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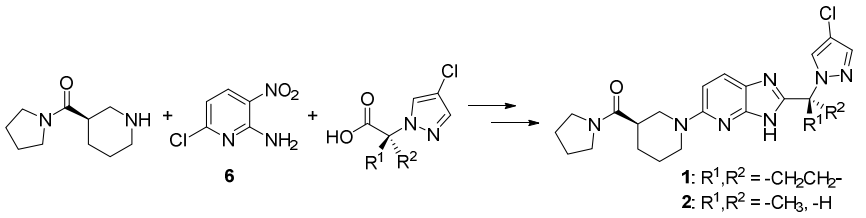
GRAPHICAL ABSTRACT



ABSTRACT

The scalable syntheses of two imidazopyridine inhibitors of the enzyme diacylglycerol acyltransferase 2 (DGAT-2) are described. 6-Chloro-3-nitro-2-aminopyridine was the starting material for the convergent synthesis of the central imidazopyridine ring. Differentiation in reactivity of the C2- and C3-nitrogen substituents on the pyridine ring and the development of mild cyclodehydration conditions to form the imidazole ring were critical problems that were

addressed to deliver a 3-kg batch of compound **1** (PF-06424439) and a 0.1-kg batch of compound **2** (PF-06450561).

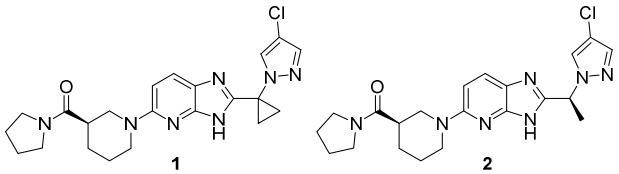
KEYWORDS

imidazopyridine, azabenzimidazole, DGAT, diacylglycerol acyltransferase

INTRODUCTION

The enzymes diacylglycerol acyltransferase 1 and 2 (DGAT-1 and DGAT-2) catalyze the final step in triglyceride synthesis. Inhibition of one or both of these enzymes has been proposed as a treatment for metabolic disease.[1] Several small molecule inhibitors of DGAT-2 have been disclosed recently.[2,3,4,5,6] This manuscript describes the synthetic route development toward scalable syntheses of the imidazopyridines PF-06424439 (**1**)[7] and PF-06450561 (**2**)[8] which were evaluated in efficacy and safety studies, leading to decreased cholesterol and triglyceride levels in preclinical species.

Figure 1. DGAT-2 inhibitors.



RESULTS AND DISCUSSION

The discovery synthesis of **1** and related compounds (Scheme 1) employed a modular route that allowed diversification of both the left- and right-hand sides of the molecule to investigate SAR.[7]

From a process chemistry perspective, the bond constructions leading to intermediate **7** were amenable to scale, providing a route to multi-kilogram quantities of **7** as shown in Scheme 1. Starting with the left-hand side of the molecule, the commercially available *N*-Boc protected (*R*)-piperidine-3-carboxylic acid **3** was activated with CDI and underwent amide coupling with pyrrolidine to give amide **4**. Deprotection with hydrochloric acid in isopropanol led to isolation of the HCl salt of **5** (84% yield over 2 steps). S_NAr reaction of **5**•HCl with commercially available 2-amino-6-chloro-3-nitropyridine **6** in acetonitrile with triethylamine at 40 °C afforded the solid product **7** in 66% yield after crystallization from ethyl acetate (4.6 kg; 99.1% purity by HPLC, 99.5% e.e.).

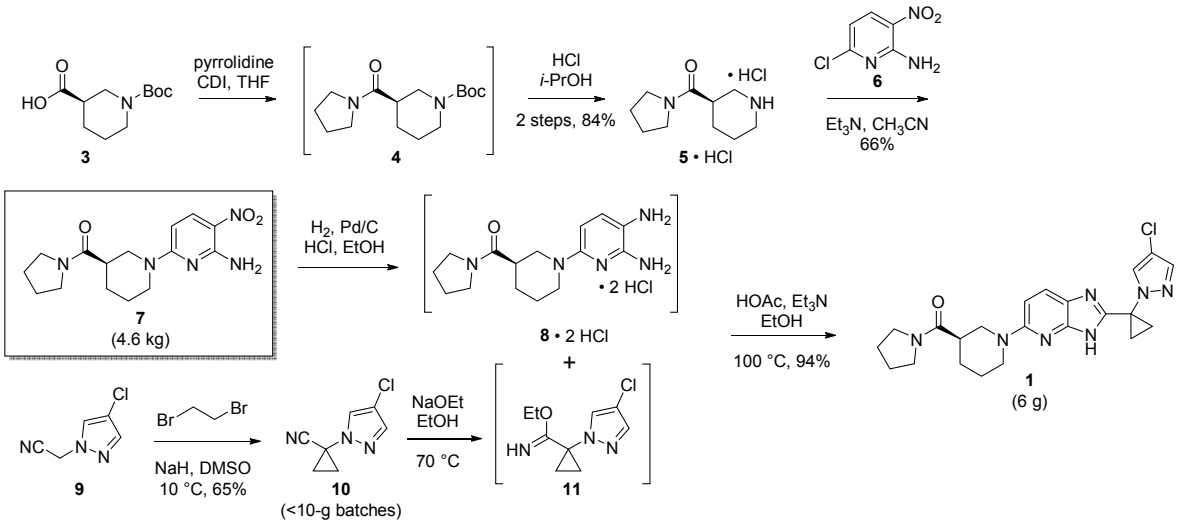
From intermediate **7**, the remainder of Scheme 1 shows the discovery conditions for synthesis of **1**.[7] The nitro group of **7** was reduced with hydrogen over palladium-on-carbon to afford triamine **8**; the free base of this electron-rich compound was unstable to air, and **8** was therefore isolated as its dihydrochloride salt. The salt proved to be stable to storage for at least a few months, but without conclusive data on its long-term stability, compound **7** was targeted as the key intermediate to stage material.

Imidate **11** was utilized as an efficient cyclization partner to incorporate the right-hand side of the molecule. The cyclopropyl-pyrazole was prepared by bis-alkylation of the acetonitrile **9** with sodium hydride and 1,2-dibromoethane to give the desired cyclopropylnitrile **10**, with DMSO the solvent that provided the highest yield. This exothermic reaction required cooling below the freezing point of (pure) DMSO, and safety concerns about the use of NaH–DMSO[9] led us to synthesize compound **10** in batches of less than 10 grams as a safety precaution. Efforts to identify base–solvent combinations that would be more amenable to scale and that afforded suitable reaction profiles were not successful (LiHMDS, KHMDS, LTMP, DBU, KOH; THF,

toluene, acetonitrile, DMF, DMPU). The main reaction by-products were nitrile "dimers" arising from addition of an intermediate anion to the nitrile functional group of another molecule (of either the starting material or desired product, in varying ratios depending on the specific reaction conditions). Addition of the substrate **9** to the base did have some influence on formation of the nitrile dimers, but did not eliminate these by-products; the NaH–DMSO conditions provided the cleanest overall reaction profile.

