution was then further concentrated in a vacuum to 14 L. The residual material was dissolved in DCM (58 L) and stirred in the presence of water (58 L) and saturated brine (11.6 L). The layers were separated after 30 min, and the aqueous phase was extracted with DCM (58 L). The combined organics were successively washed with water (58 L) and saturated brine (11.6 L). The organic solution was atmospherically concentrated to 12L, diluted with EtOAc (17.4 L), further distilled to 12 L, diluted with EtOAc (17.4 L) and reconcentrated 23 L. The resulting suspension was cooled to 0 °C, and stirred for 1 h. The crystalline material was isolated by filtration, rinsed with ice-cold EtOAc (5.8 L), and then dried under vacuum at 40−45 °C to yield the title compound (3.12 g, 77%) as a white crystalline solid, mp 232 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.62 (m, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.30−7.23 (m, 5H), 7.19 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 1H), 6.51 (s, 1H), 6.20 (s, 1H), 3.65 (s, 3H), 3.41 (s, 3H), 3.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.86, 149.96, 143.06, 139.72, 139.25, 136.62, 136.41, 133.72, 132.61, 132.36, 130.48, 129.26, 128.90, 128.50, 125.97, 122.77, 121.48, 119.25, 114.66, 83.00, 78.77, 75.93, 33.97, 29.86.

(*R*)-6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethynylphenyl-1-methyl)-1H-quinolin-2-one D-Tartaric Acid Salt (2). To a solution of **1** (7.6 kg, 16 mol) in THF (120 L) and water (3 L) was added a solution of D-tartaric acid (3.09 kg, 21 mol) in water (5.7 L). The resulting slurry was stirred for 12 h at room temperature and then diluted with EtOAc (152 L). The resulting solution was distilled while adding fresh EtOAc

so as to maintain a constant volume of 280−320 L and until a total of 1000 L of distillate had been collected. At this stage, the reaction mixture was further concentrated to 150 L, cooled to room temperature, and stirred for 3 h. The crystalline material was collected by filtration, rinsed with EtOAc (60 L), and then dried under vacuum at 40−45 °C to yield drug substance **2** (8.78 kg, 88%) of colorless material, mp 178 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (s, 1H), 7.63−7.55 (m, 3H), 7.47−7.32 (m, 5H), 7.20 (s, 1H), 7.14 (d, J = 9.0 Hz, 2H), 6.85 (br s, 1H), 6.54 (s, 1H), 6.06 (s, 1H), 4.29 (s, 2H), 4.28 (s, 1H), 3.65 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.20, 161.22, 149.80, 144.48, 140.83, 139.87, 139.49, 137.28, 136.42, 132.79, 132.39, 130.73, 129.97, 129.65, 129.08, 128.65, 125.35, 122.84, 121.66, 119.03, 115.85, 83.58, 82.08, 75.71, 72.94, 34.03, 29.94.

6-(4-Chlorobenzoyl)-4-(3-(trimethylsilylethynyl)-phenyl)-1-methyl-1H-quinolin-2-one (14). To a dry round-bottom flask were successively charged under nitrogen 6-(4-chloro-benzoyl)-4-(3-bromo-phenyl)-1-methyl-1H-quinolin-2-one (**5**) (100 g, 221 mmol), EtOAc (1.5 L), triethylamine (400 mL), (trimethylsilyl)acetylene (46.8 mL, 331 mmol), $Pd(Ph_3)_2Cl_2$ (3.10 g, 4 mmol), and CuI (841 mg, 4 mmol). The resulting mixture was heated to reflux for 18 h and then allowed to cool to room temperature. Darco G-60 (33 g) and Celite (33 g) were then added, and the mixture was further stirred for 40 min. The solid material was removed by filtration and rinsed with EtOAc (200 mL). The combined organic solutions were washed with hydrochloric acid (875 mL, 4 M) followed by a saturated aqueous ammonium chloride solution (200 mL) and were dried ($MgSO_4$) and filtered. The filtrate was concentrated at ambient pressure (final volume: 300 mL), then cooled to room temperature at which point a slurry develops. Hexanes were charged (800 mL) over 20 min, the slurry was stirred for 2 h and then stirred further at 0 °C for 30 min. The crystalline material was isolated by filtration and washed with an ice-cold solution of 20% ethyl acetate in hexane (300 mL) and then dried under reduced pressure to yield the title compound (90.52 g, 87%) as a colorless solid, mp 177−178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.5 Hz, 1H), 7.94 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.57−7.50 (m, 3H), 7.49 (d, J = 8.5 Hz, 2H), 7.43−7.33 (m, 3H), 6.73 (s, 1H), 3.83 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.43, 161.79, 150.33, 143.36, 139.11, 136.56, 135.65, 132.85, 132.27, 131.44, 130.70, 129.13, 128.89, 124.01, 122.30, 119.70, 115.06, 104.35, 95.83, 30.03, 0.16.

