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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.8b00386 • Publication Date (Web): 27 Nov 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

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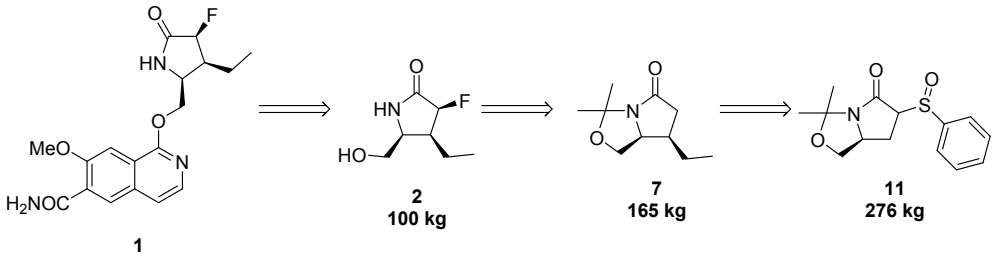


Keywords: diastereoselective, fluorination, cuprate, conjugate addition, sulfoxide, elimination, γ-lactam

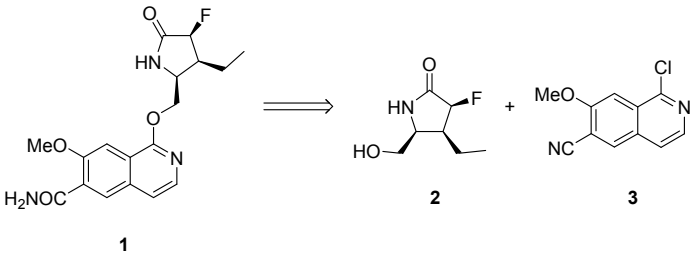
Abstract:

An improved process for the large scale synthesis of 1-{[(2S,3S,4S)-3-ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (**1**), a candidate currently in clinical development, was developed. Key objectives were to eliminate chromatographic purifications, to maximize the reproducibility of each step, and to improve the yield and efficiency of each step relative to the previous discovery syntheses of **1**. This work was focused on improvements to the synthesis of the stereochemically complex lactam **2**. Steps of particular concern were the preparation of the unsaturated lactam **6**, the cuprate conjugate addition reaction to produce **7**, and the conversion of **7** to **8** with a high degree of diastereoselection. The solutions to these challenges have permitted the synthesis of **2** in excess of 100 kg, which in turn has permitted **1** to be prepared in sufficient amounts to support further development.

Introduction:

Interleukin-1 receptor associated kinase 4 (IRAK-4) is a serine threonine kinases that plays a key role in innate immune signaling. IRAK-4 is activated by the interleukin (IL-1) family receptors (IL-1R, IL-18R, and IL-33R), as well as the Toll-like receptors (TLRs). Inhibition of IRAK-4 blocks the production of inflammatory cytokines such as type I interferons, tumor necrosis factor (TNF), IL-1, IL-6, and IL-12 that are key drivers of autoimmune and inflammatory diseases. IRAK-4 is an attractive therapeutic target for diseases associated with dysregulated inflammation, such as systemic lupus erythematosus and rheumatoid arthritis.[1] Recently, we described the synthesis and biological activity of 1-{[(2*S*,3*S*,4*S*)-3-ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (PF-06650833, **1**).[2] The principal challenges with the synthesis of **1** arise from the need to control the stereochemistry of the lactam fragment **2**, which contains three contiguous stereocenters, the integrity of which must be maintained throughout the synthesis (Scheme 1).

Scheme 1: Retrosynthesis of **1**



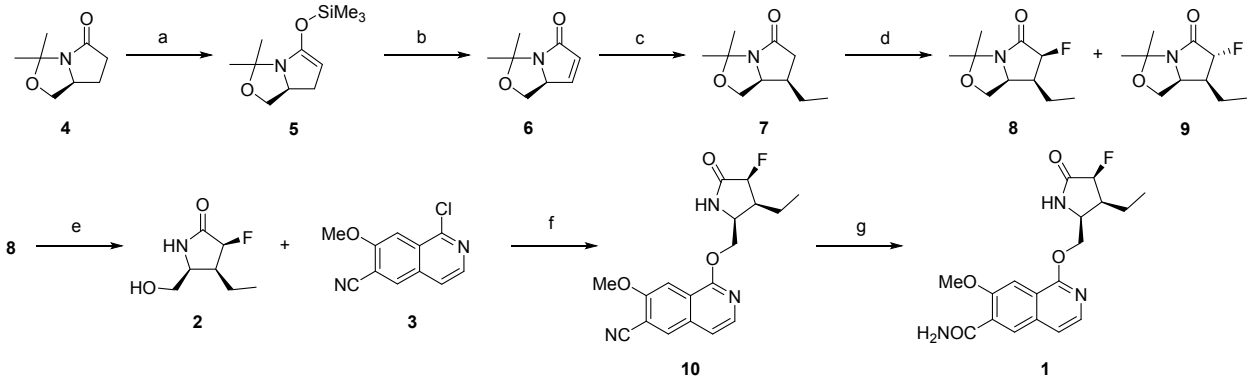
The stereocenter at C-5 is derived from the chiral pool, starting with (*S*)-pyroglutamic acid. The stereocenter at C-4 is then introduced *via* a diastereoselective cuprate conjugate addition reaction. Lastly, the stereocenter at C-3 is introduced by enolate formation and reaction with an appropriate electrophile.

Results and Discussion:

The original synthesis of **1** was carried out as shown in Scheme 2, starting with the known keto-aminal of (*S*)-pyroglutaminol **4**.[3] The olefin was introduced in 73% yield by a modified Tsuji oxidation[4] of the trimethylsilyl enol ether **5**, rather than the more customary approach *via* a selenoxide elimination.[5] The resulting unsaturated lactam **6** was treated with an excess (1.5 equivalents) of an organocopper reagent prepared from equimolar amounts of lithium (2-thienyl)cyanocuprate[6] (LiThCN) and ethylmagnesium chloride in the presence of 2.0 equivalents of chlorotrimethylsilane (TMSCl) at -70 °C to afford the ethyl substituted lactam **7** in 90% yield with high (30:1) *syn* diastereoselection.[7] Certain α,β-unsaturated γ-lactam substrates have been shown to undergo productive conjugate addition reactions with organocopper reagents in the absence of TMSCl.[8] However, the addition of TMSCl has been found to be necessary for productive reaction of N-alkyl α,β-unsaturated γ-lactams, which otherwise suffer γ-deprotonation.[9] The combination of organocopper reagents with TMSCl has been found to accelerate and

improve conjugate additions,[10] and may accelerate the collapse of the *d*-π complex with concurrent C-C bond formation.[11] Thus the TMSCl mediated conjugate addition of organocopper reagents to N-alkyl α,β-unsaturated γ-lactams has been well established.[12] These reactions must be conducted at temperatures below -55 °C to prevent alkylation of the TMSCl by the organocopper reagent.[10] The conjugate addition of organocopper reagents to **6** was previously unknown and occurred with a reversal of the diastereoselection observed previously.[7, 12]

Scheme 2: First Discovery Synthesis of **1**[a]



[a]Conditions: (a) LDA (1.2 equiv), TMSCl (1.3 equiv), THF, -60 °C, 30 min; (b) allyl methyl carbonate (1.1 equiv), $Pd(OAc)_2$ (0.05 equiv), THF, 65 °C, 2 h, 73% (2 steps); (c) LiThCN (1.5 equiv), EtMgCl (1.5 equiv), TMSCl (2.0 equiv), THF, -78 °C, 6 h, 90%; (d) LDA (1.8 equiv), NFSI (1.25 equiv), THF, -78 °C, 1 h, 23% (**8**), 45% (**9**); (e) pTsOH (0.05 equiv), MeCN, H_2O, 90 °C, 2 h, 97%; (f) **3** (0.9 equiv),

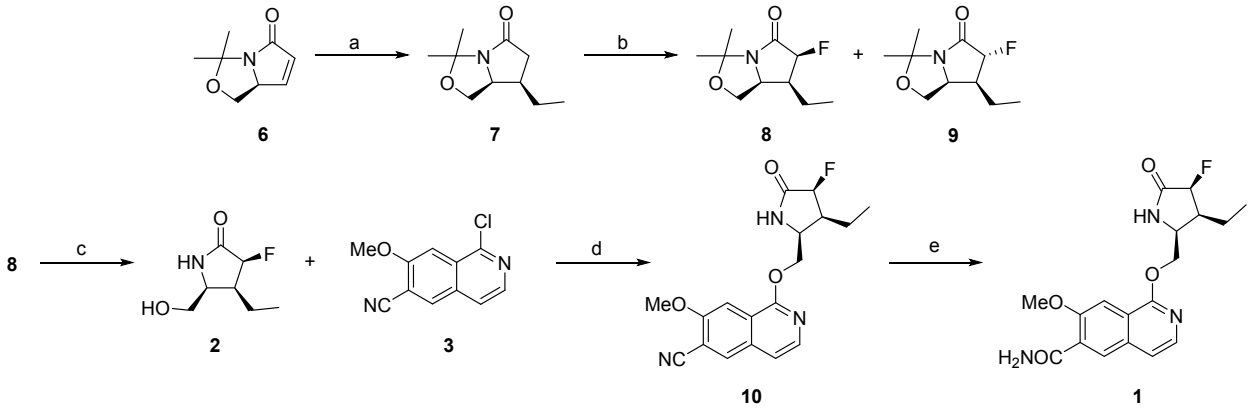
KHMDS (2.0 equiv), DMF, THF, -10 °C, 30 min, 84%; (g) H_2O_2 (10 equiv), K_2CO_3 (4.0 equiv), DMSO, 20 °C, 2 h, 97%.

