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Practical Syntheses of a CXCR3 Antagonist

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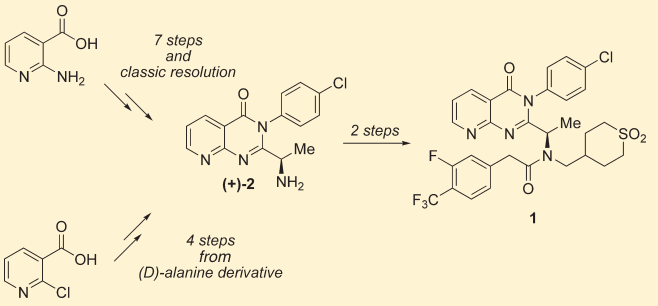
Supporting Information

ABSTRACT: Two new, reliable syntheses of a pyrido[2,3-*d*]-pyrimidine inhibitor of the CXCR3 receptor are described. A nine-step synthesis of the CXCR3 inhibitor (**1**) from 2-aminonicotinic acid was demonstrated on a multikilogram scale and incorporates a classic resolution to deliver the enantioenriched active pharmaceutical ingredient (API). A second synthesis of the CXCR3 inhibitor starts from (+)-(D)-Boc alanine and 2-chloronicotinic acid and utilizes a Goldberg coupling. This second synthesis, performed on a gram scale, intersects the former route at a common intermediate thereby completing a formal synthesis of the enantioenriched API in higher overall yield without the need for a resolution.



INTRODUCTION

Identified by Loetscher[1] in the mid-1990s, the CXCR3 chemokine receptor can be found predominantly in activated T cells ($CD4^+$ and $CD8^+$). The overexpression of this receptor is linked to several autoimmune disorders including psoriasis, rheumatoid arthritis, multiple sclerosis, and solid organ transplantations. CXCR3 animal knockout mice studies indicate that an antagonist of this receptor may inhibit T-cell migration and thereby attenuate the incidence and severity of these diseases. As part of our research program toward discovering effective inhibitors of this receptor,[2] **1** was identified as a potent inhibitor of the CXCR3 receptor (Scheme 1). To support further toxicological studies, a practical and efficient synthesis was required.

Initial synthetic efforts to provide small quantities of preclinical candidate **1** and analogues followed the strategy outlined in Scheme 1: disconnection of **1** at the tertiary amide reveals primary amine **2** along with phenylacetic acid **3** and sulfone aldehyde **4**. Amine **2** is derived from nucleophilic addition of 4-chloroaniline to oxazinone **5**. Oxazinone **5** arises from a condensation of commercially available 2-aminonicotinic acid **6** and D-Boc-alanine **7**. Key problems identified in this synthesis were the enantiomeric erosion observed during the low-yielding conversion of **7** to primary amine **2** as well as the propensity of oxazinone **5** to hydrolyze upon exposure to mildly basic aqueous wash to give ring-opened products. Although this route was sufficient for the small-scale preparation of **1**, attempts to provide quantities for further studies via this route resulted in amplification of the issues mentioned above. Moving forward, we aimed to develop a reliable, scalable synthesis of **1** via primary amine **2** that did not proceed by way of unstable oxazinone intermediate **5**.

Herein we report two novel syntheses of **1**. The first entails a racemic synthesis of *rac*-**2**, which proceeds by way of a 2-ethyl pyrido[2,3-*d*]pyrimidine and incorporates a classic resolution of a primary amine intermediate. The second begins with commercially available (+)-(D)-Boc alanine and preserves the stereocenter through four transformations to intersect the former route at (+)-**2**.

RESULTS AND DISCUSSION

Synthesis of *rac*-2. Having identified limitations in scaling up known protocols for the synthesis of pyrido[2,3-*d*]pyrimidines,[3] we considered alternate entries to access this heterocyclic core that would satisfy our scale-up needs. Cognizant of the tendency of the secondary stereocenter to undergo epimerization during the synthesis of **2**, we devised a strategy toward *rac*-**2** that hinged on its successful resolution. Such an approach to efficiently access *rac*-**2** was envisioned to go by way of pyrido[2,3-*d*]pyrimidine **8**, which could arise from a condensation of 2-aminonicotinamide **9** with a propionic acid equivalent (Scheme 2).

Toward that end we first set out to synthesize the appropriate 2-aminonicotinamide precursor with which to condense with a propionic acid equivalent. 2-Aminonicotinic acid **6** was coupled with 4-chloroaniline by using EDC HCl to give a 72% yield of amide **9** (Scheme 3).[4] After screening a variety of conditions, we found that reacting amide **9** with a mixture of triethylorthopropionate and acetic acid was most effective in promoting the desired transformation. Ultimately this procedure was used to provide >2 kg of pyrido[2,3-*d*]pyrimidine **8** from **9** in 93% yield.[5]

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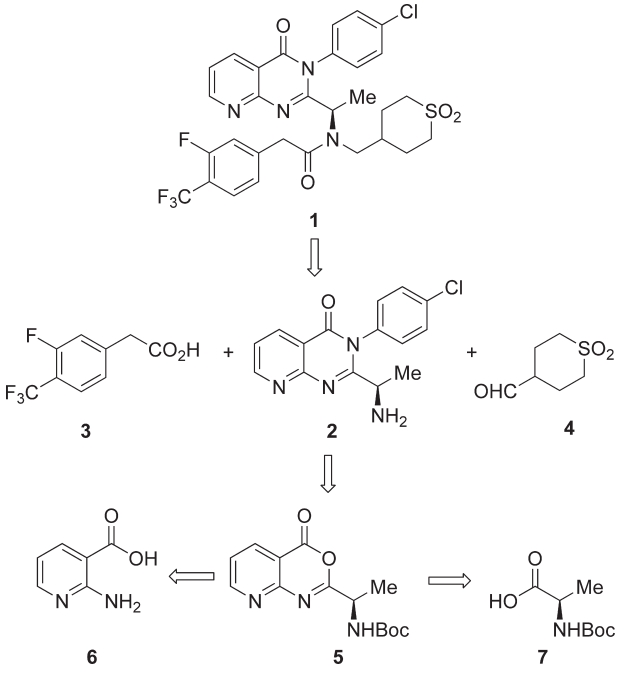
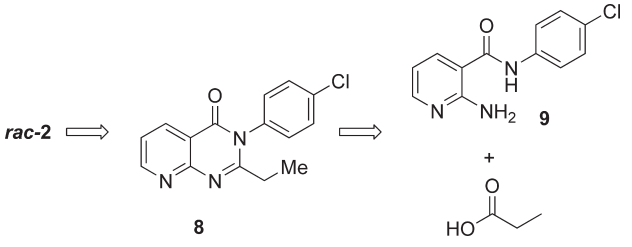
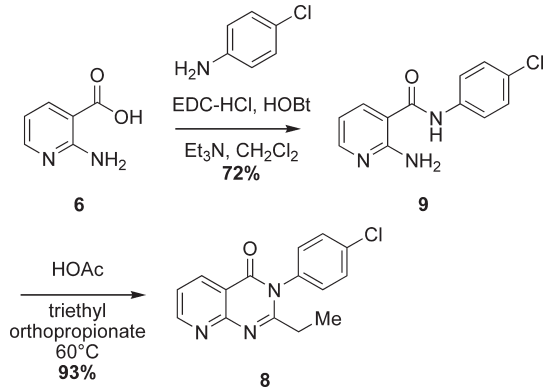
Scheme 1. First Generation Route to 1



