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Development of a Pilot-Scale Preparation of *N*-[[(5*S*)-3-[4-(1,1-Dioxido-4-thiomorpholinyl)-3,5-difluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, PNU-288034, an Oxazolidinone Antibacterial Agent

Cuong V. Lu,* Jiong J. Chen,† William R. Perrault, Brian G. Conway, Mark T. Maloney, and Ying Wang

Chemical Process Research and Development, Pfizer, Kalamazoo, Michigan 49001, U.S.A

Abstract:

As part of Pfizer's continuing efforts in the oxazolidinone area, we have developed an efficient synthesis of PNU-288034 and successfully implemented it on pilot scale. The key step was a novel, acid-catalyzed, double Michael addition of 2,6-difluoroaniline with divinyl sulfone to install the desired dioxidothiomorpholinyl ring. Regioselective nitration provided the desired para-nitrogen, which was converted to the penultimate carbamate using standard chemistry. The resulting carbamate proved to be an excellent substrate for the recently reported oxazolidinone synthesis. As is normally the case, removing impurities to achieve our quality targets for API was a challenge, but unexpectedly, some impurities also caused significant processing difficulties as well. In the end, a safe and robust process was developed which provided clinical-quality material in five linear steps with an overall yield of 41% and was proven reproducible in multiple pilot-plant campaigns.

Introduction

Zyvox (linezolid) represents the first antibacterial with a new mechanism of action to be approved by the FDA in over 30 years. It has successfully treated serious Gram-positive infections in thousands of patients since its commercial launch in early 2000. The related oxazolidinone, PNU-288034, was recently targeted for further clinical development and required preparation on multikilogram scale. With a short development timeline, it was important to quickly identify a synthetic route that was both robust and safe for immediate lab-scale synthesis, while maintaining the potential to rapidly scale to pilot-plant quantities. The target oxazolidinone was originally made via two related routes (Schemes 1 and 2).[1,2]

The initial route (Scheme 1) involved 10 linear chemical steps with an overall yield of only 10%. A poor 38% yield was obtained for the initial three steps to generate the compound **2**. Due to poor nitration and displacement of triflate with thiomorpholine, an alternative route (Scheme 2) was utilized for initial large-scale lab work. The para-fluoro displacement was demonstrated on multigram scale with excellent results. This alternative route (Scheme 2) required only five synthetic steps and provided an overall yield of 58%. Although the alternative route provided excellent overall yield, the lack of inexpensive, commercially available of trifluoronitrobenzene and the use of osmium for the final step made this route unattractive for large-scale preparations. Ultimately, a new process (Scheme 3) was developed for larger pilot-scale work.

Results and Discussion

Having previously demonstrated effective methodology for the preparation of the oxazolidinone ring system,[3] we concluded that an improved method for the construction of the left half of the molecule was clearly the key to an effective process route. Our strategy was to use relatively inexpensive 2,6-difluoroaniline and divinyl sulfone in a double Michael addition fashion to give the dioxido-4-thiomorpholinyl ring with the correct oxidation state in a single step (Scheme 3). The rational for this strategy was based on a paper by Ford-Moore in 1949,[4] where the author reported a 56% yield of desired product along with 10% bis-adduct when a 1:1 ratio of vinyl sulfone and aniline were heated under neat conditions. Straley and Fisher also patented a similar reaction.[5] However, no electron-deficient aniline system has been reported to undergo this transformation. The critical question was whether our substrate, with decreased nucleophilicity, would undergo the double Michael addition.

We are pleased to report that the activated double Michael addition of 2,6-difluoroaniline to vinyl sulfone did proceed in good to excellent yield (Scheme 3).[6] The procedure scaled well, and our initial pilot-plant campaign, using the aluminum chloride-catalyzed conditions, provided a 62% isolated yield of compound **11** of 98 area% purity by GC. In the course of the reaction, a significant amount of black tar-like residues were formed which required a dichloromethane/silica gel treatment. In three subsequent pilot runs, yields ranged from 51 to 60% with purities greater than 95%. Subsequently, we discovered and developed a superior method utilizing 85% phosphoric acid as the catalyst and the media.[7] The new conditions provided an increase in yield (89%), higher-purity

* To whom correspondence should be addressed. E-mail: cuong.v.lu@pfizer.com. Telephone: (860)-686-1826. Fax: (860)-441-5779.