Fluorination to afford **8** was accomplished in 23% yield by enolate formation with 1.8 equivalents of LDA at -70 °C followed by treatment with 1.25 equivalents of N-fluoro(bis(benzenesulfonyl)imide) (NFSI), a well established reagent for the fluorination of γ-lactam enolates.[13] In this reaction, diastereoselection was relatively poor (2:1) and favored the undesired *anti* isomer **9** (45% yield). Nevertheless, sufficient **8** could be obtained in this way to support medicinal chemistry efforts. Cleavage of the acetonide protecting group under acidic conditions (catalytic pTsOH in aqueous MeCN at 90 °C) yielded the alcohol **2** in 97% yield following purification by chromatography. The synthesis was completed by coupling the alcohol **2** to the chloroisoquinoline **3**[14] via a S_NAr reaction using 2.0 equivalents of potassium hexamethyldisilazide (KHMDS)[15] in a mixture THF and DMF at -10 °C to afford the intermediate **10** in 84% yield.[16] No epimerization of the fluoro group was observed under these conditions.[17] Nitrile hydrolysis using 10 equivalents of H_2O_2 and 4.0 equivalents of K_2CO_3 in DMSO[18] at 20 °C completed the synthesis and provided **1** in 97% yield following purification by chromatography.

Four improvements were made in order to facilitate the synthesis of larger amounts of **1** to support *in vivo* and preclinical safety studies (Scheme 3).[14] First, the organocopper reagent was prepared from copper(I) bromide – dimethyl sulfide complex[19] (2.0 equivalents) and ethylmagnesium bromide (4.0 equivalents) in THF at -5 °C. This allowed us to move away from the relatively dilute conditions of the LiThCN chemistry and eliminated some additional problems associated with that reagent: the need to generate the LiThCN reagent, to remove thiophene from the crude product, and to manage a cyanide containing waste stream. This provided the ethyl lactam **7** in 88% yield with the same high diastereoselection observed previously. Second, the unwanted *anti* fluorination isomer **9** was epimerized to provide more of the desired all *syn* isomer **8** by means of a kinetic protonation (Scheme 4). The *anti* fluoro isomer **9** was converted to the enolate **11** with 1.1 equivalents of LDA at -70 °C in toluene, followed by protonation with 2.0 equivalents of a sterically hindered acid (2,6-di-*t*-butyl-4-methylphenol, BHT) at a temperature below -65 °C. This procedure afforded a 44% yield of **8** and 27% of the *anti* isomer **9** following chromatography. This procedure improved the throughput of the desired isomer **8**, albeit at the cost of an added step and further silica gel chromatography.[20] Third, the acetonide was cleaved with catalytic TFA in aqueous MeCN at 65 °C. This allowed the lactam alcohol **2** to be isolated in 98% yield by concentration followed by crystallization and drying without need for chromatography. Lastly, nitrile hydrolysis of **10** was effected using MsOH as reagent and solvent at 60 °C instead of using

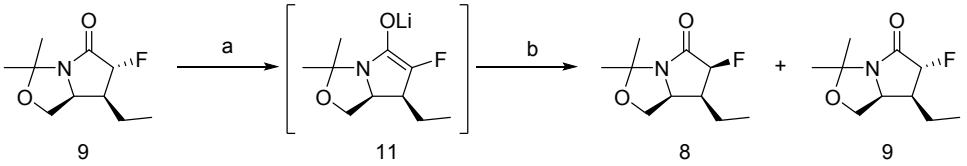
the K_2CO_3 - H_2O_2 - DMSO conditions used previously, which were perceived to be less desirable for scale up.[21] The crude **1** was isolated by extraction and purified by recrystallization to provide **1** in 91% yield.

Scheme 3: First Generation Scale Up Synthesis of **1**[a]



[a]Conditions: (a) CuBr • Me_2S (2.0 equiv), EtMgBr (4.0 equiv), TMSCl (1.5 equiv), Et_2O, THF, -70 °C, 4 h, 88%; (b) LDA (1.05 equiv), NFSI (1.05 equiv), THF, -70 °C, 2 h, 37% (**8**), 54% (**9**); (c) TFA (0.2 equiv), MeCN, H_2O, 65 °C, 4 h, 98%; (d) **3** (0.9 equiv), KHMDS (2.0 equiv), DMF, THF, -10 °C, 75 min, 90%; (e) MsOH (7.5 equiv), 60 °C, 26 h, 91%.

Scheme 4: Epimerization of **9** to **8** by Kinetic Protonation[a]



9 11 8 9

[a]Conditions: LDA (1.1 equiv), $PhCH_3$, -78 °C, 2.5 h; (b) 2,6-di-*t*-butyl-4-methylphenol (2.0 equiv), -65 °C, 3.5 h, 44% (**8**), 27% (**9**).

In order to provide sufficient **1** for further development, a significant route optimization effort was undertaken. Key objectives of this work were to maximize the reproducibility of each step, eliminate the chromatographic purification of intermediates, improve the yield and efficiency of each step, and reduce raw material costs. Three transformations warranted especial attention:

(1) The preparation of the unsaturated lactam **6** via the Tsuji oxidation was difficult to carry out on larger scales, due to the need to obtain the intermediate silyl enol ether **5** free from both diisopropylamine and lithium chloride.[22] This required distillation of the diisopropylamine and THF solvent with hexanes followed by filtration of a hexane solution of **5** to remove the lithium chloride. Failure to completely remove these intermediate by-products would result in stalling of the Tsuji catalytic cycle and recovery of the starting lactam **4**.

(2) The cuprate conjugate addition reaction faced two major hurdles to further scale up. The greatest concern was the preparation the organocopper reagent at temperatures between -3 and -30 °C,

followed by cooling of the resulting organocopper solution to -70 °C prior to the sequential addition of TMSCl followed by lactam **6**. This was problematic due to the amount of time required to accomplish both the preparation of the organocopper reagent and also the subsequent cooling operation, time periods that necessarily increased with increasing scales. The organocopper solution was found to degrade with time and therefore decomposition of the reagent became exacerbated at larger scales due to the increased times required to prepare and cool larger volumes. Lacking an in-process control procedure to reliably determine the potency of the organocopper reagent, this was viewed as a serious risk for failure of this step. In addition, the use of stochiometric or super-stochiometric amounts of copper salts would result in unacceptably large waste streams. The use of large amounts of CuBr • Me_2S in particular would have been prohibitively expensive and have required scrubbing procedures to trap the evolved Me_2S.

(3) The most significant problem was clearly the fluorination of **7** to produce the desired all *syn* lactam **8**. Further use of NFSI to accomplish this transformation would have resulted in unacceptable reagent costs and could have exceeded supply capacity. More importantly, the use of NFSI provided the desired isomer **8** as the minor diastereomer and the diastereomeric ratio was not materially influenced by selection of reaction conditions. While the BHT mediated epimerization procedure (*vide supra*) was successfully implemented in early synthetic work, both the NFSI fluorination and epimerization procedures required extensive chromatographic purifications which were not deemed acceptable for

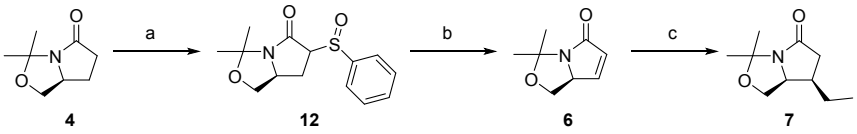
larger scale work. Initially a dynamic kinetic epimerization by crystallization procedure was investigated, which capitalized on the fact that the desired **8** is a solid (mp 55 - 57 °C) while the undesired isomer **9** is an oil at 20 °C. However, this procedure proved to be difficult to scale up and was better suited to upgrading material that contained primarily **8** than it was to the conversion of large excesses of **9** to **8**.

