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The Synthesis of a Dopamine D_2 Partial Agonist for the Treatment of Schizophrenia

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Abstract:

The synthesis of the phosphoric acid salt of dopamine D_2 partial agonist 2-{4-[4-(7-fluoro-naphthalen-1-yl)-piperazin-1-yl]-butoxy}-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one (1) is reported. The most prominent feature of the molecule is a seven-membered ring urea functionality that has been prepared *via* an efficient one-pot, three-step transformation. The original synthesis from the Medicinal Chemistry group provided precursor 13 in 10 steps and 2% overall yield, required four chromatographies and employed unsafe reagents such as 2-iodoxybenzoic acid (IBX) and $HClO_4$. The optimized synthetic route for the preparation of phosphate salt 1 consists of 12 linear steps with a 10% overall yield. Safer and more robust reaction conditions have been developed with only one required chromatography. Another key step in the synthesis is the coupling of iodide 25 with naphthalenopiperazine 12 to provide 13. Due to the difficulty to purify this intermediate, a protocol had to be developed to obtain crude material with the required purity, suitable for use in the subsequent salt formation step. Finally, considerable work was carried out to determine the most stable polymorph of the API. As a result, a robust set of conditions has been developed for the formation of phosphoric acid salt 1, providing the desired polymorph in excellent yield and purity.

Introduction

Dopamine D_2 receptor antagonists and partial agonists have been used clinically for treating central nervous system (CNS) disorders, such as schizophrenia and bipolar disorder. In particular, schizophrenia is a chronic, highly debilitating mental disorder that is equally common in men and women and affects 1% of the population.[1] There are two million people affected in the United States alone, which results in 330,000 hospitalizations each year.[2] Thirty percent of the patients do not respond adequately to current antipsychotic treatments or have continued needs for improvement in core symptoms such as negative symptoms, cognitive decline, and/or overall schizophrenic symptomatology. Safety remains a major concern, since chronic treatment with current agents[3] can lead to tardive dyskinesia, blood dyscrasias, weight gain, diabetes mellitus, akathisia, dyslipidemia, QT interval prolongation and Parkinsonism.[1,4] Therefore, there is a clear need for new and better options to treat this serious disorder.

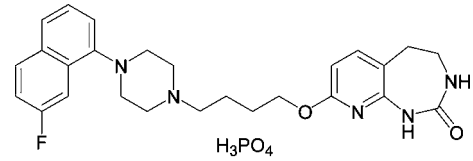

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Figure 1. **Structure of dopamine D_2 partial agonist 1.**

Recently, the phosphoric acid salt of 2-{4-[4-(7-fluoro-naphthalen-1-yl)-piperazin-1-yl]-butoxy}-5,6,7,9-tetrahydro-1,7,9-triaza-benzocyclohepten-8-one (**1**) (Figure 1) has been identified at Pfizer as a dopamine D_2 partial agonist candidate for the treatment of schizophrenia. This contribution describes the route development work for the preparation of this compound in kilogram quantities for clinical studies.

Medicinal Chemistry Route. Prior to the identification of phosphoric acid salt **1** as the desired target, the efforts of the Medicinal Chemistry group were directed toward the preparation of free base **13** (Scheme 1).[5] The synthesis started with commercially available 2,6-dichloropyridine (**2**), which was treated with concentrated ammonia at high pressure and temperature for 2 days to give 2-amino-6-chloropyridine (**3**) in fair yield.[6] The amino group was converted to the corresponding pivalamide **4** and subsequent low-temperature formylation of the pyridine ring with DMF afforded aldehyde **5**, which was purified by chromatography.[7a] Chloride displacement with 4-benzyloxy-1-butanol in DMF[8] followed by Wittig olefination under cryogenic conditions with (methoxymethyl)triphenylphosphonium chloride and PhLi as base generated methyl vinyl ether

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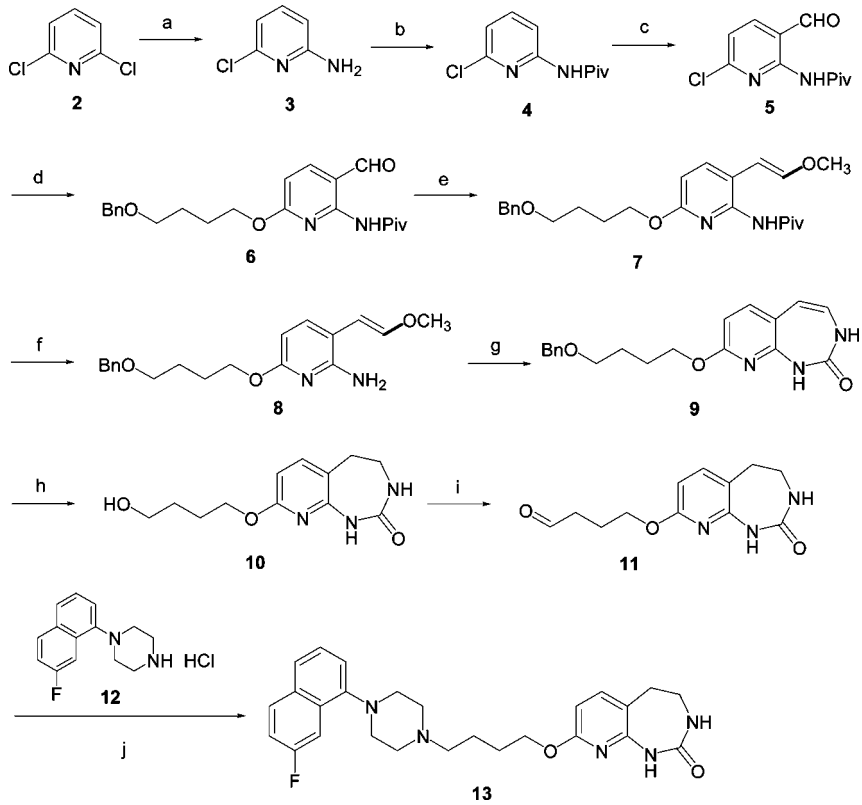
Scheme 1. **Medicinal Chemistry Route to Free Base 13**[a]



[a] Reagents and conditions: (a) cc NH_4OH, 180 °C, 48 h, steel bomb, 64%. (b) Pivaloyl chloride, TEA, CH_2Cl_2, 0 to 20 °C, 94%. (c) (i) *n*-BuLi (1.6 M in hexanes), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, THF, −70 °C; (ii) DMF, −70 to 20 °C, 30%. (d) 4-Benzyloxy-1-butanol, NaH, DMF, 0 °C, 67%. (e) $PH_3P(CH_2OCH_3)Cl$, PhLi, Et_2O, −60 to 20 °C, 80%. (f) 2 N NaOH, EtOH, reflux, 18 h, 74%. (g) (i) $Cl_3CCONCO$, CH_2Cl_2, 20 °C; (ii) $HClO_4$, Et_2O, 20 °C; (iii) NaOH, H_2O/MeOH, 90%. (h) H_2, 10% Pd/C, MeOH, 35 °C, 100%. (i) IBX, MeCN, reflux. (j) **12**, $NaBH(OAc)_3$, TEA, DCE/THF, 20 °C, 30% (2 steps).

7 as a mixture of *E*/*Z* isomers.[9] Because both **6** and **7** are oils, they were purified by chromatography on silica. Pivalamide **7** was treated with dilute NaOH in ethanol at reflux[10] to provide the unstable intermediate aminopyridine **8**, which was carried forward without purification. **8** was then subjected to a one pot, three-step sequence that involved: (a) the reaction with trichloroacetyl isocyanate[11] to give an acyclic trichloroacetylated urea intermediate; (b) the unmasking of the latent aldehyde functionality with perchloric acid[12] followed by intramolecular attack of the amino group of the urea on the aldehyde to give a trichloroacetylated seven-membered ring urea intermediate; (c) the addition of NaOH in methanol to remove the trichloroacetyl group on the urea and give intermediate **9** in excellent yield (a more in-depth discussion on this step is presented in Scheme 6 in the Kilo Laboratory Route section below). Hydrogenation of the double bond and debenzylation to deprotect the hydroxy group could be done simultaneously to afford alcohol **10** in quantitative yield. The oxidation of **10** with IBX[13] to generate aldehyde **11** followed by reductive amination[14] in the presence of naphthalenopiperazine **12**[15] gave the target compound albeit in low yield after chromatographic purification. As an alternative to chromatography, **13** could also be purified by recrystallization from either CH_2Cl_2 or $CHCl_3$, but the very low recovery and the toxicity of these two solvents made this protocol impractical. This synthetic approach consisted of 10 linear steps with a 2% overall yield.