The imidate **11** could be formed from nitrile **10** under either acidic (HCl) or basic (NaOEt) conditions in ethanol; in both cases the primary by-product was the ethyl ester resulting from hydrolysis of the imidate, presumably due to adventitious water. Preparation of fresh ethanolic solutions of HCl (from acetyl chloride or trimethylsilyl chloride) or NaOEt (from sodium metal) mitigated ester formation. Attempts to isolate neat forms of the imidate salts, however, demonstrated that the salts were hygroscopic. Therefore, treatment of the nitrile **10** with freshly prepared sodium ethoxide in ethanol afforded the imidate **11** which was used immediately without purification in cyclization with the dihydrochloride salt of **8** to afford **1** in 94% yield (6.3 g) for the cyclization.[7]

Scheme 1. Optimized route to intermediate **7** and discovery conditions for synthesis of **1**.

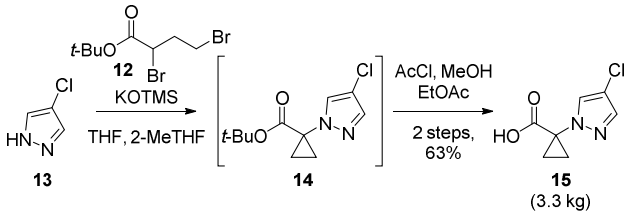


The discovery route was sufficient to deliver material for rodent exploratory toxicology studies, but there were concerns regarding science of scale for longer term development. Of modest concern was the stability of triaminopyridine **8**; exposure of the free base of this intermediate to air produced discoloration that could not be purged from the final API. Another concern was the sensitivity of imidate **11** to hydrolysis. Of greatest concern, however, was the possibility for uncontrolled exothermic decomposition with the NaH–DMSO conditions[9] utilized during the bis-alkylation of the nitrile.

To avoid all of these potential problems, an alternative synthesis of the fused imidazole ring utilizing the corresponding carboxylic acid in place of the imidate was developed. Commercially available *t*-butyl 2,4-dibromobutanoate (**12**) was a useful starting material for route development,[10,11,12] although sourcing multiple kilograms was difficult. Base, solvent, and temperature screen of the reaction of **12** with 4-chloro-pyrazole (**13**) revealed that stronger bases (e.g., NaH, LiHMDS, KHMDS, LDA) led to the undesired cyclization product *t*-butyl 1-bromocyclopropane-1-carboxylate derived from initial enolate formation followed by intramolecular alkylation (which did not undergo further displacement by the pyrazole). With

increasing temperatures, impurities derived from apparent S_NAr reaction of the chloro-pyrazole moiety were observed. Ultimately, potassium trimethylsilanolate as base (2.0 equiv) in THF–2-MeTHF at 15–22 °C led to the two desired alkylations: alkylation of the pyrazole by the 2-bromo group which was activated by the adjacent ester, followed by intramolecular alkylation of the enolate by the terminal bromide, to afford the cyclopropyl-pyrazole **14** (Scheme 2). After aqueous workup and solvent exchange, the *t*-butyl ester was cleaved with hydrogen chloride in ethyl acetate and the product acid **15** precipitated directly from the reaction solution as its HCl salt. Upon drying under vacuum at 40 °C, both residual solvent and volatile HCl were evaporated, to afford the neutral form of acid **15** (63% yield over 2 steps, 3.3 kg).

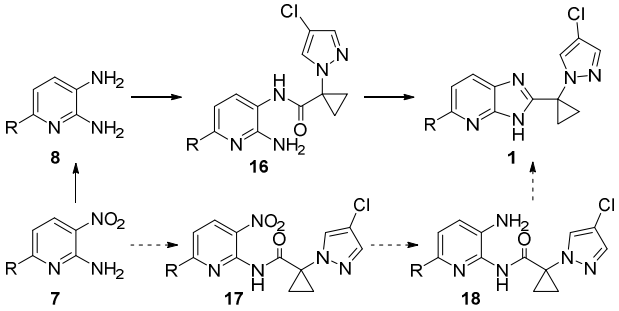
Scheme 2. Synthesis of cyclopropylcarboxylic acid **15**.



Various sequences involving amide formation followed by cyclization were considered to convert the carboxylic acid **15** to the product imidazopyridine **1** (Scheme 3). The greater nucleophilicity of the 3-amino group over the 2-amino group in pyridines is well established,[13,14] and several standard amidation conditions were employed by the discovery team for the regioselective acylation of diamine **8**, to afford amide **16**. However, the conditions identified for the subsequent dehydration–cyclization step were harsh and low-yielding (e.g., NaOMe, *i*-BuOH, 110 °C, <50% yield) and were deemed unsuitable for a development route. The need for vigorous cyclization conditions was presumably a result of the low nucleophilicity of the 2-

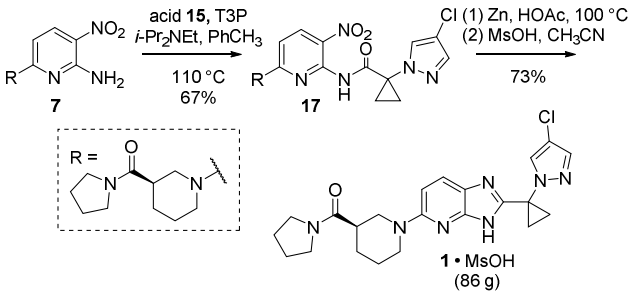
amino group and possibly the steric hindrance of the amide. However, we believed that if the 2-amido derivative **17** could be formed first, then the 3-amino group of **18** would be sufficiently nucleophilic to cyclize to the desired fused imidazole under milder conditions.

Scheme 3. Alternative route options for amidation–cyclization to imidazopyridine core.



Amidation of the poorly nucleophilic amino-nitro-pyridine **7** with cyclopropylcarboxylic acid **15** was effected by 1-propanephosphonic acid cyclic anhydride (T3P) at 110 °C in moderate yield (Scheme 4). Reduction of the nitro group with zinc in acetic acid at 100 °C led directly to cyclized imidazopyridine product **1**. Following aqueous workup, the product **1** was crystallized as its methanesulfonic acid salt, affording the final API in 73% yield over the two steps (86 g of **1**•MsOH).

Scheme 4. Reduction–cyclization of 2-amido-3-nitro intermediate **17** to imidazopyridine **1**.



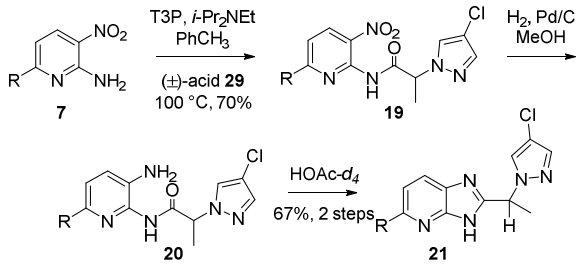
This route provided sufficient material for exploratory toxicology studies; however, it had significant limitations with regard to scalability. The amide bond of **17** was very labile and was hydrolyzed back to the starting amine and carboxylic acid under exposure to mildly acidic or

basic aqueous conditions, such as during the reaction workup. The instability of this amide led to run-to-run variation in yield and raised concerns about the viability of scaling this sequence. Further, the addition of zinc powder to the acetic acid solution of **17** in the nitro reduction step had a significant exotherm (from 23 °C to 79 °C) prior to external heating, and the workup to isolate **1** following this reaction was laborious.