Scheme 2. Approach to the Synthesis of *rac*-2

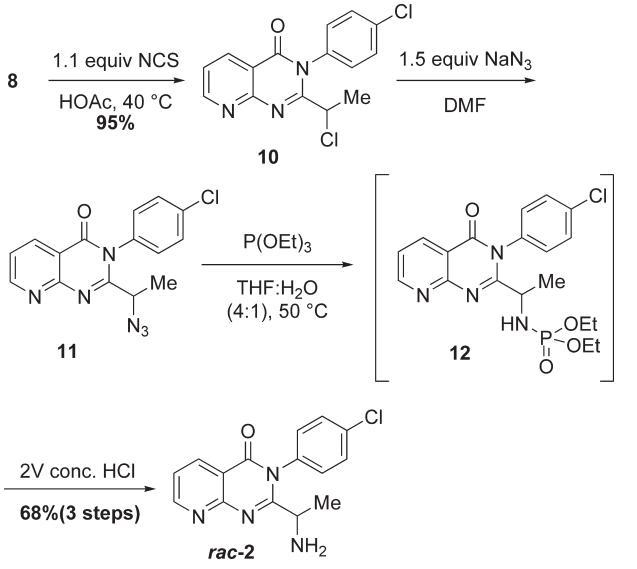


Scheme 3. Synthesis of Pyrido[2,3-*d*]pyrimidine 8

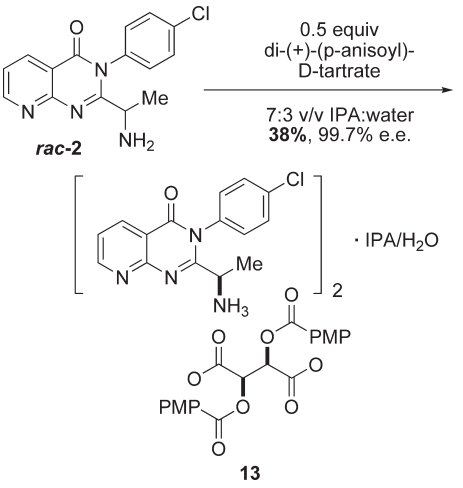


Installation of the amino group was then accomplished via a two-step process. Reacting **8** with *N*-chlorosuccinimide (NCS) in acetic acid cleanly afforded chloride **10**, which was crystallized from solution by the addition of water to achieve a 95% isolated yield (Scheme 4). Reacting **10** with sodium azide[6] effected

Scheme 4. Functionalization of 8 To Give *rac*-2



Scheme 5. Classic Resolution of *rac*-2



displacement of the chloride to provide **11**. Employing triethylphosphite to reduce azide **11** produced the desired phosphoramide **12** as determined by LC/MS.[7] Cleavage of the phosphoramide was accomplished in situ with concentrated HCl to afford the desired primary amine *rac*-**2** in 68% yield over the three steps. With the desired racemic amine in hand, efforts to develop a chiral resolution commenced.

Classic Resolution of *rac*-2. Initial screening of enantiopure acids for the resolution of *rac*-**2** led to the identification of di-(+)-(*p*-anisoyl)-D-tartrate (DAT). It was found that stirring *rac*-**2** with 0.5 equiv of this tartrate in acetonitrile afforded a 19% yield of the desired diastereomer of a 2:1 amine:DAT salt having a 95% ee at the amine stereocenter. Further investigations into solvent combinations identified IPA:water, and developmental work ensued that entailed measuring the mother liquor enantiomeric excesses of a range of IPA:water concentrations at 15 volumes.[8] The mother liquor had an enrichment of 60−63% ee in the undesired amine DAT salt using 7:3 v/v IPA:water

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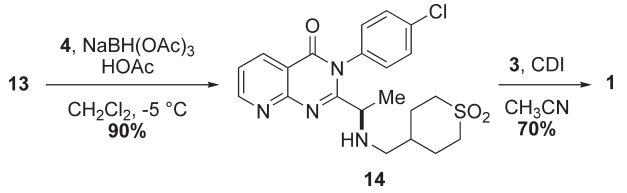
Scheme 6. Final Steps to 1



(Scheme 5). Interestingly, a sharp drop in liquor concentration and ee was observed when the concentration of IPA in the aqueous mixture exceeded 70% v/v. The outcome of a resolution of *rac*-**2** having a mother liquor ee of 63% enriched in the undesired enantiomer provides a maximum yield of 37.5−38.5%, or 75−77% of theoretical, of resolved **2** (**13**). In practice, the resolution of *rac*-**2** was performed as described above with 5 kg of *rac*-**2** to ultimately deliver 3.9 kg (38% yield, 99.7% ee) of amine:DAT salt **13** for use in the subsequent reductive amination step.

Reductive Amination of Aldehyde 4 and Amine-DAT Salt 13. With technology in place to access large quantities of aldehyde **4**[9] via its corresponding bisulfate adduct,[10] we turned our attention to the reductive amination. Early protocols called for preformation of the imine by reacting aldehyde **4** with amine-DAT salt **13** for 1 h in THF at 0 °C prior to addition of the reducing agent, $NaBH(OAc)_3$, and acetic acid. After further agitating the solution for 1 h at 0 °C, up to 90% conversion of the amine-DAT salt **13** to secondary amine **14** was observed by HPLC. However, two impurities arise from this protocol[11] that increase in concentration with prolonged aging of the preformed imine or if the reaction is carried out above 0 °C for any extended length of time. To eliminate the formation of these impurities, the order of addition was altered such that 1.4 equiv of aldehyde **4** in dichloromethane was charged to a solution of amine-DAT salt **13**, HOAc, and $NaBH(OAc)_3$ in dichloromethane over ∼3 h while maintaining the internal temperature below −5 °C (Scheme 6).[12] Under these improved conditions, quantitative conversions of **13** and assay yields of up to 99.7% of **14** were observed.

Due to difficulties encountered in identifying and isolating a crystalline salt of **14** with satisfactory properties, direct isolation of the secondary amine freebase was required. This was accomplished by a distillative solvent switch of the dichloromethane extracts into methanol, followed by concentration and crystallization from a methanol−ethanol solution at 40 °C. Yields were typically on the order of 90% isolated, with the balance of material in the mother liquor and washes. The batches also contained 1−2% of *ent*-**14** due to racemization under the reaction conditions, which was well rejected along with the other chemical impurities leading to >99.5% LCAP (liquid chromatography area percentage) isolated penultimate intermediate.

