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Synthesis of a Bicyclic Piperazine from L-Aspartic Acid and Application of a Fluoride-Promoted S_NAr Coupling

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ABSTRACT: The process development is reported of a pivotal C−N bond formation involving ((7*R*,9a*S*)-octahydro-1*H*-pyrido[1,2-*a*]pyrazin-7-yl)methanol (**2**) undergoing nucleophilic aromatic substitution with 3-chlorobenzo[*d*]isoxazole (**3**) to furnish ((7*R*,9a*S*)-2-(benzo[*d*]isoxazol-3-yl)octahydro-1*H*-pyrido[1,2-*a*]pyrazin-7-yl)methanol (**4**) as a key intermediate for a family of compounds (**1**). Essential to the success of the coupling is the use of fluoride in combination with a phase transfer catalyst. The development of an alternative route to bicyclic piperazine **2** that uses L-aspartic acid (**20**) as a starting material to avoid the need for a classical salt resolution is described.

INTRODUCTION

Bicyclic piperazines such as **2** are frequently incorporated as a rigid scaffold into the framework of pharmaceutical targets.[1] While Pd-catalyzed methodologies have recently dominated the literature as a reliable means of coupling piperazine building blocks such as **2** with aryl halides,[2] there are occasions where conventional nucleophilic aromatic substitution (S_NAr) approaches can be competitive in efficiency with the metal-catalyzed strategies.[3] Some substrates, such as electron-rich aryl chlorides, are more amenable to undergo S_NAr reactions than cross-couplings due to electronic and steric effects of the substrates[4] that impede the ability to undergo oxidative addition with a Pd catalyst.[5]

While carrying out process research and development for a route to a family of potential antipsychotic agents,[6] **1** (R = aryl or heterocycle), we encountered a challenging coupling between bicyclic piperazine **2** and 3-chlorobenzo[*d*]isoxazole (**3**). The original route provided to us by the Medicinal Chemistry team utilized an S_NAr approach for coupling **2** and **3** (Scheme 1).[1d] The coupling required high temperatures (130−140 °C) to proceed and was not reproducible in yield or rate due to sensitivities to residual water levels and other factors. The route lacked efficiency in that oxidation state adjustments were required to correctly obtain the desired stereochemistry of the bicyclic piperazine and a protecting group was employed to mask a secondary amine that would eventually need to be coupled to **3**.

RESULTS AND DISCUSSION

For the first bulk campaign we elected to introduce benzisoxazole **3** at the start of the processing steps to include a chromophore for analytical tracking purposes (Scheme 2) and to facilitate isolations with the increased crystallinity.[7] From an economical perspective, it was advantageous to carry out the low-yielding coupling between **3** and bicyclic piperazine **11** earlier to avoid carrying bulk along that would eventually be lost and to shift higher-yielding steps toward the end of the synthesis. This would also have the advantage of minimizing the introduction of impurities toward the end of the route where control of impurities is essential. The revised route began with the coupling between racemic bicyclic piperazine **11** and **3** by heating to 130−140 °C in pyridine and DBU (1 equiv).[8] During our laboratory development efforts of this coupling between **11** and **3**, we had observed yields ranging from 35 to 60%. It was only after unsuccessfully scaling up the first batch that we realized the extreme sensitivity of the reaction to residual solvents such as methylene chloride and water. To improve the reliability of the coupling, potassium carbonate (2 equiv) was introduced to the process to act as a water scavenger. Not only does water impede the coupling reaction, but bicyclic piperazine **11** can undergo alkylation with methylene chloride to afford an adduct.[9] Residual methylene chloride was present during processing of the first batch due to **3** being isolated as a solution in methylene chloride, and the solvent had not been completely removed by distillation prior to the coupling. In later batches, we avoided this problem by substitution of methylene chloride with a blend of *tert*-butyl methyl ether and heptane for the isolation of **3** as a solution.[10] With these process changes the yield was increased from 10% in the first batch up to 65% in the second batch.

After the coupling of **11** and **3** to furnish **16**, a classical salt resolution with D-tartaric acid provided **17** in 45% (90% theoretical) yield, effectively removing the undesired enantiomer that had been carried along for several steps. The sequence of oxidation, epimerization, and reduction resulted in a yield of 70% to provide the penultimate intermediate **4**, with a minimal amount of the yield loss being attributed to a methyl thiomethyl ether side product of the oxidation step.[11] These steps were performed following protocols previously reported[7] with the exception of removing boron by temporarily forming an HCl salt