Our group employed this route to explore the chemistry as well as to prepare small quantities of API, and several modifications were quickly implemented to turn it into a safer process. Thus, 1-methyl-2-pyrrolidinone (NMP) was substituted for DMF for the preparation of aldehyde **6** to avoid the potentially dangerous NaH/DMF combination.[16] Also, 4 M HCl in dioxane was employed as a replacement for $HClO_4$ in diethyl ether. Finally, a different oxidation protocol for the preparation of aldehyde **11** was developed through the use of SO_3·pyridine complex[17] or the traditional Swern conditions with oxalyl chloride[18] to avoid the handling of shock-sensitive IBX. Even after these changes, several limitations were still envisioned that

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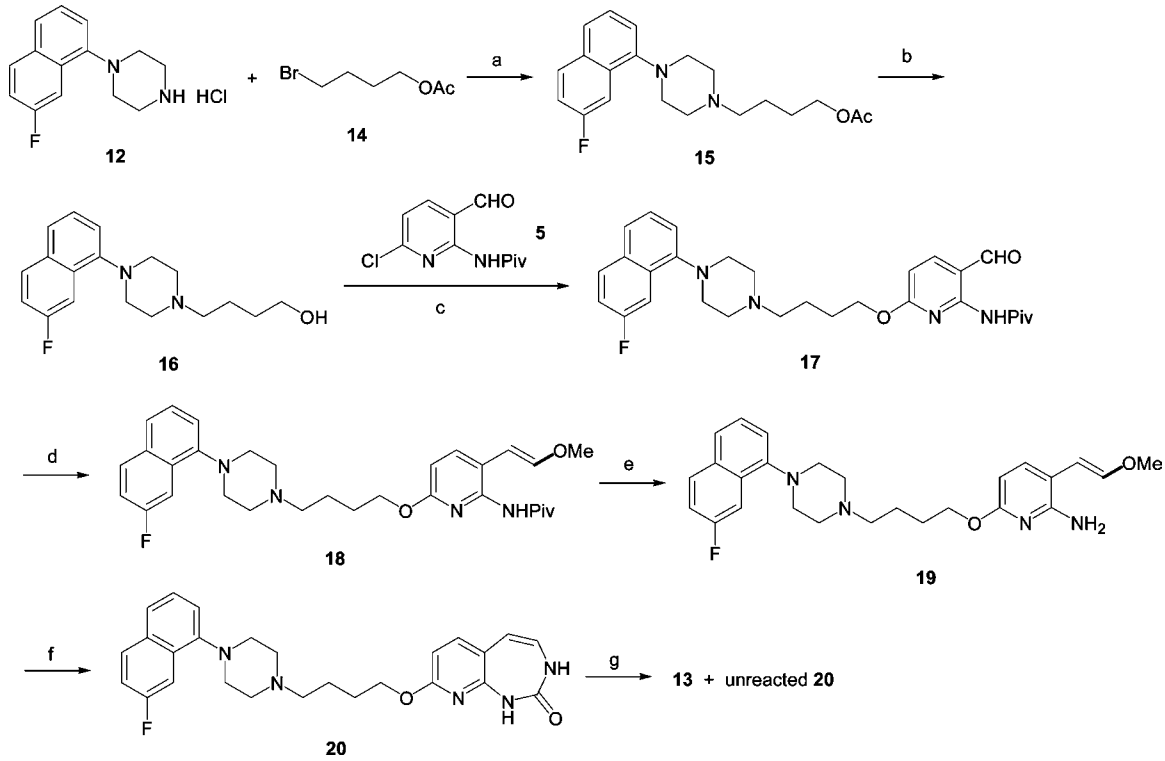
Scheme 2. **Convergent Approach for the Synthesis of 13**[a]



[a] Reagents and conditions: (a) TEA, NMP, 20 °C. (b) K_2CO_3, MeOH/H_2O, 20 °C. (c) **5**, KO*t*-Bu, THF, 0 to 20 °C, 70% (3 steps). (d) $Ph_3P(CH_2OCH_3)Cl$, PhLi, THF, −60 to 20 °C, 90%. (e) 50% NaOH, EtOH, reflux. (f) (i) $Cl_3CC(O)NCO$, CH_2Cl_2, 20 °C; (ii) $HClO_4$, Et_2O, 20 °C; (iii) MeOH, 20 °C, 50% (2 steps). (g) H_2, Pd/C, MeOH, 40 °C or NH_4HCO_2, MeOH, reflux.

would not make this route amenable to scale, such as a high pressure, time-consuming step in specialized equipment, two cryogenic steps, four chromatographies, the use of pyrophoric phenyllithium in diethyl ether, a reductive amination step that gave lower yields and purities as scale increased and, most important, the very low overall yield. Thus, when our group was requested to prepare larger amounts of **13** to support clinical studies, we decided to look for other approaches to assemble this molecule.

Alternative Approaches to 13. Since the original process consisted of a long sequence of linear steps, we first looked at the possibility of a more convergent route. As a result, the alternative approach shown in Scheme 2 was implemented.

The synthesis started with the reaction between piperazine hydrochloride **12** and 4-bromobutyl acetate (**14**). After a base and solvent screen, it was found that the best conditions for this coupling were triethylamine in 1-methyl-2-pyrrolidinone (NMP) at 20 °C, which gave crude ester **15** as an oily solid. The hydrolysis of the ester group in **15** was carried out with potassium carbonate in aqueous methanol to produce alcohol **16** as a dark-brown oil which, without further purification, was allowed to react with aldehyde **5** to give ether **17** in 70% yield after chromatography for the three steps combined. Aldehyde **17** was then subjected to the same sequence of steps as in Scheme 1 to provide unsaturated cyclic urea **20**. The final double-bond reduction step to generate **13** proved to be more difficult than expected. Several conditions (catalytic hydrogenation, phase transfer hydrogenation) were tried to force the reaction to completion, but in all cases, the reactions stalled at 90−95% conversion. When higher temperatures or longer reaction times were employed, more impurity formation was observed. In addition, the purging of unreacted **20** through recrystallization could only be accomplished at the expense of a low recovery. Due to the lack of crystallinity of some of the intermediates, which prevented the development of efficient methods of purification, the need for chromatography after the Wittig reaction to prepare **18**, and the inefficient reduction step, this route was not pursued further.

Other approaches that were tested for the preparation of the seven-membered ring urea moiety are shown in Scheme 3. We tried to introduce the two-carbon chain at the 3-position of the pyridine ring through the use of chloro- or bromoacetaldehyde diethyl acetal[19] or bromoacetonitrile,[20] but only starting material **4** was recovered, and no desired products **21** or **22** were detected. Also, a Henry reaction[21] between aldehyde **5** and nitromethane was attempted to generate nitroalkene **23**, but substrate decomposition was observed.

Kilo Laboratory Route to Phosphoric Acid Salt 1. Based on these unfavorable results and the pressing need to deliver large amounts of material for clinical studies, we decided to optimize the original Medicinal Chemistry route to turn it into a more robust process. At the same time, the phosphoric acid salt **1** had been identified as the preferred form of the API, and a protocol for the reproducible preparation of the targeted solid form had to be developed as well. After optimization of the

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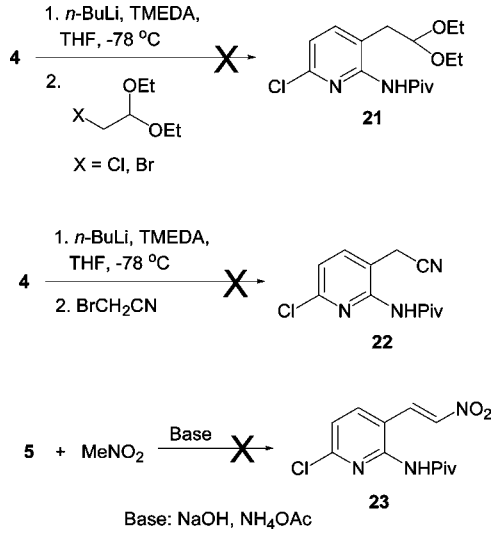
Scheme 3. **Alternative Approaches for the Preparation of the Seven-membered Ring Urea**



reaction conditions, a modified kilo laboratory route was implemented, which is shown in Scheme 4.