† Current address: GlaxoSmithKline, 709 Swedeland Rd, King of Prussia, PA 19406.

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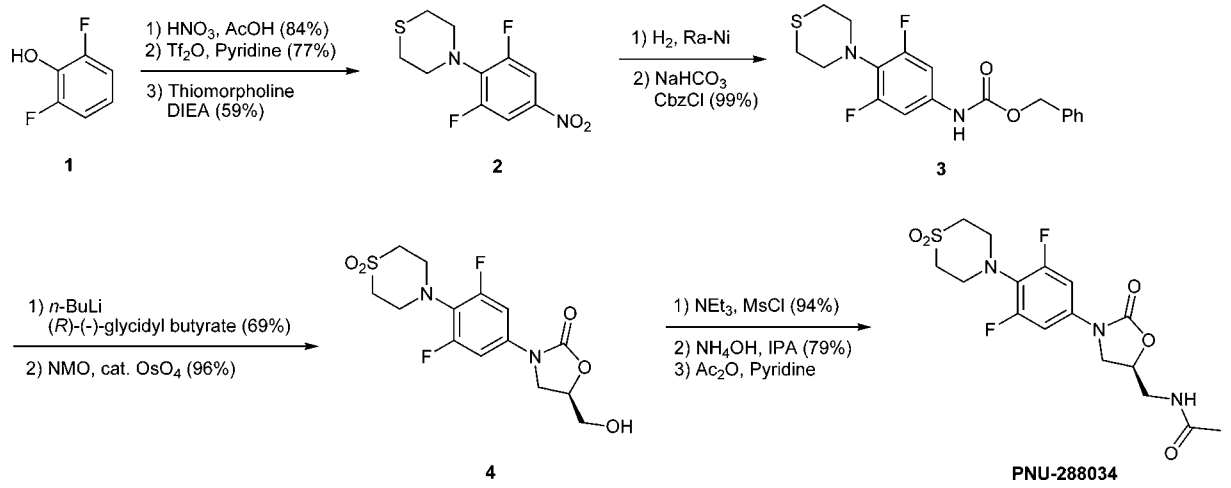
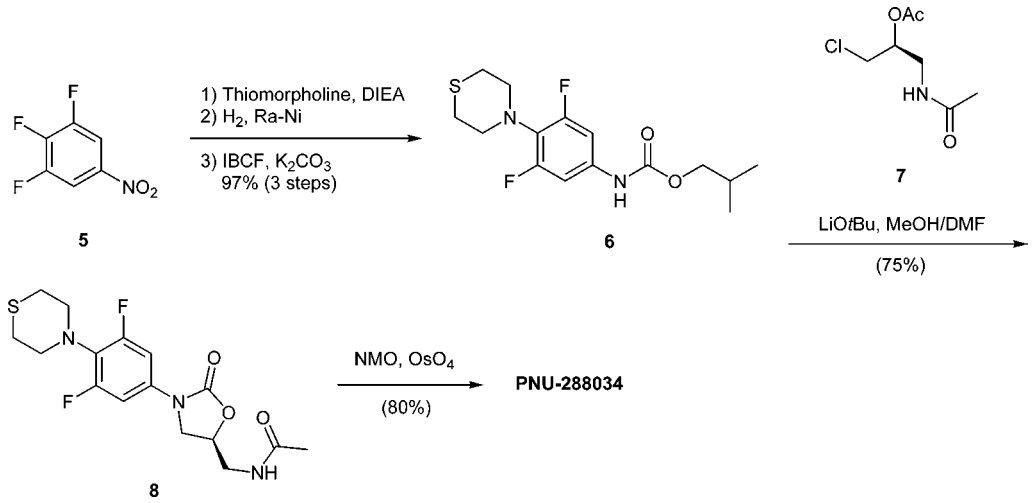
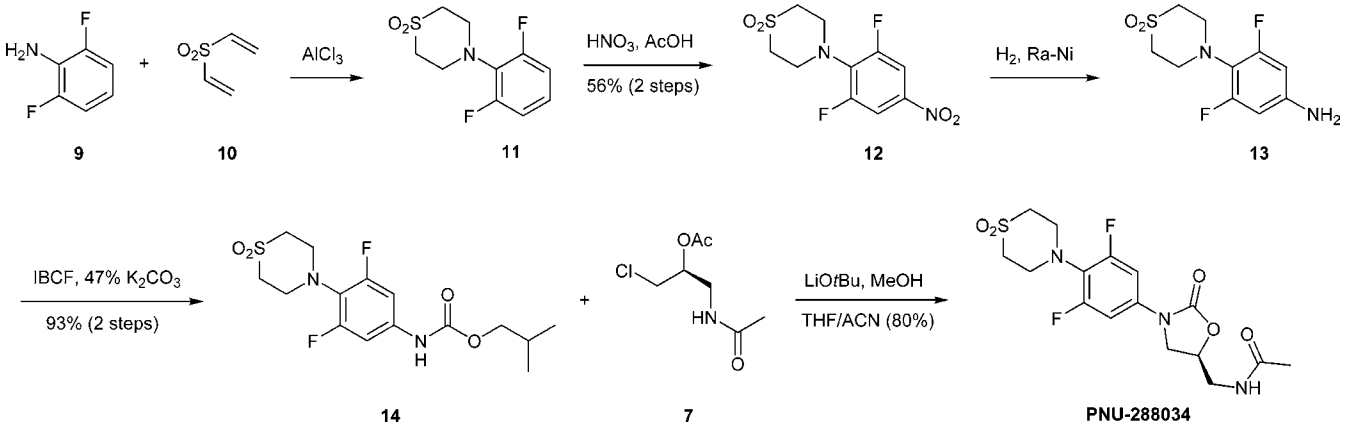
Scheme 1. **Initial route**