Amide Bond Formation. Early methods utilized EDC·HCl to promote amide bond formation between secondary amine **14** and 4-trifluoromethyl(3-fluoro)phenyl acetic acid (**3**) to form **1**. Under these conditions the amide coupling reaction proceeded in yields ranging from 80% to 85%. Upon further investigation we identified 1,1-carbonyldiimidazole (CDI) as a more readily available and cost-effective coupling agent to effect this transformation.[13] Thus, phenylacetic acid **3** was slowly added to a slurry of CDI in acetonitrile, after which time quenching an aliquot into cyclohexylamine revealed complete conversion of **3** to the corresponding cyclohexyl amide by HPLC analysis. A solution of secondary amine **14** in acetonitrile was charged to the solution of activated **3** over 1 h and the mixture was aged for 20 h, after which time 99% conversion of **14** was observed. After seeding the reaction mixture with 2 wt % of a suspension of **1** in water, addition of water continued until a 59 wt % aqueous mixture resulted. After holding for 16 h, product **1** was isolated by filtration in 83% yield.

However, we observed a higher than expected amount (7 wt %) of a single impurity, **15**, whose structure was determined by direct synthesis of the product formed upon treating **1** with K_2CO_3 in MeOH (Figure 1). Stress studies conducted prior to the campaign in which **1** was stirred with 1 equiv of imidazole resulted in the formation of only 1.4 wt % of **15** over 18 h. Product **15** was presumably formed due to the excess of imidazole in the water/acetonitrile mixture which facilitated a base-mediated prototropic rearrangement of **1** (see Figure 1). This hypothesis was later confirmed by additional stress studies that demonstrated the propensity of **1** to rearrange to **15** at higher imidazole levels (see the Supporting Information). To reduce the levels of **15** in **1** a purification procedure was implemented that involved suspending **1** in 5 volumes of IPA, which reduced the amount of **15** to approximately 3 wt % after filtration. Following the IPA suspension, **1** was recrystallized from 27 wt % aqueous ethanol at 20 volumes. This protocol allowed us to deliver 2.6 kg of **1** in overall 70% yield containing <0.5 wt % of impurity **15**.

Synthesis of 1 from (+)-D-Boc-Alanine. Concomitant with the multikilo delivery of **1**, we developed a second route to this molecule with several goals in mind. First, we were interested in replacing 2-amino nicotinic acid with a less expensive substituted pyridine starting material. Also, making use of a D-alanine derivative as the source of chirality in the molecule was appealing in that a chiral resolution could be circumvented. Finally, we recognized that a long-term route would need to eliminate the use of azide chemistry for safety considerations. We ultimately developed an approach to primary amine (+)-**2** that addressed each of these concerns.[14]

Given the advantages of employing 2-chloronicotinic acid instead of 2-aminonicotinic acid as a starting material, the development of a C−N coupling strategy with a derivative of the former was attractive.[15] A survey of the literature revealed that palladium catalysis was competent at promoting such a coupling between primary amides and 2-chloropyridines.[16] Thus, alanine amide **17**[17] was reacted with methyl 2-chloronicotinate **16**[18,19] in the presence of 2 mol % of $Pd(OAc)_2$, 4 mol % of Xantphos, and 2 equiv of potassium carbonate. Stirring these reagents in toluene at 80 °C resulted in a >95% assay yield of the desired coupled product **18** (Scheme 7). Although employing THF as solvent gave slightly lower assay yields of **18** (92%), this was the solvent of choice in order to facilitate a distillative solvent switch to isopropyl acetate (IPAc) at the completion of the reaction. Following aqueous washes, the IPAc solution was subjected to a crystallization protocol using heptane as antisolvent to achieve a 70% isolated yield of **18** with the remaining material being in the aqueous washes (3%), mother liquor (8%), and filter cake washes (7%). The enantiomeric integrity of the alanine starting material was retained through the transformation to **18** (>99:1 er).

To carry out the formation of the *N*-4-chlorophenyl nicotinamide moiety, it was necessary to add a solution of methyl ester **18** to a prestirred solution of excess 4-chloroaniline and isopropylmagnesium chloride in THF. After allowing the resulting solution to warm

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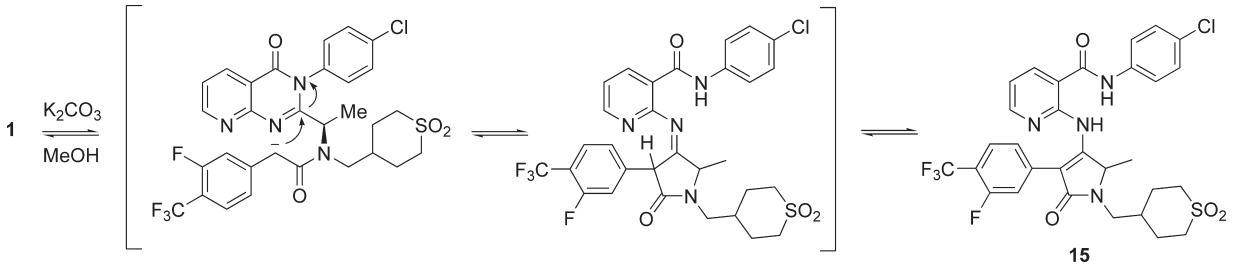
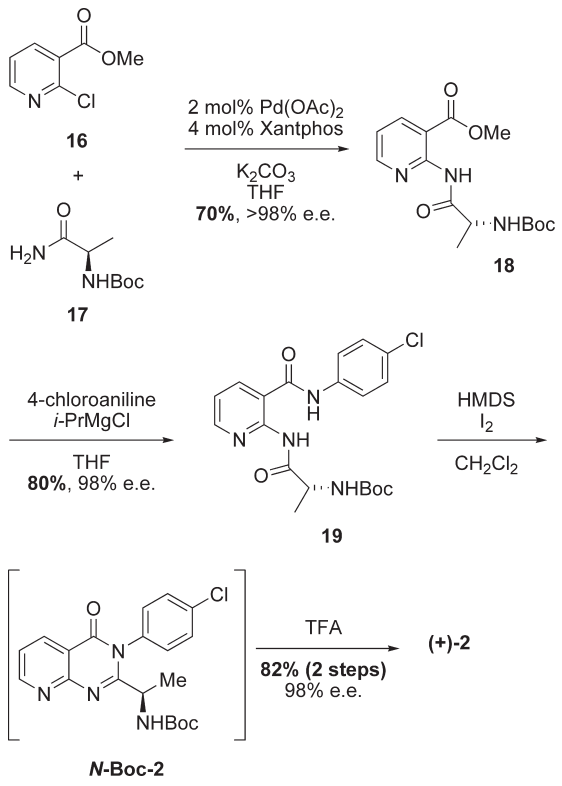


Figure 1. Proposed formation of impurity **15**.