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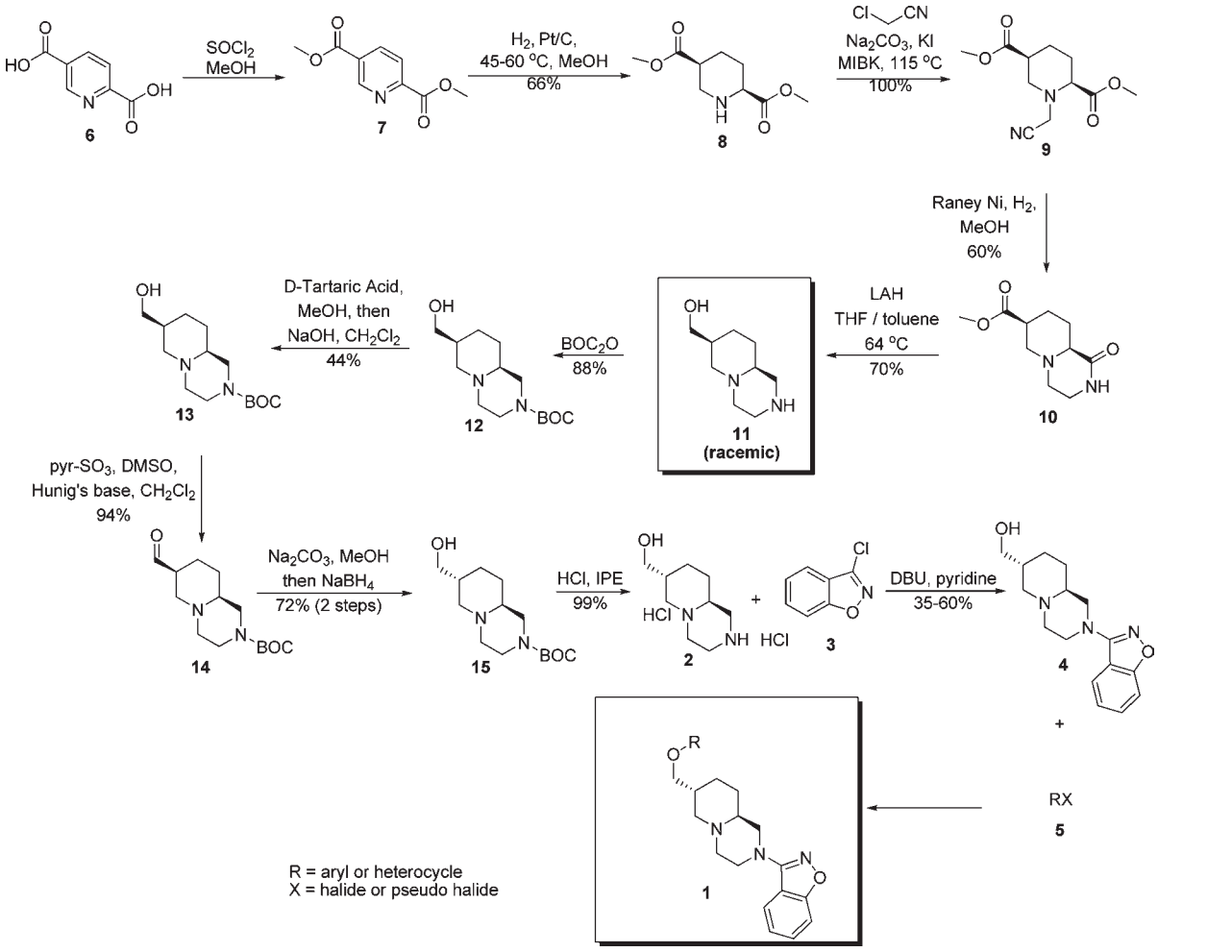
Scheme 1. Medicinal Chemistry route to 1



of **4** and then breaking the salt.[12] Containment of the dimethylsulfide byproduct of the oxidation was managed by using a bleach scrubber during vacuum distillation in the workup. The final coupling between **4** and **5** was often carried out in DMAC with a base such as potassium *tert*-butoxide or KHMDS to afford a series of potential drug candidates (**1**).

Optimization of the Coupling Between Bicyclic Piperazine 2 and 3 Using Fluoride and PTC. After this first scale-up experience we considered new routes that would avoid the need to adjust oxidation states and directly provide bicyclic piperazine **2** with the correct stereochemistry. A more immediate goal was to further optimize the coupling between **2** and **3** to realize a more robust and higher-yielding process. As a priority, we set out to study the coupling, since any route would require this essential bond formation. Metal-catalyzed cross-coupling strategies were investigated, but chlorobenzisoxazole **3** was found to be unreactive with all Pd catalysts examined.[13] Recognizing that this avenue was not viable, we refocused our efforts on nucleophilic aromatic substitution reactions.

Fluoride has been reported to accelerate arylation reactions and various other couplings, often in a solubilized form such as TBAF.[14] Considering that use of fluoride may promote the S_NAr coupling of **2** and **3** under milder conditions, various solvents were examined in combination with TBAF and other fluoride sources.[1b,15] Initially, **3** was coupled with *N*-methylpiperazine as a model substrate for **2**. The trials with *N*-methylpiperazine and **3** using TBAF showed that the coupling proceeded well in THF, DMAC, DMF, DMSO, acetonitrile, ethanol, isopropanol, and acetone. When examining the coupling of **2** and **3**, the reaction was more sensitive to water as well as the choice of solvent to facilitate the coupling, while also requiring higher temperatures. The coupling was found to work optimally in acetonitrile since it is suitable to remove water as an azeotrope by distillation. As an alternative to TBAF which is highly hygroscopic and often purchased in a hydrated form, KF was used in combination with a PTC such as tetrabutylammonium chloride, tetraethylammonium chloride or benzyltriethylammonium chloride.[16] We favored using tetraethylammonium chloride since it has better stability at higher temperatures and can be dried with heating under vacuum to remove water prior to use without decomposition. The bromide salts of the PTCs failed to perform the desired coupling, limiting the selection of PTCs to chlorides. While precedent for a fluoride-catalyzed amination by Senanayake and co-workers[14] showed evidence for conversion of a heteroaryl chloride to a more reactive heteroaryl fluoride intermediate, we were never able to observe a 3-fluorobenzisoxazole intermediate under the reaction conditions we used.