During the optimization of this nitro-amide route toward **1**, another compound of interest was identified (**2**),[8] along with a project need to evaluate both compounds for differentiation in efficacy and safety studies. Structurally, compound **2** differs from **1** by the presence of a methyl group in place of the cyclopropane, creating a second stereocenter in the molecule. Our confidence in developing a synthesis of the single enantiomer of the necessary carboxylic acid precursor for **2** was high; however, we felt that the most substantial question was whether the cyclization to form the imidazole ring could be achieved without epimerization of the methyl-bearing stereocenter. Simple initial experiments provided significant insight on this topic. First, the final compound **2** was not configurationally stable when heated at 100 °C in acetic acid-d_4 for 2 h (analogous to the reduction–cyclization conditions in Scheme 4), as demonstrated by complete incorporation of deuterium at the methine stereocenter (^{1}H NMR); this result reinforced the need to modify the nitro-amide route. Second, sequential reduction and cyclization from a 2-amido-3-nitro intermediate under milder conditions without epimerization was successfully achieved. Using racemic acid, nitro-amide **19** was prepared under T3P amidation conditions (Scheme 5). Hydrogenation over palladium-on-carbon to reduce the nitro group afforded the amino amide **20** which did not undergo detectable cyclization under the reduction conditions. However, after 2 h in acetic acid-d_4 at room temperature, complete cyclization of **20** to **21** was

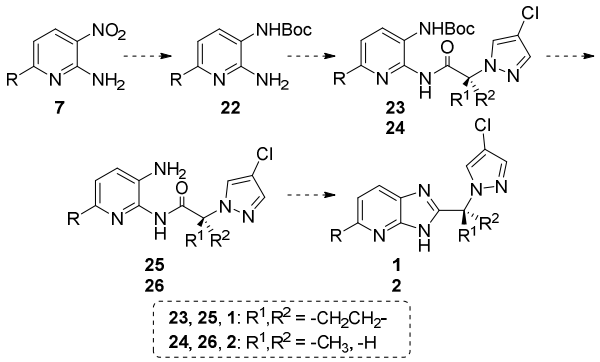
observed without detectable incorporation of deuterium at the methine position, as evaluated by ^{1}H NMR integration.

Scheme 5. Proof of principle for epimerization-free cyclization to imidazopyridine.



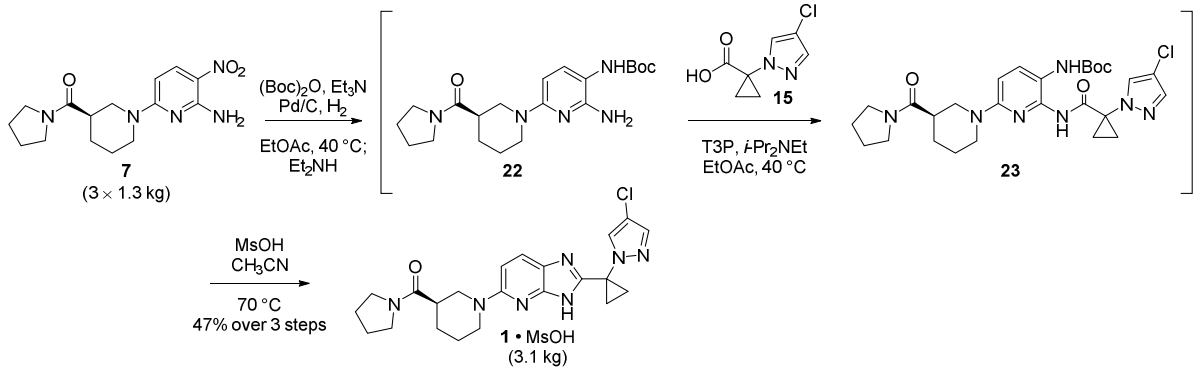
Collectively, the observations regarding the reactivity of the 2- and 3-amino groups on the pyridine ring to this point strongly suggested the sequence of steps outlined in Scheme 6. Reduction of the nitro group of **7** and in situ regioselective protection (for example, as a *t*-butyl or benzyl carbamate) would take advantage of the greater nucleophilicity of the 3-amino group and would avoid exposing the intermediate triamine to air. The enhanced nucleophilicity of the 2-amino group in the 2-amino-3-carbamate derivative **22** as compared to that in the 2-amino-3-nitro derivative **7** would allow a more robust amidation reaction. Deprotection followed by cyclization was expected to afford the desired imidazopyridine product.

Scheme 6. Plan for final iteration of imidazopyridine synthesis.



This route concept was implemented for the synthesis of compound **1** as shown in Scheme 7. Under GMP conditions, nitro compound **7** was hydrogenated over palladium-on-carbon in the presence of Boc-anhydride and triethylamine to afford the desired 3-carbamate **22**. After filtration, excess Boc-anhydride was quenched by the addition of *N,N*-diethylamine. The ethyl acetate solution of 2-amino-3-carbamate intermediate **22** was telescoped directly into the amidation step, with T3P at 40 °C (as compared to 110 °C for amidation of 2-amino-3-nitro substrate **7** in Scheme 4). After aqueous workup and a solvent switch from ethyl acetate to acetonitrile, cleavage of the Boc group of **23** and subsequent cyclization was effected with methanesulfonic acid at 70 °C. Cooling to 20 °C induced crystallization to provide **1**•MsOH in 47% yield (3.1 kg) over the three telescoped steps from compound **7**.

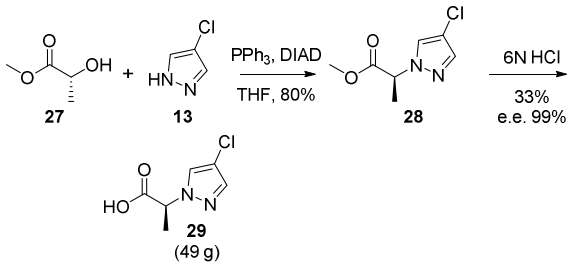
Scheme 7. GMP synthesis of compound **1**.