With these limitations in mind, research was conducted to identify appropriate solutions to permit the synthesis of **1** to be conducted successfully in amounts of thirty kilograms or more. As a result of this effort, solutions to these principal issues were identified and further optimization of other steps was accomplished to facilitate the purification and isolation of intermediates and eliminate chromatography. The solutions to the three principal issues noted previously were the following:

(1) The thermal elimination of the previously unknown sulfoxide **12** provided convenient introduction of the olefin to access unsaturated lactam **6** (Scheme 5). The sulfoxide was readily prepared from **4** by a base mediated condensation with 1.5 equivalents of methyl benzenesulfinate[23] using NaH[24] in THF at around 45 °C to afford the sulfoxide **12** after quenching with water, acidification with AcOH, extraction, and crystallization from a mixture of heptane and MTBE to afford the sulfoxide **12** in 72% yield as an equal mixture of two diastereomers as determined by ^{1}H NMR.[25] Formation of sulfoxides such as **12** in one step by enolate condensation has been little used in γ-lactams,[26] with two step procedures

involving sulfide formation and subsequent oxidation being more common.[27] The one step condensation procedure which avoids the need for an oxidation step was preferred. While it might be anticipated that $PhSO_2Me$ could react to transfer a methyl group, no Me transfer products were observed. Elimination of **12** to provide **6** was accomplished by heating a toluene solution of **12** at 110 °C[28] in the presence of 3.0 equivalents of anhydrous disodium phosphate[29] until the elimination was completed, after which the mixture was cooled, diluted with heptane, and **6** was extracted into a 1:6 (v/v) mixture of methanol and water.[30] The aqueous solution was then extracted with CH_2Cl_2 with the addition of NaCl to facilitate phase separation.[31] The CH_2Cl_2 extract was dried with Na_2SO_4 and partially concentrated prior to solvent exchange with THF. The resulting THF solution of **6** was taken into the next step as – is.

Scheme 5: Preparation of **7** by Telescoped Sulfoxide Elimination and Cuprate Addition[a]



[a]Conditions: (a) $PhSO_2Me$ (1.5 equiv), NaH (2.1 equiv), THF, 45 °C, 11 h, 72%; (b) Na_2HPO_4 (3.0 equiv), PhMe, 110 °C, 14 h; (c) EtMgBr (1.2 equiv), TMSCl (1.1 equiv), CuI (0.07 equiv), -70 °C, 4.5 h, 87% (2 steps).

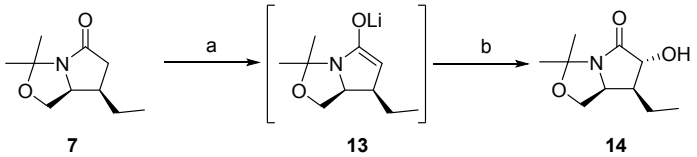
(2) The keys to successful scale up of the cuprate addition were the discoveries that this reaction could be carried out with catalytic amounts of copper(I) and that CuI was entirely satisfactory for this purpose.[32] While the use of catalytic amounts of copper(I) salts has been reported for the conjugate addition of Grignard reagents to N-sulfonyl α,β-unsaturated γ-lactams,[33] the use of catalytic amounts of copper(I) salts to effect the conjugate addition of Grignard reagents in the presence of TMSCl has not been widely practiced.[34] This is likely due to concern about the potential of TMSCl to silylate the Grignard reagent directly to afford an organyltrimethylsilane, and in small scale work there is little incentive to investigate the use of catalytic amounts of copper(I) salts. However, a review of the literature suggested that the direct alkylation of TMSCl by Grignard reagents was rather slow at temperatures of 0 °C or below.[35] Thus we had reason to anticipate that a mixture of EtMgBr, TMSCl, and catalytic Cu(I) could be maintained at < -60 °C without consumption of the TMSCl by either the EtMgBr or the organocopper species present. Experimentation showed that indeed a mixture of excess EtMgBr and catalytic (<10 mole percent) CuI could be prepared at -60 °C and treated with TMSCl at -70 °C without significant reaction between the TMSCl with the Grignard reagent, which would have prevented a successful conjugate addition reaction upon addition of **6**. This procedure eliminated the time dependent cuprate formation and cooling steps, reduced the amount of TMSCl and Grignard regent employed, and greatly reduced the amount of copper salts required for successful reaction while still delivering **7** with

excellent yields and diastereoselectivity. The substitution of the more readily available CuI for CuBr • Me_2S reduced costs and eliminated the need to control Me_2S with no effect on reaction profile. As performed, a suspension of 7 mole percent[36] of CuI in THF was cooled to -60 °C and treated with 1.2 equivalents of 1 M EtMgBr in THF. The mixture was cooled to -70 °C and TMSCl (1.1 equivalents) was added, followed by the THF solution of **6** prepared previously. The mixture was kept at -70 °C until **6** had been consumed, after which the reaction mixture was transferred into a solution of NH_4Cl. Following completion of the quench, the mixture was filtered and extracted with MTBE. The extract was washed with brine, filtered, and solvent exchanged with THF to provide a THF solution of **7** in 87% yield and 94% purity with no detectable amounts of other stereoisomers of **7** present.

(3) Among the options that could be considered to convert **7** to **8**, the introduction of an alcohol function *anti* to the ethyl group, followed by displacement with inversion to afford the *syn* fluoride was considered the most desirable (Scheme 6). A significant cost savings could be realized by changing from an electrophilic to a nucleophilic fluorination reagent if (a) a highly diastereoselective synthesis of the alcohol **14** could be realized, and (b) deoxofluorination of **14** could be accomplished with excellent preservation of stereochemical integrity. Previous work during the medicinal chemistry effort had shown that diastereoselective *anti* functionalization of the enolate **13** could be achieved with some reagents, including *anti* selective hydroxylation with bulky oxaziridine reagents.[37] A significant effort was therefore

put into the identification of a highly diastereoselective enolate oxidation procedure, one which could be carried out safely and which employed an inexpensive, readily available oxidizing agent.[38] Initial work using oxygen at -70 °C to oxidize the lithium enolate **13** gave a 4:1 ratio of diastereomers in favor of **14**. However, the use of lithium *t*-butylperoxide (*t*-BuOOLi) afforded **14** with greater than 30:1 diastereoselectivity. To be successful, this reaction required anhydrous *t*-butyl hydroperoxide which was recognized to be a potential safety hazard on large scale.[39] Accordingly, the reaction sequence was adapted to a flow process that simultaneously generated an anhydrous solution of *t*-butyl hydroperoxide in nonane *in situ* using a membrane pervaporation procedure, and consumed this solution by reaction with the lithium enolate **13**. The ultimate result of that work was a flow process that accomplished (1) the drying of the *t*-butyl hydroperoxide feedstock, (2) the formation of the lithium enolate **13** from **7** using lithium hexamethyldisilazide (LiHMDS), and (3) the subsequent oxidation of **13** to afford **14** in 74% yield, as a solution that was carried directly to the fluorination step.

Scheme 6: Diastereoselective Oxidation of **7** to **14**[a]

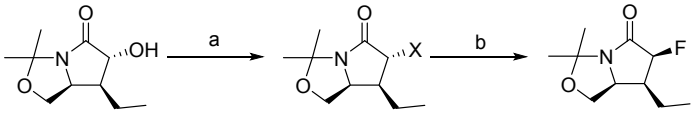


7 **13** **14**

[a]Conditions: (a) LHMDS (2.2 equiv), THF, -20 °C; (b) LiOOtBu, nonane, -20 °C → 0°C, 70% (2 steps).

While many reagents are available to accomplish deoxofluorination, those formally derived from SF_4 are known to generally possess undesirable thermal stability profiles.[40] Initial efforts to convert the alcohol **14** to the fluoride **8** with inversion therefore converted the alcohol **14** to the triflate **15a** with triflic anhydride and 2,6-lutidine, which then underwent S_N2 fluorination with triethylamine trihydrofluoride to afford **8** in 60% yield.[41] (Scheme 7). This procedure was an improvement over the original NFSI chemistry with its attendant chromatography needs; however, the use of triethylamine trihydrofluoride as a fluoride source and triflic ahydride, while manageable for large scale, were not considered ideal.[42] The use of inexpensive nonafluorobutanesulfonyl fluoride offered a more suitable option for the conversion of **14** to **8** on large scale. This reagent has seen steady acceptance as a deoxofluorinating reagent since its introduction,[43] most commonly with DBU or DIEA used as the base.