Scheme 2. **Alternative route**



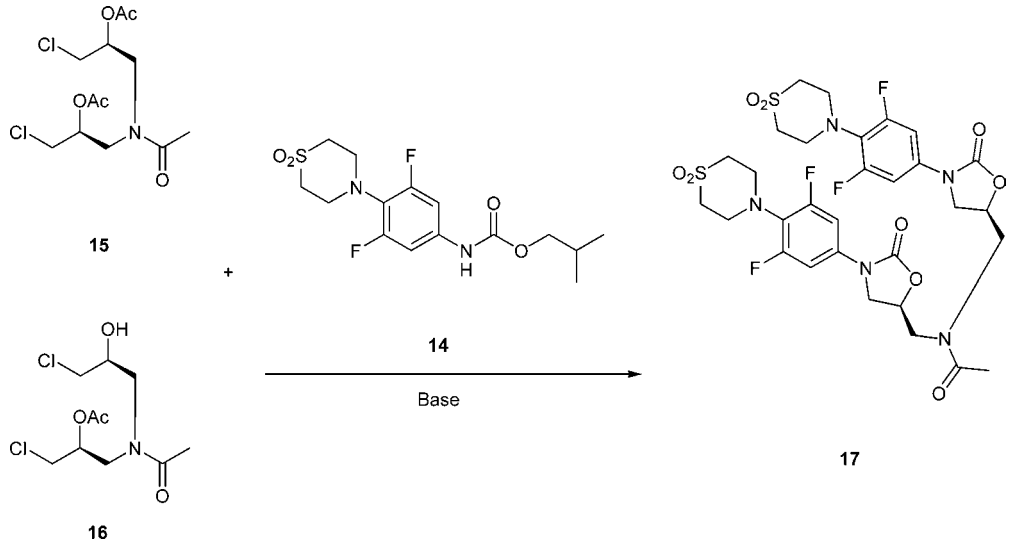
Scheme 3. **Process route to PNU-288034**



product, simplicity of product isolation, and greater throughput.

