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Evaluation and Rapid Scale-Up of the Synthesis of the Pyrrolopyrimidines U-101033E and U-104067F

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Abstract:

Large quantities of pure bulk drug were required to initiate development for possible indications as antiasthma and neuroprotective agents. Safety concerns and reproducibility problems encountered with the laboratory procedures (Bundy, G. L.; et al. *J. Med. Chem.* 1995, *38*, 4161) forced the development of a reliable large-scale process which within six months produced >100 kg of U-104067 free base in a single campaign. During the course of this work, procedures were also developed which allowed for the bulk preparation of analytically pure, pharmaceutically acceptable salt forms of both of the title compounds.

Introduction

2,4-Di-1-pyrrolidinyl-9-[2-(4-morpholinyl)ethyl]-5,6,7,8-tetrahydro-9*H*-pyrimido[4,5-*b*]indole (**7**) and the related oxidized 9-[2-(4-morpholinyl)ethyl]-2,4-di-1-pyrrolidinyl-9*H*-pyrimido[4,5-*b*]indole (**8**) were discovered by an ongoing effort in Discovery Research at Pharmacia and Upjohn. Both possess neuroprotective and antiasthma properties in vitro,[2] and large quantities of pharmaceutically acceptable salt forms of these drugs were required for evaluation, development, and registration. The Chemical Research Preparations group at Pharmacia and Upjohn has as its mission the safe, effective, and timely synthesis of large quantities of pure bulk pharmaceuticals to support the R&D efforts of Discovery Research, and we were therefore requested to prepare approximately 100 kg of the chosen candidate. As is usually the case, our starting point for the synthesis was the procedures provided by the medicinal chemists themselves. With minimal modification they allowed for the timely preparation of multigram quantities of pure material in large laboratory equipment. Procedures were then developed in our laboratory for the preparation of pharmaceutically acceptable salt forms of the free bases. The salts had to be pure, stable, bioavailable, and nonhygroscopic to suit the Pharmaceutical Development group, and from a process chemistry standpoint they should also be easy to handle. This initial synthetic campaign provided us with 100 g quantities of each of the final pyrrolopyrimidines, but more importantly it afforded a variety of useful information relevant to the anticipated eventual scale-up into our pilot plant, which has up to 4000 L capability. Herein we present the results of the initial laboratory campaign, the problems which prompted its modification for scale-up, and our solutions to those problems. The procedures which were developed in our laboratories allowed for the preparation of >100 kg of U-104067F, the eventually chosen candidate, in 48.8% overall yield. This large-scale campaign, which involved 17 pilot plant runs, was conducted in just over four months. The entire project from initial development to delivery required just over one year to complete and provided sufficient material to support an IND filing and initiation of human clinical trials only 14 months after the discovery of the compounds.

Results and Discussion

The synthesis of U-101033 and U-104067 from 2,4,6-trichloropyrimidine is depicted in Scheme 1 and starts with a remarkably selective, heterogeneous double displacement by pyrrolidine. This chemistry had been worked out previously by others in Chemical Process R&D in conjunction with another project,[3] but the large-scale isolation/purification procedure for the product was determined to be excessive for the present work. In the initial work, the small (typically 3−5%) amount of the regioisomeric 4,6-bis-pyrrolidino product was selectively hydrolyzed during the workup by heating with mineral acid. This circumvents a very difficult purification problem encountered late in the synthesis. This treatment, however, adds at least an entire shift to processing and requires 315 L of concd HCl/105 kg lot, followed by neutralization with 157 L of 50% sodium hydroxide. However, in the synthesis of the fused tricyclic nucleus common to U-101033 and U-104067, the symmetrical trisubstituted counterpart is incapable of participating in the cyclization. Therefore, the progeny of the symmetrical byproduct do not pose a purification dilemma in the synthesis of U-101033 and U-104067.

Displacement of the remaining chlorine in **3** can be readily accomplished simply by heating neat with 4-(2-aminoethyl)-morpholine. On a laboratory scale, this method affords near quantitative yields of fully substituted product after ethyl acetate/water partition, concentration, and heptane slurry upgrading. However, very high temperatures and/or long reaction times are required to get the displacement to proceed. Little reaction was evident below 140 °C, and attempts to conduct the chemistry in a variety of high-boiling diluents with and without added carbonate base were uniformly unsuccessful. Especially disturbing, however, was the fact that, even on a modest 1 kg laboratory scale, the exotherm as the reaction initiated proved nearly uncontrollable. It was therefore necessary to develop a viable displacement alternative to chemistry which performed well but was limited in scale. We found that activation of 4-(2-aminoethyl)mor-

(1) Bundy, G. L.; et. al. *J. Med. Chem.* **1995**, *38*, 4161.
(2) *Toxicologist* **1996**, *30*, 84.
(3) Pearlman, B. A.; Padilla, A. G. U.S. Patent 5225555, July 6, 1993.

