Organic Process Research & Development **2006**, *10,* 814–821

Development of a Synthetic Process towards a Hepatitis C Polymerase Inhibitor

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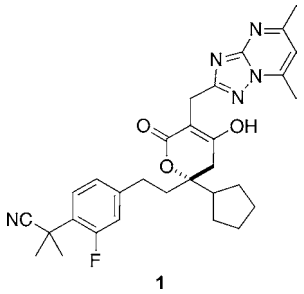
Abstract:

The synthesis of 2-(4-{2-[(2*R*)-2-Cyclopentyl-5-(5,7-dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylmethyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl]-ethyl}-2-fluoro-phenyl)-2-methyl-propionitrile (1) on multikilogram scale is described. Initial synthesis of this clinical candidate for inhibition of the hepatitis C viral polymerase (HCVP) protein was executed via a racemic synthetic route coupled with chiral HPLC separation. Due to the achiral route and instability of key intermediates, the initial route was determined to be unsuitable for large-scale manufacture. An alternate route was developed utilizing a convergent Heck coupling, resolution of a carboxylic acid via diastereomeric salt formation, and an efficient chemical recycling of the undesired enantiomer.

Introduction

Inhibitors of viral enzymes necessary for replication are of interest as clinical drug candidates. Our medicinal chemistry colleagues recently reported a series of compounds active as inhibitors of the hepatitis C viral polymerase (HCVP) enzyme.[1] Due to the activity of compound **1** as an HCVP inhibitor, larger quantities of this compound were requested for toxicology testing and clinical evaluation.



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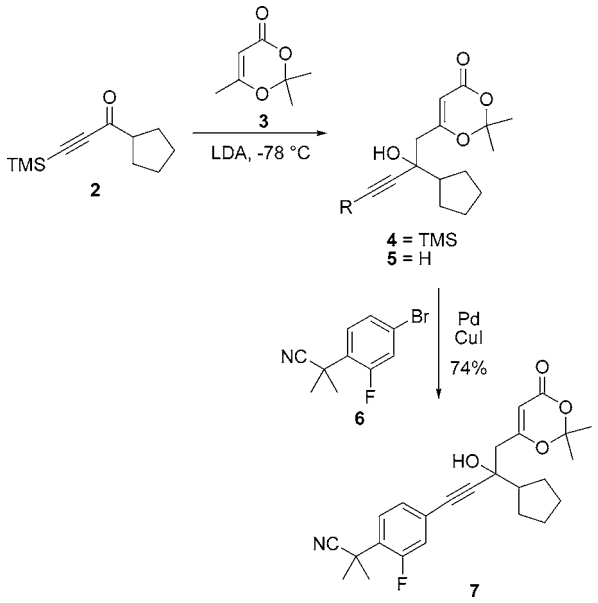
The initial preparations of **1** were via racemic syntheses coupled with chiral HPLC separation of the final material on sub-gram scale. In addition, the route was not readily amenable to asymmetric synthesis and contained some intermediates with stability concerns with respect to large-scale manufacture. This led us to develop a new route for the synthesis of the clinical candidate, which is the subject of this manuscript. As is common in the rapid-development environment of the modern pharmaceutical industry, a pilot-plant suitable route had to be developed to this complex target under significant time constraints. The described route met the immediate project goals while providing intermediates with the potential for future developments in asymmetric synthesis.

Scheme 1



Results and Discussion

The initial synthesis of **1** is briefly described in Scheme 1.[1] Alkynone **2**, available in one step from cyclopentanecarbonyl chloride and TMS/acetetylene, was treated under cryogenic conditions with the anion of dioxinone **3** to provide racemic **4**. After TMS deprotection, Sonogashira coupling with **6** (available by a two-step procedure from commercially available 2-fluoro-4-bromobenzyl bromide) provided **7**. The strategy of using **5** as the precursor to the dihydropyrone allowed incorporation of a large variety of aryl halides in the Sonogashira coupling, thus exemplifying the value of this scheme for medicinal chemistry purposes. Unfortunately, alkyne **5** was somewhat unstable to storage or high temperatures (DSC exothermic onset at 132 °C, 1912 J/g) and the coupled product **7** also had a low DSC onset (100 °C), making such intermediates undesirable for large-scale manufacture.

The completion of the medicinal chemistry synthesis is outlined in Scheme 2. Hydrogenation of the alkyne was followed by basic hydrolysis to remove the acetonide and facilitate closure to the dihydropyrone **8**. This substrate was

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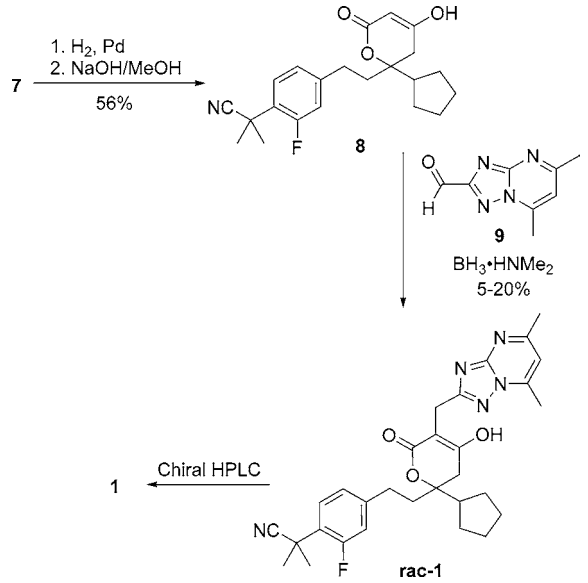
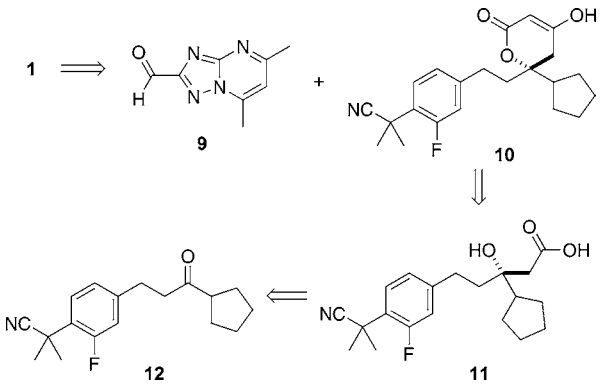
(1) Borchardt, A. J.; Gonzalez, J.; Li, H.; Linton, M. A.; Tatlock, J. H. PCT Int. App. WO 2004/074270, 2004.