Regioselective Nitration of Compound 11. Various nitration conditions were screened before we chose nitric acid in acetic acid for development as it provided the best results. In particular, an RC1 study demonstrated that these conditions had the smallest adiabatic heat potential (−46.4 kcal/mol). Initially, the reaction required as many as 20 equiv of nitric acid, but upon optimization, we found that only 5 equiv of nitric acid were needed. The large discrepancy in nitric acid appeared to depend directly upon the purity of the starting material **11**. Although the GC quality of starting material **11** was relatively similar lot-to-lot, certain lots of compound were more highly colored, and these were found to require more nitric acid. Interestingly, even with pure colorless **11**, complete consumption of starting material could not be achieved even with excess acid and prolonged heating since the starting material tended to occlude in the precipi-

Scheme 4. **Dimer formation**



tated product **12**. However, the unreacted starting material posed no downstream difficulties, and the crude product was carried on without further purification.

Nitro Reduction. The search for an effective catalyst for the hydrogenation of the nitro functionality to give aniline **13** resulted in over 100 reactions being conducted in Parr shaking pressure hydrogenation vessels. Results from these screenings indicated that clean starting material could be reduced completely with a variety of catalysts, whereas less pure lots often gave incomplete reduction due to potential catalyst poisoning. In the early stages of development using impure starting material, reactions using either 5% Pd/C or 5% Pt/C as catalyst in THF as solvent produced mostly the hydroxylamine intermediate. Attempts to increase conversion by increasing reaction time, reaction temperature, hydrogen pressure, and catalyst loading met with little success. Raney Ni (Grace 2800) was identified as the most reliable catalyst to give complete conversion for both high- and low-purity nitroaniline **13** without competing desulfurization. When these conditions were used in the initial pilot campaign using a stainless steel stirred pressure vessel, the reaction proceeded much faster than previous development work would have predicted, presumably due to better mass transfer. After clarification, the crude THF solution of **13** was used directly in the next step. The solution of aniline **13** is stable, although oxygen sensitive, rapidly darkening upon exposure to the atmosphere.

Schotten-Baumann Acylation of 13. Schotten-Baumann acylation with dilute aqueous K_2CO_3 in THF required a large excess of isobutyl chloroformate (IBCF). However, when the commercial 47% aqueous K_2CO_3 solution was used, only 1.15 equiv of IBCF were needed. When reaction was complete, a simple phase separation removed most of the water and inorganic salts. Following solvent exchange of the THF for IPA via distillation, crystallization from a 3:1 mixture of IPA/water allowed for the removal of unreacted **11**, carried through from the first step, and any remaining inorganic salts to provide **14** of >99 area% purity by HPLC. However, the isolated product was consistently bright yellow. Although effective at color removal, the use of toluene or toluene/THF mixtures to extract **14** from the crude reaction mixture resulted in emulsions. Thus, we chose to stay with the 2-propanol/water crystallization in the pilot-scale reactions and carry the resultant colored material into the next step.

During the initial pilot-scale Schotten-Baumann reactions, approximately 5% of starting material remained under the conditions that gave complete conversion in the lab and an additional 0.24 equiv of IBCF were added. Since this was a heterogeneous reaction, the difference in mass transfer between the lab runs and the pilot runs likely caused this conversion problem. We mimicked the pilot-plant mixing at laboratory scale by using a long cylindrical flask with baffles, and we found that incomplete conversion could be duplicated with high temperature and slow agitation or low temperature and high agitation. Not surprisingly, it appears that the competing reaction between water and IBCF is more pronounced towards the end of the reaction. For the third pilot campaign, higher-purity compound **12** was used, and interestingly, the previous scale-up conversion problem was not observed.