Scheme 7: Conversion of **14** to **7** with Inversion of Configuration[a]



14 **15** **8**

a, X = OTf
b, X = $OSO_2C_4F_9$

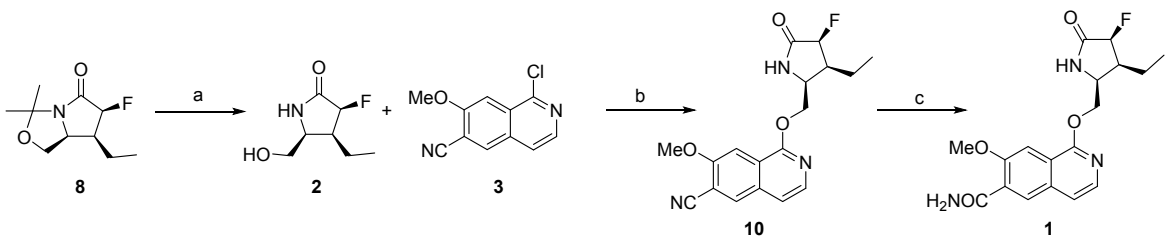
[a]Conditions: (a) Tf_2O (1.2 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, -5 °C, 10 min (for **15a**); $C_4F_9SO_2F$ (1.3 equiv), TMEDA (1.4 equiv), PhMe, 20 °C, 23 h (for **15b**); (b) Et_3N • 3HF (1.5 equiv), 2,6-lutidine (3.0 equiv), 2-MeTHF, 20 °C, 3 h (for **15a**), 60% (2 steps); No further reagents (for **15b**), 72%.

This reagent permitted the alcohol activation and S_N2 displacement by fluoride ion to be accomplished in a single step, without need for the isolation of the intermediate sulfonate ester or the use of an anhydrous, organic solvent - soluble fluoride ion source. Optimized conditions for the transformation introduced the *anti* alcohol **14** as a solution in 2-MeTHF and THF from the flow oxidation step. This was diluted with toluene and treated with TMEDA[44] (1.4 equiv) followed by nonafluorobutanesulfonyl fluoride (1.3 equiv) at 20 °C for 16 h. Following water washing and extraction, crystalline **8** could be isolated in 72% yield and 98% purity by the partial distillation of solvent, addition of heptane and crystallization at 0 °C.[45]

The remaining steps in the synthesis of **1** were the hydrolysis of the acetonide protecting group of **8**, the S_NAr reaction between **2** and **3** to afford **10**, and final nitrile hydrolysis of **10** to afford **1**. These steps were carried out with relatively little modification from previous work, with the exception that nitrile hydrolysis step was effected using H_2SO_4 instead of MsOH. The lactam alcohol **2** was isolated as a

crystalline solid from the acetonide hydrolysis. Optimized conditions for the acetonide cleavage used TFA (0.2 equiv) in 3% aqueous MeCN, after which **2** was isolated by crystallization from *i*-PrOAc and heptane in 79 to 90% yield. The S_NAr reaction was conducted as described previously using 2.2 equivalents of KHMDS at -10 °C, with the workup modified to permit isolation of the intermediate **10** as a crystalline solid. The reaction mixture was diluted with EtOAc, then quenched into a solution of NaH_2PO_4 (4.0 equiv.) in water. The EtOAc was partially distilled, toluene was added and the mixture was distilled further to remove EtOAc and crystallize **10** in 73% yield. The purified **10** was dissolved in H_2SO_4 (19 equiv.) and heated to 80 °C until nitrile hydrolysis was complete. The cooled mixture was diluted into NH_3 solution (47 equiv.) at 5 °C, then crystallized by the addition of EtOH, warmed to dissolve the solids present, and then allowed to cool to permit **1** to crystallize. The solid was filtered, washed with water and dried prior to recrystallization from EtOH and water with decolorizing carbon to afford the purified **1** in 82% yield.

Scheme 8. Conversion of **8** to **1**[a]



[a]Conditions: (a) TFA (0.2 equiv), H_2O (6.7 equiv), MeCN, reflux, 5 h, 79%; (b) KHMDS (2.2 equiv), THF, DMF, -10 °C, 6.5 h, 73%; (c) H_2SO_4, 80 °C, 4 h, 82%.

Summary

An improved process for the large scale synthesis of 1-{[(2S,3S,4S)-3-ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (**1**), a clinical candidate, was developed. Key objectives for improvement of the discovery synthetic route were: (1) a scaleable procedure for the synthesis of the unsaturated lactam **6**; (2) an improved procedure to accomplish the conjugate addition reaction to produce **7** in good yield and with high diastereoselectivity, with reduced use of copper salts and no dependence upon cooling times; (3) the preparation of **8** from **7** in good yield and with high diastereoselectivity; (4) the elimination of the intensive chromatography attendant to the preparation and purification of **8**, and (5) the reduction of costs associated with raw materials and processing. A sulfoxide elimination provided a suitable method for the preparation of **6**, while the conjugate addition could be carried out with only catalytic amounts of CuI which eliminated the troublesome dependence upon cooling times associated with this step. The preparation of **8** from **7** was achieved by the highly diastereoselective oxidation of enolate **13** to **14** with *t*-BuOOLi in a flow process, after which activation and S_N2 inversion of **14** with nonafluorobutanesulfonyl fluoride provided **8**.

Successful scale up of the final three steps and purification by recrystallization allowed **1** to be prepared in batches of greater than 30 kg at a time.[46]

Experimental Section

All new compounds were characterized by proton (^{1}H) NMR spectra using Bruker spectrometers and are reported in parts per million (ppm) relative to the residual resonances of the deuterated solvent. Carbon (^{13}C) NMR spectra (proton decoupled) were recorded similarly. Elemental Analyses were performed by Intertek, 291 Rte. 22 East, PO Box 470, Whitehouse, NJ 08888. Low-resolution mass spectrometry analyses were conducted on Waters Acquity UPLC and SQ systems. High-resolution mass spectrometry analyses were conducted on an Agilent 6220 TOF mass spectrometer in positive electrospray mode. The system was calibrated to greater than 1 ppm accuracy across the mass range prior to analyses. The samples were separated using UHPLC on an Agilent 1200 system prior to mass spectrometric analysis.

All water used in these preparations was purified water. Solvents used were commercial anhydrous grades that were used as received. Residual water was determined using Karl Fischer titration (KF). Residual solvents were determined by GCMS. Chiral purity determinations were made by gas chromatography.[47]

All previously reported compounds prepared in this work were identical in their compound characterization to properties reported previously.[2,7]

(7aS)-3,3-dimethyl-6-(phenylsulfinyl)tetrahydro-3H,5H-pyrrolo[1,2-c]oxazol-5-one (12): A clean and dry 8000 L glass-lined reactor was evacuated to 0.05 to 0.08 MPa and then filled with nitrogen to normal pressure. This was repeated 3 times. The reactor was sampled for oxygen content to ensure it was ≤ 1.0%. The reactor was rinsed with THF (83.0 kg), and the rinsing liquor was discharged to establish a residual water content of ≤ 0.05%. Sodium hydride (60% in oil, 109.6 kg containing 65.8 kg NaH, 2742 mol, 2.0 equiv) was added at 15 to 30 °C under nitrogen. The mixture was adjusted to 10 to 20 °C, and THF (2698 kg) was added. After the addition, the mixture was bubbled with nitrogen for 1 h, then heated to 50 to 55 °C and maintained at that temperature for 0.5 to 1 h.

A solution of **4** (205.9 kg, 1327 mol, 1.0 equiv) in THF (767 kg) was prepared in a dry 3000 L reactor under nitrogen. The mixture was stirred until it was homogenous, then was added into the 8000 L reactor at 50 at 55 °C at a rate of 110 to 200 kg/h. Once the addition was complete, the mixture was maintained at 50 to 55 °C for 0.5 to 1 h, then cooled to 45 to 50 °C. A solution of methyl benzenesulfinate (319.6 kg, 2046 mol, 1.5 equiv) in THF (915.6 kg) was added into the mixture in five portions at a rate sufficient to maintain the temperature at 45 to 55 °C, while allowing 0.5 to 1 h between additions to allow hydrogen

evolution to subside between additions. Once the addition was complete, the mixture was stirred at 35 to 48 °C with periodic nitrogen sparging. After about 6 h, the mixture was sampled every hour for HPLC analysis until the content of **4** was ≤ 1%.