Toward the synthesis of **2**, development of a fit-for-purpose enantioselective synthesis of acid **29** to support delivery of material for in vivo safety studies was straightforward, although the procedures were optimized for enantiomeric purity and speed to delivery of the initial batch rather than for overall yield (Scheme 8). The Mitsunobu reaction of lactate derivatives with nitrogen-based nucleophiles has ample precedent;[15,16,17] thus, (*R*)-methyl lactate **27** underwent

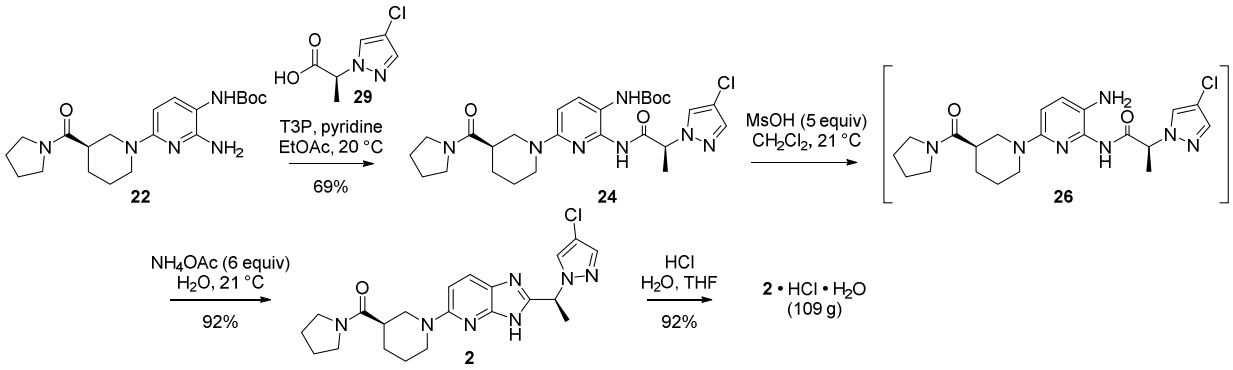
stereo-invertive displacement with 4-chloro-pyrazole **13**. Acidic hydrolysis of the ester **28** followed by crystallization afforded the desired acid **29** with 99% e.e., but a low yield (33%, 49 g) due to material losses in workup and crystallization.

Scheme 8. Fit-for-purpose enantioselective synthesis of acid **29**.



The route outlined in Scheme 6 was adapted to the synthesis of **2** with minor modifications to the reaction conditions employed toward **1** to account for the difference between cyclopropyl and methyl substituents (Scheme 9). Amidation of **22** proceeded with T3P at room temperature (rather than 40 °C) with the less sterically hindered chiral acid **29**; substitution of pyridine in place of *N,N*-diisopropylethylamine as base helped to suppress epimerization.[18,19] The amide product **24** precipitated from the reaction mixture, providing an isolation point for purging impurities and any undesired stereoisomers. Methanesulfonic acid efficiently induced Boc cleavage, although no cyclization occurred at room temperature. However, deprotection with methanesulfonic acid (5 equiv) in dichloromethane followed by addition of aqueous ammonium acetate solution (6 equiv) to buffer the acidity led to smooth cyclization to **2** without detectable epimerization. Chromatographic purification was acceptable for the amount of material required for initial in vivo studies (83 g, 92% yield, >99% d.e.). The final compound **2** was then crystallized as a monohydrate, monohydrochloride salt from THF–water.

Scheme 9. Synthesis of compound **2**.



In summary, we have described the iterative identification of routes for the synthesis of two DGAT-2 inhibitors. The cyclization of various derivatives of 2,3-diaminopyridines to form an imidazopyridine ring system was the critical problem that was addressed. The final routes described leveraged the differential nucleophilicity of the 2- and 3-amino groups to deliver 3 kg of compound **1** and 0.1 kg of compound **2**.

EXPERIMENTAL SECTION

General Experimental Methods. All chemicals, reagents, and solvents were purchased from commercial sources and were used without further purification unless otherwise noted. ^{1}H NMR data are reported relative to residual solvent signals, and are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. Silica gel chromatography was performed using a medium pressure Biotage or ISCO system and columns pre-packaged by various commercial vendors including Biotage and ISCO.

Synthesis of 1•MsOH. (R)-(1-(2-(1-(4-Chloro-1H-pyrazol-1-yl)cyclopropyl)-3H-imidazo[4,5-b]pyridin-5-yl)piperidin-3-yl)(pyrrolidin-1-yl)methanone methanesulfonate.

Step 1: (R)-tert-Butyl 3-(pyrrolidine-1-carbonyl)piperidine-1-carboxylate (4). (*R*)-1-(tert-Butoxycarbonyl)piperidine-3-carboxylic acid (6.0 kg, 26 mol, 1 equiv) was added in portions to a mixture of CDI (5.1 kg, 31 mol, 1.2 equiv) in THF (48 L) at a temperature of 18–22 °C. The mixture was held at that temperature for 3 h, then pyrrolidine (2.28 kg, 32 mol, 1.2 equiv) was

added while maintaining a temperature of 18–25 °C, and the resulting reaction mixture was held at that temperature for 2 h. Cyclohexane (48 L) and aqueous K_2CO_3 solution (prepared from 4.8 kg K_2CO_3 and 48 L H_2O) were then added sequentially, and the mixture was stirred for 30 min before separation of the layers. The organic layer was then washed with another portion of aqueous K_2CO_3 solution (4.8 kg K_2CO_3 and 48 L H_2O). The combined aqueous layers were extracted with cyclohexane (30 L). The combined organic layers were then washed with aqueous NaCl solution (prepared from 3.0 kg NaCl and 30 L H_2O). The organic layer was dried over Na_2SO_4 (2.0 kg), then the cyclohexane was removed by distillation under reduced pressure at 45 °C. i-PrOH (43 L) was added and the mixture was stirred for 30 min. The presence of **4** was confirmed by HPLC analysis: HPLC retention time: 6.0 min (Column: Halo C18, 4.6 × 150 mm, 2.7 μm; Mobile Phase A: 0.1% H_3PO_4 and 2% CH_3CN in H_2O, Mobile Phase B: CH_3CN; Gradient: 20%B to 90%B over 7 min, then held for 3 min; Flow: 0.8 mL/min; Temperature: 25 °C; UV detection at 210 and 226 nM). This material was used in the next step without further purification. Analytical data from a separate batch: ^{1}H NMR (400 MHz, MeOH-d_4) δ 4.04 (m, 2H), 3.56 (m, 2H), 3.38 (m, 2H), 2.77 (m, 2H), 2.57 (m, 1H), 1.92 (m, 5H), 1.71 (m, 1H), 1.64 (m, 1H), 1.47 (m, 1H), 1.44 (s, 9H). MS $(M+H)^+$ 283.3.

*Step 2: (R)-Piperidin-3-yl(pyrrolidin-1-yl)methanone hydrochloride (**5**•HCl).* Over a period of 1 h, concentrated hydrochloric acid (9.8 kg, 102 mol, 4 equiv) was added to a solution of **4** (26 mol, 1 equiv) in i-PrOH from the previous step, maintaining a temperature of 20–25 °C. The reaction mixture was heated to 50–55 °C and was held at that temperature for 6 h. Solvent was removed by distillation under reduced pressure at 50 °C. Four cycles of solvation and then distillation under reduced pressure at 50 °C were conducted sequentially: i-PrOH (2 × 14.5 L), toluene (18.5 L), and THF (12.0 L). Another portion of THF (12.0 L) was added and the mixture was stirred at 25–30 °C for 1 h. The mixture was centrifuged and the mother liquor was removed; the resulting cake was washed with THF (3.7 L), then was dried at 40–50 °C to afford **5**•HCl (4.8 kg, 84% over two steps). HPLC retention time: 1.7 min (Column: Halo C18, 4.6 × 150 mm, 2.7 μm; Mobile Phase A: 0.1% H_3PO_4 and 2% CH_3CN in H_2O, Mobile Phase B: CH_3CN; Gradient: 20%B to 90%B over 7 min, then held for 3 min; Flow: 0.8 mL/min; Temperature: 25 °C; UV detection at 210 and 226 nM). Analytical data from a separate batch:

^{1}H NMR (400 MHz, MeOH-d_4) δ 3.58 (m, 2H), 3.42 (m, 2H), 3.22 (m, 3H), 3.09 (m, 2H), 1.89 (m, 8H). MS $(M+H)^+$ 183.3.