Published on Web 06/15/2006
10.1021/op0600761 CCC: $33.50

Scheme 2



Scheme 3



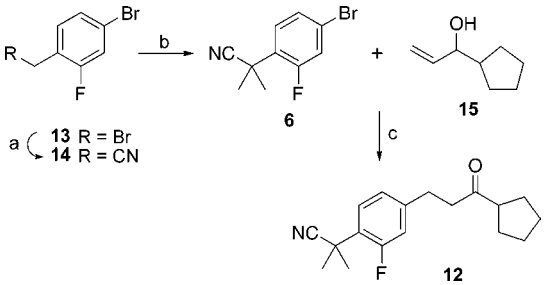
then reductively coupled with heterocyclic aldehyde **9** to form racemic **1**. Chiral HPLC separation of the enantiomers provided the first milligram quantities of this candidate in enantiomerically pure form.

In evaluating this synthetic route for multikilogram scale, several improvements were envisioned. We chose to synthesize the core without the use of the alkyne intermediates, thus avoiding these high-energy compounds. In addition, an approach was needed to address the chirality of the molecule earlier in the synthesis. A retrosynthesis was developed centered on preparation of a chiral tertiary alcohol **11** as outlined in Scheme 3. Literature precedent on two other 6,6-disubsituted dihydropyrone-core molecules suggested resolution of a β-hydroxy acid fragment such as **11** would be amenable to larger-scale synthesis.[2] The β-hydroxy acid **11** could be synthesized from prochiral ketone **12**.

Ketone **12** was synthesized by a three-step sequence from commercially available benzyl bromide **13** (Scheme 4).

(2) (a) Fors, K. S.; Gage, J. R.; Heier, R. F.; Kelly, R. C.; Perrault, W. R.; Wicnienski, N. *J. Org. Chem.* **1998**, *63*, 7348−7356. (b) Prasad, J. V. N. V.; Boyer, F. E.; Domagala, J. M.; Ellsworth, E. L.; Gajda, C.; Hamilton, H. W.; Hagen, S. E.; Markoski, L. J.; Steinbaugh, B. A.; Tait, B. D.; Humblet, C.; Lunney, E. A.; Pavlovsky, A.; Rubin, J. R.; Ferguson, D.; Graham, N.; Holler, T.; Hupe, D.; Nouhan, C.; Tummino, P. J.; Urumov, A.; Zeikus, E.; Zeikus, G.; Gracheck, S. J.; Saunders, J. M.; VanderRoest, S.; Brodfuehrer, J.; Iyer, K.; Sinz, M.; Gulnik. S. V.; Erickson, J. W. *Bioorg. Med. Chem.* **1999**, *7*, 2775−2800.

Scheme 4[a]



[a] Reagents and conditions: (a) NaCN, Bu_4NBr (85%); (b) MeOTs, NaOtBu; (c) $Pd(OAc)_2$, LiCl, LiOAc, NEt_3.

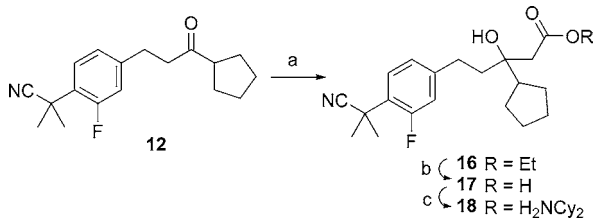
Displacement of the bromide was initially effected using NaCN in DMF in moderate yield. A much higher-yielding procedure was developed using phase-transfer conditions, reacting **13** with NaCN and catalytic Bu_4NBr (2.5%) in a CH_2Cl_2/water cosolvent (1:1 mixture, 1 mL/g **13**) to cleanly provide the desired phenylacetonitrile **14**. After extractive workup, nitrile **14** could be crystallized from a low volume of diisopropyl ether (IPE). Interestingly, **14** could not be crystallized from other common solvents in our hands, and IPE was unique in producing crystals. The high solubility of **14** in most organic solvents let to complete dissolution, even in small volumes of nonpolar solvents such as hexanes or heptane. This procedure was reproduced at a contract site to generate 35 kg of **14** in >99.5% purity.

The next step involved installation of the dimethyl moiety. Because the product (**6**) is an oil, a procedure was developed for scale-up that could provide a solution suitable for use directly in the subsequent step after the alkylation. This transformation could be performed with a variety of bases; however, we noted that the anion of **14** was unstable and rapidly produced dark solutions, presumably via self-condensation, leading to reduced yield. A better procedure was to deprotonate the phenylacetonitrile in the presence of the methylating agent, thereby eliminating buildup of the anion. Methyl tosylate was chosen as the methyl source due to its low vapor pressure and ease of handling on larger scale. Thus, a solution of **14** and methyl tosylate was treated with sodium *tert*-butoxide (NaOtBu) which led to a rapid reaction that cleanly provided the desired product **6**. After reaction completion, DABCO was added to quench any remaining methyl tosylate prior to aqueous workup. The reaction of methyl tosylate with DABCO was monitored by HPLC analysis and deemed complete within 30 min. Hexanes was chosen for extraction of the nonpolar product, leaving most impurities in the aqueous phase. On laboratory scale, the hexanes could be stripped to dryness to provide **6** in nearly quantitative yield. For large-scale manufacturing, the hexanes was displaced via distillation with DMAC, which was the desired solvent for the subsequent transformation.

To produce **12**, a Heck reaction[3] was performed with bromide **6** and cyclopentyl vinyl methanol **15**.[4] Although the reaction does proceed with simple $Pd(OAc)_2$/base conditions, the catalyst is much more stable in the presence of added chloride ligands. In addition to chloride ligands, the use of

(3) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265−272.

Scheme 5 [a]



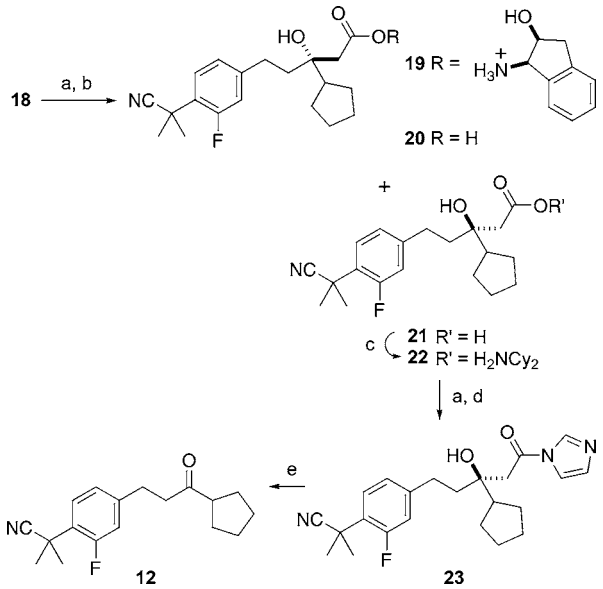
[a] Reagents and conditions: (a) i. LiHMDS, EtOAc, −35 °C; ii. add to **12**; (b) aq. NaOH, 50 °C; (c) $HNCy_2$ (68%, 5 steps).