Oxazolidinone Preparation. Application of the literature conditions to carbamate **14** gave excellent yields and high conversions to the oxazolidinone.[3] Three significant impurities (Scheme 4 and Figure 1) were formed in the reaction and were isolated by chromatography. The source of dimer **17** was shown to arise from the coupling of triacetylated **15**

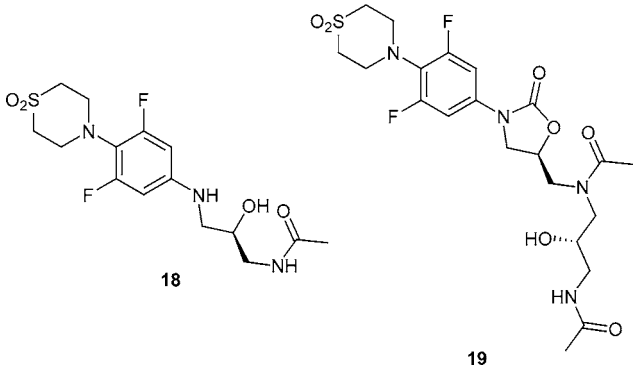


Figure 1. **Identified impurities.**

or diacetylated **16** with intermediate **14**. These two dimer impurities were formed during the preparation of **7**. The formation of impurity **18** was derived from hydrolysis of PNU-288034 during the oxazolidinone ring-formation reaction (Figure 1). Over alkylation of PNU-288034 with the coupling reagent **7** provided impurity **19**.

Following partial solvent exchange of the DMF for IPA via distillation, product losses to the filtrate were found to be fairly high. By using *n*-butanol to azeotrope the residual DMF, the level of product loss in the filtrate was decreased to ca. 7%, and the isolated yields were consistently between 86 and 92% of >99 area % purity by HPLC. Despite high chromatographic purity, the product was colored and retained solvent. It was found that the product tended to form tight solvates regardless of crystallization solvent. Attempts to decolorize with charcoals yielded little to moderate success.

Due to the presence of color impurities and residual solvent within the final product, various mixed aqueous solvent recrystallization conditions were attempted with minimal success. Through solubility studies, we found that PNU-288034 partitions preferentially at ca. 85% in the aqueous phase of a refluxing toluene/water mixture. However, the processing volume required was too large (ca. 60 L/kg) due to the low water solubility of PNU-288034. Addition of MeOH to the biphasic mixture increases solubility of PNU-288034. Thus, an alternative toluene/water/methanol extraction was developed which effectively removed nonpolar impurities such as residual carbamate **14** and most of the colored impurities. Residual **14** could be recovered and recycled from this extract.

Another problem associated with the original IPA crystallization method was the necessity of a separate recrystallization step to remove residual solvent to obtain the anhydrous product. Consequently, two methods were developed for product isolation. The first procedure involved charcoal decolorization of a THF solution of PNU-288034 followed by addition to water to precipitate anhydrous off-white product. However, this method did not allow for any purity upgrading in the crystallization and was abandoned. The second method involved azeotropic distillation to remove residual toluene followed by cooling of the aqueous methanol solution to provide anhydrous solids. The solids obtained were very fine crystals, which was problematic due to a long filtration time. By slowing the cooling rate to ca. 5−10 °C per hour and utilizing seed crystals, nice filterable anhydrous solids with residual solvent levels well within ICH guidelines were obtained.

Conclusions

Despite a host of impurity challenges, clinical-quality PNU-288034 was prepared on pilot-plant scale involving five chemical steps and one crystal habit change in an overall yield of 34%. This is a dramatic increase from previous preparations. With additional process development, the current synthetic route involves five chemical steps and provides an overall yield of 41%. The chemistry has proven to be safe and robust with both excellent overall yield and quality and has been demonstrated in two pilot-plant campaigns. With the implementation of further improvements for the first step, the overall process has a potential overall yield of 62%.