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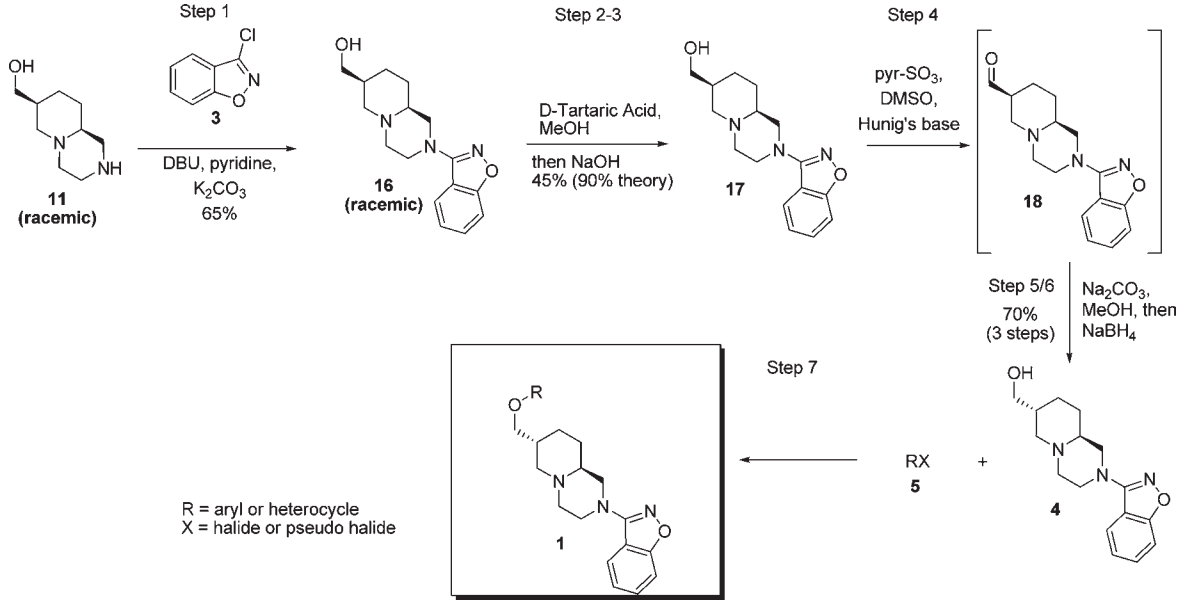
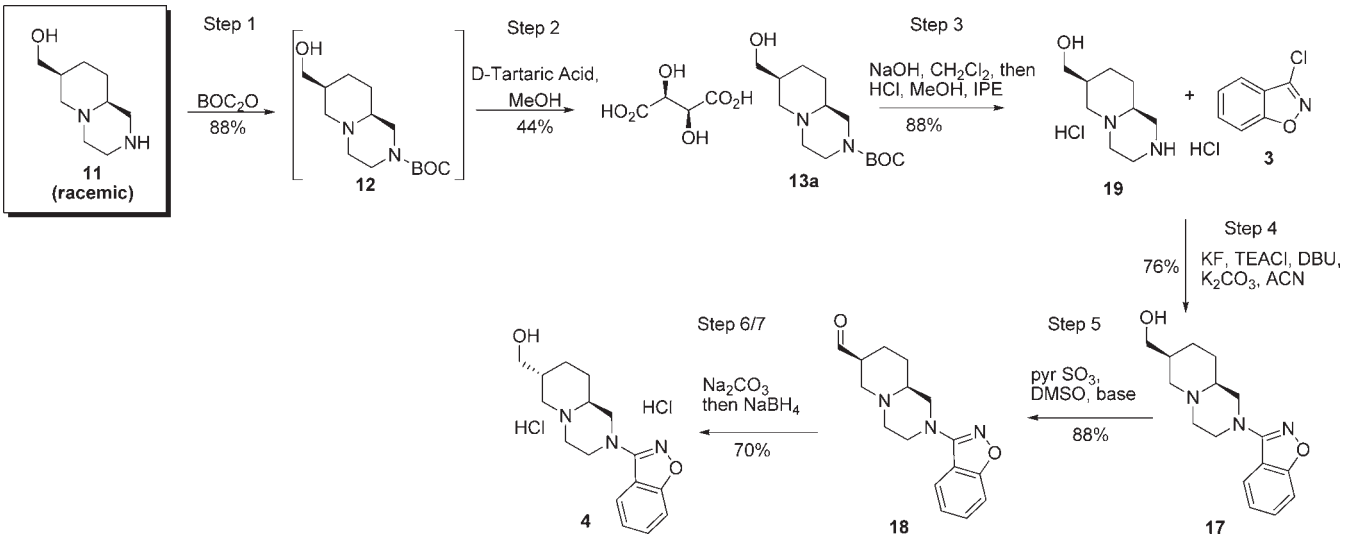
Scheme 2. First-generation process route to 1



Scheme 3. Incorporation of PTC coupling into process route



The optimized procedure for this process involved dissolving the substrates in acetonitrile with potassium carbonate, DBU, KF, and tetraethylammonium chloride and distilling acetonitrile to remove the water azeotrope. The inclusion of DBU was not essential to the success of the coupling, however, as in the original process (Schemes 1 and 2), DBU was found to increase the rate of the coupling. The coupling was carried out relatively concentrated so that the salts raised the boiling point of the reaction mixture to the range of 90−96 °C. Using an excess of **3** was found to result in coupling at both the amine and primary alcohol moieties of bicyclic piperazine **19**. Consequently, the stoichiometry of **3** was limited to 1.2−1.3 equiv which limited coupling at the alcohol group to a level of less than 4% in solution. After heating the reaction at a reflux for 12−24 h, the product (**17**) was extracted into aqueous HCl and neutralized for extraction into ethyl acetate. The product (**17**) was crystallized as a free base in 76% yield. This process was implemented in our next campaign (Scheme 3) and provided 9.00 kg of advanced intermediate **17** from 10 kg of **19**. The steps enabling the conversion of **17** to **4** were essentially identical to what had been carried out during the prior campaign.

Development of an Alternative Route to the Bicyclic Piperazine (2). With the couplings of the side chains developed, the next objective was to find a more direct route to the bicyclic piperazine core, **2**. The existing route to the racemic core (**11**) uses many hazardous reagents with low-yielding steps (Scheme 1). Even after preparation of **11**, a resolution and an epimerization are necessary to install the requisite stereochemistry. While it is likely