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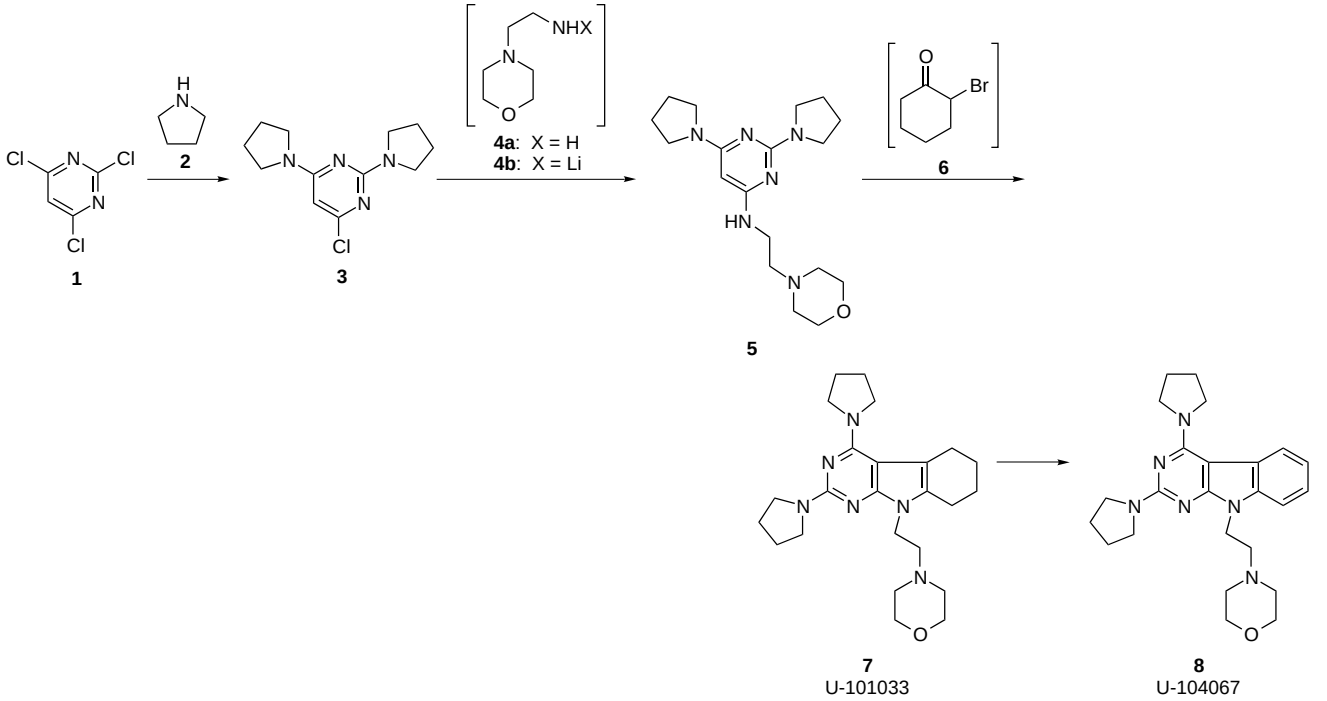
Scheme 1. **Preparation of U-101033 and U-104067**



pholine (**4a**) as the lithium amide **4b** allowed the displacement to be conducted at a reasonable temperature. The reaction is somewhat unusual as, at low temperature in heptane, neither **4a**, **4b**, nor **5** is soluble. *n*-Butyllithium and a heptane solution of **3** are successively added to **4a**, and the resulting slurry is heated to reflux to effect the displacement. As expected, the procedure still requires an excess of the morpholine reagent, but the 6-fold requirement in the neat reaction was decreased to 2.5 equiv with this activated alternative. More importantly, the chemistry can be conducted safely and under easily attainable process conditions. When the reaction is complete, the resulting heptane slurry of the desired 2,4-di-1-pyrrolidinyl-6-[[2-(4-morpholinyl)-ethyl]amino]pyrimidine (**5**) is filtered, and the product is dissolved off the filter. The workup consists of a simple partition between methylene chloride and water to remove coprecipitated inorganic salts. The isolated yield on 66 kg input averaged 95% for the three-lot campaign conducted in 4000 L equipment.