Once the reaction was complete by HPLC analysis, the mixture was cooled to -5 to 0 °C. While maintaining the temperature at -5 to 5 °C, water (414.4 kg) was added into the mixture to quench the reaction. Then the mixture was stirred for 20 to 30 min at -5 to 5 °C. The mixture was purged with nitrogen until the hydrogen content was ≤0.5%. Acetic acid (227.4 kg, 3784 mol, 2.8 equiv) was added at a rate of 20 to 50 kg/h to adjust the verified pH to 4 to 6. Stirring was then continued for 20 to 30 min at -5 to 5 °C. The mixture was then concentrated at ≤ 35 °C under reduced pressure (≤ 0.08 MPa) until the remaining volume was between 600 and 1000 L. Water (2065.0 kg) and CH_2Cl_2 (2755.4 kg) were added, stirred for 0.5 to 1 h at 15 to 30 °C, and settled for 0.5 to 1 h before separation of the CH_2Cl_2 phase. The aqueous phase was extracted with additional CH_2Cl_2 (1374.7 kg) and stirred and settled as before. The combined CH_2Cl_2 extracts were concentrated at ≤ 40 °C under reduced pressure (≤ 0.08 MPa) until the remaining volume was between 600 and 800 L. MTBE (1378.8 kg) was added and the mixture was stirred concentrated as before until the remaining volume was between 600 and 1000 L. The mixture was sampled for residual CH_2Cl_2 and KF analysis until residual CH_2Cl_2 was ≤ 10% and water was ≤ 0.15%.

Heptane (847.0 kg) was added and the mixture was stirred for 10 to 20 min before cooling to 5 to 10 °C for 1 to 2 h. The mixture was filtered with a stainless steel centrifuge. The filter cake was rinsed with MTBE (307.2 kg) until purity analysis by HPLC showed ≥ 95% purity. The filter cake was dried in a rotary conical dryer at 35 to 45 °C under reduced pressure (≤ 0.08 MPa) until sampling for residual solvents and KF analysis showed residual MTBE ≤ 0.5%, residual heptane ≤ 0.5%, and residual water ≤ 0.1%. There was obtained 268.1 kg (72%) of **12** as a fine white powder, melting point 153 - 155 °C. Both the ^{1}H and ^{13}C NMR data were consistent with the presence of two diastereomers in present in equal proportions. ^{1}H NMR (500 MHz, CD_3OD) δ 7.68 - 7.73 (m, 2 H), 7.53 - 7.65 (m, 8 H), 4.39 (dd, *J* = 10.76, 8.31 Hz, 1 H), 4.16 - 4.28 (m, 2 H), 4.08 (dd, *J* = 8.31, 5.62 Hz, 1 H), 3.51 (dd, *J* = 9.29, 8.31 Hz, 1 H), 3.39 (dd, *J* = 9.78, 8.31 Hz, 1 H), 2.40 (ddd, *J* = 14.43, 7.34, 2.20 Hz, 1 H), 2.23 (ddd, *J* = 12.84, 10.64, 8.07 Hz, 1 H), 2.01 (ddd, *J* = 14.43, 10.03, 7.34 Hz, 1 H), 1.69 (ddd, *J* = 12.84, 8.19, 6.60 Hz, 1 H), 1.65 (s, 3 H), 1.64 (s, 3 H), 1.45 (s, 3 H), 1.43 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (126 MHz, CD_3OD) δ = 167.6, 166.9, 142.3, 141.9, 133.0, 132.6, 130.8, 130.7, 125.6, 125.3, 93.4, 93.4, 73.9, 73.0, 71.1, 70.7, 62.6, 60.3, 27.3, 27.0, 24.2, 23.9, 19.3, 19.2. IR (neat): 1690, 1043 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01; S, 11.48. Found: C, 60.12; H, 6.25; N, 5.02; S, 11.67. HRMS (ESI/QTOF) m/z: $[M+H^+]$ Calcd for $C_{14}H_{17}NO_3S$ 280.1002; Found: 280.1000.

(S)-3,3-dimethyl-1,7a-dihydro-3H,5H-pyrrolo[1,2-c]oxazol-5-one (6): A clean and dry 8000 L glass-lined reactor was prepared under N_2 as described above. The reactor was charged with toluene (379.9 kg) and sampled to establish residual water at ≤ 0.05%. Additional toluene (2145.9 kg) was added to the reactor and stirred for about 10 min. Anhydrous Na_2HPO_4 (447.2 kg, 3149 mol, 3.0 equiv) was added at 15 to 30 °C, followed by **12** (290.5 kg, 1064 mol, 1.0 equiv). The mixture was heated to 80 to 85 °C, and maintained for 1 h, then heated further to 95 to 115 °C. After 14 h, HPLC analysis showed ≤ 1.0% of **12** remaining. The mixture was cooled to 10 to 30 °C and filtered through a stainless steel filter, and the reactor was rinsed with toluene (507.3 kg). The filter cake was washed with the rinsing liquor and the combined filtrates were concentrated at ≤ 45 °C under reduced pressure until the remaining volume was between 600 and 1200 L. The solution was cooled to 15 to 25 °C, diluted with heptane (3979.6 kg), stirred for 30 min, and cooled to -5 to 5 °C. The mixture was extracted three times with equal portions of a solution prepared from methanol (663.4 kg) and water (4834.0 kg), pre-cooled to -5 to 5 °C. Each extraction operation was stirred for 30 to 40 min and then allowed to settle for 15 to 30 min before separation of the phases. The combined aqueous phases were extracted with CH_2Cl_2 (3857.0 kg) for 20 to 30 min, then NaCl (86.8 kg) was added and stirred for 5 to 10 min to facilitate phase separation. The aqueous phase was extracted twice more with CH_2Cl_2 (1937.8 kg, 1886.6 kg). Each time the mixture was stirred for 15 to 30 min and allowed to settle for 15 to 30 min prior to phase separation. The combined

CH_2Cl_2 extracts were adjusted to 10 to 20 °C and dried with anhydrous Na_2SO_4 (100.0 kg) with stirring for 30 min until KF analysis showed ≤ 1.0% water remaining. The mixture was filtered with a stainless steel filter and the filter was washed with CH_2Cl_2 (771.4 kg). The combined CH_2Cl_2 filtrates were concentrated at ≤ 35 °C under reduced pressure (≤ 0.06 MPa) until the remaining volume was between 450 and 700 L. THF (777.0 kg) was added and the distillation was continued until the remaining volume was between 450 and 700 L. Two additional cycles of THF addition (775.0 kg, 776.8 kg) and distillation were conducted until analyses for residual water, MeOH and CH_2Cl_2 showed each to be present at ≤ 0.10%. The resulting solution of **6** was cooled to 15 to 25 °C, the reactor was rinsed with additional THF (101.4 kg), the rinsing liquor was combined, and the solution was chilled to -30 to -10 °C.

(7R,7aS)-7-ethyl-3,3-dimethyltetrahydro-3H,5H-pyrrolo[1,2-c]oxazol-5-one (7): A clean and dry 8000 L glass-lined reactor was prepared under N_2 as described above. The reactor was charged with THF (174.0 kg) at 15 to 30 °C and sampled to establish residual water ≤ 0.05%. Additional THF (532.6 kg) was added and N_2 was bubbled at bottom of reactor to degas for 20 min, after which CuI (8.0 kg, 73.1 mol, 0.07 equiv) was added through a solid addition funnel. After addition, the funnel was rinsed with THF (4.0 kg). The mixture was cooled to -65 to -60 °C, after which 1 M ethyl magnesium bromide in THF (1329.0 kg, 1245 mol, 1.2 equiv) was added into the reactor at a rate of 400 to 800 kg/h while maintaining the