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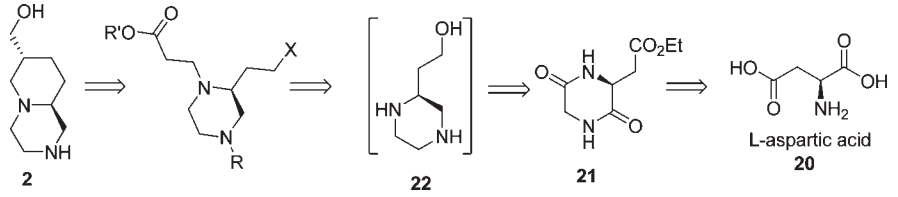
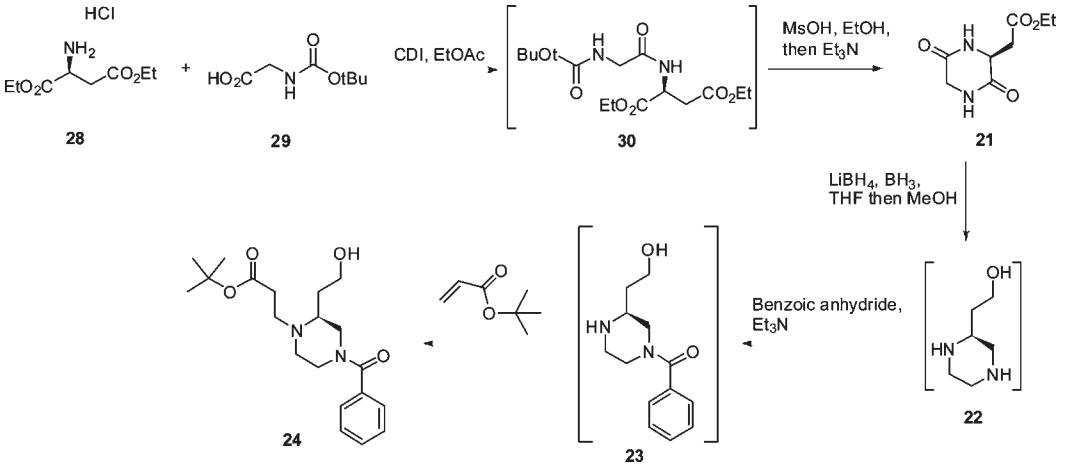
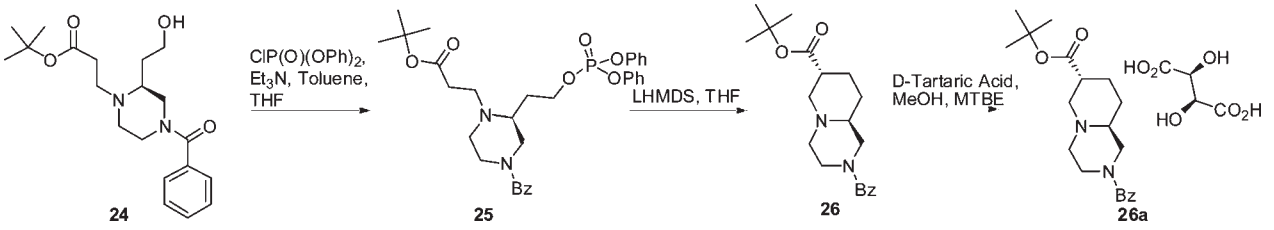
Scheme 4. Retrosynthetic analysis of bicyclic piperazine core 2



Scheme 5. Coupling, cyclization, reduction, and Michael addition to afford piperazine 24



Scheme 6. Tandem phosphate formation, cyclization, and salt formation



that a vendor could handle the sulfur oxidation, epimerization, and subsequent reduction to furnish **2**, we wished to demonstrate a route avoiding these operations.

One option that seemed appealing involved using L-aspartic acid (**20**) as the source of chirality for the bicyclic piperazine (Scheme 4). Coupling L-aspartic acid with glycine and subsequent cyclization to afford **21** followed by reduction to give piperazine **22** has been demonstrated.[17] We speculated that **22** could be used to prepare the bicyclic piperazine core (**2**) by undergoing addition with an acrylate followed by ring closure through an intramolecular enolate alkylation. Such a process was realized as shown in Schemes 5 and 6. The opening steps followed procedures analogous to those reported to furnish **21**.[18] For the reduction of **21**, $LiBH_4$ was used initially to ensure complete reduction of the ester, and borane−THF was subsequently charged to complete reduction of the two amides to afford **22** (Scheme 5). As an alternative to purchasing borane, we had demonstrated the use of boron trifluoride etherate as an additive to $LiBH_4$ to form borane *in situ*. This approach seemed to work best in our hands, but the vendor wished to avoid the use of fluoride salts for the scale up.[19] After heating to complete the reduction, the reaction mixture was quenched into methanol and distilled to remove some of the boron as trimethylborate. In this same pot was added triethylamine and benzoic anhydride which selectively protects the less hindered nitrogen of **22** and sets up for a Michael addition with acrylate at the unprotected nitrogen. The protection proceeded during the slow dosing of benzoic anhydride over 3 h under ambient conditions in methanol and limited the formation of a bis-amide side product to a level of no more than 3%.[20] Once the benzamide was formed, *tert*-butyl acrylate was added to introduce the remaining carbons for the bicyclic piperazine scaffold. Heating to 50−60 °C enabled the Michael addition to reach completion within 24−48 h. The yield of **24** on lab scale was often 60−65% for steps 4−6, but the yield was only 49−58% in the pilot plant on a 25−50 kg scale.

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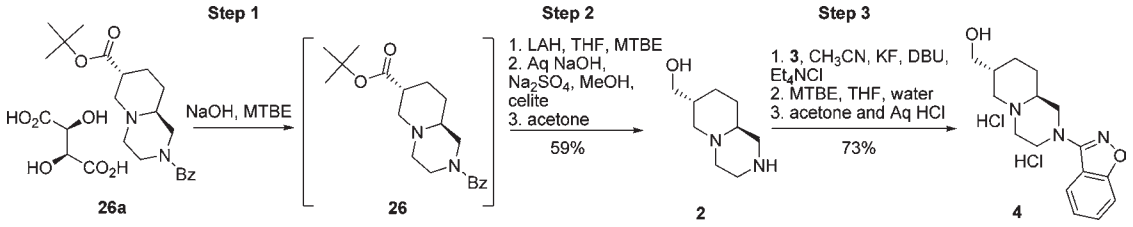
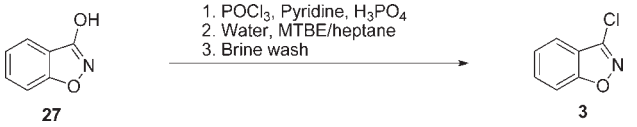
Scheme 7. Scale up of new route to 4