*Step 3: (R)-(1-(6-Amino-5-nitropyridin-2-yl)piperidin-3-yl)(pyrrolidin-1-yl)methanone (**7**).* Et_3N (4.65 kg, 46 mol, 2.1 equiv) was added over a period of 1 h to a mixture of **5**•HCl (4.8 kg, 22 mol, 1.0 equiv) and CH_3CN (48 L), maintaining a temperature of 15–20 °C. The mixture was held at that temperature for 30 min, then was warmed to 38–42 °C. 6-Chloro-3-nitropyridin-2-amine (3.8 kg, 22 mol, 1 equiv) was added portion-wise, and the mixture was held at 38–42 °C for 3 h. The mixture was then cooled to 15–20 °C and an aqueous solution of NH_4Cl (prepared from 6.24 kg NH_4Cl and 48 L H_2O) and EtOAc (48 L) were added sequentially, and the layers were stirred and then separated. The aqueous layer was further extracted with EtOAc (2 × 24 L). The combined organic layers were washed with an aqueous solution of NaCl (prepared from 4.8 kg NaCl and 24 L H_2O) and then were dried with Na_2SO_4 (1.92 kg). The organic layer was collected and the solvent was evaporated under reduced pressure at 40 °C. EtOAc (14.4 L) was added to the crude product, and the mixture was heated to 35–40 °C and was held at that temperature for 15 min. The mixture was cooled to 20–25 °C and was held at that temperature for 6 h, then was cooled to 10–15 °C and was held at that temperature for 1 h. The resulting suspension was centrifuged and the mother liquor was removed. The resulting cake was washed with chilled EtOAc (4.8 L) and then was dried at 40–50 °C to afford **7** (4.6 kg, 66%). HPLC retention time: 5.3 min (Column: Halo C18, 4.6 × 150 mm, 2.7 μm; Mobile Phase A: 0.1% H_3PO_4 and 2% CH_3CN in H_2O, Mobile Phase B: CH_3CN; Gradient: 20%B to 90%B over 7 min, then held for 3 min; Flow: 0.8 mL/min; Temperature: 25 °C; UV detection at 210 and 226 nM), purity 99.1%. Chiral HPLC retention time 40.6 min (Column: Chiralpak AD-H, 250 × 4.6 mm, 5μ; Mobile phase, 20% EtOH–heptane with 0.1% formic acid; 1.0 mL/min; 40 °C; UV detection at 230 nM); (*S*)-enantiomer retention time 28.9 min; e.e. >99%. Analytical data from a separate batch: ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.05 (d, *J*=9.6 Hz, 1H), 6.23 (d, *J*=9.6 Hz, 1H), 4.71 (app br s, 1H), 4.41 (app br s, 1H), 3.65 (m, 1H), 3.52 (m, 1H), 3.36 (m, 2H), 3.01 (m, 2H), 2.68 (m, 1H), 1.91 (m, 7H), 1.58 (m, 1H). MS $(M+H)^+$ 320.4.

*Step 4: tert-Butyl 1-(4-chloro-1H-pyrazol-1-yl)cyclopropanecarboxylate (**14**).* 4-Chloro-1H-pyrazole (2.87 kg, 28.0 mol, 1 equiv) and tert-butyl 2,4-dibromobutyrate (9.89 kg, 32.8 mol, 1.2 equiv) were dissolved in 2-MeTHF (26.0 L) and the resulting solution was cooled to 5 °C. A

suspension of KOTMS (9.58 kg, 67.2 mol, 2.4 equiv) in THF (23.5 L) was added over 30 min while maintaining the temperature below 15 °C. The resulting slurry was stirred at 22 °C for 12 h. The presence of **14** was confirmed by HPLC analysis (HPLC retention time: 8.8 min (Column: Halo C18, 4.6 × 150 mm, 2.7 µm; Mobile Phase A: CH_3CN, Mobile Phase B: 0.05% MsOH in H_2O; Linear Gradient: 5:95 A:B to 95:5 A:B over 9 min, then held for 1 min; Flow: 1.0 mL/min; UV detection at 210, 226, and 254 nM)). Aqueous HCl solution (2M, 22.5 L, 45.0 mol, 16 equiv) was added while maintaining the temperature at or below 22 °C. The aqueous layer was removed and the organic layer was washed with 13% aqueous NaCl solution (9.6 L). The wash layer was removed and the resulting solution of tert-butyl 1-(4-chloro-1H-pyrazol-1-yl)cyclopropanecarboxylate was distilled under reduced pressure at 40 °C until a volume of approximately 8 L was achieved. Residual THF solvents were exchanged for EtOAc (one 9.6-L portion, followed by continuous addition of a 19.0-L portion to maintain a constant volume) by distillation under reduced pressure at 40 °C. The volume was reduced to approximately 8 L to afford a solution of **14** and EtOAc, which was used in the next step without further purification. Analytical data from a separate batch: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.44 (s, 1H), 1.75 (app q, *J*=4.3 Hz, 2H), 1.57 (app q, *J*=4.3 Hz, 2H), 1.40 (s, 9H). MS $(M)^+$ 242.

*Step 5: 1-(4-Chloro-1H-pyrazol-1-yl)cyclopropanecarboxylic acid (**15**).* A solution of **14** (from the previous step, 28 mol, 1 equiv) in EtOAc (13 L, followed by a 2-L rinse) was added to a solution of anhydrous HCl (prepared by adding acetyl chloride (9.0 L, 126 mol, 4.5 equiv) to a solution of MeOH (6.2 L, 154 mol, 5.5 equiv) and EtOAc (19.0 L)) over a period of 10 min while maintaining a temperature at or below 20 °C. Over a period of 12 h at that temperature, a precipitate formed. The presence of **15** was confirmed by HPLC analysis of the mixture (HPLC retention time: 5.5 min (Column: Halo C18, 4.6 × 150 mm, 2.7 µm; Mobile Phase A: CH_3CN, Mobile Phase B: 0.05% MsOH acid in H_2O; Linear Gradient: 5:95 A:B to 95:5 A:B over 9 min, then held for 1 min; Flow: 1.0 mL/min; UV detection at 210, 226, and 254 nM)). The mixture was cooled to 10 °C and was held at that temperature for 2 h. The solids were collected by filtration, rinsing the reaction vessel with EtOAc (9.6 L). The solids were dried under a N_2 flow, and then were dried in a vacuum oven at 40 °C to remove residual solvent and HCl, to afford **15** (3.3 kg, 63% over 2 steps). Analytical data from a separate batch: ^{1}H NMR (500 MHz, $CDCl_3$)

δ 11.01 (br s, 1H), 7.52 (s, 1H), 7.48 (s, 1H), 1.88 (app q, *J*=4.8 Hz, 2H), 1.69 (app q, *J*=4.8 Hz, 2H). MS $(M)^+$ 186.