Scheme 7



to ambient temperature and 2 h of stirring, an 87% assay yield of bisamide **19** was observed. Bisamide **19** was isolated in 80% yield and 98% ee after acidic workup and silica gel chromatography.

Next, we required a dehydrative cyclization and conditions for Boc group cleavage to arrive at key intermediate primary amine **2**. A survey of conditions revealed that heating **19** in either HOAc or isobutyric acid achieved the desired transformation to the pyrido[2,3-*d*]pyrimidine core (*N*-Boc-**2**); however, chiral HPLC analysis revealed that this product had undergone racemization. Thus, milder conditions were sought that would not disrupt the stereocenter. Following a report by Argade,[20] we subjected bisamide **19** to hexamethyldisilazane and iodine in dichloromethane and observed clean (>99%) conversion to the desired cyclized product after 16 h of stirring. Pleasingly, no epimerization occurred during this transformation. This product was carried on without further purification to the deprotection in which a solution of crude *N*-Boc-**2** in dichloromethane was treated with TFA. After 1 h of stirring, HPLC analysis revealed full conversion to primary amine (+)-**2**. The product was subjected to an acid−base extraction sequence in order to remove colored impurities that formed during the dehydrative cyclization. The organic extracts were concentrated in vacuo to approximately three volumes, and then product (+)-**2** was precipitated with nine volumes of MTBE and isolated by filtration in 82% yield over the 2 steps, with the remainder of material in the mother liquors.

CONCLUSION

We have developed two new practical syntheses of the CXCR3 antagonist **1**. The first, which begins with racemic starting materials, constructs the pyrido[2,3-*d*]pyrimidine cores from a 2-amino nicotinamide and triethyl orthopropionate. The selective functionalization of the ethyl moiety of pyrido[2,3-*d*]pyrimidine **8** provided access to the requisite primary amine *rac*-**2** in four steps and 72% overall yield. Furthermore, a classic resolution of this primary amine (*rac*-**2**) was developed and implemented on a 5 kg scale. A practical and reliable synthesis of sulfone aldehyde **4** was developed that improves upon known procedures to synthesize its precursor acid, **14**, and then incorporates the formation of a crystalline bisulfite adduct **16** as a purification and hold point. Coupling partners **13** and **4** were then combined in a reductive amination to give secondary amine **14**. A CDI-mediated coupling to form the final amide bond to give **1** was employed in place of the existing EDC HCl technology. Using these methods the synthesis of the CXCR3 antagonist **1** was demonstrated on a multikilogram scale.

Our second synthesis of **1**, in which the stereocenter is derived from the readily available enantiopure building block (+)-D-alanine, makes use of a challenging C−N coupling reaction that allowed us to employ 2-chloronicotinic acid as a cheaper alternative to 2-aminonicotinic acid. By preserving the stereocenter through the isopropylmagnesium chloride mediated amide bond formation with 4-chloroaniline and the subsequent dehydrative cyclization and Boc group cleavage, we accessed (+)-**2** in enantioenriched form without the need for a resolution. The free primary amine (+)-**2** is known to perform in the reductive amination with **4** and amide bond coupling with **3** to arrive at **1**, thereby completing the formal synthesis of our target compound. Although this route requires additional research to support large-scale production of the API, it demonstrates a practical means to access **1** as a starting point for future process development.

EXPERIMENTAL SECTION

(*R*)-2-(*N*-1-(3-(4-Chlorophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one)-*N*-(1,1-dioxohexahydro-1λ^6-thiopyran-4-yl)methyl)-2-(3-fluoro-4-(trifluoromethyl)phenyl)acetamide (1). To a 100 L reactor was charged **14** (2595 g, 92.4 wt %, 5.8 mol) followed by acetonitrile (32 L, 12 vol). To remove the residual EtOH from the previous step, approximately half of the acetonitrile was vacuum distilled at 25−30 °C.

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Additional acetonitrile was charged (16 L, 6 vol) and distillation was repeated to afford a solution of **14** (141 mg/mL) that contained 0.2 wt % EtOH. The solution was cooled to 15 °C and held overnight.

A solution of **3** (1547 g, 7.0 mol) and CH_3CN (3.2 L) was added to a slurry of CDI (1226 g, 7.6 mol) and CH_3CN (2.6 L, 1 vol) over 10 min, and the mixture was stirred for an additional 10 min at which time 1.4% of **3** remained by HPLC analysis. A solution of **14** (141 mg/mL in CH_3CN) was added over 1 h followed by additional CH_3CN (3.2 L) to rinse the vessel. The reaction mixture was maintained for 20 h at which point 0.1% **14** remained. Water (2.6 L, 1 vol) was charged to the reactor over 0.5 h followed by a slurry of 2 wt % **1** (55 g) in water (4.4 L) to achieve a 59 wt % aqueouws mixture. The reaction mixture was aged for 16 h, then the solids were filtered and washed with 7:3 water:acetonitrile (12.7 L) and water (12.9 L) and then dried in the vacuum oven at 40 °C. The solids (3570 g) were then slurried in IPA (26 L, 0.016 wt % water) for 2 h, filtered, washed with IPA (8.6 L), and dried in a vacuum oven at 40 °C overnight. The solids (3685 g) were then dissolved in EtOH (46 L), heated to 65 °C, and filtered through a 5 μL polypropylene filter. Water (13.5 L) was charged to the solution at 61 °C followed by 2 wt % of **1** (109 g) suspended in water (0.5 L). Water (0.3 L) was charged into the vessel to wash the remaining seeds into the reactor to give a 27 wt % water mixture. The slurry was cooled to 22 °C and agitation continued for an additional 16 h before the solids were isolated by filtration and dried in a vacuum oven at 40 °C overnight to afford 2585 g of **1** (99.7 wt % 70.9% corrected isolated yield) as a white solid (mp (DSC) 206−257 °C,, exothermic decomposition, maximum 236 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (d, J = 7.24 Hz, 3H), 1.65 (d, J = 6.65 Hz, 1H), 1.71 (s, 2H), 1.80−2.01 (m, 3 H), 2.05−2.13 (m, 1H), 2.50 (d, J = 2.93 Hz, 1H), 2.78 (d, J = 13.11 Hz, 1H), 3.07−3.21 (m, 3H), 3.43−3.60 (m, 2H), 3.66−3.75 (m, 1H), 3.78 (s, 2H), 4.96 (q, J = 7.24 Hz, 1H), 6.79−6.88 (m, rotamer), 6.98−7.06 (m, 2H), 7.14 (dd, J = 8.61, 2.54 Hz, rotamer), 7.22 (dd, J = 8.41, 2.54 Hz, 1H), 7.35 (dd, J = 8.51, 2.45 Hz, rotamer), 7.44 (dd, J = 7.82, 4.69 Hz, 1H), 7.49−7.60 (m, 3H) 7.66−7.72 (m, rotamer), 7.75 (dd, J = 8.41, 2.54 Hz, 1H), 8.56 (dd, J = 7.92, 2.05 Hz, 1H), 8.65 (dd, J = 8.02, 1.76 Hz, rotamer), 8.94 (dd, J = 4.70, 19.6 Hz, 1H), 9.09 (dd, J = 4.50, 1.96 Hz, rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 28.0, 28.2, 37.4, 40.3, 49.4, 51.0, 51.1, 54.2, 77.2, 116.3, 117.8, 122.6, 125.0, 127.3, 129.7, 130.6, 130.7, 134.0, 136.0, 136.7, 141.0, 141.1, 156.4, 157.2, 161.8, 162.5, 170.8; IR 3264, 2929, 1624, 1584, 1514, 1491, 1395, 1367, 1320, 1290, 1253, 1110, 1093, 1093, 1046, 828, 773, 712, 662 cm^{-1}; exact mass m/z calcd for $C_{30}H_{28}ClF_4N_4O_4S$ $[M + H]^+$ 651.14504, found 651.14540.