The conversion of **24** to the bicyclic piperazine was accomplished by activation of the primary alcohol as a phosphate followed by intramolecular alkylation of an enolate (Scheme 6).[21] After formation of phosphate **25** and removal of the triethylammonium salt by filtration, the resulting solution of **25** was added at 0 °C to a solution of LHMDS in hexane. Surprisingly, no cyclization occurred until THF was charged to the solution of LHMDS and **25**, probably due to a need for changing the aggregation state of the LHMDS; however, if THF was added to the LHMDS prior to the charge of **25**, then more side products tended to form.[22] The mode of the quench of the cyclization was essential for dictating the diastereoselectivity in the product. The optimal quench was carried out by charging the reaction mixture to chilled water, which typically provides a 20:1 ratio of diastereomers, whereas quenching with addition of water to the reaction mixture allowed opportunity for epimerization during the quench. After workup and distillation of solvent to remove water, the product (**26**) was crystallized as the D-tartrate salt in methanol and MTBE to furnish **26a** in ~50% yield from **24**. The yield of **26a** was much lower on production scale than in the lab since more epimerization occurred during the preparation of **21** in the pilot plant due to longer stir times at low pH.[17] Fortunately, the isolation of **26a** as a salt did enable the purge of the undesired enantiomer of **26** and the mother liquors of the filtercake contained the enantiomer of **26** in 93% optical purity, suggesting that this is an effective diastereomeric salt resolution. On lab scale about 10−13% of the undesired enantiomer was present prior to salt formation of **26**, but on pilot-plant scale this amount rose to ~20%. It was found subsequently that use of a slightly milder acid, such as TFA, avoided epimerization during conversion of **30** to **21**. As a result of the partial racemization, the yield of **26a** over the three steps was only 39−43% in the pilot plant. The level of the undesired enantiomer of **26** was 0.7−1.0% in each batch after isolation of crude **26a**. With recrystallization of **26a** from methanol and MTBE in 97% yield, the level of the enantiomer of **26** was reduced to 0.3%, with total chemical impurities (other than the enantiomer) at a level of 0.3% (by HPLC area %).

Scale Up of the New Route to 4. After preparing 40 kg of **26a**, this intermediate was reduced to provide the bicyclic piperazine core, **2** (Scheme 7). Originally Vitride[23] was used to reduce **26** to the *N*-benzyl-protected core and the benzyl group was subsequently cleaved by Pd/C-catalyzed hydrogenolysis to provide **2**. A more efficient route was developed by adding a solution of **26** to chilled LAH in THF. By maintaining a cold reaction mixture, the ester was rapidly reduced as expected, and the benzamide was semi-reduced to provide a hemi-aminal which upon quench was hydrolyzed to give bicyclic piperazine **2** and benzaldehyde. After the quench, sodium sulfate was added to the mixture to assist with filtration of the aluminum salts and methanol was added to avoid precipitation of the product. After displacing the methanol with acetone, **2** crystallized as a free base in 59% yield.

Scheme 8. Preparation of 3



In preparation for the coupling between **2** and **3**, it was necessary to convert 3-hydroxybenzo[*d*]isoxazole (**27**)[24] to **3** using $POCl_3$ (Scheme 8). The addition of phosphoric acid to $POCl_3$ enabled the reaction to be homogeneous and allowed the chemistry to proceed at a lower temperature,[25] which avoided side products.[26] We treated **3** as a potential irritant since related compounds have proven to be hazardous in this respect.[27] For this reason we had planned to prepare **3** as a solution to avoid isolation and use the crude product solution in the subsequent coupling reaction.

With both **2** and **3** in hand, we proceeded with the most pivotal bond-forming step. The coupling was carried out by combining **2** with the solution of **3** as well as KF, tetraethylammonium chloride, and DBU in acetonitrile. The residual solvent introduced with **3** was distilled along with some of the acetonitrile to remove any water. While on lab scale the use of potassium carbonate was beneficial to exclude water; we found that potassium carbonate was unnecessary on manufacturing scale due to the efficiency of removing water as an azeotrope by distillation with acetonitrile. After the reaction had been heated for ~19 h, the coupling was worked up, and the organic phase was diluted with acetone to crystallize **4** as the di-HCl salt in 73% yield and >99% purity on 12-kg scale. Throughout the extraction sequence of the workup, it was important to maintain the batch at 35 ° C to avoid precipitation of the product prior to the intended crystallization.

CONCLUSIONS

In summary we have demonstrated an approach to carrying out a challenging bond formation between bicyclic piperazine **2** and chlorobenzisoxazole (**3**) using a fluoride promoter that is solubilized through the use of a phase transfer catalyst. With this process improvement, the yield was improved from a highly variable range of 35−60% to 73−76%. This methodology should translate well to related systems and illustrates how the combination of a phase transfer catalyst with fluoride can facilitate nucleophilic aromatic substitution reactions. In addition, we developed an alternative approach to preparing **2**, which is often used as a rigid scaffold in pharmaceutical targets. This new

synthesis of **2** avoids the need for a classical salt resolution and provides the desired stereochemistry using L-aspartic acid to set all stereochemistry without the need for oxidations or epimerizations, thus wasting less of **3** in subsequent adjustments to stereochemistry. A reduction step is required to transform an ester into a primary alcohol, but this simultaneously cleaves a benzoyl protecting group that provides a chromophore for analytical tracking of intermediates as well as regiochemical control of Michael addition with *tert*-butyl acrylate. Furthermore, the undesired stereoisomers are well controlled during the isolation of **26a** as a D-tartrate salt, prior to the reduction step to afford **2**. All of the materials used in the preparation of **2** are inexpensive commodities, including the L-aspartic acid that is used to define the stereochemistry. The new synthesis of **2** was applied to the preparation of **4** on 12-kg scale.

EXPERIMENTAL SECTION

General Procedures. All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 spectrometer at 400 and 100.6 MHz, respectively. Intermediates were analyzed by reverse phase HPLC on an Agilent 1100 series instrument according to the following conditions: column Atlantis-C18 4.6 mm × 150 mm i.d., 3 μm; eluent A, 0.1% aqueous phosphoric acid; eluent B, acetonitrile; flow rate 1.0 mL/min; wavelength, 287 nm; column temperature, 30 °C; injection volume, 10 μL; at t = 0 min, 10% eluent B; at t = 25 min, 70% eluent B; at t = 26 min, 85% eluent B; at t = 27 min, 10% eluent B.