ligating bases (TEA, Hunig's base, $MeNCy_2$) provided enhanced reactivity at lower catalyst loading. The optimized conditions for laboratory transformations were $Pd(OAc)_2$ (2.5%), LiCl (2 equiv), NEt_3 (1.5 equiv), and heating to ∼90 °C. One drawback was that these conditions led to a very rapid reaction (15−60 min), with a noticeable temperature rise of 30 °C. Examination of this reaction in an RC1 reactor determined the maximum adiabatic temperature rise for the transformation to be 84 °C. Since such an exothermic reaction had the *potential* to overwhelm the temperature transfer fluid in a pilot-plant setting, we chose to modify the reaction conditions to slow the transformation. By dosing in the TEA, the reaction could be run in bursts where the exotherm could be controlled more reliably. As the reaction proceeded, HBr was produced which quenched the triethylamine and effectively removed it as a ligating base, significantly slowing the reaction until additional amine was added. Using the amine base as the limiting reagent had negative repercussions for the catalyst stability and often led to the reaction stalling. To solve this dilemma, we found that the addition of a non-amine co-base (LiOAc) significantly stabilized the catalyst system and allowed reaction completion with a single initial charge of palladium. Therefore, by using $Pd(OAc)_2$ with LiOAc and dosing in the NEt_3, the Heck reaction was performed on 40-kg scale without incident. Unfortunately, ketone **12** was an oil, and therefore direct isolation was not ideal. A procedure was developed whereby **12** was isolated as a solution suitable for use in the next reaction. This workup procedure included Darco/Celite addition and filtration to remove Pd, aqueous extractive workup, and distillation to azeotropically dry the MTBE solution. The solution of **12** in MTBE was then used directly in the next transformation.

Conversion of the prochiral ketone **12** to the β-hydroxy acid **17** was achieved using a two-step, one-pot procedure (Scheme 5). Addition of the lithium-enolate of ethyl acetate to ketone **12** was followed by quench of the reaction with aqueous NaOH to hydrolyze the ester. The attempted use of acetic acid dianion led to significant quantities of ketone deprotonation and thus poor conversion. Although asymmetric aldol additions to the ketone were planned, time restrictions limited exploration of such alternatives to future research. As the carboxylic acid **17** was a thick oil, we sought

(4) Compound **15** was synthesized at multiple contract sites using a two-step procedure (addition of cyclopentyl grignard to DMF to produce cyclopentylcarbaldehyde, followed by addition of vinylmagnesium bromide) as outlined in these general literature procedures: Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M. *Synthesis*, **1984**, *3*, 228−230; Midland, M. M.; Koops, R. W. *J. Org. Chem*. **1990**, *55*, 5058−5065.

Scheme 6 [a]

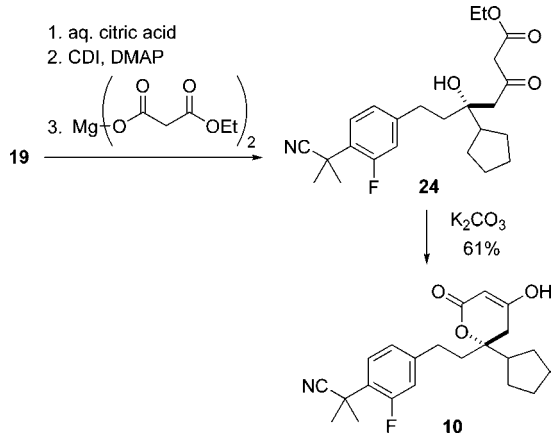


[a] Reagents and conditions: (a) aq. citric acid; (b) (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (38%); (c) $HNCy_2$; (d) CDI; (e) NaHMDS.

an alternative isolation of this intermediate. Precipitation of acid **17** as the dicyclohexylammonium (DCA) salt provided a robust isolation, which represented the first isolated compound in the scheme since intermediate **14**. Thus, the telescoped bulk procedure for the methylation of **14**, Heck reaction of **6** and **15**, enolate addition, hydrolysis, and isolation produced 59 kg of **18** in 99% purity for an overall yield of 68% over the five steps.

With a robust procedure to synthesize the β-hydroxy acid **17** coupled with the isolation/purification as the DCA salt, the next key transformation entailed identification of an appropriate resolution of this intermediate. It was important to effectively remove the dicyclohexylamine from the system prior to resolution, as the presence of this amine would cause precipitation of a racemic salt. Common mineral acids (HCl, H_2SO_4, H_3PO_4) were explored to break the DCA salt via aqueous extraction, but produced dicyclohexylammonium salts that were still partially soluble in the organic phase. By switching to citric acid, an effective salt break was achieved in a single extraction due to the high water solubility of the dicyclohexylammomium citrate salt. With a clean procedure to produce free acid **17**, several common commercially available chiral amines were screened for resolution via diastereomeric salt formation, and promising initial results were obtained using (*S*)-methylbenzylamine. Although the diastereomeric salt was obtained in high ee (95%), the maximum yield was only 17%. Further screening led to identification of (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol as an excellent resolving agent for **17**, requiring only 0.5 equiv of amine to obtain **19** in >95% ee. Recrystallization provided a salt with >99% ee. For generation of bulk material (Scheme 6), the dicyclohexylamine salt **18** was broken with aqueous citric acid and the solution of acid **17** dried azeotropically by distillation at atmospheric pressure followed by resolution with (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol. The salt was then recrystallized to provide 20 kg of **19** (38% overall yield) in >99% ee.

Scheme 7



Although we were quite satisfied with the yield and reproducibility of the described resolution, the undesired enantiomer **21** represented a valuable fragment. We envisioned ways to recycle this portion and found one solution that allowed the majority of the unique structure to be salvaged (Scheme 6). The filtrate from the resolution solution was purified by isolation of the DCA salt **22** in 50% yield (85% recovery of material in the filtrate). After salt break and azeotropic drying, the solution of acid **21** was treated with CDI to form acylimidazole intermediate **23**. The acylimidazole intermediate was sufficiently activated to participate in a retro-aldol reaction with catalytic base to provide ketone **12**. Treatment of ketone **12** with the previously described conditions for aldol addition, hydrolysis, and isolation as the DCA salt provided racemic **18** in 87% overall yield from **22**. As larger quantities of this candidate are required, we believe this recycle procedure will become cost-effective despite the extra steps required for utilization.