The optimized synthesis started with 2,6-dichloropyridine (**2**), which was converted into 2-amino-6-chloropyridine (**3**) in the presence of concentrated NH_4OH in a sealed, stainless steel reactor by heating to 180 °C. Intermediate **3** crystallized from the solution upon cooling and was easily isolated by filtration. Up to 10% of 2,6-diaminopyridine was formed as a side product, but it was easily purged in the filtrates due to its higher solubility in water. With the goal of accelerating the manufacture of this intermediate, the progress of the reaction was monitored at different intervals, and it was found that it was complete after only 12 h compared to the 48 h that was reported by our Medicinal Chemistry group, which resulted in an increased yield. One of the possible reasons for this increase in yield may be the production of less 2,6-diaminopyridine when the reaction time is shortened. At the same time, it was found that 180 °C was the optimal temperature since the reaction proceeded at a considerably slower rate below this value and hardly proceeded at all below 120 °C. Another finding was that vigorous stirring is necessary to push the reaction to completion since in one instance and, due to a malfunction of the overhead stirrer, the process stalled at partial conversion. Even though this transformation required the use of specialized equipment, we decided to proceed with it since it worked well and to outsource this intermediate for our kilo laboratory campaign. Unfortunately, due to the limited availability from commercial sources (only 7 out of the 9 kg that was required could be supplied by the manufacturer at the start of the campaign), we were forced to run several 200-g batches due to equipment size limitations in our own laboratories to quickly prepare 2 kg of this material to meet our needs. The reaction is reproducible up to this scale under this condition and regardless of the source of 2,6-diaminopyridine.[22]

A different approach found in the literature for the preparation of **3** involves the reaction between epichlorohydrin and a mixture of NaCN and hydrochloric acid (35%) to generate 3-hydroxyglutaronitrile[23] which, in the presence of dry hydrogen chloride in ether,[24] provides the HCl salt of **3**. Due to the risks associated with the generation of HCN and the low overall yield (28% for the two steps combined), this route was ruled out.

Intermediate **3** was then treated with pivaloyl chloride to provide pivalamide **4**. Screening of inorganic bases (Na_2CO_3, K_2CO_3, $KHCO_3$, $NaHCO_3$) identified $NaHCO_3$ as the base of choice, and a simple filtration to remove the inorganic salts and precipitation of the product from heptane afforded material in excellent yield and purity. A drop in yield was observed when this process was run on scale compared to laboratory experiments (86% vs 90−94%), where there was essentially no difference in performance between $NaHCO_3$ and TEA. Even though the reason for this lower yield is still unclear, a possibility is a slower crystallization rate on large scale. On the other hand, the use of $NaHCO_3$ had the advantage that this intermediate could be isolated without the need for an aqueous workup, which both simplified the number of operations and reduced the amount of waste considerably. Another finding during the kilo laboratory campaign was that, unlike in laboratory experiments, a strong gas evolution was observed during the addition of the pivaloyl chloride after an induction period. This led to some foaming and solvent reflux that was easily controlled by the reflux condenser of the reactor.

The optimization of the subsequent formylation step focused on both improving the yield and attempting to run the reaction at higher temperature. Better yield and purity were obtained when 4-formylmorpholine[7b] was employed in place of DMF. During laboratory experiments it was noticed that the addition of a THF solution of 4-formylmorpholine to the dianion of **4** at −70 °C caused the mixture to thicken considerably, which prevented a good mixing even with an overhead stirrer. Even though this same event was observed on scale, an efficient agitation during the morpholine addition ensured a good mixing of the reagents, and the integrities of the shaft and blade were never compromised. Another key factor for the successful outcome of this reaction was the predrying of the 4-formylmorpholine over 4 Å molecular sieves (water content <0.01% by Karl Fischer analysis), since the presence of water resulted in incomplete consumption of the starting material and lower purity. Unfortunately, when the reaction was run at higher temperature (−40 to −20 °C instead of −70 °C), lower yield and purity were obtained as well. As alternatives to the pivalamide group,[25] the formylation step was also examined with the corresponding carbamate or carbonate, but decomposition was observed in both cases.

The chloride displacement with 4-benzyloxy-1-butanol was modified to avoid the use of NaH in combination with solvents

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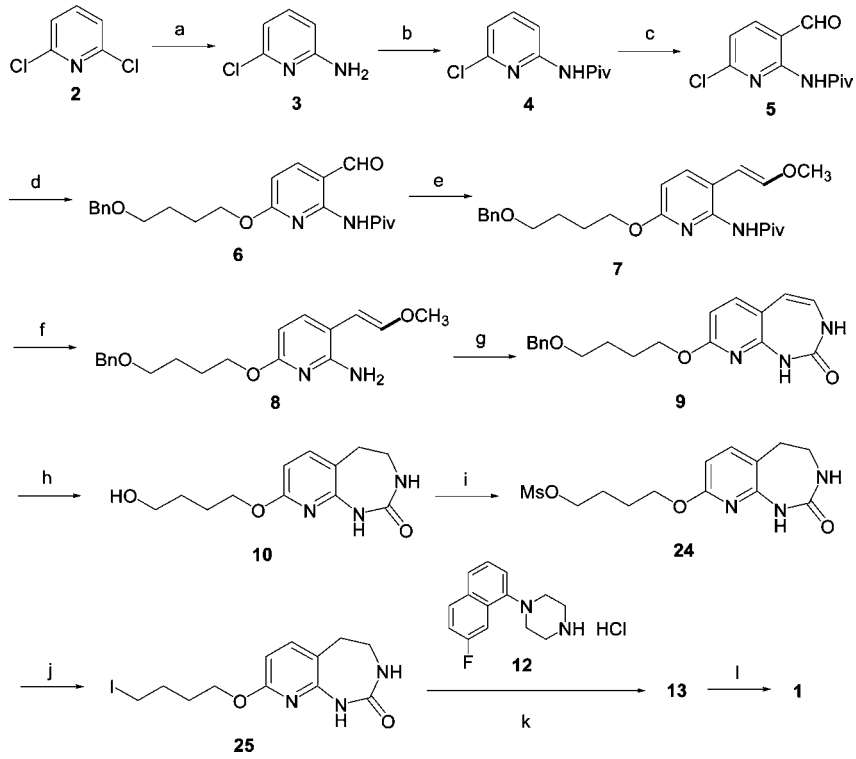
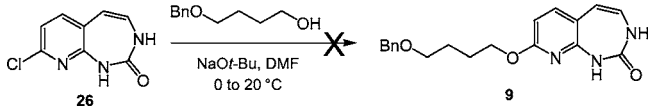
Scheme 4. **Kilo Lab Route for the Preparation of 1**[a]



[a] Reagents and conditions: (a) cc NH_4OH, 180 °C, 12 h, steel bomb, 77%. (b) Pivaloyl chloride, $NaHCO_3$, CH_2Cl_2, −5 to 20 °C, 86%. (c) (i) *n*-BuLi (1.6 M in hexanes), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, THF, −70 to −20 °C; (ii) 4-formylmorpholine, −70 to 20 °C, 49%. (d) 4-Benzyloxy-1-butanol, NaO*t*-Bu, DMF, 0 to 20 °C. (e) $Ph_3P(CH_2OCH_3)Cl$, KO*t*-Bu, THF, 0 °C, 61% (2 steps). (f) 50% NaOH, EtOH, reflux, 1 h. (g) (i) $Cl_3CCONCO$, THF, 20 °C; (ii) 4 M HCl, EtOAc, 5 to 20 °C; (iii) MeOH, 20 °C, 81% (2 steps). (h) H_2, 10% Pd/C, MeOH, 40 °C, 95%. (i) MsCl, TEA, THF, 30−35 °C, 84%. (j) NaI, acetone, reflux, 71%. (k) 12, K_2CO_3, MeCN, 70 °C, 95%. (l) (i) 1 M H_3PO_4, MeOH/EtOAc, 50 °C; (ii) cooling to 20 °C over 5 h, 87%.

Scheme 5. **Failed Approach for the Preparation of Intermediate 9**



such as NMP or DMF. It was observed that sodium *tert*-butoxide in DMF performed well in this transformation to afford ether **6** as a dark-brown oil. In addition, the presence of the aldehyde group, due to its electron-withdrawing nature, was fundamental for the success of this transformation, since when this same reaction was attempted on chloride **26** (Scheme 5), no detectable amount of **9** was produced even upon heating to 50 °C. In the Medicinal Chemistry route, intermediate **6** was purified by chromatography since it is an oil. We discovered that the crude material telescoped as a THF solution was a good substrate for the subsequent Wittig olefination, and as a result, the chromatographic purification could be eliminated.

Without isolation, aldehyde **6** underwent a Wittig reaction with (methoxymethyl)triphenylphosphonium chloride to provide masked aldehyde **7** as a 3:2 mixture of *E*/*Z* isomers. Potassium *tert*-butoxide[26] proved a good substitute for phenyllithium, and the reaction could be carried out in THF at 0 °C instead of at cryogenic temperatures as reported in the original synthesis. Since Wittig product **7** is an oil and the use of the crude material proved inadequate to afford good-quality intermediates in the following steps, the chromatographic purification of this intermediate was essential. This operation was carried out on silica and with 4:1 heptane/ethyl acetate as mobile phase.[27] Upon concentrating the fractions that contained desired product, the residual heptane and ethyl acetate were displaced with toluene, and olefin **7** was used in the next step as a toluene solution. The combined yield for the chloride displacement and Wittig olefination steps was 61%, in comparison with the 53% that was obtained when intermediate **6** was also purified via chromatography. We speculate that the difference in yield may be due to the instability of **6** in the presence of silica. The instability of this intermediate was further confirmed when material purified by chromatography darkened and showed degradation by HPLC analysis after a few weeks on storage. Wittig product **7** also showed signs of degradation (darkening and decreased purity by HPLC) upon storage over prolonged periods of time.