Experimental Section

4-(2,6-Difluorophenyl)thiomorpholine-1,1-dioxide (11). To a glass-lined reactor, aluminum chloride (12.9 kg, 96.7 mol), toluene (92 L), vinyl sulfone (12.96 kg, 109.7 mol), and 2,6-difluoroaniline (12.44 kg, 96.4 mol) were added and then heated to 110 °C for 24 h followed by cooling to 0−5 °C. The reaction mixture was slowly quenched with water (42 L) upon which the mixture thickened; dichloromethane (315 L) was added to solubilize the mixture followed by additional water (191 L). The phases were then separated, and the aqueous layer was back extracted with DCM (2 × 105 L). The combined organic layers were treated with sodium sulphate and filtered, and the cake was washed with DCM (139 L). The filtrate was concentrated during which precipitation was observed, and DCM (93 L) was added to obtain a homogeneous solution. The DCM solution was then subjected to column chromatography using SiO_2 and DCM as the elutent. The combined fractions were vacuum distilled, and EtOAc (225 L) was added to obtain a homogeneous solution. The solution was then treated with charcoal and filtered through a bed of Celite; the cake was washed with EtOAc (85 L) and the filtrate vacuum distilled. To the heated solution was added hexane (50 L), and the mixture was slowly cooled to 0−5 °C. The resulting slurry was filtered, washed with a cold solution of EtOAc (32 L) and hexane (16.4 L), and dried in a Calmic Dryer at 40 °C overnight to give **11** as a beige powder (14.7 kg, 62%) of >98 area% purity by GC. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.10 (m, 3H), 3.51 (m, 4H), 3.21 (m, 4H). The phosphoric acid procedure was not developed in time for the campaign, but the procedure can be found in ref 7.

4-(2,6-Difluoro-4-nitrophenyl)thiomorpholine-1,1-dioxide (12). To a mixture of acetic acid (212 L) and **11** (14.7 kg, 59.6 mol) was slowly added fuming nitric acid (24.8 L) while maintaining reaction temperature <30 °C. After the addition was completed, precipitation and a small exotherm were observed, and the resulting slurry was stirred at room temperature for 48 h. Slowly, the reaction was quenched with water (390 L), and the slurry was then filtered, washed with water (2 × 74 L) followed by ethanol (2 × 25 L), and then dried in a Calmic Dryer at 45 °C overnight to give **12** as a yellow powder (16.2 kg, 93.4%); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.06 (m, 2H), 3.70 (m, 4H), 3.26 (m, 4H); ^{13}C NMR (DMSO-d_6, 75.4 MHz) δ 154.1 (d, J_{C-F} = 247 Hz), 139.7 (d, J_{C-F} = 12 Hz), 132.9, 108.4 (d, J_{C-F} = 30 Hz), 51.1, 48.5; ^{19}F NMR (DMSO-d_6, 300 MHz) δ −117.4. HRMS (FAB) Calcd for $C_{10}H_{10}F_2N_2O_4S$ [M]: 292.0329. Found: 292.0332. Anal. Calcd for $C_{10}H_{10}F_2N_2O_4S$: C, 41.10; H, 3.45; N, 9.59; F, 13.00. Found: C, 41.19; H, 3.48; N, 9.55; F, 13.10.

4-(1,1-Dioxidothiomorpholin-4-yl)-3,5-difluoroaniline (13). To a glass-lined 30-gal autoclave was added **12** (7.0 kg, 24 mol). To a one-gal Nalgene bottle was added Raney nickel 2800 (1.4 kg) and ethanol (3.5 L), and the slurry was hand stirred and settled. The supernatant was separated, THF (3.5 L) was added to the solid, and the slurry was stirred

and settled. The supernatant was separated, and THF (3.5 L) was added to the solid. The slurry was added to the autoclave followed by additional THF (66 L), and the mixture was stirred at 40 °C with 40 psig H_2 until deemed complete by HPLC with <1% of hydroxylamine intermediate. The mixture was then filtered, and the reactor and filter were rinsed with THF (2 × 20 L) and combined with the THF filtrate for use directly in the next step. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.15 (m, 2H), 5.52 (m, 2H, D_2O exchangeable), 3.30 (m, 4H), 3.15 (m, 4H). ^{19}F NMR (DMSO-d_6, 300 MHz) δ −120.9. HRMS (FAB) Calcd for $C_{10}H_{12}F_2N_2O_2S$ [M^+]: 263.0666. Found: 263.0665. Anal. Calcd for $C_{10}H_{12}F_2N_2O_2S$: C, 45.79; H, 4.61; N, 10.68; F, 14.49. Found: C, 45.63; H, 4.65; N, 10.45; F, 14.60.