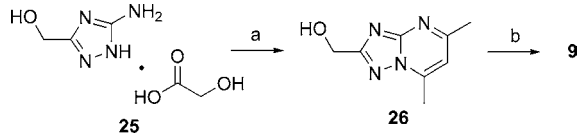
With enantiomerically pure β-hydroxy acid **19** in hand, we utilized a dihydropyrone synthesis analogous to that reported in the literature (Scheme 7).[2b,5] Thus, the chiral salt was broken via acidic aqueous extraction and the carboxylic acid activated as the acyl imidazole. The yield of the acylimidazole formation was significantly improved by using catalytic DMAP, which minimized formation of anhydrides. The acylimidazole intermediate was then treated with the magnesium salt of monoethyl malonate. After condensation, spontaneous decarboxylation provided β-keto ester **24**. For large-scale manufacture, the gas evolution was controlled by adjusting the addition rate of the acylimidazole intermediate to the magnesium malonate reagent. After formation of **24**, the crude product was treated with base to convert the ester into the cyclized dihydropyrone **10**. After crystallization, 9.1 kg of **10** were isolated in >98% purity, corresponding to a 61% yield over the four-step procedure from **19**.

To complete the synthesis of **1**, fragments **9** and **10** need to be combined as described in the retrosynthesis (Scheme 3).

Synthesis of Triazolopyrimidine 9. The triazole **25** was synthesized via the previously published procedure in high yield from aminoguanidine bicarbonate and glycolic acid.[6]

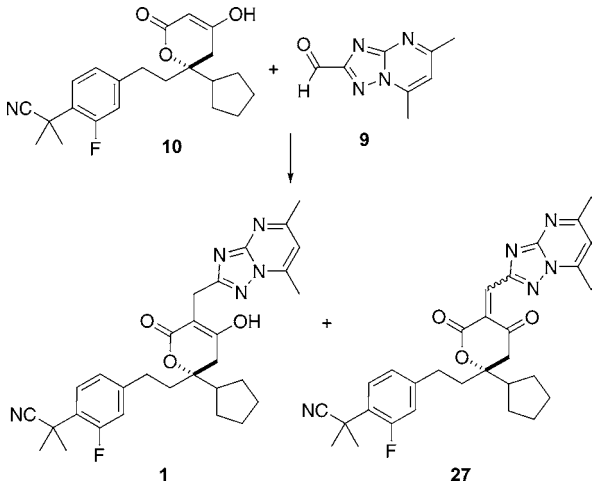
(5) Brooks, D. W., Lu, L. D. L., Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72−74.

Scheme 8 [a]



[a] Reagents and conditions: (a) HOAc, EtOH, 2,4-pentanedione (83%); (b) cat. Tempo, $PhI(OAc)_2$ (78%).

Scheme 9



Condensation of the triazole with 2,4-pentanedione was also accomplished via a reported procedure (Scheme 8).[7] The next step required oxidation of the alcohol of **26** to produce the desired aldehyde **9**. Unfortunately, the starting material (**26**) and product (**9**) are extremely soluble in water and cannot be effectively removed via organic extraction. This water solubility was quite limiting, as many oxidation conditions require some type of water workup to remove the reactants or catalysts. As a result, we chose to use an organic-soluble oxidant [cat. Tempo and $PhI(OAc)_2$][8] and optimized the solvent system for product isolation. Thus, the reaction was carried out in CH_2Cl_2, and after reaction completion MTBE was added as an anti-solvent to precipitate the desired product while retaining the reaction byproducts in the organic solution. Using this method, over 7 kg of **9** were produced.

Completion of Synthesis. The final convergent coupling was via a reductive alkylation of **10** with **9** (Scheme 9). Mild reducing agents (borane complexed with amines) were utilized to effect this transformation. We screened borane·amine sources [BH_3 complexed with $N(CH_3)_3$, $HN(CH_3)_2$, or $tBuNH_2$] in various solvents, and chose $BH_3{\cdot}N(CH_3)_3$ due to the superior profile. Attempted use of other reducing agents such as $NaHB(OAc)_3$ led to no significant product. One of the main byproducts of these reactions was tentatively identified as the Knoevenagel condensation product **27** by mass spectroscopy and NMR analysis of crude mixtures. Interestingly, attempted reduction of the Knoevenagel product under the same reaction conditions does not provide the desired product, implying that the reaction to produce **1**

(6) Allen, C. F. H.; Beilfuss, H. R.; Burness, D. M.; Reynolds, G. A.; Tinker, J. F.; VanAllan, J. A. *J. Org. Chem.* **1959**, *24*, 793−6.
(7) Lippmann, E.; Becker, V. *Z. Chem.* **1974**, *14*, 405−406.
(8) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974−6977.

proceeds via reduction of an intermediate prior to the elimination that forms the unsaturated product **27**. In the optimized laboratory procedure, dihydropyrone **10** was dissolved in a methanol/THF mixture, followed by addition of the $BH_3{\cdot}N(CH_3)_3$ reagent. Aldehyde **9** was then added to the mixture, thus minimizing the amount of simple Knoevenagel condensation. The excess borane was digested with aqueous HCl and the crude product isolated via precipitation after further water addition. The low solubility of **1** in most solvents at concentrations desired for plant operation limited the usefulness of extractive workups and necessitated this direct-precipitation workup. After filtration and recrystallization, **1** was isolated in 60−65% overall yield. In preparing this chemistry for plant scale, we were limited by the equipment available and operational safety concerns. Aldehyde **9** was not very soluble in the reaction solution, and addition of several kilograms of **9** as a solid was not a viable alternative on this particular scale. Additionally, the potential of the borane reagent to liberate hydrogen gas required us to handle this material in a vessel with nitrogen-gas sweep once solvent was introduced. As a result of these limitations, the addition order was reversed, and the solution of dihydropyrone **10** and $BH_3{\cdot}N(CH_3)_3$ was added to the solid **9**. This alternate addition order caused a reduction in yield of 5−10% in laboratory experiments due to a slightly higher level of impurities. On larger scale the new addition order provided 7.3 kg of the desired product **1** via the direct precipitation method in 56% yield. This material was then recrystallized from MeOH/EtOAc in 74% recovery to provide 5.4 kg of the product **1** in >98% purity. The modest yield on the recrystallization was due to the necessity of obtaining the high purity we required for clinical-quality material. However, the filtrate still contained a large amount of reasonably pure **1**, and reworking the filtrate provided an additional 500 g of **1** in >99% purity as a second crop.