The original procedure for the displacement and subsequent cyclization with 2-bromocyclohexanone and trisubstituted pyrimidine **5** proved to be unreliable in our hands. We had suspected that preparing 2-bromocyclohexanone via Br_2/MeOH[4] treatment of cyclohexanone and *vacuum distillation*[5] prior to use by our Medicinal Chemistry colleagues would not be a desirable large-scale procedure, and our initial encounter with this chemistry confirmed our suspicions. Running the condensation/cyclization reaction in acetonitrile with a full 2 equiv each of *undistilled* 2-bromocyclohexanone and Hunig's base afforded conversions routinely only in the 34−40% range. HPLC analysis of the crude reaction mixture indicated that, except for a few minor impurities totalling only about 5 area %, the predominant species were product and starting material. The reaction appeared to stall and simply could not be coaxed further either by the use of longer reflux times or by increasing the stoichiometry.

We therefore sought a procedure which would allow the preparation of 2-bromocyclohexanone of sufficient purity to allow its use directly in the displacement/cyclization reaction. To this end, cyclohexanone trimethylsilyl enol ether was generated from cyclohexanone and TMSCl/triethylamine in refluxing THF,[6] and after workup and isolation it was then converted in quantitative yield to 2-bromocyclohexanone **6** upon portionwise treatment with *N*-bromosuccinimide.[7] It must be stressed that neither HBr/acetic acid nor Br_2[8] treatment of the enol ether afforded 2-bromocyclohexanone of acceptable quality. In fact, if the enol ether does not remain in stoichiometric excess in the NBS procedure, complex reaction mixtures of polybrominated material unsuitable for our purposes are obtained with it as well. We obtained superior results in the bromination if the quantity of TMS enol ether were accurately known, and the best way to accomplish this was via distillation of the starting material. Although it may appear that we are simply trading one vacuum distillation for another, the TMS enol ether is stable indefinitely and is not lacrimatory as is the bromide. The distillation is routine in the lab, but for pilot scale we contracted out the synthesis of the enol ether to Farr Research, who have distillation technology superior to ours. In this fashion, we were able to advance order the precursor to our unstable reagent, generate the 2-bromocyclohexanone as needed, and hold it cold overnight until its use in the coupling/cyclization reaction.

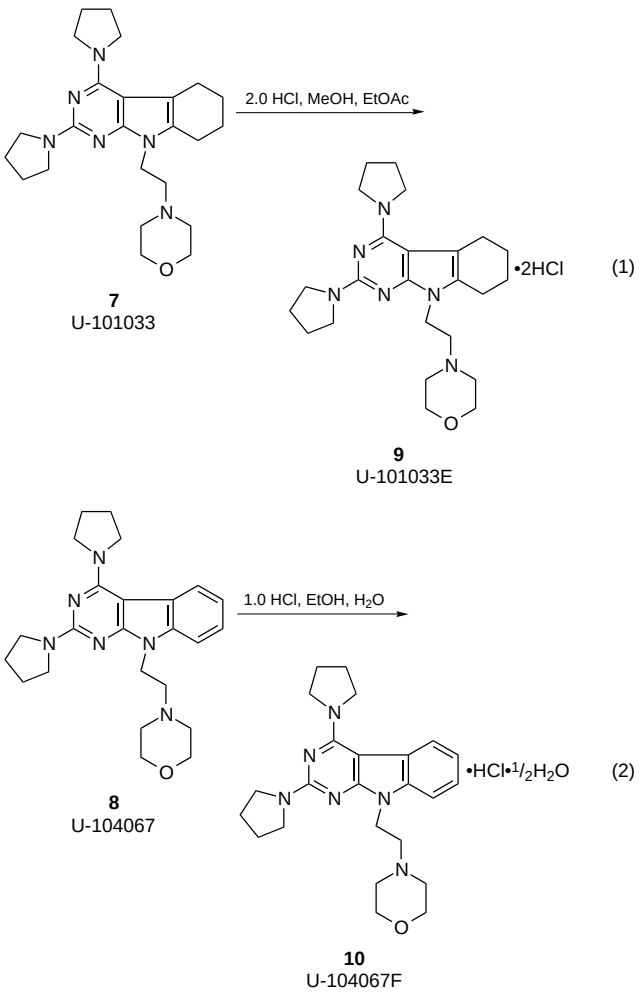
We had determined, early on, the stoichiometric requirement of the bromination reaction, and it was apparent that an inverse addition of the NBS would have to be employed. *However, a potentially serious safety problem was encoun-*