(*S*)-Diethyl 2-Aminosuccinate Hydrochloride (28). To ethanol (150 L) cooled to 0−10 °C was added acetyl chloride (60 kg) over 1 h at no more than 30 °C. This was added to a solution of L-aspartic acid (20) (50.0 kg) and ethanol (150 L) over 15 min. The resulting solution was heated to a reflux for 3 h. The reaction mixture was concentrated by atmospheric distillation until the reaction pot reached a temperature of 88 °C (~275 L of solvent distilled). Isopropyl acetate (350 L) was added and redistilled until the reaction pot reached a temperature of 88−89 °C (~350 L of solvent distilled). Isopropyl acetate (350 L) was added, and the resulting mixture was cooled to 22 °C over 1 h. After stirring for 18 h, the crystals were cooled to 0 °C and stirred an additional 3 h before filtering. The vessel and filtercake were washed with isopropyl acetate (25 L). The crystals were dried under vacuum at 40−50 °C to give 28 as white crystals (80.0 kg, 94%). mp 78−80 °C; $[\alpha]^{22}_{D}$ = +11.5 ☒ (c = 1.25, water); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 169.7, 168.9, 62.6, 61.6, 49.1, 34.8, 14.6, 14.5. Analysis of the spectroscopic data matched reported data.[17]

(*S*)-Ethyl 2-(3,6-dioxopiperazin-2-yl)acetate (21). A suspension of **28** (52 kg) and triethylamine (26.6 kg) in ethyl acetate (200 L) was stirred for 30 min at 35−45 °C. To a solution of **29** (35 kg) in ethyl acetate (90 L) was added carbonyldiimidazole (35.65 kg) as a solution in ethyl acetate (90 L) over 1 h at 20−30 °C. This reaction mixture was stirred at 20−30 °C for 30 min and then was transferred to the suspension of **28** over 30 min. The combined reaction mixture was stirred for 1 h and then was quenched with water (50 L) and methanesulfonic acid (74 kg). The aqueous layer was discarded. The organic layer was concentrated under vacuum at 15−35 °C and displaced with ethanol so that the final volume was ~200 L. The product residue in ethanol (~140 L) was treated with methanesulfonic acid (23.3 kg). The resulting reaction mixture was heated to 60−70 °C for ~1 h; then triethylamine (61.5 kg) was added, and heating was continued at a reflux for 5 h. The reaction mixture was gradually cooled to 0 °C to crystallize the product and stirred for 4 h. The crystallized product was isolated by filtration. The filtercake was washed with ethanol (17.5 L) followed by heptane (35 L). After drying under vacuum at 50−55 °C, **21** was isolated as a white, crystalline solid (27.4 kg, 68%). Mp 187−188 °C; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 170.7, 167.7, 166.6, 60.8, 51.4, 45.2, 37.2, 14.7; Anal. Calcd for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 13.99; Found: C, 47.77; H, 5.97; N, 13.90; $[\alpha]^{22}_{D}$ = +48 ☒ (c = 0.90; methanol). Analysis of the spectroscopic data matched reported data.[17]

(*S*)-*tert*-Butyl 3-(4-Benzoyl-2-(2-hydroxyethyl)piperazin-1-yl)propanoate (24). To a suspension of **21** (50.0 kg, 1 equiv) and THF (250 L) was charged 2.0 M lithium borohydride in THF (288 L, 2.3 equiv) at 20−25 °C. The reaction mixture was stirred for 1 h at 20−25 °C. The reaction mixture was heated to 50 °C, held for 1 h and was cooled to 40 °C. To the reaction mixture was added 1.0 M borane−THF complex (500 L, 2 equiv) at 40−50 °C over 1.25 h. The reaction mixture was stirred for 3 h at 40−50 °C. The reaction was cooled to ~0 °C. The reaction was quenched with methanol (40 L) added over 1 h at 0 °C and was allowed to warm to 20 °C. The reaction mixture was stirred for an additional h. A methanol solution of HCl (118 kg of HCl in 1000 L of methanol) was charged at 0−20 °C over 50 min. The reaction mixture was heated to ~60 °C for distillation of the volatiles (~1250 L distilled). Added methanol (2500 L) and resumed distillation (distilled ~2500 L). Triethylamine (425 L, 12 equiv) was added at 20−40 °C. The reaction was heated to 65−75 °C and held for 1 h. The reaction was cooled to 20 °C for addition of a solution of benzoic anhydride (52 kg, 1 equiv) in THF (150 L) over 3 h. After stirring for another hour at 20 °C *tert*-butyl acrylate (96 kg, 2.0 equiv) was added, and the resulting mixture was heated to 50−60 °C for 48 h. The reaction mixture was concentrated (distilled ~265 L). The reaction mixture was diluted with MTBE (1000 L) and aqueous citric acid (483 kg of citric acid in 1500 L of water). The mixture was stirred for 1 h, and then the organic layer was discarded. The aqueous layer was treated with 50% aqueous NaOH (500 L) to adjust the pH to 13−14. After addition of toluene (1250 L) to extract the product, the mixture was stirred for 1 h. After discarding the aqueous phase, the organic layer was washed with an aqueous brine solution (100 kg of NaCl in 750 L of water). The organic layer was concentrated (final volume of ~350 L). The solution of **24** (50 kg, 55% yield) was used directly in the next sequence without isolation. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.9, 170.9, 135.8, 130.0, 128.7, 127.2, 60.5, 57.2, 49.0, 48.0, 46.7, 44.7, 40.5, 33.9, 30.0, 28.3.