Conclusions

We have developed a new synthetic route to the HCVP inhibitor **1**. Key steps are the synthesis of a versatile prochiral ketone (**12**), conversion to a tertiary β-hydroxy acid followed by efficient resolution, and elaboration via a convergent reductive alkylation in the final step. We demonstrated that the undesired enantiomer after diastereomeric salt resolution can be recycled to an earlier prochiral intermediate. The process has been utilized on pilot-plant scale to produce over 5 kg of **1**. Future syntheses could focus on asymmetric addition to ketone **12** to lower the long-term manufacturing cost.

Experimental Section

All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen.

2-(4-Bromo-2-fluorophenyl)acetonitrile (14). A 5-L flask was sequentially charged with sodium cyanide (342.19 g, 6.982 mol), Bu_4NBr (49.29 g, 0.1529 mol), water (800 mL), and CH_2Cl_2 (800 mL). After dissolution, the solution was cooled to 10 °C. In a separate vessel, CH_2Cl_2 (320 mL) was added to 4-bromo-2-fluorobenzyl bromide (**13**, 1628.87 g, 6.080 mol) and the mixture stirred and heated to room temperature until dissolved. The 4-bromo-2-fluorobenzyl bromide/CH_2Cl_2 solution was charged to an addition funnel and added slowly to the stirred cyanide solution to control the reaction exotherm. The bath temperature was adjusted to room temperature and the reaction stirred an additional 19 h. The solution was added to a separatory funnel and the lower aqueous layer removed. To the organic phase was added an aqueous solution of 1% $NaHCO_3$ (8 g $NaHCO_3$ in 800 mL water) and isopropyl ether (IPE, 1600 mL),[9] and the phases were mixed well. The aqueous phase is now the top layer. The layers were separated, and the lower organic phase was added back to the separatory funnel and extracted again with an aqueous 1% $NaHCO_3$ solution (800 mL). The phases were separated, and the organic layer was added to a 5-L flask set up for distillation. The solution was distilled at atmospheric pressure down to an internal volume of ~1.6 L. To the solution was added IPE (800 mL) and the distillation continued until the internal volume was ~1.5 L. Additional IPE (500 mL) was added and the solution distilled down to an internal volume of 1.6 L to effectively complete displacement of the CH_2Cl_2 with IPE. The solution was allowed to cool to 29 °C over 2 h, and then seeded with crystalline **14**. The solution was allowed to cool with vigorous stirring overnight. The slurry was then cooled in an ice/water bath to an internal temperature <10 °C for 1.5 h. The cold slurry was filtered, and the solids were rinsed with cold isopropyl ether (2 × 250 mL, <5 °C). The solids were dried under vacuum (no heat, solid melts <40 °C) to provide 1104.80 g (85%) of product as an off-white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 2), 7.27−7.42 (m, 3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0 (d, J = 4.9), 116.9, 117.4 (d, J = 15.4), 119.8 (d, J = 24.0), 123.0 (d, J = 9.3), 128.5 (d, J = 3.8), 131.4 (d, J = 3.8), 159.6 (d, J = 249). Anal. Calcd for C_8H_5BrFN: C, 44.89; H, 2.35; N, 6.54. Found: C, 45.10; H, 2.40; N, 6.56.

2-(4-Bromo-2-fluorophenyl)-2-methylpropanenitrile (6). A 500-gal reactor was charged with **14** (35.0 kg, 163.52 mol), THF (35 gal), DMF (37 gal), and MeOTs (67 kg, 360 mol). The charge line was rinsed with THF (2 gal) to remove any residual MeOTs. The headspace was purged with nitrogen, and the solution was cooled to −10 °C. The NaOtBu (35.2 kg, 366 mol) was divided into eight equal portions that were added separately to the reaction to control the exotherm (temperature range was −10 to 11 °C). One hour after the eighth and final charge the reaction was warmed to 3.6 °C and then charged with DABCO (4.6 kg, 41 mol) to consume the remaining MeOTs. After 60 min the reactor was charged with water (37 gal) and hexanes (37 gal), and the phases were mixed well and then separated. The aqueous phase was recharged to the reactor and re-extracted with hexanes (18 gal). The organic phases from the first two extractions were combined and transferred back to the reactor and washed twice with water (18 gal). The phases were separated, and the organic layer was concentrated under vacuum (400 Torr)

(9) The use of isopropyl ether can be hazardous. All fresh solvent, distillates, and waste streams were treated with peroxide-formation inhibitors. Please use with caution.

until no significant solvent distillation occurred. This solution of **6** was held overnight and used without further processing in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90−7.00 (m, 2), 7.33−7.39 (m, 1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7 (d, J = 3.3), 34.6, 120.1 (d, J = 26), 122.3 (d, J = 9.4), 122.8, 127.6 (d, J = 11), 128.2 (d, J = 3.8), 128.8 (d, J = 4.4), 160.0 (d, J = 254).

2-(4-(3-Cyclopentyl-3-oxopropyl)-2-fluorophenyl)-2-methylpropanenitrile (12). A 200-gal reactor containing **6** (theoretical 39.59 kg, 163 mol) was sequentially charged (while stirring) with DMAC (26 gal), LiCl (13.9 kg, 327 mol), LiOAc (5.4 kg, 81.8 mol), and H_2O (3 gal). The solution was then purged (subsurface) with N_2 for 30 min. The reactor was then charged with 1-cyclopentyl-prop-2-en-1-ol (**15**, 24.8 kg, 196.5 mol; the charge line was rinsed with DMAC, 2 gal), $Pd(OAc)_2$ (1800 g, 8.03 mol), Et_3N (1.7 kg, 16.8 mol, 10% of the total to be added) followed by a purge of the headspace. The reaction was heated towards 75 °C. It took a total of 60 min to heat the reaction to 75 °C. At this point, a second addition of NEt_3 (3.3 kg, 32.61 mol, 20% of the total to be added) was added to the reaction. Fifteen minutes later, the third portion of NEt_3 (5.8 kg, 57.31 mol, 70% of the total to be added) was added to the reaction. The reaction was exothermic, producing a maximum internal temperature of 88 °C over 15 min. Two hours after the final NEt_3 addition, the reaction was cooled to 28 °C over 60 min. The reactor was charged with water (20 gal) and MTBE (20 gal). In a separate 500-gal reactor was charged DARCO (10 kg), and Celite (10 kg). The solution containing the product was transferred from the 200-gal reactor to the 500-gal reactor and charged with water (26 gal) and MTBE (26 gal). The solution was stirred well for 2 h and then filtered over a cake of Celite. The cake was washed with MTBE (35 gal). The filtrate was transferred to a clean reactor, the phases were mixed well, and the lower aqueous layer was removed. The organic phase was washed with water (18 gal × 2), and the phases were mixed well and separated. The organic layer was concentrated by atmospheric distillation until the internal volume was ∼21 gal. After cooling below reflux, an aliquot was removed and analyzed by K−F titration, showing 0.39% H_2O. An additional portion of MTBE (15 gal) was added, and distillation continued until the internal volume was again ∼21 gal. After cooling below reflux, an aliquot was removed and analyzed by K−F titration, showing 0.09% H_2O. The solution was cooled under nitrogen and held overnight at room temperature. The solution of **12** was used directly in the next reaction without further processing. A purified sample of **12** was analyed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52−1.72 (m, 9), 1.77 (s, 6), 2.73−2.92 (m, 4), 6.90−7.00 (m, 1), 7.33−7.39 (m, 1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 27.1 (d, J = 3.3), 28.7, 28.8, 34.6, 42.4, 51.4, 116.6 (d, J = 23), 123.5, 124.2 (d, J = 4.0), 125.2 (d, J = 12), 126.9 (d, J = 4.4), 144.6 (d, J = 8.2), 160.5 (d, J = 250), 212.0. Anal. Calcd for $C_{18}H_{22}FNO$: C, 75.23; H, 7.72; N, 4.87. Found: C, 75.43; H, 7.85; N, 4.68