(4) Palmer, C. S.; McWherter, P. W. *Organic Synthesis*; Wiley: New York, 1941; Collect. Vol. I, p 245.
(5) This procedure results in a significant amount of polybromination requiring the high-vacuum distillation of thermally labile 2-bromocyclohexanone.
(6) Tsuji, J.; Ohashi, Y.; Minami, I. *Tetrahedron Lett.* **1987**, *28*, 2397.
(7) Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785.
(8) Begue, J. P.; Mesureur, D. *J. Fluorine Chem.* **1988**, *39*, 271.

tered on attempted scale-up of the NBS/enol ether reaction in the lab. Upon dissolving NBS at 15% w/v in cold THF, an extremely exothermic reaction ensued, resulting in a highly colored boiling solution. A literature search failed to uncover a previous report of this NBS/THF incompatability. We offer without proof that this dangerous reaction is probably due to the presence of peroxides in the THF which initiated a radical chain reaction with NBS. The procedure therefore had to be developed with the expectation of conducting an undesirable inverse solid addition in the pilot plant. This turned out to be handily accomplished with the aid of glovebags, to keep the area of the reactor sight glass oxygen-free, and Canty Quick-Port sight glasses, which allow one to quickly open and close the reactor manhole. In this fashion, the cooled THF solution of TMS enol ether could be safely treated incrementally with portions of NBS under an inert atmosphere and the stoichiometric reaction requirement could be met.

Using 2-bromocyclohexanone prepared by this scalable, convenient two-step process provided high and reliable conversions in the condensation/cyclization reaction, but the yields were still too low for what was at the time the final step in the sequence. Since water is generated in the cyclization, we speculated that its removal would increase conversion either by driving the equilibrium or by increasing the lifetime of 2-bromocyclohexanone under the harsh reaction conditions. In the event, when the reaction was conducted by gently refluxing through 3A molecular sieves, the conversions and yields were noticeably improved and a ratio of product to starting material of about 4:1 was obtained. With such high conversions, the product U-101033, **7**, now crystallized directly from the reaction mixture upon cooling and isolated yields increased to the 65% range. In addition, product quality was extremely high (>98 area % by HPLC). The final iteration of the condensation/cyclization involved incremental addition of reagents. Hunig's base and 2-bromocyclohexanone, 1.33 equiv each, are heated with 1 equiv of substrate for a period of time and then cooled; a second charge of base and 2-bromocyclohexanone are then added, and the reaction mixture is reheated. This final procedure allowed us to drive the reaction to ratios of product to starting material in the range of 8−10:1. Of course, refluxing through molecular sieves on pilot plant scale is a cumbersome undertaking, but not necessary in this case. The favorable binary azeotrope of water/acetonitrile allows one to simply set the reactor in distillation mode and gently azeotrope off the water atmospherically. The yields at this point averaged 78% for our three 85 kg input runs in 4000 L equipment.

During our first laboratory campaign, a final salt form of U-101033 had not yet been selected. Since we had ample free base, close collaboration with our Discovery Research colleagues allowed us to choose a salt and develop a reliable method for its generation. The salt of choice was the dihydrochloride, which exhibited excellent stability and solubility characteristics, but unfortunately had the annoying drawback of retaining solvent. The only acceptable nonalcoholic solvent for which the free base shows appreciable solubility is ethyl acetate, in which the salt is essentially insoluble. Alcoholic solvents had been ruled out since U-101033 exhibited a tendency to degrade in hot alcohol,



as attempted recrystallization of U-101033E from methanol resulted in material of lower quality than one started with! Simply generating the salt in ethyl acetate, in addition to being too voluminous for routine large-scale operation, produced an uncrackable ethyl acetate solvate. In an effort to, in part, make the volumes for the final salt formation more manageable, mixed solvent systems were examined. We were delighted to discover that warm ethyl acetate containing 10 vol % methanol proved to be an excellent system for this chemistry. Not only does it possess the desirable solubility characteristics of a methanol system while at the same time retaining the desirable stability characteristics of the ethyl acetate system, but it also produces an *unsolvated* form of the dihydrochloride. The salt is generated in the warm mixed methanol/ethyl acetate system from which it precipitates. An azeotropic removal of the methanol assures a high recovery of analytically pure material.