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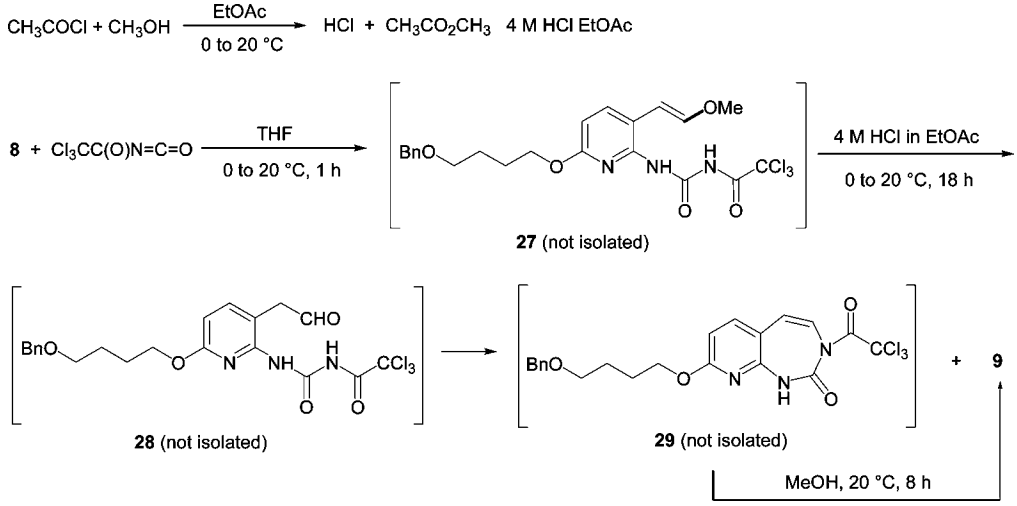
(27) The chromatographic purification conditions were as follows: Column: Hipersep 600 LP with an internal diameter of 60 cm. Stationary phase: Merck flash silica (63−200 μm, 80 kg). Mobile phase: 4:1 heptane/ethyl acetate, with a flow rate of 3 L/min (nitrogen pressure). UV detection wavelength: 335 nm. Polar impurities were removed in the first injection, and the fractions that contained early eluting impurities and desired product were concentrated. A solvent exchange into toluene was performed to give, after concentration, a final volume of 20 L. The column was back washed with 3 volumes of acetone and, after re-equilibration with 4:1 heptane/ethyl acetate, the 20 L from the first injection was divided into two portions and passed through the column with an acetone back wash with re-equilibration in between.

Scheme 6. **Step-wise Sequence for the Preparation of Cyclic Urea 9**



The synthesis continued with the hydrolysis of the pivalamide group in **7** with 50% sodium hydroxide in ethanol at reflux. By increasing the base concentration, the reaction time was reduced from **18** to only 1 h without affecting the purity or yield of aminopyridine **8**. Intermediate **8** is a waxy solid that also has a strong tendency to darken upon standing, and for this reason, it was telescoped into the next step as a toluene solution and used immediately.

With crude **8** in hand, the stage was set for the three-step, one-pot process for the formation of cyclic urea **9** (Scheme 6). The synthesis of seven-membered ring ureas has been reported in the literature. They can be prepared from bromourethanes and KNH_2,[28] semicarbazides *via* treatment with sodium nitrite followed by spontaneous decomposition and cyclization of the resulting nitrene,[29] the reaction of 1,4-diamines with triphosgene[30] or 1,1′-carbonyldiimidazole[31] and oxidative rearrangement of bicyclic six-membered ring ureas in the presence of *N*-bromosuccinimide.[32] In our case, we opted for a novel approach that involved the treatment of aminopyridine **8** with trichloroacetyl isocyanate[33] in THF at 0 °C to give trichloroacetylated urea **27**, which could be detected by LC−MS. Without isolation, to **27** was added a 4 M HCl solution in ethyl acetate, freshly prepared from acetyl chloride and methanol,[34] to afford aldehyde **28**.[35] Commercially available 4 M HCl solution in dioxane can also be used to carry out this deprotection step, but the use of this solvent was avoided due to its carcinogenicity. Aldehyde **28** is a short-lived species that cyclized *in situ* to give a mixture of cyclic trichloroacetylated urea **29**, also detected by LC−MS, and **9**. Since the conversion of **29** to **9** was a slow process under the reaction conditions, we investigated ways to promote this transformation. It was found that a simple addition of methanol to the reaction mixture at 20 °C was sufficient to complete the removal of the trichloroacetyl group and give **9** in very good yield. Unlike the original protocol, the need for a strong base such as NaOH was circumvented. To the best of our knowledge, this is an unprecedented, one-pot approach for the synthesis of seven-membered ring ureas.

The synthesis continued with the simultaneous hydrodebenzylation and double bond hydrogenation of **9** over 10% Pd/C in methanol to give alcohol **10** in almost quantitative yield. This intermediate has very low solubility in most solvents, and after a solvent exchange, it could be easily isolated in high yield and purity from an MTBE slurry. Due to reactor volume limitations at the time of the campaign, this same protocol had to be repeated to convert all available substrate.

To avoid the difficult-to-scale reductive amination, it was decided to replace aldehyde **11** (Scheme 1) with iodide **25** (Scheme 4) in the coupling with piperazine **12**. Thus, crude alcohol **10** was converted to mesylate **24** under standard conditions.[36] The mesylation of **10** only went to completion when the internal temperature was maintained in the 30−35 °C range during the MsCl addition, whereas at lower temperatures the process stalled at approximately 90−95% conversion. The addition of more MsCl had no appreciable effect on the conversion of unreacted alcohol. At this point we do not have a satisfactory explanation for this observation. One possible reason is the presence of some residual water or methanol from the previous hydrogenation step, even though the Loss on Drying test for alcohol **10** showed only a 0.03% weight loss.

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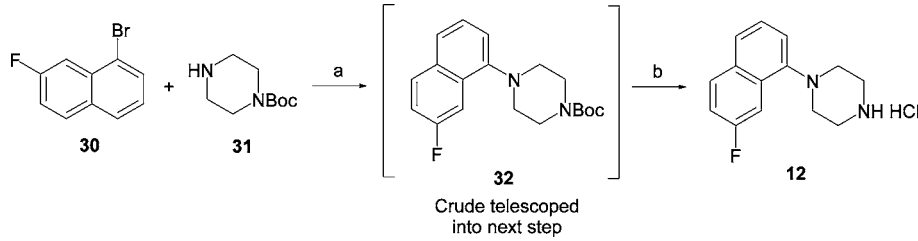
(35) At this point it is unknown whether this intermediate is present in solution as the aldehyde species or as a cyclic aminal. Additional studies with techniques such as ReactIR would be necessary to clarify this point.
(36) Hayakawa, M.; Kaizawa, H.; Kawaguchi, K.; Ishikawa, N.; Koizumi, T.; Ohishi, T.; Yamano, M.; Okada, M.; Ohta, M.; Tsukamoto, S.; Raynaud, F. I.; Waterfield, M. D.; Parker, P.; Workman, P. *Bioorg. Med. Chem.* **2007**, *15*, 403.

Scheme 7. **Preparation of Piperazine Hydrochloride 12**[a]



[a] Reagents and conditions: (a) NaO*t*-Bu, 1,1′-bis(di-*tert*-butylphosphinoferrocene) palladium dichloride, toluene, reflux. (b) (i) HCl gas, EtOH, 0 °C to rt; (ii) Si-thiol silica gel (Pd scavenger), 35 °C, THF/water, 81% (3 steps).

We did not investigate other alternatives such as the tosylate since mesylates are usually more reactive and MsCl, being a liquid, is easier to handle on scale than TsCl.

Iodide **25** was prepared by treating mesylate **24** with sodium iodide in acetone at reflux.[37] Once the reaction was complete, **25** was precipitated from solution through the addition of water. Based on previous laboratory work, we were concerned about the impurity profile of the iodide and the possibility of not being able to purge some of the byproducts in the next step. As a result, we decided to upgrade its purity *via* recrystallization from acetonitrile, which gave material of excellent purity (97.5% a/a) in 71% yield. Even though on laboratory scale the purity of this intermediate was always ≥99% by HPLC (a/a), the slightly lower purity of this batch did not compromise the quality of the free base **13** produced in the next step.