(7*R*,9a*S*)-*tert*-Butyl 2-Benzoyloctahydro-1*H*-pyrido[1,2-*a*]-pyrazine-7-carboxylate D-Tartrate (26a). Triethylamine (28 kg, 38.5 L, 2 equiv) was added to a solution of **24** (50 kg, 1 equiv) in toluene (300 L) and cooled to 0 °C. To the solution was added diphenylchlorophosphate (44.5 kg, 1.2 equiv). The reaction was stirred for 1 h and was warmed to 20−25 °C. The reaction developed a suspension and was stirred for 15 h. The reaction mixture was filtered to remove salts, and the filtercake was rinsed with toluene (50 L). This solution was charged over 1 h to a 1.0 M solution of LHMDS in hexane (392 kg, 550 L, 4 equiv) at 0 °C. THF (125 L) was added to the cold reaction mixture over 30 min at 0 °C. The reaction mixture was held at 0−10 °C for 2 h.

The reaction mixture was quenched into aqueous sodium hydroxide (18.4 kg 30% NaOH and 395 L water) at 0−10 °C. After the quench, the mixture was warmed to 25 °C and stirred for 1 h. The mixture was settled and the aqueous layer was discarded. The organic phase was concentrated under vacuum (to a volume of ∼150 L) and was diluted with isopropanol (650 L). This solution was concentrated under vacuum again (to a target volume of ∼100−150 L). Methanol (300 L) was added, and again the solution was concentrated under vacuum (until ∼100−150 L remained). The solution was heated to 45−55 °C and a solution of D-tartaric acid (20.8 kg) in methanol (125 L) was added to the warm reaction mixture. The reaction mixture was cooled to 20 °C and crystals formed. The suspension was stirred for 1 h and then MTBE (250 L) was added. This mixture was stirred for 1 h and then was cooled to −10 °C to stir for 1 h. The crystals were filtered and washed with MTBE (50 L). The product was dried in the vacuum oven at 40−50 °C for 24 h to afford **26a** as white crystals (27.3 kg, 40%). mp 147−150 °C. Anal. Calcd for $C_{24}H_{34}N_2O_9$: C, 58.29; H, 6.93; N, 5.66; Found: C, 58.07; H, 7.05; N, 5.35. Optical purity was analyzed by normal phase HPLC on an Agilent 1100 series instrument according to the following conditions: column Chiralpak AD 4.6 mm ×250 mm; eluent, diethylamine:isopropanol:hexanes (1:150:1850); flow rate 0.5 mL/min.; wavelength, 240 nm; column temperature, 30 °C; injection volume, 50 μL; **26** elutes at 20.1 min and **ent-26** elutes at 21.6 min. The level of **ent-26** was 0.7−1.0% initially in crude **26a**. With recrystallization of **26a** from methanol and MTBE, the level of **ent-26** was reduced to 0.3%.

3-Chlorobenzo[*d*]isoxazole (3). Phosphorus oxychoride (22.9 kg, 2 equiv) and 85% phosphoric acid (1.02 L, 0.20 equiv) were sequentially added to 3-hydroxybenzo[*d*]isoxazole (**27**) (10.0 kg). Pyridine (6.10 L, 1 equiv) was added over 1 h at 20−50 °C. The reaction mixture was heated to 80−85 °C and held for 12 h. The reaction was cooled to 35−50 °C and quenched over 1 h into a mixture of MTBE (35 L), heptanes (45 L), and water (50 L) at 35−50 °C. The reaction mixture was stirred for 1 h at 35 °C, then cooled to 20−25 °C before discarding the aqueous layer. Stirred the organic layer with an aqueous brine solution (5 kg of sodium chloride in 40 L of water) for 1 h and then discarded the aqueous layer. The organic layer was transferred to a drum to be used in the next step without isolation. Assumed theoretical yield of **3** (11.4 kg). The product may be isolated by concentration of the mixture to yield a low-melting solid. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.0, 150.1, 131.4, 124.7, 121.0, 112.0, 110.7; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, 1H, J = 7.9 Hz), 7.61−7.55 (m, 2H), 7.41 (d, 1H, J = 8.7 Hz), 7.38 (t, 1H, J = 7.9 Hz), 5.8 (bs, 1H). Analysis of the spectroscopic data matched reported data.[7]

(7*R*,9a*S*)-*tert*-Butyl 2-Benzoyloctahydro-1*H*-pyrido[1,2-*a*]-pyrazine-7-carboxylate (26). The tartrate salt, **26a**, (40.7 kg; 82.3 mol) was suspended in MTBE (203.5 L) and water (285 L). An aqueous solution of sodium hydroxide (9.9 kg; 246.9 mol in 41 L water) was added to the suspension over 45 min at 15−22 °C. The mixture was stirred 1 h to dissolve all solids and then was settled. The light-yellow aqueous phase (pH should be 14) was discarded. The light-yellow organic layer was stirred for 1 h with added sodium sulfate (40.7 kg). The mixture was filtered and the sodium sulfate filtercake was washed with THF (40.7 L). The wash was added to the filtrate containing **26** in a MTBE/THF solution. Used the solution of **26** directly in the reduction to afford **2** without isolation.