temperature at -45 to -65 °C. Additional THF (10.6 kg) was used to rinse the addition port and the mixture was stirred for 40 to 60 min before being cooled to -78 to -65 °C. Me_3SiCl (124.0 kg, 1141 mol, 1.1 equiv) was added dropwise into the mixture. THF (10.0 kg) was used to rinse the addition line and the mixture was stirred for 1 to 2 h at -78 to -65 °C. The pre-cooled solution of **6** was added while maintaining the temperature at -78 to -65 °C. The vessel containing the solution of **6** was rinsed twice with THF (47.2 kg, 47.6 kg) and the washes were added into the reaction mixture. After 4.5 h, GCMS analysis showed that ≤ 1.0% of **6** remained. The reaction mixture was added into a pre-cooled (-10 °C) solution of NH_4Cl (95.4 kg) in water (953.0 kg) at a rate of 50 to 200 kg/h. The reactor was washed with THF (48.4 kg) and the wash liquor was combined with the mixture. The mixture was warmed to 10 to 20 °C and stirred for 2 h before being filtered through Celite® (23.8 kg). The filter cake was washed with MTBE (590.3 kg) and the filtrate was stirred for 1 h at 10 to 30 °C, then settled for 1 h before separation. The aqueous phase was further extracted with twice with MTBE (355.6 kg, 355.4 kg), stirring and settling before separation as before. The combined organic phases were washed with a brine solution prepared from NaCl (200.6 kg) and water (804.0 kg) prior to concentration at ≤ 40 °C under reduced pressure (≤ -0.08 MPa) until the remaining volume was 600 to 800 L. The mixture was filtered through Celite® (40.0 kg). The filter cake was washed five times with MTBE (236.4 kg, 235.5 kg, 234.9 kg, 235.0 kg, 234.4 kg). The last washing was sampled for **7** content and found to be < 0.1%. The combined organic phases

were concentrated at ≤ 40 °C under reduced pressure (≤ 0.08 MPa) until the remaining volume was 350 to 500 L. THF (694.8 kg) was added and concentration was repeated until the remaining volume was 350 to 500 L. Further addition of THF (695.0 kg, 694.8 kg) and concentration were conducted until analyses showed residual water ≤ 0.05% and MTBE ≤ 0.5%. Repeated additions of heptane (329.1 kg, 164.4 kg, 164.0 kg, 163.8 kg, 165.2 kg) and concentration to the same residual volume were conducted, after which THF (401.0 kg) was added and the mixture was cooled to 15 to 25 °C. There was obtained 635.0 kg of a solution of **7** containing 165.1 kg (87%) of **7** of 94% HPLC purity and 100% ee.

(6R,7S,7aS)-7-ethyl-6-hydroxy-3,3-dimethyltetrahydro-3H,5H-pyrrolo[1,2-c]oxazol-5-one (14): Two solutions of **7** prepared as above, containing in total 318.2 kg (1736 mol) of **7**, were converted to **14** in six approximately 53 kg batches as previously described.[36] Following workup and purification there was obtained 241.1 kg (1210 mol, 70%) of **14** as a solution in toluene containing approximately 24% by weight of **14**.

(6S,7S,7aS)-7-ethyl-6-fluoro-3,3-dimethyltetrahydro-3H,5H-pyrrolo[1,2-c]oxazol-5-one (8): A clean and dry 5000 L glass-lined reactor was prepared under N_2 as described above. A solution of **14** (118.1 kg, 593 mol, 1.0 equiv) in toluene (372.6 kg) was added, followed by additional toluene (704.0 kg). After

stirring for 20 min, perfluorobutane sulfonyl fluoride (231.6 kg, 767 mol, 1.3 equiv) and TMEDA (95.6 kg, 823 mol, 1.4 equiv) were added at 20 to 30 °C. After 23 h, HPLC analysis showed 7% of **14** remaining and the concentration of **14** did not change with further sampling. Water (1170.7 kg) was added at 20 to 30 °C, the mixture was stirred for 1 h and allowed to settle for 2 h before separation. The aqueous phase was extracted twice more with additional toluene (1011.9 kg, 509.4 kg), stirring and settling as before. The combined toluene solutions were transferred into a clean 5000 L reactor and washed twice with water (1189.9 kg, 354.8 kg), stirring and settling as before. The toluene solution was concentrated at ≤ 50 °C under reduced pressure (≤ 0.08MPa) until the remaining volume was between 150 and 250 L. Precipitated solids were dissolved by heating and stirring at 45 to 55 °C prior to the addition of heptane (237.6 kg). The mixture was sampled for toluene content until the remaining toluene content was between 10 and 18%. Once the toluene content was within specification, the mixture was cooled to 0 to 10 °C and maintained at that temperature for 2 h. Additional heptane (321.9 kg) was charged into the mixture over 5.5 h, then maintained at 0 to 10 °C for 2 h. The mixture was then cooled to -5 to -10 °C over 2.25 h before being filtered with a centrifuge. The filter cake was washed with heptane (79.8 kg) before being transferred into a rotary conical dryer. It was dried at 15 to 30 °C, under reduced pressure (≤ 0.06MPa) for 11 h until analyses for residual solvents detected no residual toluene or heptane. There was obtained 86.5 kg (72%) of **8** of 98% HPLC purity as brown crystals. ^{1}H NMR (400MHz,

DMSO) δ = 5.40 (dd, *J* = 7.4, 51.5 Hz, 1H), 4.09 - 3.98 (m, 2H), 3.67 - 3.56 (m, 1H), 3.67 - 3.56 (m, 1H), 2.75 - 2.64 (m, 1H), 1.54 (s, 3H), 1.51 - 1.40 (m, 1H), 1.36 (s, 3H), 1.34 - 1.21 (m, 1H), 0.87 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101MHz, DMSO) δ = 164.9 (d, *J* = 24.2 Hz), 92.4 (d, *J* = 195.1 Hz), 90.3, 64.1, 57.3, 41.2 (d, *J* = 16.1 Hz), 26.1, 23.1, 15.0 (d, *J* = 8.8 Hz), 12.5 (d, *J* = 2.9 Hz). ^{19}F NMR (H decoupled, 376 MHz, $CDCl_3$) δ -199.61.

(3S,4S,5S)-4-ethyl-3-fluoro-5-(hydroxymethyl)pyrrolidin-2-one (2): A clean and dry 1000 L glass-lined reactor was prepared under N_2 as described above and charged with CH_3CN (349.4 kg). A solution of **8** (73.5 kg, 365 mol, 1.0 equiv) in CH_3CN (126.4 kg) was added and stirred for 1 h at 10 to 30 °C, after which water (44.2 kg, 6.7 equiv) was added. After stirring for 30 min, CF_3CO_2H (8.3 kg, 73 mol, 0.2 equiv) was added and stirred for 30 min before being heated to reflux. After 5 h, HPLC analysis showed ≤ 0.1% of **8** remaining. The mixture was cooled to 25 to 35 °C and transferred to a clean reactor, along with CH_3CN (73.4 kg) used to wash the reactor. The CH_3CN solution was combined with a second CH_3CN solution resulting from similar processing of 86.5 kg (430 mol) of **8** for work up and crystallization. The combined solutions were concentrated at ≤ 40 °C under reduced pressure (≤ 0.08MPa) until the remaining volume was between 180 and 230 L. Three additional portions of CH_3CN (380.7 kg, 371.8 kg, and 376.9 kg) were added and distilled similarly. KF analysis showed 0.3% residual water present. Two portions of

iPrOAc (415.2 kg, 414.6 kg) were added and distilled similarly. Further iPrOAc (417.0 kg) was added; residual CH_3CN could not be detected. The solution was warmed to 45 to 55 °C and maintained for 1 h before being cooled to 25 °C over 4 h. Heptane (216.1 kg) was added over 2.75 h after which the mixture was stirred for 30 min at 25 °C. The mixture was further cooled to 0 to 10 °C and stirring was continued to promote crystallization. After 6.5 h, analysis of the supernatant liquid showed ≤ 3% of **2** present. The crystalline **2** was filtered with an agitating filter dryer. The reactor was washed with a mixture of iPrOAc (189.1 kg) and heptane (72.5 kg) and the washing was cooled to 0 to 10 °C. The filter cake was washed with this chilled solvent mixture before being dried at 25 to 30 °C for 12 h. Analyses showed residual CH_3CN 0.0%; iPrOAc 0.2%; heptane 0.0%; and water 0.1%. The solid was cooled to 15 to 30 °C and sieved until it was of uniform texture and appearance to provide 100.6 kg (79%) of **2** of 100% HPLC purity as brown crystals. ^{1}H NMR (400 MHz, DMSO) δ = 8.41 (br. s., 1H), 4.74 (br. s., 1H), 4.73 (dd, *J* = 5.1, 53.5 Hz, 1H), 3.56 - 3.44 (m, 2H), 3.30 - 3.21 (m, 1H), 2.45 - 2.26 (m, 1H), 1.53 - 1.40 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101MHz, DMSO) δ = 170.6 (d, *J* = 19.1 Hz), 90.4 (d, *J* = 179.0 Hz), 62.8 (d, *J* = 1.5 Hz), 56.9, 42.7 (d, *J* = 19.1 Hz), 16.0 (d, *J* = 7.3 Hz), 12.2. ^{19}F NMR (H decoupled, 376 MHz, $CDCl_3$) δ -198.72. LCMS: 162 (MH^+).