(+)-2-(1-(*R*)-Aminoethyl)-3-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one ((+)-2). Hexamethyldisilylazide (7.6 mL, 36.5 mol, 3.0 equiv) was added to a solution of **19** (5.1 g, 12.18 mol, 1.0 equiv), I_2 (4.6 g, 18.3 mol, 1.5 equiv), and CH_2Cl_2 (77 mL). The reaction mixture was maintained for 18 h, then washed with 10 wt % aqueous $Na_2S_2O_3$ (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo to a brown oil, which was dissolved in CH_2Cl_2 (50 mL) and treated with trifluoroacetic acid (25 mL). The reaction mixture was maintained for 1 h, then poured into HCl (1 N aqueous, 50 mL). The layers were separated, and then the aqueous layer was basified to pH 10 with NaOH (5 N aqueous) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were reduced in vacuo to 10 mL, then MTBE (50 mL) was added slowly to precipitate the product. The mixture was filtered and washed with MTBE (5 mL) to yield 3.0 g of (+)-**2** (82%) as a pale yellow solid (mp (DSC) 175−206 °C, exothermic decomposition, maximum 182 °C). All spectral data for (+)-**2** match that of *rac*-**2**, and the enantiomeric ratio was determined to be 99:1 by using the chiral SFC method described for **13**.

2-(1-Aminoethyl)-3-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (*rac*-2). Sodium azide[6] (480 g, 7.38 mol, 1.5 equiv) was added to a solution of **10** (1575 g, 4.92 mol, 1.0 equiv) and DMF (6500 mL). The reaction mixture was maintained at 20 °C for 23 h, then poured into water (40 L). The mixture was filtered then the filtrate was washed with water (3 × 2.0 L) and taken directly to the next step without drying. Diagnostic data for intermediate azide **11** (mp (DSC) 149−163 °C, minimum 160 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (d, J = 3.0 Hz, 1H), 8.53 (dd, J = 8.0, 2.0 Hz, 1H), 7.66 (m, 5H), 4.00 (q, J = 6.5 Hz, 1H), 1.55 (d, J = 6.5 Hz, 3H); signals for 2 N*H* protons not observed; ^{13}C (100 MHz, DMSO-d_6) δ 161.8, 157.5, 156.6, 156.1, 136.1, 134.7, 134.2, 131.0, 130.6, 129.6 (2C), 123.1, 116.4, 55.5, 17.0; IR 3445, 3259, 2097, 1680, 1599, 1584, 1566, 1488, 1432, 1367, 1256, 1088, 796 cm^{-1}; exact mass m/z calcd for $C_{15}H_{12}ClN_6O$ $[M + H]^+$ 327.07611, found 327.07524.

Triethylphosphite (1880 g, 11.3 mol, 2.3 equiv) was slowly added to a mixture of **11** (1607 g, 4.9 mol, 1.0 equiv), THF (8.0 L), and water (6.5 L). The reaction mixture was maintained at 60 ± 5 °C for 20 h then cooled to 0 °C. Concentrated HCl (3.0 L) was added slowly keeping the internal temperature between 0 and 5 °C, and the resulting mixture was allowed to warm to ambient temperature and stirred for 15 h. The reaction mixture was concentrated in vacuo and to the residue was added water (3.5 L) and DCM (12.0 L). The biphasic mixture was cooled to 5 °C, and NaOH (2.6 kg) in water (3.0 L) was added slowly to keep the internal temperature at 10 ± 5 °C to basify the aqueous layer to pH 9. The layers were separated, and the DCM layer was dried with Na_2SO_4, concentrated in vacuo. The residue was washed with MTBE (3 × 1 L) and EtOAc (2 × 1 L) and dried under vacuum to afford 1010 g of *rac*-**2** (68%, 3 steps) as a light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (dd, J = 4.7, 2.0 Hz, 1H), 8.56 (dd, J = 7.9, 2.0 Hz, 1H), 7.56 (dd, J = 7.4, 1.6 Hz, 2H), 7.44 (dd, J = 8.1, 4.7 Hz, 1H), 7.25 (m, 2H), 3.74 (q, J = 6.6 Hz, 1H), 1.35 (d, J = 6.6 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 165.2, 162.7, 157.7, 156.6, 137.0, 136.2, 134.6, 130.7, 130.5, 130.1, 129.8, 122.7, 116.2, 49.2, 23.6; IR 3446, 3260, 2990, 2097, 1682, 1599, 1584, 1566, 1432, 1256, 1088, 795 cm^{-1}; exact mass m/z calcd for $C_{15}H_{14}ClN_4O$ $[M + H]^+$ 301.0856, found 301.0837.

3-(4-Chlorophenyl)-2-ethylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (8). HOAc (100 g, 1.5 mol, 0.25 equiv) was added to a mixture of **9** (1530 g, 6.2 mol, 1 equiv) and 1,1,1-triethoxypropane (4350 g, 24.8 mol, 4 equiv). The reaction mixture was heated to 60 °C, maintained for 18 h, and then cooled to 20 °C and stirred for an additional 48 h. The mixture was filtered, then the filtrate was washed with hexane (2 × 1.0 L) and dried under vacuum to afford 1490 g of **8** (84%) as an off-white solid (mp (DSC) 172−183 °C, minimum 179 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (dd, J = 4.5, 2.0 Hz, 1H), 8.48 (dd, = 7.6, 2.1 Hz, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.54 (m, 3H), 2.38 (q, J = 7.6 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H); ^{13}C (100 MHz, DMSO-d_6) δ 162.0, 160.9, 157.2, 155.9, 136.0, 135.9, 133.8, 130.6 (2C), 129.7 (2C), 122.2, 115.6, 28.9, 10.4; IR 3445, 3259, 2990, 1682, 1599, 1584, 1566, 1487, 1432, 1367, 1254, 1087, 1015, 820 cm^{-1}; exact mass m/z calcd for $C_{15}H_{14}ClN_3O$ $[M + H]^+$ 286.07471, found 286.07395.