((7*R*,9a*S*)-Octahydro-1*H*-pyrido[1,2-*a*]pyrazin-7-yl)methanol (2). A solution of **26** (82.3 mol) in MTBE and THF was distilled atmospherically to remove water as an azeotrope until the temperature reached 66−68 °C (all MTBE and water were removed). The solution of **26** was added over 1 h to a solution of 10% lithium aluminum hydride solution in THF (69.4 L; 164.62 mol) diluted with additional THF (194 L) at −5 to 5 °C. The reaction was stirred for 1 h. The reaction mixture was warmed to 15−20 °C over 30 min once the reaction was determined to be complete by GC/MS (used a DB-5MS column 30 m × 0.25 mm × 0.25 μm film, flow rate of 1 mL/min, temperature ramp from 100 to 280 °C at a rate of 5 °C/min, **26** elutes at 24 min and **2** elutes at 13 min). A mixture of water (7 L) in THF (63.5 L) was added to the reaction mixture over 1 h at 025 °C. Gas evolution was observed (be cautious of hydrogen evolution). After stirring the mixture 1 h an aqueous solution of sodium hydroxide (1 kg; 25 mol in 7 L water) was added over 15 min followed by water (7 L) which was added over 15 min. The quenched reaction mixture was stirred at 15−25 °C for 3 h. Sodium sulfate (40.7 kg) and methanol (65.1 L) were added to the quenched reaction mixture. The suspension was filtered after stirring 2 h. The cake was washed with a mixture of THF (204 L) and methanol (20.4 L). The combined filtrates were concentrated by atmospheric distillation at 50−67 °C (until ∼120 L remain). A constant volume (120 L) was maintained with gradual addition of THF (81.4 L) while atmospheric distillation continued to ensure complete removal of methanol (temperature reached 66−68 °C). Solids crystallized from solution during the distillation once the methanol was removed. Acetone (204 L) was gradually added maintaining a constant volume (120 L) during the atmospheric distillation to ensure complete removal of THF. Distillation was continued until the distillation temperature was between 56 and 58 °C. The slurry was cooled to 20 °C over 1 h and stirred as a suspension for 4 h before filtering. The filtered off-white solids were washed with acetone (3 × 40.7 L) and dried under vacuum at 40 °C for 16 h to afford **2** (8.3 kg, 59%). $[\alpha]^{20}_D$ = +8.4 ± 0.1 (*c* = 1.00; CH_3OH); mp 157−158 °C; ^{13}C NMR (CD_3OD, 100 MHz): δ 65.1, 62.3, 59.0, 55.4, 50.7, 44.8, 38.7, 28.7, 26.9. Analysis of the spectroscopic data matched reported data.[7]

((7*R*,9a*S*)-2-(Benzo[*d*]isoxazol-3-yl)octahydro-1*H*-pyrido-[1,2-*a*]pyrazin-7-yl)methanol Dihydrochloride (4). Potassium fluoride (27.3 kg; 469.9 mol), tetraethylammonium chloride (21.6 kg; 117.5 mol), DBU (8.6 kg; 56.4 mol), and **2** (8.0 kg; 47.0 mol) are charged to a dry Hastelloy vessel with acetonitrile (152 L). The suspension was concentrated by atmospheric distillation (until approximately 65 L remain), and then cooled to 45 °C. A solution of **3** in MTBE/heptane (47.6 kg of solution; 7.9 kg of **3**; 51.7 mol) was added to the reaction mixture, and atmospheric distillation was resumed (until approximately 50 L remained). The thick suspension remaining was stirred at reflux (90−96 °C) for 15 h, then cooled to 35−40 °C. Charged MTBE (56 L) and THF (24 L), followed by water (120 L) and stirred the mixture for 30 min at 35−40 °C. The lower aqueous layer was discarded. Acetone (80 L) was added to the organic layer followed by the slow addition of 37 wt % hydrochloric acid (23.6 L; 28.2 mol) over 30 min at 15−20 °C to precipitate the product as the dihydrochloric acid salt. The suspension was stirred 4 h before the solids were filtered, washed with acetone (40 L), and dried under vacuum at 40 °C for 18 h. Isolated **4** as white crystals of the dihydrochloride salt (12.3 kg, 73%). $[\alpha]^{20}_D$ = −1.5 ± 0.1 (*c* = 1; H_2O); mp >280 °C dec; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 164.0, 160.7, 131.0, 123.5,

123.4, 115.8, 110.9, 63.6, 61.1, 56.3, 52.3, 50.7, 45.6, 36.9, 26.0, 25.1; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.2, 161.3, 129.8, 122.5, 122.4, 116.3, 110.7, 66.3, 60.5, 58.9, 54.4, 53.8, 48.4, 39.2, 29.1, 26.9. Analysis of the spectroscopic data matched reported data.[7]

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(13) In our hands **3** does not appear to undergo oxidative insertion by Pd readily. One test examined the coupling of **3** with phenyl boronic acid. Even using this outstanding coupling partner failed to give more than trace product using electron-rich ligands such as Xphos.

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(18) The process began with esterification of L-aspartic acid and coupling with BOC-glycine using CDI followed by deprotection under acidic conditions and cyclization with neutralization using triethylamine. It was later realized that the deprotection of the BOC group with MsOH could lead to some epimerization of the stereocenter, depending on the temperature control of the MsOH addition as well as the total stir time at elevated temperature prior to adding triethylamine for cyclization. Use of TFA or a milder acid than MsOH resulted in no epimerization.

(19) The vendor had concerns of fluoride etching the glass-lined vessel and would require the use of a steel or Hastelloy vessel which was not as readily available for the scale up.

(20) The slow dosing of the benzoic anhydride ensures that no more than about 3% of bis-benzoylated amide side product forms. Adding the benzoic anhydride over 1 h resulted in ~7% or more of the bis-benzoylated amide forming.

(21) Aside from the phosphate, we had prepared the mesylate, chloride, and tosylate derivatives of **24**; however, none of these cyclized as readily as the phosphate.

(22) In addition to controlling the addition of THF to LHMDS and **25**, it is important to maintain a lower temperature during the addition of the THF when cyclization occurs.

(23) Vitride is also sold as Red-Al, which is a 65 wt % solution of bis(2-methoxyethoxy)aluminum hydride in toluene.

(24) While **27** is commercially available, we typically prepared this building block as follows: methyl salicylate was treated with hydroxylamine hydrochloride in aqueous base to obtain a hydroxamic acid adduct which is crystallized upon treatment with aqueous HCl. This intermediate is cyclized to **27** by slow addition of CDI in THF/acetonitrile with heating and is crystallized from water/acetonitrile by addition of aqueous HCl.

(25) The addition of phosphoric acid to $POCl_3$ for improving the efficiency of the conversion to the chloride has been reported previously, see: Andersen, K.; Begtrup, M. *Acta Chem. Scand.* **1992**, *46*, 1130.

(26) At higher temperatures (100−120 °C) chlorination of the benzisoxazole ring occurred, and these side products were found to be difficult to purge downstream in the process.

(27) We have had experience handling 3-chlorobenzo[*d*]isothiazole which is a known irritant sold by numerous suppliers and suspected that 3-hydroxybenzo[*d*]isoxazole may possess similar hazards in handling.