Isobutyl 4-(1,1-dioxidothiomorpholin-4-yl)-3,5-difluorophenylcarbamate (14). To the THF filtrate containing **13** (12.6 kg, 48 mol) was added 47% potassium carbonate solution (14.1 kg, 48 mol), and the mixture was heated to 45 °C. Slowly, isobutyl chloroformate (7.2 kg, 53 mol) was added to the mixture while maintaining a reaction temperature between 45 and 55 °C. Additional IBCF shots were added (4 × 0.7 kg) every 1.5 h until the starting material was <2% by HPLC and agitation was maintained for an additional 2 h. Once deemed complete, the reaction was slowly quenched with water (45 L) and cooled, and the phases were separated. The organic layer was solvent exchanged into IPA. Additional IPA (75 L) and water (50 L) were added, and the slurry was heated at 80 °C. After digestion, the slurry was slowly cooled, filtered, washed with cold IPA (2 × 30 L), and dried at 60 °C to give yellow compound **14** (14.2 kg, 82%) of 99 area% purity by HPLC. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.90 (s, 1H, D_2O exchangeable), 7.14 (m, 2H), 3.86 (d, 2H), 3.43 (m, 4H), 3.18 (m, 4H), 1.90 (m, 1H), 0.92 (d, 6H). ^{19}F NMR (DMSO-d_6, 300 MHz) δ −119.21. HRMS (FAB) Calcd for $C_{15}H_{20}F_2N_2O_4S$ [M^+]: 363.1190. Found: 363.1164. Anal. Calcd for $C_{15}H_{20}F_2N_2O_4S$: C, 49.72; H, 5.56; N, 7.73; F, 10.48. Found: C, 49.72; H, 5.63; N, 7.67; F, 10.57.

***N*-({(5S)-3-[4-(1,1-Dioxidothiomorpholin-4-yl)-3,5-difluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (PNU-288034, Initial Pilot-Scale Prep).** Compound **14** (10.5 kg, 29 mol), Li*Ot*Bu (6.96 kg, 87 mol), and branched octane were charged to a glass-lined reactor and cooled to ca. 20 °C. Then DMF (10 L) was slowly added over 25 min and the resultant slurry stirred for 30 min. Methanol (1.86 kg, 58 mol) was slowly added over 25 min and the slurry further cooled to ca. 15 °C. **7** (11.22 kg, 58 mol) and DMF (9.4 L) were charged into another glass-lined reactor. The mixture was stirred at 25−30 °C for 60 min for complete dissolution. This light-yellow solution was slowly added to the burgundy slurry over 90 min while maintaining internal reaction temperature between 15 and 20 °C. The reaction mixture was stirred at temperature range overnight. Once the reaction was determined to have stalled, glacial HOAc (3.48 kg, 58 mol) was slowly added over 30 min. The layers were separated, and the upper organic phase was back extracted with MeOH (14 L) and water (4.7 L). The combined lower aqueous/organic phase was extracted with DCM (32 L) and water (32 L). The layers were separated, and the aqueous phase was re-extracted with DCM (2 × 11 L). The combined organic layers were concentrated, and *n*-BuOH (210 L) was then slowly added during distillation while maintaining a total volume of ca. 80 L. Once addition was complete, the slurry was concentrated to a final volume of ca. 58 L and cooled to 40 °C. IPA (53 L) was then added over 30 min and the solution slowly cooled to 0 °C over 2 h. The solids were then filtered, washed with cold IPA (3 × 53 L), and dried with 60 °C N_2 flow to give 9.3 kg of PNU-288034 (79% yield) of 98 area% purity by HPLC.