Dicyclohexylammonium[5-(4-(2-cyanopropan-2-yl)-3-fluorophenyl)-3-cyclopentyl-3-hydroxypentanoate] (18). A 300-gal reactor was charged with LiHMDS (1.0 M in THF, 231.7 kg, 260 mol) and purged with nitrogen. The reactor was cooled to −30 °C, and EtOAc (29.2 kg, 331 mol) was slowly added to the reaction vessel. During the EtOAc addition the internal temperature rose to −26 °C for 10 min but then was cooled back down to −39 °C. After complete EtOAc addition, a solution of **12** (crude MTBE solution from prior reaction, theoretical 163 mol, precooled to 3 °C) was slowly added over 40 min to the reactor containing the enolate solution and rinsed over with THF (4 gal). The internal temperature gradually rose to −33 °C during the addition of the solution of **12**. After 1 h at −30 °C the reactor was warmed to −12.5 °C, and 1 M NaOH (80 gal) was added and the mixture heated to 50 °C. After 17 h the reaction solution was cooled to 23 °C and charged with MTBE (116 gal). The phases were mixed well and separated. Water (116 gal) was added to the organic layer, and the phases were mixed well and separated. To the combined aqueous phases was added concentrated aqueous HCl (∼4.75 gal) until the pH = 2. Once the desired pH was observed, IPE (116 gal) was charged, and the solution was mixed well then separated. The organic layer was dried ($MgSO_4$, 9 kg), stirred well for 1 h, and then filtered and the cake rinsed with IPE (19 gal). This filtrate was charged back to the reactor and rinsed over with IPE (5 gal). While stirring well, dicyclohexylamine (59 kg, 325 mol) was added and the charge line rinsed with IPE (2 gal). After 10 min, significant solids were observed. The solution was stirred at room temperature for 2.5 h. The solution was cooled until the internal temperature remained below 5 °C for 2 h. The slurry was filtered, and the solids were rinsed with cold IPE (24 gal, 5 °C). The solids were dried for 4 days at 46 °C to provide 59.0 kg (68.6% from **14**) of **18** as a white powder (98.4% HPLC purity). ^{1}H NMR (300 MHz, CD_3OD) δ 1.20−1.44 (m, 10), 1.48−1.74 (m, 10), 1.78 (s, 6), 1.81−1.92 (m, 7), 2.07−2.18 (m, 6), 2.38 (dd, 2, J = 15.1, 8.7), 2.72 (ddd, 2, J = 13.4, 7.2, 3.0), 3.16−3.25 (m, 3), 7.07 (m, 2), 7.40 (t, 1, J = 9.0);^{13}C NMR (75 MHz, CD_3OD) δ 26.4, 27.0, 27.7, 28.3, 28.4, 28.5, 31.5, 32.0, 36.1, 43.5, 44.6, 55.3, 75.8, 117.8 (d, J = 23), 125.3, 126.1 (d, J = 2.7), 126.7 (d, J = 12), 128.2 (d, J = 3.9), 148.2 (d, J = 8.3), 162.8 (d, J = 247), 181.5. Anal. Calcd for $C_{32}H_{49}FN_2O_3$: C, 72.69; H, 9.34; N, 5.30. Found: C, 72.73; H, 9.42; N, 5.33

5-(4-(2-Cyanopropan-2-yl)-3-fluorophenyl)-3-cyclopentyl-3-hydroxypentanoic acid (17). A 500-gal reactor was charged with **18** (59.0 kg, 111.6 mol) and MTBE (160 gal). The slurry was stirred at 22 °C and 10% aqueous citric acid (57 gal) was added. The mixture was stirred for 60 min. The phases were separated, and the lower aqueous phase was removed. The organic solution was washed with water (5 gal), the phases were separated, and the organic phase was concentrated by distillation under atmospheric pressure to ∼40 gal. K−F titration of an aliquot showed 0.67% water. The solution of **17** (theor. 111.6 mol) was used directly in the next step.

***(R)*-5-(4-(2-Cyanopropan-2-yl)-3-fluorophenyl)-3-cyclopentyl-3-hydroxypentanoic acid-[(1*R*,2*S*)-1-amino-2,3-dihydro-1H-inden-2-ol] salt (19).** A 200-gal reactor was charged with (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (7.9 kg, 53

mol) and THF (55 gal). The slurry was heated to 50 °C, at which point the mixture was heated another 2 h until a homogeneous solution was observed. To the heated solution was added a solution of **17** (theor. 111.6 mol, in MTBE, 40 gal total volume, from previous step) at such a rate that the internal temperature was maintained above 47 °C. The stirred mixture was seeded with **19** in a slurry of MTBE (0.5 gal) immediately after complete addition of the MTBE/**17** solution. After seeding, another portion of MTBE (73 gal) was charged. After the second MTBE addition was complete, heating was discontinued and the mixture gradually cooled to room temperature over 2 h. The mixture was stirred for 8 h at 23 °C. The mixture was filtered, and the solids were rinsed with 1:1 MTBE/THF (18 gal). The filter was blown down with nitrogen for 1 h, and then the solids were removed from the filter and used directly in the subsequent recrystallization.