The second coupling partner to generate **13**, piperazine hydrochloride **12**, was synthesized on scale through a procedure developed in our laboratories that involved a Pd-catalyzed cross-coupling reaction between 1-bromo-7-fluoronaphthalene (**30**) and 1-Boc-piperazine (**31**) and subsequent deprotection under acidic conditions (Scheme 7).[15]

With **12** and **25** in hand, an investigation of the reaction conditions for their coupling was conducted. Because of the difficulty to purify free base **13** by recrystallization, the goal was to develop conditions that provided good quality material that could be used in the final salt formation step without any further purification. Thus, several bases (triethylamine, diisopropylethylamine, Li_2CO_3, Na_2CO_3, K_2CO_3 and Cs_2CO_3) and solvents (MeCN, $CHCl_3$, acetone, DMF, NMP, 1,2-dichloroethane) were screened for this. The best condition was the use of 1.05 equiv of piperazine **12** in the presence of K_2CO_3 and MeCN at 70 °C for 4 h, which minimized impurity build-up. Once all the iodide had been consumed, the addition of water precipitated **13** from solution and provided this material in excellent yield and purity.

Thermodynamically Stable Polymorph Determination. Prior to the formation of phosphate salt **1**, it was desired to identify the thermodynamically stable polymorph and subsequently develop a protocol for its reproducible preparation. The thermodynamically stable polymorph under ambient conditions is generally targeted for pharmaceutical development if it is known. Although this solid form is the least soluble at ambient conditions, it is also the least likely form to convert during processing, formulation, scale-up or storage. The accelerated kinetics of solution-mediated phase transformation have recently been employed as an efficient means for identifying the thermodynamically most stable polymorph.[38] Stable form screening experiments exploit the fact that a suspension that is saturated with respect to a metastable polymorph is supersaturated with respect to the stable polymorph. This supersaturation is most efficiently removed in solvents in which the compound of interest is the most soluble, especially those in which the solubility is greater than 8 mmol.[39] Eventually, the least soluble form will crystallize at the expense of the more soluble metastable form(s) such that the equilibrium suspension consists only of the thermodynamically stable form.

Forms A (monohydrate), B (anhydrate), and C (anhydrate) of phosphate salt **1** had been encountered previously during small-scale crystallization and salt formation experiments. Form A was initially recovered from salt formation experiments using acetonitrile and water mixtures. Scale-up of this procedure from 200 mg to 10−14 g resulted in incomplete salt formation. Form B of phosphate salt **1** was recovered from small-scale suspensions of Form A in neat ethyl acetate and tetrahydrofuran. Attempts to reproduce Form B on a scale larger than 100−200 mg were unsuccessful and yielded anhydrous Form C. Forms A and B were never recovered again as pure phases and were not fully characterized. It was noted that Forms A and B were observed to be somewhat high in phosphorous content.

Stable form screening experiments were employed to identify the thermodynamically stable polymorph as well as establish preliminary relative stability of the other crystalline forms. Compound **1** was suspended in 15 different solvents (Table 1) for two weeks, and the resulting solids were collected and analyzed using PXRD. Suspensions were prepared using material that was a mixture of Forms A and C. Form C was recovered from 13 of these solutions. A dihydrate (Form D) and a methanol solvate (Form E) were recovered from water and methanol suspensions, respectively.

Form C of compound **1** was the only anhydrous/nonsolvated form recovered from the stable form screen; however, the solubility in these systems was poor. Therefore, compound **1** was suspended in ethanol at 50 °C for 1 week (solubility =

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(39) The term "mmol" is used in a broad sense in the literature to represent the minimum solubility needed to ensure confidence in stable form screening, and it refers to millimol/L. It assures that a certain number of molecules go into solution rather than a mass.

Table 1. **Stable Polymorph Screen Summary of Compound 1**

solvent system	solubility mg/mL	solubility mmol	form
water	3.5	6.23	D
acetone	0.25	0.45	C
acetonitrile	1.5	2.67	C
dichloromethane	<0.1	–	C
ethyl acetate	<0.1	–	C
ethanol	2	3.56	C
hexane	<0.1	–	C
isopropanol	1.25	2.23	C
methyl ethyl ketone	<0.1	–	C
glyme	<0.1	–	C
methyl *tert*-butyl ether	<0.1	–	C
tetrahydrofuran	1	1.78	C
toluene	<0.1	–	C
methanol	>11.8	–	E
ethanol (55 °C)	4.64	8.27	C

8.3 mmol) and, from this suspension, Form C was obtained, further supporting the hypothesis that it was the stable anhydrous form of compound **1**.

Form D (dihydrate) and Form E (methanol solvate) of compound **1** were the thermodynamically stable forms in a pure water and methanol environments, respectively. Form E was relevant from a synthesis standpoint, and its preparation from Form C was investigated. Thus, Form C was suspended in 6.3, 10 and 20% methanol solutions in ethyl acetate. Only Form C was recovered, indicating that a substantial amount of methanol was required to convert it to Form E. A methanol solvate was then avoidable and would not be considered for dosing in humans.

The dihydrate (Form D) of compound **1** was potentially more problematic. Solid-state transition to Form D dihydrate may occur since water is ubiquitous in the environment. Furthermore, stable hydrates are less soluble in water relative to anhydrous forms of the same material. Although the magnitude of the aqueous solubility difference between Forms C and D was unknown, there was a strong desire to avoid the potential decrease in bioavailability of the stable hydrate.

The hydration state of an anhydrous/hydrate system depends on the water activity (abbreviated a_w) of the surrounding system in relation to the critical water activity (abbreviated ca_w) of hydrate formation. The ca_w of a hydrate/anhydrous pair at a given temperature is a state thermodynamic variable. If the ca_w for compound **1** was hypothetically 0.45 at 25 °C, then exquisite thermodynamic control could be used to recover and store the desired form. For example, crystallization conditions with $a_w < 0.45$ would favor anhydrous Form C. Furthermore, storage of Form C in relative humidity <45% would guarantee no form change to dihydrate in this scenario.

Water activities in binary aqueous and organic solutions have been described in the literature as an effective method to determine ca_w of a hydrate/anhydrous system.[40] Forms C and D were suspended in solutions with a_w ranging from 0.2 to 0.83 for approximately 24 h (Table 2). Additionally, anhydrous

(40) (a) Grant, D. J. W.; Higuchi, T. *Solubility Behavior of Organic Compounds*; Wiley: New York, 1990. (b) Ghosh, S.; Grant, D. J. W. *Int. J. Pharm.* **1995**, *114*, 185. (c) Zhu, H.; Yuen, C.; Grant, D. J. W. *Int. J. Pharm.* **1996**, *135*, 151. (d) Zhu, H.; Grant, D. J. W. *Int. J. Pharm.* **1996**, *139*, 33.

Table 2. **Thermodynamic Stability Relationships Between Forms C and D at Various a_w values**

solvent system	water activity (a_w)	initial form	recovered form
ethanol−water	0.2	C	C
isopropanol−water	0.2	C	C
ethanol−water	0.2	C+D	C+D
isopropanol−water	0.2	C+D	C+D
ethanol−water	0.3	C+D	C+D
isopropanol−water	0.3	D	D
isopropanol−water	0.3	D	D
isopropanol−water	0.4	C	D
methanol−water	0.5	C	D
isopropanol−water	0.83	C	D
92% RH (2 weeks)	0.92	C	C

Form C was stored in a 92% relative humidity (RH) chamber for 2 weeks ($a_w = 0.92$). Form conversion to dihydrate was observed in solutions where a_w was 0.4 and higher. No form changes were observed in solutions below a_w of 0.4. Therefore ca_w was likely somewhere between 0.2 and 0.4. However, Form C did not convert to dihydrate in the solid state after being stored at 92% RH for two weeks.

Project timelines and compound availability in early development necessitated that a ca_w range was identified in lieu of definition of the finite thermodynamic point. The hypothetically low ca_w range presented possible challenges for storage of desired Form C of compound **1**. However, solid-state transformation to dihydrate was not seen even though the compound was stored well above the hypothetical ca_w. Furthermore, the relatively fast kinetics of transformation in solution failed to induce transformation to dihydrate when a_w was less than 0.4.

In summary, Form C was robustly prepared in anhydrous solvents, Forms A and B easily converted to Form C, and Form D was thermodynamically stable in water activities relevant to environmental conditions (see Figure 2 for a summary of the stability relationship between Forms A, B, C and D). However, the kinetics of transformation were slow, especially in the solid state. Routine desiccated storage conditions could then be employed to maintain humidity such that the desired anhydrous form of compound **1** was preserved. Therefore, Form C was identified as the target solid form for early development.