We were thus able to begin supplying large quantities of bulk drug to the toxicologists. Unfortunately, disaster hit the project at this point when it was determined in 30-day studies that the drug exhibited an unusual dose dependent toxicity, and further study of U-101033E was suspended.

Upon discovery of the toxicity of U-101033, the ongoing analogue program in Medicinal Chemistry was already prepared to offer a replacement: the unsaturated version U-104067 (**8**). This compound, in fact, is the degradation product one obtains in small amounts upon attempted upgrading of U-101033. It would seem that a compound so difficult to avoid in the U-101033 sequence would be trivial

to synthesize. Medicinal Chemistry reported that oxidation of U-101033 with chloranil or DDQ provided good yields of U-104067 *after silica gel chromatography*. We had, much to our chagrin, experienced chromatographing one of the intermediates in an early U-101033 campaign and were convinced that any procedure involving chromatography in this highly polar series was doomed from a practical standpoint, and we quickly turned our attention to potential catalytic methods of oxidation. After all, U-104067 is simply the aromatized form of U-101033. It can be generated on exposure of U-101033 to air, and we felt that it would be a suitable donor for a transfer hydrogenation procedure.

Ordinarily one thinks of transfer hydrogenation as being a reductive technique, but with respect to the donor (generally cyclohexene or more safely methylcyclohexene) the reaction is an oxidation. We felt that aromatization of the six-membered ring in U-101033 would provide a driving force for the reaction and therefore set about to find conditions which would allow for this energetically favorable and presumably facile reaction to occur. Under a variety of transfer hydrogenation conditions employing various heterogeneous catalysts at a range of catalyst loadings, using various hydrogen acceptors, various solvents, water, acid and base enhancement, and various temperatures and times in a glass bomb, the reaction could at best be pushed to only about 50% completion. These reactions were, however, extremely clean. It was clear, however, that due to the toxicity of U-101033, its presence in U-104067 could not be tolerated and so conversions in the oxidation had to be near quantitative. Out of safety concerns we had been reluctant to run this reaction under a pad of nitrogen open to the atmosphere, but since our experiments had demonstrated the reluctance of this system to oxidize, particularly below about 140 °C, we felt that the liberated hydrogen could be dissipated by a nitrogen sweep. Our first successful experiment employed 50 wt % of 10% Pd/C in decalin at reflux and allowed complete conversion (>99 area % by HPLC) to U-104067 in approximately 4 h, a time frame that we felt would preclude any dangerous buildup of hydrogen gas. The recovery was low, however, even after copious cake washes with ethyl acetate. But slurrying the solka floc/catalyst cake in methylene chloride allowed recovery of the missing mass after filtration, and we finally had an acceptable laboratory isolation procedure for **8**. Concentration on a rotary evaporator under house vacuum followed by high-vacuum rotary evaporation yielded clean decalin-soluble U-104067 free base. Over time many refinements were made to the reaction conditions, the most significant of which was an acetonitrile recrystallization of already >98 area % pure U-101033 prior to the oxidation. Eventually, the conditions settled on for the dehydrogenation were 30 wt % of 5% Pd/C at 153 °C (internal temperature attainable with 100 psi of steam in the pilot plant) in decalin solvent.

Our large-scale laboratory runs had demonstrated the feasibility of pilot scale operation of this chemistry, but we still lacked a practical large-scale isolation procedure. This was readily developed, however, as an extraction of the filtrate of the methylene chloride washed cake with 1 N HCl separated the product from the organic solvents. Neutralization (NaOH) in the presence of fresh methylene chloride solvent allowed us to isolate a solution of exceptionally clean U-104067 free base.