2-Amino-*N*-(4-chlorophenyl)nicotinamide (9). Et_3N (1993 g, 19.7 mol, 2 equiv) was added to a mixture of **6** (1360 g, 9.9 mol, 1 equiv), 4-chlorobenzenamine (1257 g, 9.9 mol, 1 equiv), EDCI·HCl (2070 g, 10.8 mol, 1.1 equiv), HOBt (122 g, 0.9 mol, 0.1 equiv), and DCM (8.0 L). The mixture was stirred for 21 h then concentrated in vacuo. The residue was triturated with water (2.5 L) and the resulting mixture was filtered. The filtrate was washed with water (2.5 L), 5% Na_2CO_3 (2 × 2.0 L), water (2 × 2.5 L), and MTBE (2 × 2.0 L) and dried under vacuum overnight to afford 1540 g of **9** (72%) as a white solid (mp (DSC) 207−218 °C, minimum 214 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (br s, 1H), 8.13 (dd, J = 6.5, 2.0 Hz, 1H), 8.04 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 9.1 Hz, 2H), 7.40 (d, J = 9.1 Hz, 2H), 6.99 (br s, 2H), 6.67 (dd, J = 7.5, 4.5 Hz, 1H); ^{13}C (100 MHz, DMSO-d_6) δ 165.3, 157.4, 150.4, 136.8, 135.9, 127.1, 125.8, 120.8, 110.0, 108.6; IR 3444, 3258, 1639, 1611, 1515, 1491, 1441, 1397, 1309, 1251, 1089, 1014, 821 cm^{-1}; exact mass m/z calcd for $C_{12}H_{11}ClN_3O$ $[M + H]^+$ 248.05906, found 248.05842.

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2-(1-Chloroethyl)-3-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (10). *N*-Chlorosuccinimide (765 g, 5.72 mol, 1.1 equiv) was added over 3 h to a solution of **8** (1484 g, 5.20 mol, 1.0 equiv) and HOAc (5600 mL) at 40 °C, maintaining the internal temperature between 50 and 53 °C, then maintained at 40 °C for an additional 19 h before it was cooled to 20 °C and poured into water (15 L). The mixture was filtered, then the filtrate was washed with water (2 × 7.5 L), 1% NaOH (10 L), and water (2 × 5 L) and dried under vacuum to afford 1580 g of **10** (95%) as a white solid (mp (DSC) 201−219 °C, minimum 217 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (dd, J^1 = 2.0 Hz, J^2 = 4.5 Hz, 1H), 8.61 (dd, J^1 = 2.1 Hz, J^2 = 8.1 Hz, 1H), 7.55 (m, 4H), 7.16 (dd, J^1 = 2.5 Hz, J^2 = 8.5 Hz, 1H), 4.59 (q, J = 7.0 Hz, 1H), 1.95 (d, J = 7.0 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 162.7, 158.0, 157.3, 156.8, 137.1, 136.6, 134.0, 131.4, 130.6, 130.5, 126.5, 123.6, 116.9, 52.7, 22.0; IR 3444, 3260, 1682, 1601, 1587, 1568, 1433, 1367, 1259, 1088, 798, 719 cm^{-1}; exact mass m/z calcd for $C_{15}H_{12}Cl_2N_3O$ $[M + H]^+$ 320.03574, found 320.03467.

2-(*R*)-(1-Aminoethyl)-3-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one Dibenzoyl-(+)-*p*-methoxy-D-tartrate Water/Isopropanol Solvate (13). Di-(+)-(*p*-anisoyl)-D-tartrate (3.95 kg, 92 wt %, 8.7 mol) was dissolved in aqueous IPA (39 L, 38.4 wt % water). A total of 4.8 L of this DAT solution was added to a 100 L reactor containing a solution of *rac*-**2** (5.22 kg, 17.4 mol) and aqueous IPA (33 L, 38.4 wt % water) and seeded (266 g of **13**). An additional 2 L of DAT solution was added to wash the seed into the reactor, and the remaining DAT solution was added over 3.5 h. The reaction mixture was stirred for an additional 10 h at which time the mother liquor was assayed by chiral HPLC at 64% ee, enriched in the undesired enantiomer. The reaction mixture was heated to 42 °C for 1.5 h and cooled over 1.5 h to 22 °C. The reaction mixture was filtered through a 25 μm filter at rate of approximately 2.2 L/min. The filter cake was washed with aqueous IPA (2 × 12.5 L, 38.4 wt % water) and the solids dried at 40 °C for 4 d to afford 3.93 kg (38%, 99.7% ee as determined on a Berger SFC, Chiralcel AD-H, 5 μm, 4.6 × 250 mm, 35 °C, 4 mL/min, 100 psi, isocratic mixture of 65:35 CO_2:0.1% isopropylamine/MeOH) of IPA/water solvate **13** as a white solid (mp (DSC) 131−149 °C, minimum 139 °C).