With this information in hand, the preparation of Form C of the phosphoric acid salt of **1** was carried out by dissolving free base **13** in ethyl acetate at 50−55 °C followed by the addition of a 1 M solution of phosphoric acid in methanol. Due to its poor solubility in this medium, the salt crystallized immediately from the solution. and after a slow, controlled

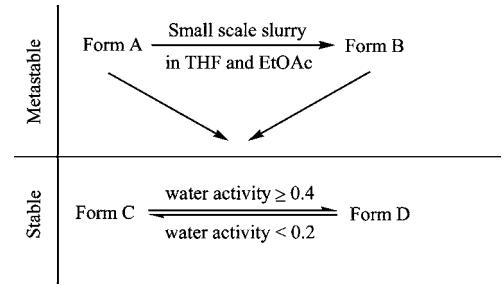

Figure 2. **Thermodynamic stability relationship between anhydrous and hydrated forms of compound 1.**

cooling to 20 °C over 5 h, the final API was obtained in excellent yield and purity.

Conclusions

In conclusion, an optimized protocol for the preparation of D_2 partial agonist **1** has been developed that overcomes many of the synthetic limitations present in the original route, such as the low overall yield, the use of unsafe reagents and conditions and the need for multiple chromatographic purifications. However, further work would have to be carried out to turn it into a truly scalable process, which includes alternatives for the preparation of 2-amino-6-chloropyridine (**3**) under milder conditions and without resorting to the use of specialized equipment, the elimination of the remaining chromatography and the generation of aldehyde **5** under noncryogenic temperatures. In addition, a more convergent route would be desirable. But, at the same time, the improvements that were implemented during the kilo-laboratory campaign increased the overall yield from 2 to 10% and allowed for the quick preparation of multikilogram quantities of API to make possible the timely advance of the associated drug development program. Due to the discontinuation of this program, no further work will be carried out in the near future to address these issues.

Experimental section

Reaction completion and product purity were evaluated by HPLC using the following conditions: column: YMC PackPro C18, 150 mm × 4.6 mm, 3 μm; wavelength: 215 nm; temperature: 25 °C; injection volume: 10 μL after diluting the sample with 50:50 water/acetonitrile to a concentration of approximately 0.35 mg/mL of product; eluent (A) water (0.1% TFA) (B) ACN (0.1% TFA), gradient: (0 min) (A) 70%, (B) 30%; (30 min) (A) 20% (B) 80%; (35 min) (A) 20% (B) 80%; (35.1 min) (A) 70% (B) 30%; (45 min) (A) 70% (B) 30%.

Synthesis of 2-Amino-6-chloropyridine (3). A 4-L stainless steel reactor was charged with 2,5-dichloropyridine (**2**) (200.0 g, 1.35 mol) and aqueous, concentrated ammonium hydroxide (1 L). The reactor was sealed, and the mixture was heated at 180 °C for 12 h with good stirring. The contents of the reactor were cooled to 20 °C, and the resulting solid was filtered, washed with water (3 × 100 mL) and dried under vacuum (15 Torr) at 45 °C to give 134.1 g (77%) of **3** as a light green solid. Mp: 72−75 °C. HPLC retention time: 2.67 min. HPLC purity: 99.6% a/a. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (br s, 2H), 6.35 (d, J = 7.91 Hz, 1H), 6.58 (d, J = 7.58 Hz, 1H), 7.31 (t, J = 7.75 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.8, 112.9, 140.2, 149.4, 159.1. MS (ES+): 129.4 $(M + H)^+$.

Synthesis of Pivalamide 4. To a mixture of 2-amino-6-chloropyridine (**3**) (9.00 kg, 70 mol) and sodium bicarbonate (11.76 kg, 140 mol) in CH_2Cl_2 (87 L) at −5 °C under nitrogen was added pivaloyl chloride (12.67 kg, 105 mol) while the internal temperature was held below 25 °C. The resulting mixture was then stirred at 20 °C for 5 h. The suspension was filtered to remove the inorganic solids, and these solids were washed with CH_2Cl_2 (16 L). The filtrates were concentrated at reduced pressure to a final volume of 27 L. Heptane (18 L) was added, and the distillation was resumed until the volume in the reactor was 22 L. This protocol was repeated once more to a final volume of 22 L, and the resulting suspension was stirred at 20 °C for 1 h. The solid was filtered, washed with heptane (12 L) and dried under vacuum (15 Torr) at 40 °C to give 12.80 kg (86%) of pivalamide **4** as a pale-yellow solid. Mp: 85−87 °C. HPLC retention time: 15.25 min. HPLC purity: 99.8% a/a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 6.96−7.01 (m, 1H), 7.59 (d, J = 7.87 Hz, 1H), 7.96 (br s, 1H), 8.12 (d, J = 8.24 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 40.0, 112.1, 119.7, 141.1, 148.9, 151.6, 177.2. HRMS (EI) exact mass calcd for $C_{10}H_{14}ClN_2O$ (M + H) 213.0795, found 213.0788.

Synthesis of Aldehyde 5. To a solution of pivalamide **4** (12.75 kg, 60.2 mol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (7.0 kg, 60.2 mol) in THF (154 L) at −70 °C under nitrogen was added *n*-BuLi (1.6 M in hexanes, 94.0 L, 150.5 mol) while the internal temperature was held below −60 °C. The mixture was warmed to −20 °C over 2 h and stirred at this temperature for an additional 2 h. The mixture was then cooled to −70 °C, and a solution of 4-formylmorpholine (20.8 kg, 180 mol) in THF (13 L) was slowly added while the internal temperature was maintained below −60 °C. The resulting thick suspension was warmed to 20 °C and stirred for 18 h. The dark brown mixture was cooled to 0 °C, and saturated ammonium chloride (80 L) and 1 M HCl (12 L) were added to bring the pH down to 7 ± 0.5 while the internal temperature was held below 10 °C. The two layers were allowed to separate, and the aqueous layer was extracted with toluene (64 L). The aqueous layer was extracted with additional toluene (32 L), and the combined organic extracts were concentrated at reduced pressure until the volume reached 45 L. Toluene (29 L) was added to the mixture, and the distillation was resumed until the volume reached 45 L. Hexanes (64 L) was added over 30 min, and the resulting suspension was stirred at 20 °C for 30 min. The solid was filtered, washed with a 2:1 MTBE/hexanes mixture (51 L) and dried under vacuum (15 Torr) at 20 °C to give 7.15 kg (49%) of aldehyde **5** as a tan solid. Mp: 137−138 °C. HPLC retention time: 10.11 min. HPLC purity: 92.7% a/a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 7.14 (d, 1H), 8.01 (d, J = 8.06 Hz, 1H), 9.87 (s, 1H), 10.87 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 40.8, 116.6, 119.3, 145.3, 151.9, 155.9, 176.7, 192.2. HRMS (EI) exact mass calcd for $C_{11}H_{14}ClN_2O_2$ (M + H) 241.0744, found 241.0738.

Synthesis of Aldehyde 6. To a solution of 4-benzyloxy-1-butanol (4.09 kg, 22.7 mol) in DMF (19 L) at 0 °C under nitrogen was added a freshly prepared solution of NaO*t*-Bu (6.55 kg, 68.1 mol) in DMF (16 L) while the internal temperature was held below 10 °C. The resulting mixture was stirred at 0−5 °C for 30 min, and a solution of aldehyde **5** (7.10 kg, 29.5 mol) in DMF (14.3 L) was slowly added while the internal temperature was maintained below 10 °C. The reaction was warmed to 20 °C and stirred for 1 h. The mixture was cooled to 5 °C, and water (103 L) and MTBE (82 L) were added. The layers were separated, and the aqueous layer was extracted with MTBE (36 L). The combined organic extracts were washed with water (38 L) and saturated brine (44 L), and the solvent was removed at reduced pressure until the batch

volume reached 24 L. THF (30 L) was added, and the distillation was resumed until the batch volume reached 28 L to give a THF solution of aldehyde **6** that was used without further purification in the next step. HPLC retention time: 27.55 min. HPLC purity: 60.5% a/a. An analytical sample was purified by flash chromatography on silica (heptane/ethyl acetate 9/1 as mobile phase) to fully characterize this intermediate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.73−1.93 (m, 4H), 3.52 (d, J = 6.41 Hz, 2H), 4.52 (s, 4H), 6.46 (d, 1H), 7.21−7.35 (m, 5H) 7.78 (d, J = 8.24 Hz, 1H) 9.69 (s, 1H) 11.49 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.6, 27.6, 27.7, 41.1, 67.5, 70.1, 73.0, 105.5, 111.0, 127.7, 127.8, 128.5, 138.7, 145.7, 153.2, 167.0, 176.9, 191.8. HRMS (EI) exact mass calcd for $C_{22}H_{28}N_2O_4$ (M + H) 385.2127, found 385.2125.