Recrystallization of 19. A 200-gal reactor was charged with **19** (wet cake from above) and isopropyl alcohol (IPA, 153 gal). The slurry was stirred and heated over 2 h to reach 80 °C. After 45 min at 80 °C, the solids were completely dissolved. The solution was seeded with **19** in a slurry of IPA (0.25 gal), and the stirred mixture was cooled to room temperature over 2 h and granulated for 6 h. The mixture was then filtered, and the solids were rinsed with IPA (6 gal). The solids were dried at 50 °C for 4 days to provide 19.8 kg (38%) of **19** as a white crystalline solid. Chiral HPLC analysis of the acid showed product with >99% ee. ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.36−1.62 (m, 8), 1.62−1.74 (m, 2), 1.70 (s, 6), 1.90−2.04 (m, 1), 2.17 (d, 1, J = 15.3), 2.23 (d, 1, J = 15.3), 2.58−2.68 (m, 2), 2.89 (dd, 1, J = 3.3, 16.2), 3.07 (dd, 1, J = 5.8, 16.2), 4.39 (d, 1, J = 5.5), 4.52 (dt, 1, J = 3.3, 5.6), 7.03−7.47 (m, 7); ^{13}C NMR (75 MHz, d_6-DMSO) δ 26.4, 27.0 (d, J = 16.0), 27.5 (d, J = 1.0), 30.4, 33.9, 40.0, 41.9, 43.9, 48.5, 58.3, 72.1, 73.3, 116.9 (d, J = 21.0), 124.6, 125.4, 125.5, 125.6, 125.8 (d, J = 6.0), 127.4, 127.7 (d, J = 4.0), 129.1, 141.0, 142.2, 147.4 (d, J = 8.0), 160.8 (d, J = 247), 177.4. Anal. Calcd for $C_{29}H_{37}FN_2O_4$: C, 70.14; H, 7.51; N, 5.64. Found: C, 70.10; H, 7.46; N, 5.64

(*R*)-5-(4-(2-Cyanopropan-2-yl)-3-fluorophenyl)-3-cyclopentyl-3-hydroxypentanoic Acid (20). A 200-gal reactor was charged with **19** (19.8 kg, 39.9 mol) and MTBE (58 gal). The mixture was stirred at room temperature, and aqueous citric acid (10 kg citric acid in 26 gal H_2O) solution was added. After stirring for 3 h, the mixture was allowed to settle for 30 min, and the lower aqueous layer was removed. The organic phase was washed with water (2 gal), mixed well, and separated. The organic solution was transferred to a clean reactor, and the solution was distilled under atmospheric pressure to 15 gal, removing water azeotropically. An aliquot was removed and showed 0.63% water by K−F titration. This solution of **20** was used directly in the next step. ^{1}H NMR (300 MHz, CD_3OD) δ 1.50−1.76 (m, 7), 1.79 (s, 6), 1.92 (m, 2), 2.18 (m, 1), 2.61 (q, 2, J = 14), 2.76 (t, 2, J = 8.0), 4.92 (s, 3), 7.08 (m, 2), 7.41 (t, 1, J = 8.3); ^{13}C NMR (75 MHz, CD_3OD) δ 27.5 (d, J = 8.3), 28.0, 28.3, 28.5 (d, J = 2.2), 31.6, 36.2, 42.4, 43.4, 76.0, 118.2 (d, J = 23), 125.7, 126.5 (d, J = 2.7), 127.3 (d, J = 12), 128.7 (d, J = 3.8), 148.2 (d, J = 7.7), 162.7 (d, J = 248), 176.3.

(*R*)-Ethyl 7-(4-(2-cyanopropan-2-yl)-3-fluorophenyl)-5-cyclopentyl-5-hydroxy-3-oxoheptanoate (24). A 100-gal reactor was charged with CDI (9.70 kg, 59.8 mol), DMAP (244 g, 2.00 mol), and MTBE (6 gal). An MTBE solution of **20** (13.85 kg, 39.87 mol, ~15 gal) was added to the stirred mixture over a 30-min period. The line was rinsed with THF (2 gal), and the mixture was stirred for 75 min to complete formation of the acylimidazole intermediate. A separate 200-gal tank was charged with ethyl magnesium malonate (17.1 kg, 59.66 mol) and THF (9 gal). The stirred mixture was heated to 46 °C, and the acylimidazole solution was slowly added to the ethyl magnesium malonate mixture. Stirring was continued at 48 °C for 2 h. The solution was cooled to room temperature and charged with IPE (18 gal) and 1 M HCl (32 gal), the mixture was stirred well, and the phases were separated. The organic phase was washed with H_2O (1 gal), the phases were separated, and the organic layer was distilled to 12 gal to remove water (K−F titration =0.18%). The solution of **24** was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3, J = 7.2), 1.40−1.55 (m, 3), 1.57−1.72 (m, 6), 1.86 (m, 6), 2.12 (m, 1), 2.65 (m, 2), 2.82 (d, 1, J = 5.1), 3.66 (m, 2), 3.76 (m, 3), 4.22 (q, 2, J = 7.2), 6.97 (m, 2), 7.38 (app. t, 1, J = 8.1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 25.7 (d, J = 2.0), 26.5 (d, J = 24), 27.1 (d, J = 3.0), 29.7, 34.8 (d, J = 2.0), 39.9, 47.4, 48.3, 50.8, 61.6, 74.9, 117.0 (d, J = 23), 124.1, 124.7 (d, J = 3.0), 125.6 (d, J = 11.0), 127.4 (d, J = 5.0), 145.4 (d, J = 8.0), 160.9 (d, J = 250), 167.4, 172.9, 176.0.

(*R*)-2-(4-(2-(2-Cyclopentyl-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-fluorophenyl)-2-methylpropanenitrile (10). A 200-gal reactor was charged with K_2CO_3 (8.3 kg, 60 mol), MeOH (9 gal), and the solution of **24** (16.64 kg, 39.87 mol) from the previous experiment. The mixture was heated to 50 °C for 4 h. The solution was cooled to room temperature and charged with IPE (4 gal) and water (18 gal). The mixture was stirred, and the phases were separated. The product-containing aqueous phase was extracted with IPE (2 gal). The layers were separated, and the aqueous phase was added back to the reactor. To the aqueous phase was added 2-methyl-THF (27 gal), MTBE (9 gal), and 1 M HCl (~28.5 gal) until the pH of the aqueous phase was ~3.5. The phases were mixed well, and the aqueous phase was removed. The organic phase was washed with saturated aqueous NaCl (2 gal) and then concentrated by distillation to ~14 gal. The temperature was adjusted to 52 °C, and heptane (4 gal) was added at such a rate that the internal temperature was kept above 50 °C. The solution was then seeded with solid **10** (5 g), followed by the addition of heptane (22 gal). The heating was continued for 1 h, and then the stirred mixture was allowed to gradually cool to room temperature. After stirring for 60 min at room temperature, the mixture was filtered, and the solids were rinsed with 1:1 IPE/heptane (6 gal). The solids were dried at 50 °C for 4 days to provide 9.1 kg (61% from **19**) of **10** as granular crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46−