*Step 6: (R)-tert-Butyl 2-amino-6-(3-(pyrrolidine-1-carbonyl)piperidin-1-yl)pyridin-3-ylcarbamate (**22**).* A N_2-purged reaction vessel was charged sequentially with 5% Pd-on-carbon (0.208 kg, 0.10 mol, 0.02 equiv), nitro intermediate **7** (1.3 kg, 4.1 mol, 1 equiv), EtOAc (14 L), di-tert-butyl dicarbonate (0.906 kg, 4.15 mol, 1.0 equiv), and Et_3N (0.824 kg, 8.14 mol, 2.0 equiv). An additional charge of EtOAc (1.3 L) was added to ensure all residues were rinsed into the reaction vessel. The vessel was purged and pressurized with N_2, then was purged and pressurized with H_2 to 50 psig. The reaction was heated to 40 °C and was held at that temperature for 6 h. The mixture was then cooled to 20 °C and the vessel was purged with N_2. The presence of **22** was confirmed by HPLC analysis (HPLC retention time: 5.3 min (Column: Halo C18, 4.6 × 150 mm, 2.7 μm; Mobile Phase A: CH_3CN, Mobile Phase B: 0.05% MsOH in H_2O; Linear Gradient: 5:95 A:B to 95:5 A:B over 9 min, then held for 1 min; Flow: 1.0 mL/min; UV detection at 210, 226, and 254 nM)). The mixture was filtered and was rinsed with EtOAc (6.5 L). The filtrate was transferred to another reaction vessel, rinsing with EtOAc (1 L). To quench excess di-tert-butyl dicarbonate, Et_2NH (59.5 g, 0.81 mol, 0.2 equiv) was added while maintaining a temperature of 20 °C; the mixture was held for 30 min at that temperature. Three batches of material on this scale were combined and were used in the next reaction without further purification. Analytical data from a separate batch: ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.22 (br d, *J*=8.2 Hz, 1H), 6.11 (d, *J*=8.2 Hz, 1H), 4.44 (br d, *J*=13.0 Hz, 1H), 4.13 (d, *J*=13.0 Hz, 1H), 3.73 (m, 1H), 3.54 (m, 1H), 3.43 (m, 2H), 2.84 (m, 2H), 2.69 (m, 1H), 1.89 (m, 7H), 1.57 (m, 1H), 1.51 (s, 9H). MS $(M+H)^+$ 390.0.

*Step 7: (R)-(1-(2-(1-(4-Chloro-1H-pyrazol-1-yl)cyclopropyl)-3H-imidazo[4,5-b]pyridin-5-yl)piperidin-3-yl)(pyrrolidin-1-yl)methanone methanesulfonate (**1**•MsOH).* A solution of amine **22** in EtOAc (12.2 mol, 1 equiv, 65 L total volume) was distilled under reduced pressure at 40 °C until the residual volume was approximately 8 L. An additional portion of EtOAc (48 L) was added, and the resulting solution was distilled under reduced pressure at 40 °C until the residual volume was approximately 8 L. EtOAc (33 L), acid **15** (2.28 kg, 12.2 mol, 1.0 equiv), and i-Pr_2NEt (4.74 kg, 36.7 mol, 3.0 equiv) were added sequentially. To the resulting mixture at 20 °C was added a solution of T3P in EtOAc (50% solution, 14.0 kg, 22.0 mol, 1.8 equiv; plus a 2.0-L

EtOAc rinse). The resulting mixture was heated to 40 °C and was held at that temperature for 8 h. The presence of **23** was confirmed by HPLC analysis of the mixture (HPLC retention time: 8.5 min (Column: Halo C18, 4.6 × 150 mm, 2.7 μm; Mobile Phase A: CH_3CN, Mobile Phase B: 0.05% MsOH in H_2O; Linear Gradient: 5:95 A:B to 95:5 A:B over 9 min, then held for 1 min; Flow: 1.0 mL/min; UV detection at 210, 226, and 254 nM)). The mixture was then partitioned between EtOAc (38 L) and a 10% aqueous solution of citric acid (2 × 50 L). The organic layer was then washed sequentially with a 10% aqueous solution of K_2CO_3 (31 L) and with H_2O (24 L). The organic layer was distilled under reduced pressure at 40 °C until the remaining volume was approximately 8 L. CH_3CN (49 L) was added and the solution was distilled under reduced pressure at 40 °C until the remaining volume was approximately 26 L. MsOH (1.41 kg, 14.7 mol, 1.2 equiv) was added via addition funnel, followed by a CH_3CN rinse (0.5 L). The reaction mixture was heated to 70 °C and was held at that temperature for 12 h, then was cooled to 20 °C over a period of 2 h. The resulting suspension was filtered, rinsing with CH_3CN (29 L). The solids were dried under a N_2 flow and then in a vacuum oven (40 °C) to afford **1**•MsOH (3.1 kg, 47% over two steps). HPLC retention time: 5.9 min (Column: Halo C18, 4.6 × 150 mm, 2.7 μm; Mobile Phase A: CH_3CN, Mobile Phase B: 0.05% MsOH in H_2O; Linear Gradient: 5:95 A:B to 95:5 A:B over 12 min, then held for 2 min; Flow: 1.0 mL/min; UV detection at 210 nM). Chiral HPLC retention time: 4.3 min (Column: AS-H 4.6 × 150 mm, 5 μm; Mobile Phase A: supercritical CO_2, Mobile Phase B: 0.1% i-$PrNH_2$ in MeOH; Gradient: 5%B to 45%B over 6 min, then held at 45%B for 2 min; Flow: 4.0 mL/min; Column temperature 40 °C; UV detection at 230 nM). Analytical data from a separate batch: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J*=9.0 Hz, 1H), 7.76 (s, 1H), 7.55 (s, 1H), 6.78 (m, 1H), 4.14 (m, 1H), 4.06 (m, 1H), 3.69 (m, 1H), 3.48 (m, 4H), 3.32 (m, 1H), 2.87 (s, 3H), 2.80 (m, 1H), 1.99 (m, 11H), 1.70 (m, 1H). MS $(M+H)^+$ 440.2. mp 212–214 °C. Anal. Calc. for $C_{22}H_{26}ClN_7O$•CH_4O_3S: C, 51.53; H, 5.64; N, 18.29; Cl, 6.61; S, 5.98. Found: C, 51.28; H, 5.65; N, 18.19; Cl, 6.56; S, 5.96.

Synthesis of 2•HCl•H_2O. ((R)-1-(2-((S)-1-(4-chloro-1H-pyrazol-1-yl)ethyl)-3H-imidazo[4,5-b]pyridin-5-yl)piperidin-3-yl)(pyrrolidin-1-yl)methanone hydrochloride hydrate.

*Step 1. Methyl (S)-2-(4-chloro-1H-pyrazol-1-yl)propanoate (**28**).* Diisopropylazodicarboxylate (157 g, 777 mmol, 1.3 equiv) was added to a solution of methyl (*R*)-2-hydroxypropanoate (60 g,

576 mmol, 1 equiv), 4-chloro-1*H*-pyrazole (67 g, 634 mmol, 1.1 equiv) and PPh_3 (205 g, 782 mmol, 1.4 equiv) in THF (1.5 L) at 0 °C. The mixture was stirred at ambient temperature overnight, then was concentrated. The solids were removed by filtration and were rinsed with EtOAc, and the filtrate was concentrated. The crude product was purified by chromatography (20:1 petroleum ether:EtOAc). Three batches were run on this scale and were combined to afford a yellow oil (260 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.45 (s, 1H), 5.04 (q, *J*=7.6 Hz, 1H), 3.75 (s, 3H), 1.76 (d, *J*=7.6 Hz, 3H). MS $(M)^+$ 188.