The solids were then recharged into a new glass-lined reactor along with water (390 L) and toluene (90 L). The biphasic mixture was then heated to reflux (84 °C) and ca. 40 L of solvent was removed by vacuum distillation. While maintaining a hot biphasic solution, the phases were separated, the aqueous layer was concentrated to final volume of ca. 150 L and slowly cooled to 0 °C over 14 h. The resulting off-white solids were then filtered, washed with 0−5 °C water (2 × 50 L), and dried with 60 °C N_2 flow to give 5.7 kg of anhydrous PNU-288034 (63% isolated yield) with a second crop of 2.5 kg (27% yield). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.21 (t, J = 5.6 Hz, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 4.69−4.78 (m, 1H), 4.09 (t, J = 9.0 Hz, 1H), 3.70 (dd, J = 9.0 Hz, J = 7.9 Hz, 1H), 3.47−3.51 (m, 4H), 3.40 (t, J = 5.6 Hz, 2H), 3.20−3.24 (m, 4H) 1.83 (s, 3H). ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 22.32 (s), 41.23 (s), 47.08 (s), 49.79 (s), 51.89 (s), 71.63 (s), 101.95 (d, J = 29.1 Hz), 122.06 (d, J = 14.6 Hz), 135.71 (dd, J = 14.5 Hz, J = 13.8 Hz), 153.76 (s), 157.92 (dd, J = 245.0 Hz, J = 10.2 Hz) 169.90 (s). Anal. Calcd for $C_{16}H_{19}F_2N_3O_5S$: C, 47.64; H, 4.75; N, 10.42; F, 9.42; S, 7.95. Found: C, 47.58; H, 4.82; N, 10.39; F, 9.50; S, 7.91.

***N*-({(5S)-3-[4-(1,1-Dioxidothiomorpholin-4-yl)-3,5-difluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (PNU-288034, Alternative Pilot-Scale Prep). 14** (85.0 kg, 235 mol), **7** (90.8 kg, 469 mol), CH_3CN (133 kg), and MeOH (15.0 kg, 469 mol) were charged to a glass-lined reactor and cooled to 0−5 °C. Li*Ot*Bu (56.3 kg, 704 mol) was charged into a separate glass-lined reactor and cooled to 10−20 °C followed by THF (225 kg). The resulting compound **14** solution was then charged into the slurry over 1 h followed by line rinse with THF (25 kg) and the light-brown solution was then stirred at 16 °C. Once the reaction was determined to have stalled, glacial acetic acid (28.2 kg, 469 mol) and THF (55 kg) were charged to a separate glass-lined reactor, and the solution was slowly added to the reaction mixture over 1 h followed by water (440 L). The volume was then concentrated and then extracted with toluene (512 L) and MeOH (255 L) at 60−70 °C. The layers were separated warm, and both layers were either extracted or back extracted with water (340 L), MeOH (85 L), and toluene at 60−70 °C. The aqueous layers were combined and cooled to RT and then extracted with DCM (2 × 425 L). The organic layers were combined, and the total volume was reduced. Water (1254 kg) and MeOH (654 L) were then added, and the solution was distilled under atmospheric pressure until solution temperature reached 85.5 °C. The

concentrated solution was then cooled to 60−62 °C prior to seeding of PNU-288034 (425 g) in filtered water (2 L) and then again at 58−60 °C. The solution/slurry was then slowly cooled at 5 °C/h until solution temperature reached 40−45 °C at which time the cooling rate was increased to 10 °C/h until solution temperature reached 0−5 °C. The resulting white slurry was then filtered, washed with a cold solution of filtered water (320 kg) and MeOH (106 L), and dried with heated N_2 flow to give 76 kg of anhydrous PNU-288034 (80.3% isolated yield) of 99 area% HPLC purity.

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