We had eventually settled on a final salt, the monohydrochloride, and had devised a reproducible procedure for its preparation by this time. Despite the obvious structural similarity of U-101033 and U-104067, the mixed solvent technique used to advantage in the U-101033E preparation was not applicable here. When the salt formation was conducted in the presence of any ethyl acetate, an ethyl acetate solvate was invariably obtained. This solvate could not be vacuum dried to acceptable residual solvent levels, but could be converted to other solvates by refluxing in the appropriate medium; i.e., refluxing in heptane provided a heptane solvate, refluxing in acetonitrile afforded an acetonitrile solvate, and refluxing in ethanol afforded an ethanol solvate. This last fact provided the clue that we needed to solve the problem: conduct the salt formation in pharmaceutically acceptable ethanol, as reasonable residual ethanol levels can be tolerated in bulk drug. However, further experimentation allowed us to determine that employing absolute ethanol doped with 10% water allowed isolation of not the ethanol solvate but a stable monohydrochloride *hemihydrate* of U-104067, designated as U-104067F.

This dehydrogenation/salt formation scheme worked extremely well on pilot scale as the switch to ethanol after the extractive isolation allowed an atmospheric chase of the residual methylene chloride via an ethanol distillation prior to conversion to the desired salt. No residual methylene chloride was ever detected in any of our lots of bulk drug.

Conclusions

The clinical candidates U-101033E (**9**) and U-104067F (**10**), being evaluated as potential neuroprotectives and antiasthma drugs, were prepared in both high yield and high purity on a large scale in the pilot plant. A time-consuming workup involving concentrated hydrochloric acid and 50% caustic was avoided, and a safe, reliable method for the generation of 2-bromocyclohexanone which avoided its distillation was developed and demonstrated. Yields in the critical cyclization/condensation of 2-bromocyclohexanone with **3** to produce U-101033 free base **7** were shown to be stoichiometry and water dependent. A catalytic dehydrogenation of U-101033 in which the saturated six-membered ring is aromatized was employed. This procedure provided higher yields of U-104067 free base and avoided the chromatographic purification required of the DDQ and chloranil alternatives. Finally, pharmaceutically acceptable salt forms of both the candidates were prepared.

Experimental Section

NMR spectra were obtained using a Bruker AMX 300 instrument. 2,4,6-Trichloropyrimidine was obtained from Poly Organix. Pyrrolidine was obtained from BASF Wyandot. Sodium carbonate and *n*-butyllithium were obtained from FMC. 4-(2-Aminoethyl)morpholine was obtained from Fluka. Tetrahydrofuran was obtained from Webb Chemical and used without purification. Acetonitrile and decalin were purchased from E. I. DuPont. Ethyl alcohol was purchased from AAper. All other solvents are available in bulk and were used as is. 1-(Trimethylsiloxy)cyclohexene was pre-

pared by Farr Research. *N*-Bromosuccinimide and diisopropylethylamine were purchased from Aldrich Chemical Company. Palladium on carbon was obtained from Englehard. Hydrochloric acid was purchased from Detrex Corporation.

6-Chloro-2,4-di-1-pyrrolidinylpyrimidine (3). A clean, dry, inert 4000 L glass-lined reaction vessel under an atmosphere of nitrogen was charged with sodium carbonate (122 kg, 1150 mol), made inert again, and charged with 1050 L of heptane. 2,4,6-Trichloropyrimidine (**1**, 105 kg, 572 mol) was charged via vacuum from a grounded drum, and the mixture was agitated during the addition of 200 L of water. Pyrrolidine (**2**, 98.4 kg, 1386 mol) was added via drum pump at such a rate as to keep the internal temperature below 70 °C, and the mixture was heated to a gentle reflux for 9 h. The reaction mixture was then cooled to 60 °C, 504 L of water was added, and the phases were separated. The aqueous phase was extracted at 60 °C with 105 L of heptane, and the combined organic phase was cooled to −30 °C. The product 6-chloro-2,4-di-1-pyrrolidinylpyrimidine (**3**) was isolated by filtration, and the colorless solids were washed with cold heptane. Drying at 40 °C under nitrogen afforded 132 kg (91.3% yield, first crop) of **3** which assayed at 96.4% by GC (15 m DB-1, 100−250 °C at 10 deg/min, t_R **3** 13.2 min, iso-**3** 14.4 min). ^{1}H NMR ($CDCl_3$): δ 5.63 (s), 3.53 (t, J = 2 Hz, 8H), 1.92 (m, 8H).