Synthesis of Methyl Vinyl Ether 7. To a suspension of (methoxymethyl)triphenylphosphonium chloride (11.34 kg, 33.0 mol) in dry THF (13.8 L) at 0 °C under nitrogen was added a 1 M solution of KO*t*-Bu in THF (57.3 L, 57.3 mol) while the internal temperature was maintained below 5 °C. The resulting deep-red mixture was stirred at 0−5 °C for 30 min, and the THF solution of aldehyde **6** obtained in the previous step was slowly added while maintaining the internal temperature below 5 °C. After 15 min, aqueous, saturated ammonium chloride (36 L), water (31 L) and MTBE (42 L) were added, and the layers were separated. The organic phase was washed with saturated brine (25 L), and the solvent was removed under reduced pressure until the batch volume reached 25 L. This crude material was chromatographed on silica (heptane/ethyl acetate 4/1 as mobile phase),[27] and the fractions that contained product were concentrated at reduced pressure. Residual heptane and ethyl acetate were displaced with toluene (2 × 35 L) to give 7.38 kg (61%, two steps; yield calculated based on Loss on Drying test of a small sample) of **7** as a bright-yellow toluene solution (27.45 kg). Olefin **7** was obtained as a 3/2 *E*/*Z* mixture of isomers. HPLC retention times: 23.18 and 23.53 min. HPLC purity: 95.1% a/a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28−1.35 (m, 9H), 1.71−1.90 (m, 4H), 3.53 (t, J = 6.23 Hz, 2H), 3.61 (s, 1H), 3.72 (s, 2H), 4.18−4.30 (m, 2H), 4.50 (s, 2H), 5.07 (d, J = 6.96 Hz, 0.6H), 5.57 (d, J = 13.00 Hz, 0.4H), 6.11 (d, J = 7.14 Hz, 0.6H), 6.50−6.56 (m, 1H), 6.83 (d, J = 13.00 Hz, 0.4H), 7.22−7.38 (m, 4.8H), 7.50−7.57 (m, 1H), 7.77 (br s, 0.6H), 8.03 (d, J = 8.42 Hz, 0.6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 26.6, 27.8, 39.7, 56.3, 60.7, 66.1, 66.2, 70.2, 73.0, 100.4, 100.8, 107.8, 108.6, 117.9, 119.5, 127.7, 127.8, 128.5, 137.4, 138.8, 141.3, 144.5, 144.7, 147.1, 149.1, 161.3, 161.6, 176.6, 176.7. HRMS (EI) exact mass calcd for $C_{24}H_{33}N_2O_4$ (M + H) 413.2440, found 413.2433.

Synthesis of Aminopyridine 8. To the toluene solution of **7** obtained in the previous step was added ethanol (72 L) followed by 50% NaOH solution in water (13.2 kg) while the internal temperature was held below 70 °C. The hazy mixture was heated to reflux for 1 h, and after the mixture cooled to 40 °C, toluene (38 L) and water (70 L) were added. The layers were separated, and the aqueous layer was extracted with toluene (38 L). The combined organic extracts were washed with water (3 × 18 L) and saturated brine (20 L) and dried over $MgSO_4$ (5 kg). The solution was filtered, and the solvent was removed at reduced pressure until the batch volume reached 10 L. Toluene (30 L) was added, and the solution was concentrated at reduced pressure until the batch volume reached 10 L. Karl Fischer analysis showed 0.05% water content. This toluene solution of aminopyridine **8** (3/2 *E*/*Z* mixture of isomers) was used in the next step without further purification. HPLC retention times: 11.09 and 11.26 min. HPLC purity: 90.8% a/a. An analytical sample was purified by flash chromatography on silica (CH_2Cl_2/ethyl acetate 9/1) to fully characterize this intermediate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72−1.91 (m, 4H), 3.51−3.58 (m, 2H), 3.66 (s, 1.2H) 3.73 (s, 1.8H), 4.14−4.22 (m, 2H), 4.30−4.85 (m, 4H), 5.02 (d, J = 6.96 Hz, 0.6H), 5.55 (d, J = 12.64 Hz, 0.4H) 6.04−6.12 (m, 1H), 6.73 (d, J = 12.64 Hz, 0.4H), 7.22−7.39 (m, 5H), 7.65 (d, J = 8.24 Hz, 0.6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 26.6, 27.4, 56.8, 60.6, 65.9, 66.0, 70.2, 73.1, 98.8, 99.0, 99.4, 100.4, 107.4, 108.3, 127.7, 127.8, 128.6, 138.2, 138.8, 140.9, 146.3, 149.7, 154.1, 154.4, 162.0, 162.3. HRMS (EI) exact mass calcd for $C_{19}H_{25}N_2O_3$ (M + H) 329.1865, found 329.1859.

Synthesis of Urea 9. Reactor A: to a mixture of methanol (4 L) and ethyl acetate (12 L) cooled at 10 °C under nitrogen was slowly added acetyl chloride (5.92 L, 83.3 mol) while maintaining the internal temperature below 25 °C. The resulting mixture was stirred at 20 °C for 1 h to give a 4 M HCl solution in ethyl acetate.

Reactor B: to the toluene solution of **8** that was obtained in the previous step was added THF (61 L), and the mixture was cooled to 0 °C. Trichloroacetyl isocyanate (3.77 kg, 20.0 mol) was slowly added while maintaining the internal temperature below 6 °C. The resulting mixture was warmed to 20 °C for 1 h. HPLC analysis showed complete consumption of amine **8** to give acyclic urea **27** (HPLC retention times: 28.92 and 29.06 min). The mixture was cooled to 5 °C, and the 4 M HCl solution in ethyl acetate previously prepared in Reactor A was transferred to Reactor B while the internal temperature was held below 10 °C. The mixture was warmed to 20 °C and stirred for 24 h. HPLC analysis showed full consumption of urea **27** and a 3/1 mixture of **9** and acetylated urea **29** (HPLC retention time: 24.76 min). Methanol (28 L) was added, and the reaction was stirred for an additional 8 h at 20 °C to fully convert intermediate **29** to **9**. One molar NaOH (80 L) was added to adjust the pH to 7, followed by the addition of ethyl acetate (65 L). The layers were separated, and the aqueous layer was extracted with ethyl acetate (15 L). The combined organic extracts were washed with saturated brine (25 L), and the solvent was removed at reduced pressure until the batch volume reached 10 L. Methanol (71 L) was added followed by water (35.4 L) over 30 min. The suspension was stirred at 20 °C for 30 min, and the solid was filtered, washed with a 1:1 methanol/water mixture (22 L) and dried under vacuum (15 Torr) at 40 °C to give 4.66 kg (77%, two steps) of cyclic urea **9** as a beige solid. Mp: 79−80 °C. HPLC retention time: 22.63 min. HPLC purity: 98.5% a/a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79−1.90 (m, 2H), 1.90−2.01 (m, 2H), 3.57 (t, J = 6.23 Hz, 2H), 4.30 (d, J = 6.23 Hz, 2H), 4.54 (s, 2H), 6.47 (d, J = 3.85 Hz, 1H), 6.56 (br s, 1H), 6.67 (d, J = 8.61 Hz, 1H), 7.24−7.39 (m, 5H), 7.74−7.82 (m, 2H),

9.13 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.7, 66.4, 70.1, 73.1, 104.0, 106.5, 116.9, 122.9, 127.8, 128.6, 133.0, 138.7, 144.0, 152.7, 160.6. Anal. Calcd for $C_{19}H_{21}N_3O_3$: C: 67.24; N: 12.38; H: 6.24. Found: C: 67.03; N: 12.21; H: 6.17.