2-((*R*)-(1-(1,1-Dioxohexahydro-1λ^6-thiopyran-4-yl)methylamino)ethyl)-3-(4-chlorophenyl)pyrido[2,3*d*]pyrimidin-4(3*H*)-one (14). Acetic acid (205 g, 3.4 mol, 0.1 equiv) and $NaBH(OAc)_3$ (2893 g, 13.7 mol, 2.0 equiv) were charged to a solution of **13** (3740 g of **13** ≈ 2050 g of (+)-**2**, 6.8 mol, 1.0 equiv) and DCM (18.5 L, 5 vol) at −4 °C. The contents of the reactor were aged for 30 min, then a solution of **4**[8] (1548 g, 9.5 mol, 1.4 equiv) and DCM (10900 g, 142 mg of **4**/g of solution) was charged over 1 h keeping the internal temperature below −5 °C, at which time ≤5 LCAP of **13** was observed by HPLC analysis. Saturated aqueous $NaHCO_3$ (39.3 kg, 10 vol) was charged at a rate to control gas evolution, and the reaction mixture was warmed to 24 °C. The phases were separated, and the organic phase was washed sequentially with saturated aqueous $NaHCO_3$ (41.0 kg, 11 vol) and saturated aqueous NaCl (49.9 kg, 13 vol). A distillative solvent switch to MeOH was performed, and the MeOH solution was concentrated to ∼2 volumes, diluted with EtOH (2 vol), and warmed to 40 °C. Holding this solution resulted in self-seeding; however, 2 wt % of freebase **15** (58.9 g) was charged as seed to control the process. The reaction mixture was cooled to 25 °C over 2 h then diluted with EtOH (6 vol) over 1.5 h. The reaction mixture was cooled to 0 °C and held until the supernatant concentration was ≤6 mg/g then it was filtered. The wet cake was washed with 1 volume of 0 °C ethanol and dried at 40 °C under vacuum with an N_2 sweep until ≤1 wt % loss on drying was observed to afford 2871 g of product **14** (92.4 wt %, 87.1% corrected isolated yield) was collected as a white solid (mp (DSC) 124−138 °C, minimum 133 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 6.65 Hz, 3H), 1.50−1.55 (m, 1H), 1.71− 1.83 (m, 2H), 2.03−2.12 (m, 1H), 2.17 (dd, J = 11.25, 7.34 Hz, 1H), 2.20−2.30 (m, 1H), 2.57 (dd, J = 11.25, 5.97 Hz, 1H), 2.88−2.91 (m, 2H), 2.97−3.05 (m, 2H), 3.41 (q, J = 6.52 Hz, 1H), 7.19 (dd, J = 8.61, 2.54 Hz, 1H), 7.24 (dd, J = 8.61, 2.54 Hz, 1H), 7.48 (dd, J = 7.83, 4.0 Hz, 1H), 7.57−7.61 (m, 2H), 8.59 (dd, J = 7.83, 1.96 Hz, 1H), 9.01 (dd, J = 4.60, 2.05 Hz, 1H), N*H* not visible in spectrum; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 28.1, 28.2, 36.4, 50.7, 50.8, 52.2, 53.4, 55.7, 115.9, 122.5, 129.3, 129.6, 130.4, 134.2, 136.0, 136.7, 156.3, 157.4, 162.3, 164.0; IR 3563, 2927, 1684, 1597, 1583, 1569, 1491, 1433, 1279, 1255, 1123, 1092, 851, 799 cm^{-1}; exact mass m/z calcd for $C_{21}H_{23}ClN_4O_3S$ $[M + H]^+$447.12576, found 447.12475.

(*R*)-Methyl 2-(2-(*tert*-Butoxycarbonyl)propanamido)nicotinate (18). **16** (35.1 g, 206 mmol, 1.0 equiv), **17** (42.6 g, 226 mmol, 1.1 equiv), $Pd(OAc)_2$ (924 mg, 4.1 mmol, 0.02 equiv), Xantphos (4.8 g, 8 mmol, 0.04 equiv), K_2CO_3 (56.9 g, 412 mmol, 2.0 equiv), and THF (265 mL) were combined and heated to reflux and stirred for 16 h. The reaction mixture was filtered through Celite and the filter cake was washed with IPAC (600 mL). The combined organic solutions were then washed with H_2O (300 mL) and brine (300 mL) before a full solvent switch to IPAC was performed. The slurry in IPAC (130 mL) was heated to 72 °C, and then heptane (51 mL) was added to the solution, which was seeded with **18** (575 mg) and cooled to rt before additional heptane (339 mL) was added. The slurry was stirred overnight and then filtered and the filter cake was washed with 75% heptane/IPAC (102 mL) and dried overnight in the oven at 40 °C to afford 46.1 g of **18** (70%) as a pale yellow solid (mp (DSC) 180−196 °C, minimum 193 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (br s, 1H, N*H*), 8.64 (dd, J = 4.7, 1.3 Hz, 1H, Ar*H*), 8.33 (dd, J = 8.0, 1.5 Hz, 1H, Ar*H*), 7.09 (dd, J = 8.0, 5.0 Hz, 1H, Ar*H*), 5.19 (br s, 1H, N*H*), 4.64 (br s, 1H, C*H*), 3.95 (s, 3H, CH_3), 1.51 (d, J = 7.5 Hz, 3H, CH_3), 1.47 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 166.9, 155.3, 153.1, 152.0, 139.9, 118.5, 111.8, 79.9, 52.8, 51.6, 28.3 (3C), 18.8; IR 3292, 2928, 1701, 1687, 1595, 1581, 1531, 1494, 1366, 1279, 1251, 1163, 1124, 1091, 1065, 1017, 858, 789 cm^{-1}; exact mass m/z calcd for $C_{15}H_{22}N_3O_5$ $[M + H]^+$ 324.1560, found 324.1543.

(R)-*tert*-Butyl-1-(3-((4-chlorophenyl)carbamoyl)pyridin-2-ylamino)-1-oxopropan-2-ylcarbamate (19). A solution of isopropylmagnesium chloride and THF (61 mL of a 2.0 M solution in THF, 121 mmol, 4 equiv) was added via dropwise addition funnel to a solution of **18** (9.8 g, 30 mmol, 1.0 equiv), 4-chloroaniline (5.4 g, 42 mmol, 1.4 equiv), and THF (40 mL) at 2 °C maintaining the internal temperature <25 °C. After 10 min of stirring, the cooling bath was removed and the solution was allowed to warm to ambient temperature and maintained for 2 h. The solution was poured into 1 N HCl (125 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (125 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by silica gel chromatography (1% MeOH/DCM) to afford 10.2 g of **19** (80% yield) as a light yellow solid (mp (DSC) 233−244 °C, minimum 227 °C): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (br s, 1H, N*H*), 10.40 (br s, 1H, N*H*), 8.50 (d, J = 4.5 Hz, 1H, Ar*H*), 8.01 (d, J = 4.0 Hz, 1H, Ar*H*), 7.70 (d, J = 8.5 Hz, 2H, Ar*H*), 7.37 (d, J = 8.5 Hz, 2H, Ar*H*), 7.32 (dd, J = 7.5, 4.5 Hz, 1H, Ar*H*), 4.22−4.13 (m, 1H, C*H*), 1.32 (s, 9H, CH_3), 1.16 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 165.1, 155.0, 149.5, 148.2, 138.26, 137.7, 128.3 (3C), 126.8, 124.0, 121.2, 119.7, 77.8, 50.0, 28.0 (3C), 17.3; IR 3233, 2979, 2931, 1685, 1653, 1586, 1516, 1492, 1446, 1395, 1330, 1306, 1246, 1159, 1094, 1074, 823, 773 cm^{-1}; exact mass m/z calcd for $C_{20}H_{24}ClN_4O_4$ $[M + H]^+$ 419.1486, found 419.1480.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details for compound **15** and copies of ^{1}H NMR and ^{13}C NMR spectral data of **1**, *rac*-**2**, **8**, **9**, **10**, **11**, **14**, **15**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) For more information about the development of the medicinal chemistry CXCR3 antagonist program at Amgen, see: (a) Du, X.; Chen, X.; Mihalic, J. T.; Deignan, J.; Duquette, J.; Li, A. R.; Lemon, B.; Ma, J.; Miao, S.; Ebsworth, K.; Sullivan, T. J.; Tonn, G.; Collins, T. L.; Medina, J. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 608–613. (b) Du, X.; Gustin, D. J.; Chen, X.; Duquette, J.; McGee, L. R.; Wang, Z.; Ebsworth, K.; Henne, K.; Lemon, B.; Ma, J.; Miao, S.; Sabalan, E.; Sullivan, T. J.; Tonn, G.; Collins, T. L.; Medina, J. C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5200–5204. (c) Chen, X.; Henne, K.; Medina, J. C. Patent WO 2009094168, 2009.