2,4-Di-1-pyrrolidinyl-6-[[2-(4-morpholinyl)ethyl]amino]pyrimidine (5). *Method A.* A clean, dry, 5 L three-neck round-bottom flask equipped with reflux condenser, heating mantle, thermocouple, and mechanical agitator was charged with 6-chloro-2,4-di-1-pyrrolidinylpyrimidine (**3**, 1.0 kg, 3.96 mol) and 4-(2-aminoethyl)morpholine (**4a**, 1.65 kg, 12.67 mol). The mixture was heated with stirring to 195 °C, where a very vigorous reaction occurred. The heat was removed, but the temperature continued to increase to 216 °C before leveling off. The reaction mixture was allowed to cool to 180 °C, held at this temperature for 1 h, then cooled to 70 °C, and poured into 8 L of water and 8 L of 1:1 ethyl acetate/hexane. The layers were separated, and the aqueous phase was extracted first with 6 L and then with 2 L of 1:1 ethyl acetate/hexane. The combined organic phase was washed with saturated sodium chloride solution, dried over $MgSO_4$, and concentrated under reduced pressure to 1.85 kg of crude solid. The solids were slurried with 4 L of hexane, and the product was isolated by filtration, affording 1.23 kg total (89.0% yield) in two crops.

Method B. A clean, dry, inert 4000 L glass-lined reaction vessel was charged with 4-(2-aminoethyl)morpholine (**4a**, 93 kg, 715 mol) and 1300 L of heptane. The solution was cooled to −10 °C, at which point it became a slurry, and was treated over 1.75 h with a 15% solution of *n*-butyllithium in heptane (286 kg, 669 mol). The slurry of lithium amide **4b** was then treated with a solution of 6-chloro-2,4-di-1-pyrrolidinylpyrimidine (**3**, 60 kg, 237 mol) in 650 L of heptane and heated to 82 °C for 4 h. The mixture was cooled to 0 °C and filtered under pressure, and the cake was washed with heptane and dried under nitrogen. The crude solid product was returned to the reaction vessel and partitioned between 1350 L of methylene chloride and 460 L of water. The methylene chloride phase was washed with a second 460 L portion of water and then concentrated under reduced pressure. The residue was taken up in acetonitrile, the last of the methylene chloride was chased, and the yield was determined by aliquot as 78.3 kg (95.4%). Material assayed at 99.1 area % by HPLC (Zorbax RX-C8, 60:40 acetonitrile/pH 4 buffer; 2 mL/min; t_R **5** = 2.3 min, **7** = 3.4 min, **8** = 7.3 min).

2-Bromocyclohexanone (6). A clean, dry, inert 4000 L reaction vessel under a pad of nitrogen was charged with 1-(trimethylsiloxy)cyclohexane (83.5 kg, 490 mol) and 670 kg of tetrahydrofuran and cooled to −5 °C. *N*-Bromosuccinimide (83 kg, 465 mol) was carefully added portionwise as a solid through a Cantelever sight glass over a period of 3 h, the temperature being maintained below 0 °C. The reaction was quenched by the addition of 160 kg of sodium chloride and 50 kg of sodium bicarbonate dissolved in 625 L of water, the mixture was diluted with 310 L of hexane, and the phases were separated. The aqueous phase was extracted with a second 310 L portion of hexane, and the combined organic phase was washed with 100 kg of sodium chloride and 28 kg of sodium bicarbonate dissolved in 310 L of water, filtered through a bed of $MgSO_4$, and concentrated under reduced pressure. The residue was diluted with 100 L of acetonitrile and maintained at 5 °C until used in the following step.

2,4-Di-1-pyrrolidinyl-9-[2-(4-morpholinyl)ethyl]-5,6,7,8-tetrahydro-9*H*-pyrimido[4,5-*b*]indole (7). A clean, dry, inert 4000 L reaction vessel under a pad of nitrogen was charged with 2,4-di-1-pyrrolidinyl-6-[[2-(4-morpholinyl)-ethyl]amino]pyrimidine (**5**, 570 kg of a 12.5 wt % solution in acetonitrile, 71.25 kg, 206 mol) and diisopropylethylamine (34.25 kg, 245 mol). An acetonitrile solution of 2-bromocyclohexanone (80 kg of an approximately 50 wt % solution, 40 kg, 240 mol) was added and the reaction mixture heated in distillation mode for 1 h at atmospheric pressure until ca. 20 L of distillate had been collected. The reaction mixture was cooled to 45 °C, an additional charge of diisopropylethylamine (34.25 kg, 245 mol) and an acetonitrile solution of 2-bromocyclohexanone (80 kg of an approximately 50 wt % solution, 40 kg, 240 mol) were added, the reaction mixture was reheated, and an additional 20 L of distillate was collected. The reaction mixture was cooled to −25 °C and stirred for 6 h, and the solid product was isolated by filtration, washed with cold acetonitrile, and dried at 40 °C under a stream of nitrogen, affording 74.3 kg, 84.3% yield. It was characterized as the dihydrochloride salt (**9**).