6-[(4-Chlorophenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-(trimethylsilylethynyl)-phenyl)-1-methyl-1H-quinolin-2-one (15). To a round-bottom flask were successively added imidazolium **13** mesylate (82.05 g, 319 mmol), potassium carbonate (123 g), and dichloromethane (1.4 L). The resulting suspension was heated to reflux for 6 h, then cooled to room temperature and stirred for an additional 12 h. The solid material was removed by filtration and rinsed with dichloromethane (200 mL). The combined organic solutions were concentrated at ambient pressure (final volume: 1.02 L) and then cooled to room temperature. A solution of ethylmagnesium chloride (160 mL, 2 M in THF) was added over 20 min, and the resulting slurry was stirred for an additional 30 min. At this stage, a solution of 6-(4-chlorobenzoyl)-4-(3-(trimethylsilyl)ethynyl-phenyl)-1-methyl-1H-quinolin-2-one **14** (100 g, 213 mmol) in dichloromethane (300 mL) was added, and the reaction mixture was heated to reflux for 18 h and then allowed to cool to room temperature. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (500 mL) and stirred for 10 min. The organic layer was separated, dried with magnesium sulfate (30 g), filtered, and concentrated atmospherically (final volume: 350 mL). Acetonitrile (1.0 L) was then added, and the resulting solution was concentrated atmospherically (final volume: 600 mL). Additional acetonitrile was charged (1.4 L), and the slurry was cooled to room temperature and stirred 12 h. The crystalline material was isolated by filtration, washed with acetonitrile (300 mL), and then dried under reduced pressure to yield the title compound (88.02 g, 75%) as a colorless solid, mp 189−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 9.0 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.33−7.25 (m, 10H), 7.00 (d, J = 8.0 Hz, 1H), 6.51 (s, 1H), 6.13 (s, 1H), 3.63 (s, 3H), 3.43 (s, 3H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.92, 150.14, 143.11, 139.87, 139.51, 139.32, 136.54, 136.15, 133.68, 132.48, 132.22, 130.50, 129.72, 128.90, 128.69, 128.51, 126.95, 123.87, 121.47, 119.28, 114.58, 104.40, 95.77, 76.01, 33.75, 29.84, 0.17.

6-[(4-Chlorophenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethynyl-phenyl)-1-methyl-1H-quinolin-2-one D-Tartaric Acid Salt Monohydrate (16). To a round-bottom flask were successively added 6-[(4-chlorophenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-(trimethylsilyl)ethynyl-phenyl)-1-methyl-1H-quinolin-2-one **15** (85 g, 154 mmol), K_2CO_3 (21.3 g, 154 mmol), and methanol (850 mL). The reaction mixture was stirred for 3 h and then concentrated by atmospheric distillation (final volume: 180 mL). Methylene chloride (1.0 L) was added, and the mixture was further concentrated (final volume: 500 mL). The resulting mixture was stirred with additional dichloromethane (500 mL) and water (500 mL). The phases were separated, and the aqueous layer was extracted twice with dichloromethane (2 × 250 mL). The combined organic solutions were dried with magnesium sulfate (25 g) and filtered. The filtrate was concentrated at ambient pressure (final volume: 150 mL), THF (1.5 L) was added, and the solution was further concentrated (final volume: 760 mL). A solution of D-tartaric acid (23.11 g) in water (35 mL) was added, the solution was slowly cooled to room temperature, and the resulting slurry was stirred for 12 h. The crystalline material was isolated by filtration, washed with an ice-cold solution of water in THF (7%, 200 mL), and then dried under reduced pressure to yield the title compound (41.36 g, 41%, 97.2 ee) as a colorless solid, mp 138 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (s, 1H), 7.63−7.55 (m, 3H), 7.47−7.32 (m, 5H), 7.20 (s, 1H), 7.14 (d, J = 9.0 Hz, 2H), 6.85 (br s, 1H), 6.54 (s, 1H), 6.06 (s, 1H), 4.29 (s, 2H), 4.28 (s, 1H), 3.65 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)

δ 174.20, 161.22, 149.80, 144.48, 140.83, 139.87, 139.49, 137.28, 136.42, 132.79, 132.39, 130.73, 129.97, 129.65, 129.08, 128.65, 125.35, 122.84, 121.66, 119.03, 115.85, 83.58, 82.08, 75.71, 72.94, 34.03, 29.94.

6-[(4-Chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethynyl-phenyl-1-methyl)-1H-quinolin-2-one D-Tartaric Acid Salt (2). A suspension of the hydrate **15** (40 g, 62 mmol) in ethyl acetate (2.4 L) was concentrated at ambient pressure (final volume: 800 mL), and the resulting slurry was stirred for 12 h at room temperature. The crystalline material was isolated by filtration, washed with ethyl acetate (210 mL), and then dried under reduced pressure to yield the title compound (37.3 g, 96%, 99.9 ee) as a colorless solid, mp 178 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (s, 1H), 7.63−7.55 (m, 3H), 7.47−7.32 (m, 5H), 7.20 (s, 1H), 7.14 (d, J = 9.0 Hz, 2H), 6.85 (br s, 1H), 6.54 (s, 1H), 6.06 (s, 1H), 4.29 (s, 2H), 4.28 (s, 1H), 3.65 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.20, 161.22, 149.80, 144.48, 140.83, 139.87, 139.49, 137.28, 136.42, 132.79, 132.39, 130.73, 129.97, 129.65, 129.08, 128.65, 125.35, 122.84, 121.66, 119.03, 115.85, 83.58, 82.08, 75.71, 72.94, 34.03, 29.94.

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