1-(((2S,3S,4S)-3-ethyl-4-fluoro-5-oxopyrrolidin-2-yl)methoxy)-7-methoxyisoquinoline-6-carbonitrile (10): A clean and dry 630 L glass-lined reactor was prepared under N_2 as described above. The reactor was charged with DMF (57 kg) and THF (53.3 kg) at 15 to 25 °C. After mixing, **3** (20.0 kg, 91.5 mol, 1.0 equiv) and **2** (14.7 kg, 91.5 mol, 1.0 equiv) were added and stirred for 20 min. After the water content was found to be ≤ 0.05%, the mixture was cooled to -5 to -15 °C. While at this temperature, KHMDS (20% in THF, 201.0 kg, 201.3 mol, 2.2 equiv) was added over 5 h and the pump and connecting lines were washed with 8.9 kg of THF. Stirring was continued for another 1.5 h, after which HPLC analysis showed 0.46% **3** remaining. The mixture was diluted with EtOAc (180.0 kg) and added into a precooled (0 to 5 °C) solution of NaH_2PO_4 (43.9 kg, 366 mol, 4.0 equiv) in water (200 kg) over 15 minutes, keeping the temperature at ≤ 10 °C during the quenching process. The reactor and transfer line were washed with EtOAc (18.0 kg) and the washings were added. After a pH check showed the pH of aqueous phase to be 7.8, the mixture was diluted with an additional 80 kg of water and the temperature was raised to 35 to 45 °C. The mixture was stirred for 30 min, allowed to settle for 30 min, and separated. The aqueous phase was extracted with additional EtOAc (180 kg), stirring and settling as before. The combined EtOAc solutions were cooled to 15 to 25 °C and washed with a solution of NaCl (18 kg) in water (360 kg) for 30 min. The EtOAc was distilled to a remaining volume of about 50 L under reduced pressure, after which toluene (173 kg) was added. Distillation was continued at ambient pressure until the

remaining volume was about 100 L and the distillation head temperature attained 110 °C, after which it was allowed to cool to ambient temperature and remain for 10 h. Analysis for residual EtOAc showed 0.14% remaining. The mixture was cooled to 5 to 10 °C for 1 h and transferred to a filter dryer. The reactor and filter cake were washed with additional cold (5 °C) toluene (34.6 kg). Drying was continued at 50 °C until analyses for residual solvents showed that EtOAc and THF ≤ 0.05%, DMF 0.17%, and toluene 0.22%. There was obtained 22.85 kg (73%) of **10** of 99.85% purity. ^{1}H NMR (400MHz, DMSO) δ = 8.89 (s, 1H), 8.51 (s, 1H), 7.98 (d, *J* = 5.9 Hz, 1H), 7.80 (s, 1H), 7.41 (d, *J* = 5.9 Hz, 1H), 4.90 (dd, *J* = 5.5, 53.5 Hz, 1H), 4.56 (dd, *J* = 3.3, 11.1 Hz, 1H), 4.24 (dd, *J* = 6.6, 10.9 Hz, 1H), 4.09 (td, *J* = 3.1, 6.2 Hz, 1H), 4.03 (s, 3H), 2.70 - 2.52 (m, 1H), 1.66 - 1.52 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101MHz, DMSO) δ = 171.0 (d, *J* = 19.1 Hz), 158.5, 156.9, 138.7, 134.5, 131.3, 121.4, 115.6, 114.7, 106.4, 103.6 (d, *J* = 4.4 Hz), 90.0 (d, *J* = 179.7 Hz), 66.7, 56.6, 53.9, 42.2 (d, *J* = 19.1 Hz), 16.3 (d, *J* = 8.1 Hz), 12.1. ^{19}F NMR (H decoupled, 376 MHz, $CDCl_3$) δ = -199.18. LCMS: 344 (MH^+).

1-(((2S,3S,4S)-3-ethyl-4-fluoro-5-oxopyrrolidin-2-yl)methoxy)-7-methoxyisoquinoline-6-carboxamide (1): A clean and dry 250 L glass-lined reactor was prepared under N_2 as described above. The reactor was charged with 98% H_2SO_4 (200.4 kg, 2000 mol, 19 equiv) at 20 to 30 °C, after which **10** (36.3 kg, 106 mol, 1.0 equiv) was added and stirred to dissolve. The mixture was heated at 75 to 85 °C for 4 h, then

cooled 15 to 25 °C. Analysis showed 0.49% **10** remaining. During the heating period, a chilled (0 to 5 °C) quench solution was prepared in a separate reactor from water (472 L) and 34% NH_3 solution (247.2 kg 4936 mol, 47 equiv). Water (20 L) was used to complete the transfer of the NH_3 solution. The H_2SO_4 solution was transferred to the quench solution over a period of 5.5 h, maintaining the temperature between 0 to 5 °C. The H_2SO_4 reactor was washed twice with water (161 L and 20 L) and the washings were added to the quench solution. After thorough mixing, the pH of the mixture was found to be 9.7. The temperature was increased to 25 to 35 °C and EtOH (265.2 kg) was added. The mixture was heated under reflux for 1 h, at 67 °C for 2 h, then cooled to 5 °C and held at that temperature for 30 min before being transferred to a filter drier. The precipitate was washed with twice with cold (5 °C) water (218 L per wash) before being dried at 60 °C until KF water analysis showed 0.08% water remaining. Upon cooling to 20 °C there was obtained 34.46 kg (90%) of crude **1**.

Purification was effected by suspending the crude **1** in EtOH (217.1 kg) at 20 to 30 °C. A previously prepared suspension of Darco G60 (1.7 kg) in water (48.8 L) was added, followed by 20 L of water used to wash the tank in which the Darco suspension had been prepared. The mixture was heated under reflux for 30 min, then recirculated through a Gauthier filter at 70 °C until all the Darco had been removed. The resulting solution was transferred to preheated (70 °C) vessel through a Halar filter, using a

70 °C mixture of EtOH (21.7 kg) and water (6.9 kg) to complete the transfer. Heating at 70 °C was continued for 30 min before the mixture was cooled to 56 to 60 °C, held at that temperature for 10 min, then further cooled to 50 to 55 °C and seeded with **1** (760 g, 2.1 mol). The mixture was then subjected to a constant volume distillation for 6 h at 50 °C under reduced pressure, during which time EtOH (368.5 kg) was added and distilled. The final volume remaining in the tank was 378 L and contained 8.5% water by weight. It was cooled to 3 to 7 °C for 4.5 h before being transferred to a filter drier and washed with cold (5 °C) EtOH (81.4 kg). The precipitate was dried at 45 °C until the EtOH residue was ≤ 0.05% to afford **1** (31.3 kg, 91%, 82% overall) as a white, free flowing powder. ^{1}H NMR (500MHz, DMSO) δ = 8.86 (s, 1H), 8.16 (s, 1H), 7.90 (d, J = 5.9 Hz, 1H), 7.84 (br. s., 1H), 7.74 (s, 1H), 7.70 (br. s., 1H), 7.42 (d, J = 5.9 Hz, 1H), 4.90 (dd, J = 5.9, 53.8 Hz, 1H), 4.54 (dd, J = 3.5, 11.1 Hz, 1H), 4.26 (dd, J = 6.4, 11.0 Hz, 1H), 4.13 - 4.05 (m, 1H), 3.97 (s, 3H), 2.69 - 2.54 (m, 1H), 1.68 - 1.53 (m, 2H), 1.02 (t, J = 7.3 Hz, 3H). ^{13}C NMR{^{1}H} (126MHz, DMSO) δ = 171.0 (d, J = 19.4 Hz), 166.4, 158.4, 155.1, 137.7, 131.8, 130.3, 128.4, 120.3, 115.2, 103.2 (d, J = 4.2 Hz), 90.0 (d, J = 179.2 Hz), 66.3, 56.0, 54.1, 42.2 (d, J = 19.4 Hz), 16.4 (d, J = 8.4 Hz), 12.1. ^{19}F NMR (H decoupled, 376 MHz, DMSO-d_6) δ -199.26. LCMS: 362 (MH^+).

Supporting Information:

Copies of ^{1}H and ^{13}C spectra of isolated intermediates **12**, **8**, **2**, **10**, and **1**; HPLC of **12**.

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Candidate 1-{[(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (PF-06650833), a Potent, Selective Inhibitor of Interleukin-1 Receptor Associated Kinase 4 (IRAK4), by Fragment-Based Drug Design. *J. Med. Chem*. **2017**, *60*, 5521-5542.