2,4-Di-1-pyrrolidinyl-9-[2-(4-morpholinyl)ethyl]-5,6,7,8-tetrahydro-9*H*-pyrimido[4,5-*b*]indole, Dihydrochloride (9). 2,4-Di-1-pyrrolidinyl-9-[2-(4-morpholinyl)ethyl]-5,6,7,8-tetrahydro-9*H*-pyrimido[4,5-*b*]indole (**7**, 335 g, 0.776 mol) was dissolved in 3.66 L of refluxing acetonitrile, polished by filtration through a coarse-fritted sintered glass funnel, and cooled to −27 °C. The precipitate was isolated by filtration, washed with cold acetonitrile, and dried at 40 °C under vacuum to provide 315 g of >99 area % pure **7**. The purified **7** was combined with two other small lots totalling 30.0 g and dissolved in 9.41 L of ethyl acetate and 2.05 L of methanol at 29 °C. The solution was treated all at once with anhydrous HCl in ethyl acetate (1.29 kg of a 4.53% w/w solution, 1.60 mol), cooled to room temperature, and

concentrated under reduced pressure until 4 L of distillate had been collected. It was combined with a lot identically prepared, cooled to 0 °C, and filtered. The solids were washed with cold ethyl acetate and oven-dried at 40 °C, affording 765 g (96% yield) of analytically pure **9**. Anal. Calcd: C, 57.94; H, 7.70; N, 16.89; Cl, 14.25. Found: C, 57.93; H, 7.79; N, 16.86; Cl, 13.96.

9-[2-(4-Morpholinyl)ethyl]-2,4-di-1-pyrrolidinyl-9*H*-pyrimido[4,5-*b*]indole, Hydrochloride, Hemihydrate (10). A clean, dry, inert 800 L/1200 L reactor pair was carefully charged with 12 kg of 5% Pd/C, 2,4-di-1-pyrrolidinyl-9-[2-(4-morpholinyl)ethyl]-5,6,7,8-tetrahydro-9*H*-pyrimido[4,5-*b*]-indole (**7**, 40 kg, 93.5 mol), and 300 kg of decahydronaphthalene. The reaction mixture was heated with stirring under a strong nitrogen sweep at 153 °C for 18 h, cooled to 20 °C, and diluted with 120 L of methylene chloride. The catalyst was removed by filtration over a solka floc packed Sparkler filter and the cake thoroughly washed with 240 L of methylene chloride. The filtrate was extracted with 300 L of 1.0 N hydrochloric acid, and the aqueous phase was washed with heptane, then cooled, and treated with 300 L of methylene chloride. The pH of the aqueous phase was adjusted to 11 by the addition of 24.5 kg of 50% sodium hydroxide, the phases were separated, and the organic phase was clarified by filtration through a bed of $MgSO_4$. The methylene chloride phase was concentrated under reduced pressure to a thick slurry, and 475 kg of anhydrous ethyl alcohol was added, followed by 60 L of water. The reaction mixture was concentrated at atmospheric pressure until 125 L of distillate had been collected and then was treated with 8.24 kg of concentrated hydrochloric acid diluted with 50 L of 95% alcohol. The distillation was continued until an additional 40 L of distillate had been collected, and the slurry was cooled to −30 °C for 12 h. The solid product was isolated by filtration, and the crystals were washed with cold ethanol and dried at 40 °C under nitrogen, affording 31.3 kg (72.1% yield) of analytically pure 9-[2-(4-morpholinyl)-ethyl]-2,4-di-1-pyrrolidinyl-9*H*-pyrimido[4,5-*b*]indole, hydrochloride, hemihydrate which assayed at 99.9% by HPLC. Anal. Calcd: C, 63.07; H, 7.28; N, 18.39; Cl, 7.76. Found: C, 63.32; H, 7.41; N, 18.65; Cl, 7.16.

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