1.73 (m, 7), 1.77 (s, 7), 1.91 (m, 2), 2.27 (m, 1), 2.68 (t, 2, $J = 7.8$), 2.77 (s, 2), 3.43 (d, 2, $J = 1.4$), 6.92 (m, 2), 7.39 (app. t, 1, $J = 8.2$); ^{13}C NMR (75 MHz, CD_3OD) δ 27.5, 27.6, 28.3, 28.4, 28.8 (d, $J = 13$), 31.2, 34.5, 36.1, 40.9, 86.1, 117.9 (d, $J = 23$), 125.2, 126.1 (d, $J = 2.7$), 127.2 (d, $J = 12$), 128.5 (d, $J = 4.4$), 146.6 (d, $J = 8.3$), 162.8 (d, $J = 249$), 171.2, 174.7. Anal. Calcd for $C_{22}H_{26}FNO_3$: C, 71.14; H, 7.06; N, 3.77. Found: C, 71.01; H, 7.12; N, 3.71

5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidine-2-carbaldehyde (9). A 100-L reactor was sequentially charged with CH_2Cl_2 (35.9 L), **26** (4748.8 g, 26.65 mol), and iodobenzene diacetate (9442.4 g, 29.32 mol). The mixture was warmed to ambient temperature, and Tempo (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical, 311.4 g, 2.00 mol) was added in a single charge. The reaction was maintained at 33.5 °C and stirred for 7 h. MTBE (35.6 L) was then slowly charged to the reactor, causing the product to precipitate, and the slurry stirred for an additional 30 min at 23 °C. The mixture was filtered, washed twice with 1:1 CH_2Cl_2/MTBE (2 × 4 L), and dried to yield 3734.2 g (79%) of **9** as an off-white solid. This procedure was repeated, starting with 4483.2 g of **26** which yielded 3448.0 g (78%) of **9**. ^{1}H NMR (300 MHz, d_6-DMSO) δ 2.67 (s, 3), 2.82 (d, 3, $J = 0.76$), 7.40 (d, 1, $J = 0.76$), 10.2 (s, 1); ^{13}C NMR (75 MHz, d_6-DMSO) δ 17.3, 25.7, 113.9, 148.8, 155.9, 161.1, 167.8, 187.4. Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.54; H, 4.56; N, 31.70

(*R*)-2-(4-(2-(2-Cyclopentyl-5-((5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl)-4-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl)-2-fluorophenyl)-2-methylpropanenitrile (1). A 100-gal reactor was charged with **9** (6.5 kg, 36.9 mol). A separate 50-gal reactor was charged with **10** (9.1 kg, 24.5 mol), $BH_3{\cdot}NMe_3$ (2.7 kg, 37 mol), MeOH (7 gal), and THF (5 gal). The solution in the 50-gal reactor was transferred to the 100-gal reactor, and a slight exotherm was observed to 28 °C. The mixture was allowed to stir at room temperature for 30 min and was then charged with concentrated aqueous HCl (0.25 gal). The reactor was charged with water (13.7 kg) and then seeded with **1** (2 g) to initiate crystallization. The mixture was stirred for 20 h and then was filtered; the cake rinsed with THF (4 gal) and then water (7 gal). The wet cake was transferred to a clean reactor and charged with water (18 gal) and stirred for 2 h. The slurry was filtered, washed with water (12 gal), and dried at 50 °C for 5 days to provide 7.3 kg (56%) of **1** as a white crystalline solid (purity 90% by HPLC analysis).

Recrystallization of 1. A 50-gal reactor was charged with **1** (7.3 kg, 13.7 mol), ethanol (14.5 gal, denatured with 0.5% toluene), and EtOAc (8.5 gal). The mixture was heated to 70 °C until the solution was homogeneous. The solution was then filtered through a 1-μm polishing filter, and residual product left in the tank was washed over with hot EtOAc (7 gal). The filtrate was combined and transferred to a clean 50-gal tank where it was distilled atmospherically to a volume of ~15 gal. Analysis of the solution by GC showed 40% EtOAc and 60% EtOH. The reactor was heated to 54 °C, and EtOAc (24 gal) was slowly added, maintaining the temperature in the 49−54 °C range. The solution was then cooled to 31 °C and seeded with **1** (2 g). The solution was stirred at room temperature for 12 h and then filtered, washed with EtOAc (8 gal), and dried at 50 °C for 2 days to provide 5.4 kg of **1** (74%) as a white crystalline solid (98% purity by HPLC analysis). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32−1.83 (m, 8), 1.80 (s, 6), 1.99−2.08 (m, 2), 2.33−2.48 (m, 1), 2.58 (d, 1, $J = 17.7$), 2.63−2.76 (m, 2), 2.71 (s, 3), 2.82 (d, 1, $J = 17.7$), 2.83 (s, 3), 4.14 (br s, 2), 6.87−6.98 (m, 3), 7.37 (app. t, 1, $J = 8.2$); ^{13}C NMR (75 MHz, d_6-DMSO) δ 17.1, 24.1, 25.4, 26.4 (d, $J = 4.0$), 27.4 (d, $J = 13.0$), 27.5, 29.9, 33.9, 34.0, 38.4, 46.4, 82.4, 99.2, 111.0, 117.3 (d, $J = 22.0$), 124.6, 125.8, 125.9 (d, $J = 11.0$), 127.8 (d, $J = 4.0$), 145.8 (d, $J = 9.0$), 147.1, 155.9, 160.9 (d, $J = 247$), 164.5, 166.1, 167.7, 167.9. Anal. Calcd for $C_{30}H_{34}FN_5O_3$: C, 67.78; H, 6.45; N, 13.17. Found: C, 67.69; H, 6.45; N, 12.96.

Acknowledgment

We thank Mark Macias for technical contributions to work related to this research, Daniel Yazbeck for salt screening, and Greg Young for scale-up assistance. Lisa Newell, Wen-Chin Tsai, and Bo Zhang are acknowledged for analytical support of this project. We acknowledge Bruce Fan and Derek Brown for providing the safety data related to this synthesis.

Received for review April 6, 2006.

OP0600761