Synthesis of Alcohol 10. A Parr shaker reactor was charged with a solution of urea **9** (150 g, 442 mmol) in methanol (1.6 L). Pd/C, 10% (Johnson Matthey, 1940 carbon (shell, unreduced, water wet), 15 g) was added, and the contents of the reactor were pressurized and shaken with hydrogen gas to 50 psig and heated to 35 °C. When the hydrogen uptake ceased (usually after 3 h), the mixture was filtered, and the catalyst cake was washed with methanol (250 mL). Due to reactor volume limitations, this same protocol was repeated to convert all available substrate. All the filtrates were combined together to give a crude solution of alcohol **10** in methanol. The solvent was removed at reduced pressure until the batch volume reached 4 L. MTBE (13.5 L) was added over 10 min and the resulting suspension was cooled to 10 °C and stirred for 1 h. The solid was filtered, washed with MTBE (4 L) and dried under vacuum (15 Torr) at 40 °C to give 2.96 kg (90%) of alcohol **10** as a white solid. Mp: 116−118 °C. HPLC retention time: 3.05 min. HPLC purity: 99.5% a/a. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45−1.58 (m, 2H), 1.65−1.77 (m, 2H), 2.90 (t, J = 8.79 Hz, 2H), 3.39−3.47 (m, 2H), 3.90 (t, J = 8.79 Hz, 2H), 4.12 (t, J = 6.59 Hz, 2H), 4.46 (t, J = 5.13 Hz, 1H), 6.22 (d, J = 7.87 Hz, 1H), 6.98 (br s, 1H), 7.45 (d, J = 8.06 Hz, 1H), 7.98 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.5, 25.9, 29.6, 46.2, 61.0, 66.5, 101.1, 116.7, 137.0, 154.7, 154.9, 162.2. Anal. Calcd for $C_{12}H_{17}N_3O_3$: C: 57.36; N: 16.72; H: 6.82. Found: C: 57.25; N: 16.40; H: 6.74.

Synthesis of Mesylate 24. To a solution of alcohol **10** (2.14 kg, 8.50 mol) and triethylamine (3.55 L, 25.5 mol) in THF (86 L) at 25−30 °C under nitrogen was added methanesulfonyl chloride (1.46 kg, 12.7 mol) while maintaining the internal temperature in the 30−35 °C range. After 30 min, water (9.8 L) was added, and the suspension was concentrated at reduced pressure until the batch volume reached 40 L. Water (58 L) was added over 1 h, and the suspension was stirred at 20 °C for 30 min. The solid was filtered, washed with water (20 L) and dried under vacuum (15 Torr) at 40 °C to give 2.33 kg (84%) of mesylate **24** as an off-white solid. HPLC retention time: 7.05 min. HPLC purity: 89.8% a/a. An analytical sample was purified by flash chromatography on silica (CH_2Cl_2/ethyl acetate 95/5) to fully characterize this intermediate. Mp: 158−160 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.71−1.91 (m, 4H), 2.94 (t, J = 8.57 Hz, 2H), 3.20 (s, 3H), 3.93 (t, J = 8.74 Hz, 2H), 4.09−4.35 (m, 4H), 6.28 (d, J = 7.91 Hz, 1H), 7.00 (br s, 1H), 7.51 (d, J = 7.91 Hz, 1H), 7.98 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.5, 25.3, 26.1, 37.2, 46.3, 66.1, 70.8, 101.1, 117.0, 137.1, 154.7, 162.1. HRMS (EI) exact mass calcd for $C_{13}H_{20}N_3O_5$ (M + H) 330.1124, found 330.1115.

Synthesis of Iodide 25. A mixture of mesylate **24** (2.32 kg, 7.0 mol) and sodium iodide (3.17 kg, 21.1 mol) in acetone (45.5 L) under nitrogen was heated at reflux for 3 h. The suspension was cooled to 30 °C, and the solvent was removed at reduced pressure until the batch volume reached 25 L. Water (53.5 L) was added over 1 h, and the resulting suspension was stirred at 20 °C for 30 min. The solid was filtered, washed with water (20 L) and dried under vacuum (15 Torr) at 40 °C for 12 h to give crude iodide **25**. To crude **25** was added acetonitrile (14 L), and the suspension was heated to 60 °C to give a clear solution. The solution was cooled to 10 °C over 1 h, and the solid was filtered, washed with acetonitrile (3 L) and dried under vacuum (15 Torr) at 40 °C to give 1.78 kg (71%) of iodide **25** as an off-white solid. Mp: 105−107 °C. HPLC retention time: 15.68 min. HPLC purity: 97.5% a/a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73−1.83 (m, 2H), 1.86−1.97 (m, 2H), 2.89 (t, J = 8.79 Hz, 2H), 3.16 (t, J = 6.87 Hz, 2H), 3.95−4.05 (m, 2H), 4.09 (t, J = 6.13 Hz, 2H), 6.13 (d, J = 8.06 Hz, 1H), 6.48 (br s, 1H), 7.25 (d, J = 7.87 Hz, 1H), 8.31 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8, 23.7, 30.0, 30.4, 46.0, 65.3, 101.7, 116.1, 136.1, 154.5, 155.8, 162.1. Anal. Calcd for $C_{12}H_{16}IN_3O_2$: C: 39.90; N: 11.63; H: 4.47. Found: C: 39.89; N: 11.39; H: 4.43.

Synthesis of Free Base 13. A mixture of iodide **25** (1.77 kg, 4.9 mol), piperazine **12** (1.37 kg, 5.14 mol) and potassium carbonate (2.03 kg, 14.7 mol) in acetonitrile (21.6 L) was heated to 70 °C under nitrogen. After 4 h, the reaction was cooled to 40 °C, and water (21.8 L) was added over 30 min. The resulting slurry was stirred at 20 °C for 30 min, and the solid was filtered, washed with a 1:1 water/acetonitrile mixture (5.4 L) and dried under vacuum (15 Torr) at 40 °C to give 2.17 kg (95%) of **13** as a white solid. Mp: 120−121 °C. HPLC retention time: 8.86 min. HPLC purity: 98.7% a/a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68−1.93 (m, 4H), 2.50−2.60 (m, 2H), 2.78 (br s, 4H), 3.00 (t, J = 8.92 Hz, 2H), 3.17 (br s, 4H), 4.07−4.17 (m, 2H), 4.23 (t, J = 6.22 Hz, 2H), 5.19 (br s, 1H), 6.26 (d, J = 7.88 Hz, 1H), 7.13 (d, J = 7.47 Hz, 1H), 7.19−7.29 (m, 1H), 7.32−7.41 (m, 2H), 7.55 (d, J = 8.30 Hz, 1H), 7.75−7.87 (m, 2H), 8.53 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 27.2, 46.0, 53.0, 53.9, 58.5, 66.4, 101.9, 107.3, 107.5, 116.0, 116.1, 116.4, 123.6, 125.3, 130.9, 131.8, 136.2, 149.4, 154.6, 155.4, 159.6, 162.0, 162.4. Anal. Calcd for $C_{26}H_{30}FN_5O_2$: C: 67.37; N: 15.11; H: 6.52; F, 4.10. Found: C: 67.45; N: 14.46; H: 6.56; F, 3.94. HRMS (EI) exact mass calcd for $C_{26}H_{31}FN_5O_2$ (M + H) 464.2462, found 464.2457.

Synthesis of Phosphoric Acid Salt 1. Preparation of the phosphoric acid solution in methanol: Phosphoric acid (0.45 kg, 4.59 mol) was added to methanol (4.6 L) at 20 °C under nitrogen. The mixture was stirred until all the solids dissolved to give a 1 M solution of phosphoric acid in methanol.

To a solution of **13** (2.15 kg, 4.63 mol) in ethyl acetate (64.5 L) at 50−55 °C under nitrogen was added the 1 M solution of phosphoric acid in methanol previously prepared while the internal temperature was held in the 50−55 °C range. The resulting slurry was stirred for 20 min at 50−55 °C and then cooled to 20 °C over 5 h. The solid was filtered, washed with ethyl acetate (2 × 8 L) and dried under vacuum (15 Torr) at 50 °C to give 2.28 kg (87%) of salt **1** as a white solid. Mp (DSC): 192.7 °C. HPLC purity: 98.8% a/a. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.63−1.84 (m, 4H), 2.64−2.77 (m, 2H), 2.81−3.02 (m, 5H), 3.12 (br s, 4H), 3.91 (t, J = 8.71 Hz, 2H), 4.18 (t, J = 6.01 Hz, 2H), 6.27 (d, J = 7.88 Hz, 1H), 7.04 (br s, 1H),

7.20 (d, J = 7.47 Hz, 1H), 7.37−7.46 (m, 2H), 7.49 (d, J = 7.88 Hz, 1H), 7.66 (d, J = 7.88 Hz, 1H), 7.73 (dd, J = 11.20, 2.49 Hz, 1H), 7.88−8.09 (m, 2H), 9.25 (br s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.4, 23.5, 26.8, 46.3, 51.9, 53.0, 57.2, 66.3, 101.2, 107.2, 107.4, 116.5, 116.9, 124.2, 126.1, 129.8, 129.9, 132.0, 132.1, 137.1, 154.7, 155.0, 159.5, 162.1. Anal. Calcd for $C_{26}H_{33}FN_5O_6P$: C: 55.61; N: 12.47; H: 5.92; F, 3.38; P, 5.52. Found: C: 55.21; N: 12.32; H: 5.89; F, 3.35; P, 5.24.

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Supporting Information Available

Copies of ^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **13**, **24** and **25** and PXRD data of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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