*Step 2. (S)-2-(4-Chloro-1H-pyrazol-1-yl)propanoic acid (**29**).* A suspension of **28** (160 g, 1.4 mol) in 6N aqueous HCl (2 L) was heated at reflux for 4 h. The solution was cooled to 0 °C, then was extracted with EtOAc (2 × 2 L). The combined organic layers were concentrated to afford a solid. Recrystallization (10:1 petroleum ether:EtOAc) afforded **29** as a white solid (49 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (br s, 1H), 7.54 (s, 1H), 7.51 (s, 1H), 5.11 (q, *J*=7.4 Hz, 1H), 1.80 (d, *J*=7.4 Hz, 3H). MS $(M)^+$ 174.8. Chiral SFC retention time 2.3 min (Chiralpak AD-3 150 × 4.6 mm, 3 μ, 10% MeOH-CO_2, 2.5 mL/min, UV detection at 220 nm); (*R*)-2-(4-chloro-1*H*-pyrazol-1-yl)propanoic acid retention time 3.6 min; 99% e.e.

*Step 3. tert-Butyl (2-((S)-2-(4-chloro-1H-pyrazol-1-yl)propanamido)-6-((R)-3-(pyrrolidine-1-carbonyl)piperidin-1-yl)pyridin-3-yl)carbamate (**24**).* A solution of amine **22** (118 g, 304 mmol, 1 equiv), acid **29** (60.9 g, 349 mmol, 1.15 equiv), and pyridine (113 mL, 1.40 mol, 4.6 equiv) in EtOAc (100 mL) was cooled in an ice bath. A solution of T3P (50% in EtOAc, 210 mL, 698 mmol, 2.3 equiv) was added with stirring at a rate to maintain internal temperature below 6.0 °C. As the ice bath melted, the mixture was allowed to warm to 20 °C and was stirred overnight. The resulting slurry was cooled to 0 °C and then the solids were collected by filtration, rinsing with cold EtOAc (0.5 L), to afford amide **24** as a white solid (115 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 7.76 (app br s, 1H), 7.61 (s, 1H), 7.59 (s, 1H), 7.25 (app br s, 1H), 6.58 (d, *J*=9.0 Hz, 1H), 5.08 (br q, *J*=7.0 Hz, 1H), 4.34 (app br d, *J*=13.3 Hz, 1H), 4.15 (app br d, *J*=11.7 Hz, 1H), 3.51 (m, 4H), 3.00 (dd , *J*=13.1, 11.1 Hz, 1H), 2.87 (m, 1H), 2.56 (m, 1H), 1.94 (m, 6H), 1.89 (d, *J*=7.0 Hz, 3H), 1.76 (m, 1H), 1.55 (m, 1H), 1.49 (s, 9H). MS $(M+H)^+$ 546.5.

*Step 4. ((R)-1-(2-((S)-1-(4-Chloro-1H-pyrazol-1-yl)ethyl)-3H-imidazo[4,5-b]pyridin-5-yl)piperidin-3-yl)(pyrrolidin-1-yl)methanone (**2**).* A solution of **24** (115 g, 210 mmol, 1 equiv) in CH_2Cl_2 (421 mL) was cooled to 0 °C. Methanesulfonic acid (68.3 mL, 1.05 mol, 5.0 equiv) was

added with stirring at a rate to maintain internal temperature below 5.5 °C. The resulting solution was stirred overnight at 21 °C. The solution was then cooled to 0 °C and a solution of NH_4OAc (97.4 g, 1.26 mmol, 6.0 equiv) in water (180 mL) was added dropwise at a rate to maintain internal temperature below 7 °C. The biphasic solution was warmed to ambient temperature and was stirred an additional 1 h. The layers were separated, and the organic layer was diluted with EtOAc (1 L) and was cooled to 6 °C. Saturated aqueous $NaHCO_3$ (1.5 L) and brine (1 L) were added, and the layers were separated. The organic layer was dried over Na_2SO_4, was filtered, and was concentrated. The resulting residue was purified by silica gel chromatography (0–7% MeOH:CH_2Cl_2) to afford a foam that was concentrated from EtOH (2×). Further drying in a vacuum oven afforded **2** as a foam (83.5 g, 92%; with residual ethanol). Analytical data from a sample purified to be free of residual ethanol: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.9 Hz, 1H), 7.60 (s, 1H), 7.53 (s, 1H), 6.68 (d, *J*=8.9 Hz, 1H), 5.76 (q, *J*=7.1 Hz, 1H), 4.46 (br d, *J*=13.2 Hz, 1H), 4.23 (br d, *J*=12.4 Hz, 1H), 3.61 (m, 1H), 3.48 (m, 3H), 3.08 (m, 1H), 2.95 (m, 1H), 2.65 (m, 1H), 2.04 (d, *J*=7.6 Hz, 3H), 1.88 (m, 7H), 1.560 (m, 1H). MS $(M+H)^+$ 428.3. Chiral HPLC retention time 8.9 min (Column: Lux Cellulose-2, 250 × 4.6 mm, 5μ; Mobile phase A, heptane; Mobile phase B, EtOH; Gradient (time (min)/%B), 0.00/5, 1.00/5, 10.0/100, 11.0/100, 12.5/5; 1.5 mL/min; UV detection at 210 nM); diastereomer at methyl-bearing stereocenter retention time 10.8 min; d.e. of 83.5 g batch, >99%.

*Step 5. ((R)-1-(2-((S)-1-(4-Chloro-1H-pyrazol-1-yl)ethyl)-3H-imidazo[4,5-b]pyridin-5-yl)piperidin-3-yl)(pyrrolidin-1-yl)methanone hydrochloride hydrate (**2**•HCl•H_2O).* To prepare a crystalline sample of **2**•HCl•H_2O, compound **2** (32.4 g, 75.7 mmol, 1 equiv) was dissolved in THF (0.84 L). A solution of concentrated HCl (6.62 mL, 79.5 mmol, 1.05 equiv) in THF (0.42 L) was added dropwise with stirring; a precipitate formed, then water (13.6 mL, 0.755 mol, 10 equiv) was added. The resulting mixture was stirred for 3.5 h, then the solids were collected by filtration and were dried under vacuum (32.7 g, 93%). Another portion of **2** (76.5 g, 179 mmol, 1 equiv) was dissolved in THF (2.0 L) and water (32.2 mL, 1.79 mol, 10 equiv) with stirring. A solution of concentrated HCl (15.6 mL, 188 mmol, 1.05 equiv) in THF (1.0 L) was added dropwise with stirring. The resulting red solution became cloudy and then formed a granular precipitate. After complete addition of the HCl solution, the mixture was seeded with the first batch of crystalline material described above (32.6 g, 67.6 mmol). After an additional 2 h, the

solids were collected by filtration and were dried under vacuum to afford **2**•HCl•H_2O as a crystalline solid (109.7 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 7.90 (d, *J*=9.2 Hz, 1H), 7.64 (s, 1H), 7.07 (d, *J*=9.2 Hz, 1H), 5.99 (br q, 1H), 4.33 (m, 2H), 3.53 (m, 1H), 3.44 (m, 1H), 3.30 (m, 2H), 3.01 (m, 2H), 2.61 (m, 1H), 1.95 (d, *J*=7.4 Hz, 3H), 1.77 (m, 7H), 1.52 (m, 1H). MS $(M+H)^+$ 428.4. mp 154–157 °C. Anal. Calc. for $C_{21}H_{29}Cl_2N_7O_2$, C, 52.29; H, 6.06; N, 20.32; Cl, 14.70; Found: C, 52.08; H 6.05; N, 20.13; Cl, 14.52.