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15: The S_NAr reaction of **2** with **3** was found to require a minimum of two equivalents of KHMDS to proceed to completion. The mechanism of this reaction must be more complex than simple deprotonation of the alcohol followed by S_NAr of the resulting alkoxide with **3**, since the addition of one equivalent of the base invariably resulted the reaction proceeding to 50% completion. This is suggestive, but not proof, of a cooperative double deprotonation of **2** by KHMDS that then undergoes rapid S_NAr reaction with **3**.

16: Treatment of compounds similar to **2** with KHMDS, in which the halogen is *anti* to the alcohol substituent **and** in which the lactam N cannot be deprotonated, leads to the rapid formation azabicyclic compounds; see: Choi, C.; Nuhant, P.; Mousseau, J. J.; Yang, X.; Gerstenberger, B. S.; Williams, J. M.; Wright, S. W. Synthesis of Chiral Azabicycles from Pyroglutaminols. *Org. Lett.* **2016**, *18*, 5748-5751.

17: Exposure of the acetonide **8** or **9** to bases such as KHMDS led to epimerization. The resistance of **2** to epimerization under these conditions suggests that the lactam NH is deprotonated under the conditions of the reaction.

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20: In early API campaigns, the kinetic protonation with BHT was replaced by simple epimerization of **9** with LDA to afford an approximately equal mixture of **8** and **9**. See reference 38.

21: The use of H_2O_2 introduces the possibility of abrupt pressure increases due to the potential for exothermic disproportionation of H_2O_2 to H_2O and O_2. Furthermore, the thermal stability properties of a H_2O_2 – DMSO mixture could be problematic, since DMSO is known to undergo accelerated decomposition and pressure increase in the presence of various additives, see Yang, X. –W.; Zhang, X.-Y.; Guo, Z.-C.; Bai, W.-S.; Hao, L.; Wei, H.-Y. Effects of Incompatible Substances on the Thermal Stability of Dimethyl Sulfoxide. *Thermochim. Acta* **2013**, *559*, 76-81.

22: Presumably residual amine and / or chloride ion are capable of complexing to Pd(II) and removing Pd(II) from the catalytic cycle.

23: While methyl benzenesulfinate may be viewed as atom uneconomical, other considerations overrode atom economy. The sulfinate ester must be non-enolizable, commercially available in large amounts, and not introduce odor control problems.

24: Extensive screening of bases showed that NaH provided a superior reaction profile. In particular, reactions mediated by alkoxide bases tended to stall. Sodium hydride may be handled on large scale by the use of the 60% dispersion in mineral oil packaged in solvent soluble bags of 1 or 5 kg capacity.

25: These conditions were adopted because they proved to be highly reliable at a variety of scales. It was not determined whether the stereogenic center was on carbon or sulfur.

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27: See, for example, (a) Zoretic, P. A.; Soja, P. Synthesis of 1-Methyl-3-pyrrolin-2-one. *J. Heterocycl. Chem.* **1997**, *14*, 681-682; (b) Yoshida, K.; Morikawa, T.; Yokozuka, N.; Harada, S.; Nishida, A. Stereoselective Synthesis of Chiral Hydrocarbazoles via the Catalytic Diels-Alder Reaction of Siloxyvinylindole and Cyclic Z-Olefin. *Tetrahedron Lett*. **2014**, *55*, 6907-6910.

28: These conditions are comparable to those applied to similar γ-lactam substrates, see (a) Gibson, S.; Jacobs, H. K.; Gopalan, A. S. Chiral Oxazolidinones as Electrophiles: Intramolecular Cyclization Reactions with Carbanions and Preparation of Functionalized Lactams. *Tetrahedron Lett*. **2011**, *52*, 887-

890; and (b) Ezquerra, J.; Pedregal, C.; Collado, I.; Yruretagoyena, B.; Rubio, A. First Trapping Reaction of N-Boc Ethyl 3,4-Dehydropyroglutamate with Cyclopentadiene. *Tetrahedron* **1995**, *51*, 10107-10114.

29: Extensive reaction screening showed that Na_2HPO_4 afforded a cleaner reaction profile than the more customarily used carbonate and bicarbonate bases.

30: Extensive screening showed this methanol – water mixture to be optimal for extraction of **6** into a heptane – immiscible phase. The benzenesulfenic acid (PhSOH) by-product of the elimination reaction undergoes disproportionation to afford PhS(=O)SPh, PhSSPh, and $PhSO_2SPh$. These by-products are removed by the heptane extraction. See Davis, F. A.; Yocklovich, S. G.; Baker, G. S. Synthesis of Sulfenic Acids: Flash Vacuum Pyrolysis of Aryl and Alkyl tert-Butyl Sulfoxides. *Tetrahedron Lett*. **1978**, *19*, 97 - 100.

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32: On a per mole basis, CuBr • Me_2S is approximately twenty times more expensive than CuI.

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34: See: Maillard, M. C.; Brookfield, F. A.; Courtney, S. M.; Eustache, F. M.; Gemkow, M. J.; Handel, R. K.; Johnson, L. C.; Johnson, P. D.; Kerry, M. A.; Krieger, F.; Meniconi, M.; Munoz-Sanjuan, I.; Palfrey, J. J.; Park, H.; Schaertl, S.; Taylor, M. G.; Weddell, D.; Dominguez, C. Exploiting Differences in Caspase-2 and -3 S2 Subsites for Selectivity: Structure-based Design, Solid-phase Synthesis and In Vitro Activity of Novel Substrate-Based Caspase-2 Inhibitors. *Bioorg. Med. Chem. Lett*. **2011**, *19*, 5833-5851. In this example, the authors add TMSCl and the α,β-unsaturated γ-lactam simultaneously to a mixture of the Grignard reagent and 10 mole percent of copper(I) salt.

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36. Experimentation showed that the copper mediated conjugate addition reaction could be carried out successfully with as little as 2 mole percent of CuI.

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Chien, T. V.; Zdobinsky, T.; Seebohm, G.; Nennstiel, D.; Zerbe, O.; Scherkenbeck, J. Structural Prerequisites for Receptor Binding of Helicokinin I, a Diuretic Insect Neuropeptide from Helicoverpa zea. *Eur. J. Org. Chem*. **2014**, 2714-2725; with oxaziridine, see: (c) Fujita, M.; Kitagawa, O.; Yamada, Y.; Izawa, H.; Hasegawa, H.; Taguchi, T. Synthesis of Optically Active 5-Substituted-2-pyrrolidinone Derivatives Having Atropisomeric Structure and 3,5-Cis-Selective Reaction of Their Enolates with Electrophiles. *J. Org. Chem.* **2000**, *65*, 1108-1114; with O_2, see: (d) Kawakami, K.; Takahashi, H.; Ohki, H.; Kimura, K.; Miyauchi, S.; Miyauchi, R.; Takemura, M. Studies on 8-Methoxyquinolones: Synthesis and Antibacterial Activity of 7-(3-Amino-4-substituted)pyrrolidinyl Derivatives. *Chem. Pharm. Bull*. **2000**, *48*, 1667-1672.

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Zhou, B. Evaluation of Thermal Hazard of Tert-Butyl Hydroperoxide by Using Accelerating Rate Calorimeter. *Procedia Engineering,* **2012**, *45*, 574-579.

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41. The triflate **15a** could be isolated and purified or carried on *in situ* as desired.

42: Triethylamine trihydrofluoride is both corrosive and toxic, while Ms_2O is expensive for large scale use.

43: Bennua-Skalmowski, B.; Vorbrueggen, H. A Facile Conversion of Primary or Secondary Alcohols with n-Perfluorobutanesulfonyl Fluoride/1,8-Diazabicyclo[5.4.0]undec-7-ene Into Their Corresponding Fluorides. *Tetrahedron Lett. 1995*, **36,** 2611-2614.

44: The use of TMEDA with nonafluorobutanesulfonyl fluoride has not been reported previously. In our hands DIEA afforded poor conversions while DBU was unnecessarily expensive.

45. For production purposes, the toluene solution of **8** could alternatively be solvent exchanged with THF and carried forward into the aminal cleavage procedure without isolation of the intermediate acetonide **8**.

46: Compound **1** (PF-06650833) is commercially available from Sigma Aldrich (catalog # PZ0327).

47. The gas chromatograph was fitted with a Cyclosil-B column (30 m x 0.25 mm ID x 0.25 μm) and FID detection with an inlet temperature of 230 °C and the following temperature program: 210 °C (held for 10 min), then increased temperature at a rate of 10 °C min^{-1} to 240 °C, then held at 240 °C for 15 min. Samples were injected as solutions in MeCN.