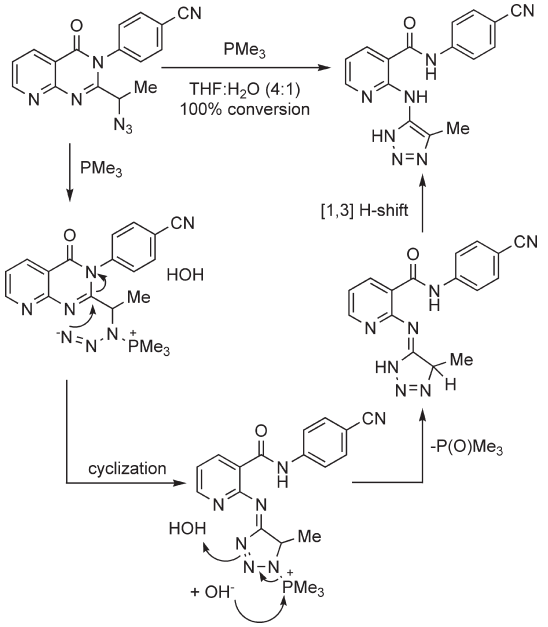
(3) Efforts to apply our recently developed aza-Wittig approach to construct the pyrido[2,3-*d*]pyrimidine core were met with failure: Chan, J.; Faul, M. *Tetrahedron Lett.* **2006**, *47*, 3361–3363. The requisite imide was unstable and prone to hydrolysis. Therefore, this strategy was abandoned.

(4) No products arising from self-coupling of 2-aminonicotinic acid were observed.

(5) Chan, J.; Gustin, D.; Divirgilio, E.; Guram, A.; Faul, M. M. *Synthesis* **2007**, *23*, 3678–3682.

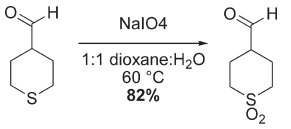
(6) Sodium azide is an extremely toxic reagent. For safety data regarding its use, see: Urben, P. G. *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Elsevier Ltd.: Amsterdam, The Netherlands, 2007; pp 1886−1888.

(7) Interestingly, attempts to reduce a related azide with trimethylphosphine exclusively produced a triazole based on ^{1}H and ^{13}C NMR spectra and the mass spectrum. This transformation presumably proceeds through the cyclization of phosphine bound azide onto the electrophilic C2 of the pyrido[2,3-*d*]pyrimidine followed by loss of trimethylphosphine oxide and tautomerization to give the triazole:



(8) One volume (abbreviated "vol") is defined as 1 mL of solvent per 1 g of solvate. In this case 15 volumes refers to 15 mL of IPA:water mixtures per gram of *rac*-**2**.

(9) Initial quantities of sulfone aldehyde **4** (<100 g) were synthesized by oxidizing the commercially available sulfide aldehyde:

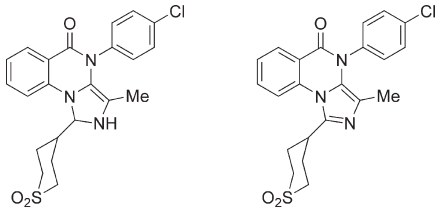


4

Subsequent process development provided procedural improvements and the use of the corresponding bisulfite adduct as a control point allowed the delivery of >4 kg of this precursor to **4**. For details see: Bio, M. M.; Hansen, K.; Gipson, J. *Org. Proc. Res. Dev.* **2008**, *12*, 892-895, along with references cited therein.

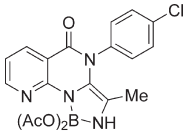
(10) At the time of this work, the use of bisulfite adducts in reductive aminations without prior conversion to the aldehyde was not known. However, since the completion of this work, a report has been published describing this application. See: Chennagiri, R. P.; Neelakandha, S. M. *Synthesis* **2009**, *23*, 4032–4036.

(11) These impurities were isolated and characterized as cyclized products **A** and **B**:



A **B**

(12) Running the reductive animation under these conditions *mandated* that the reaction temperature be kept under 0 °C to prevent the formation of another impurity (observed by LC and supported by mass spectrometry) that is speculated to be the boron complex:



C

(13) In looking at Schotten−Baumann approaches, the acyl chloride derived from 4-trifluoromethyl-3-fluorophenyl acetic acid was found to be unstable and as a result, this approach was abandoned. CDMT was also an effective coupling reagent.

(14) During the long-term route selection, an unexpected oxidative coupling of aldehydes and sulfonamides was discovered: Chan, J.; Baucom, K. D.; Murry, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14106–14107.

(15) Although a formal cost comparison between 2-aminonicotinic acid and 2-chloronicotinic acid was not performed, a preliminary investigation indicates that the latter is more readily available from a wider range of manufacturers and significantly less expensive.

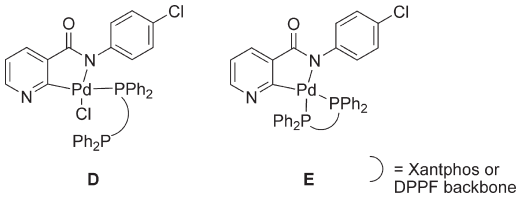
(16) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048.

(17) For Boc-protection, see: Lucet, D.; Le Gall, T.; Mioskowski, C.; Ploux, O.; Marquet, A. *Tetrahedron: Asymmetry* **1996**, *7*, 985–988. For amide formation see: Pozdnev, V. F. *Tetrahedron Lett.* **1995**, *36*, 7115–7118.

(18) 2-Chloronicotinonitrile also performed under similar conditions to couple with alanine amide **17** in 38% isolated yield.

(19) Notably, it was necessary to synthesize the methyl nicotinate **16** as attempts to directly couple either 2-chloronicotinic acid or with **17** were met with failure. Very low conversions of the starting nicotinic acid derivatives were observed at 5% palladium loadings. Furthermore, when 2-chloro-*N*-(4-chlorophenyl)nicotinamide was reacted with a full equivalent of palladium acetate and either Xantphos or DPPF

conditions, insoluble solids formed within 5 min that were tentatively assigned to be a mixture of palladacycles **D** and **E** based on $^{31}P\{^{1}H\}$ NMR resonances:



(20) Kshirsagar, U. A.; Mhaske, S. B.; Argade, N. P. *Tetrahedron Lett.* **2007**, *48*, 3243–3246.