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ABBREVIATIONS

LiHMDS, lithium hexamethyldisilazide; KHMDS, potassium hexamethyldisilazide; LTMP, lithium tetramethylpiperidide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMPU, *N,N′*-dimethylpropylene urea; LDA, lithium diisopropylamide; KOTMS, potassium

trimethylsilanolate; CDI, 1,1'-carbonyldiimidazole; T3P, 1-propanephosphonic acid cyclic anhydride; DMAP, 4-dimethylaminopyridine.

REFERENCES

1. Yen, C.-L. E.; Stone, S. J.; Koliwad, S.; Harris, C.; Farese, R. V., Jr. *J. Lipid Res.* **2008**, *49* (11), 2283-2301.

2. Kim, M. O.; Lee, S. U.; Lee, H.-J.; Choi, K.; Kim, H.; Lee, S.; Oh, S. J.; Kim, S.; Kang, J. S.; Lee, H. S.; Kwak, Y.-S.; Cho, S. *Biol. Pharm. Bull.* **2013**, *36* (7), 1167-1173.

3. Kim, M. O.; Lee, S.; Choi, K.; Lee, S.; Kim, H.; Kang, H.; Choi, M.; Kwon, E. B.; Kang, M. J.; Kim, S.; Lee, H.-J.; Lee, H. S.; Kwak, Y.-S.; Cho, S. *Biol. Pharm. Bull.* **2014**, *37* (10), 1655-1660.

4. Lee, K.; Kim, M.; Lee, B.; Goo, J.; Kim, J.; Naik, R.; Seo, J. H.; Kim, M. O.; Byun, Y.; Song, G.-Y.; Lee, H. S.; Choi, Y. *Org. Biomol. Chem.* **2013**, *11* (5), 849-858.

5. Imbriglio, J. E.; Shen, D.-M.; Liang, R.; Marby, K.; You, M.; Youm, H. W.; Feng, Z.; London, C.; Xiong, Y.; Tata, J.; Verras, A.; Garcia-Calvo, M.; Song, X.; Addona, G. H.; McLaren, D. G.; He, T.; Murphy, B.; Metzger, D. E.; Salituro, G.; Deckman, D.; Chen, Q.; Jin, X.; Stout, S. J.; Wang, S.-P.; Wilsie, L.; Palyha, O.; Han, S.; Hubbard, B. K.; Previs, S. F.; Pinto, S.; Taggart, A. *J. Med. Chem.* **2015**, *58* (23), 9345-9353.

6. Camp, N. P.; Naik, M. Preparation of pyrimidinylaminomethylpyrimidinyloxyphenylmethanesulfonamide derivatives for use as DGAT2 inhibitors. WO2015077299A1, 2015.

7. Futatsugi, K.; Kung, D. W.; Orr, S. T.; Cabral, S.; Hepworth, D.; Aspnes, G.; Bader, S.; Bian, J.; Boehm, M.; Carpino, P. A.; Coffey, S. B.; Dowling, M. S.; Herr, M.; Jiao, W.; Lavergne, S. Y.; Li, Q.; Clark, R. W.; Erion, D. M.; Kou, K.; Lee, K.; Pabst, B. A.; Perez, S. M.; Purkal, J.; Jorgensen, C. C.; Goosen, T. C.; Gosset, J. R.; Niosi, M.; Pettersen, J. C.; Pfefferkorn, J. A.; Ahn, K.; Goodwin, B. *J. Med. Chem.* **2015**, *58* (18), 7173-7185.

8. Futatsugi, K.; Huard, K.; Kung, D. W.; Pettersen, J. C.; Flynn, D. A.; Gosset, J. R.; Aspnes, G. E.; Barnes, R. J.; Cabral, S.; Dowling, M. S.; Fernando, D. P.; Goosen, T. C.; Gorczyca, W. P.; Hepworth, D.; Herr, M.; Lavergne, S.; Li, Q.; Niosi, M.; Orr, S. T. M.; Pardo, I. D.; Perez, S. M.; Purkal, J.; Schmahai, T. J.; Shirai, N.; Shoieb, A. M.; Zhou, J.; Goodwin, B. *MedChemComm* **2017**, *8* (4), 771-779.

9. "Sodium hydride" in *Bretherick's Handbook of Reactive Chemical Hazards*. 8th ed.; Elsevier: Cambridge, MA, 2017.

10. Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1983**, *48* (25), 5143-5144.

11. Rossle, M.; Del Valle, D. J.; Krische, M. J. *Org. Lett.* **2011**, *13* (6), 1482-1485.

12. Greszler, S. N.; Halvorsen, G. T.; Voight, E. A. *Org. Lett.* **2017**, *19* (10), 2490-2493.

13. Zecchini, G. P.; Torrini, I.; Paradisi, M. P. *J. Het.Chem.* **1985**, *22* (4), 1061-1064.

14. London, C.; Hoyt, S. B.; Parsons, W. H.; Williams, B. S.; Warren, V. A.; Tschirret-Guth, R.; Smith, M. M.; Priest, B. T.; McGowan, E.; Martin, W. J.; Lyons, K. A.; Li, X.; Karanam, B. V.; Jochnowitz, N.; Garcia, M. L.; Felix, J. P.; Dean, B.; Abbadie, C.; Kaczorowski, G. J.; Duffy, J. L. *Bioorg. Med. Chem. Lett.* **2008**, *18* (5), 1696-1701.

15. Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58* (10), 2900-2903.

16. Hanessian, S.; Yang, R.-Y. *Synlett* **1995**, (6), 633-634.

17. Brosse, N.; Pinto, M.-F.; Bodiguel, J.; Jamart-Gregoire, B. *J. Org. Chem.* **2001**, *66* (8), 2869-2873.

18. Dunetz, J. R.; Xiang, Y.; Baldwin, A.; Ringling, J. *Org. Lett.* **2011**, *13* (19), 5048-5051.

19. Dunetz, J. R.; Berliner, M. A.; Xiang, Y.; Houck, T. L.; Salingue, F. H.; Chao, W.; Yuandong, C.; Shenghua, W.; Huang, Y.; Farrand, D.; Boucher, S. J.; Damon, D. B.; Makowski, T. W.; Barrila, M. T.; Chen, R.; Martinez, I. *Org. Process Res. Dev.* **2012**, *16* (10), 1635-1645.