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An Efficient and Cost-Effective Synthesis of Pagoclone

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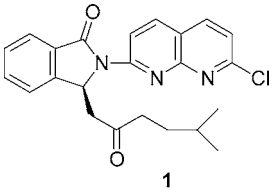
Abstract:

The compound (+)-2-(7-chloro-1,8-naphthyridin-2-yl)-3*S*-(5-methyl-2-oxohexyl)-1-isoindolinone (pagoclone) shows anxiolytic activity due to partial agonism of the benzodiazepine site of the $GABA_A$ receptor. We describe the development of an economical and practical process for a 100+ kg pilot plant production used to supply development needs. For the key reaction, a β-keto phosphonium salt was prepared by selectively reacting a primary α-bromo ketone with triphenylphosphine in the presence of a secondary α-bromo ketone. A novel Wittig reaction with a 1-isoindolinone was used to produce racemic pagoclone. The enantiomerically pure drug substance was prepared by hydrolyzing a γ-lactam and resolving the resulting enantiomeric carboxylic acids with (+)-ephedrine hemihydrate. An alternate resolution, involving chiral multicolumn chromatography (MCC) was also developed. The synthesis was completed by a racemization-free lactam formation to afford pagoclone.

Introduction

Pagoclone (**1**) is a partial agonist at the benzodiazepine site of the $GABA_A$ receptor and is active in preclinical models predictive of anxiolytic activity. This licensed compound[1] was under development for the treatment of general anxiety disorder (GAD) and panic disorder.



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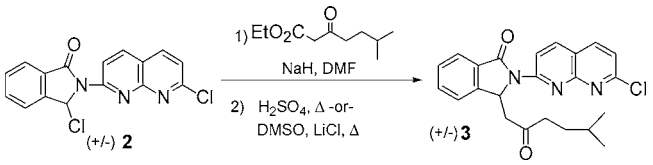
CI-1043 (pagoclone)

It was found that the known route[2] to racemic pagoclone (**3**), which involved the alkylation of dichloride **2** and subsequent decarboxylation (Scheme 1), provided low throughput and was also prohibitively expensive. Because of the large volumes of drug substance required for the development program, it was necessary to invent a more practical approach.

Scheme 1



Our approach was based on the assumption that, under certain conditions, the hydroxy-isoindolinone **4** would be in equilibrium with the aldehyde tautomer **5** (Scheme 2). If this were the case, a Wittig olefination of that aldehyde followed by a Michael-type ring closure would afford the desired racemic product, **3**.

Results and Discussion

Our process began with the synthesis of naphthyridine **6** from 2,6-diaminopyridine and malic acid using a modification of a literature procedure[3] (Scheme 3). Hazard evaluation of our reaction revealed two safety concerns that had to be addressed prior to scale-up. The first was the significant adiabatic heat rise that occurred when the diamine was added to the concd sulfuric acid (ΔT_{ad} = 192 °C). The material could not be added to a cold solvent because, somewhat surprisingly, the dissolution would require days to complete. The solution was to add the material in six portions at 40 °C and allow the exotherm (ca. 30 °C) to subside (ca. 30 min) prior to each addition. The second concern was the generation of an equivalent of carbon monoxide after the addition of the malic acid. Fortunately, evaluation of the headspace gases showed that the CO was not liberated until the reaction had reached 65 °C. Therefore, charging the malic acid to a 25 °C reaction through an open man-way was not considered to be a hazard to the operators. We found that the free base of the naphthyridine (**6**) was a very fine powder and formed a clay during filtration. The sulfuric acid salt, on the other hand, could be isolated as a fast-filtering, yellow powder simply by addition of brine to the reaction mixture.[4] The sulfuric acid salt of the product was used crude (93% pure) in the subsequent step.

The synthesis of the requisite ylide precursor, phosphonium salt (**10**), was not as straightforward as we had initially

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(1) Pagoclone was originally licensed by Warner-Lambert (now Pfizer, Inc.) from Interneuron Pharmaceuticals (now Indevus Pharmaceuticals) who in turn licensed it from Rhone-Poulenc Rorer (now Aventis).

(2) Bourzat, J.-D., et al. (Rhone-Poulenc Sante). U.S. Patent 4,960,779, October, 1990.

(3) The free base of compound **6** has been reported: Newkome, G.; Garbis, S.; Majestic, V.; Fronczek, F.; Chiari, G. *J. Org. Chem.* **1981**, *46*(5), 833. This protocol, in our hands, produced a low yield of product contaminated with large amounts of Na_2SO_4.

(4) It was also observed that, because of the low basicity of the compound, a water wash of the filter cake would remove the acid and form the free-base clay (with substantial product loss). To avoid the clay formation, the sulfuric acid salt was chosen as the form for isolation.

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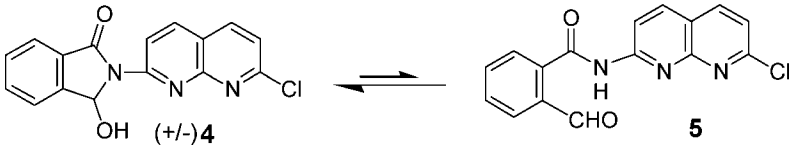
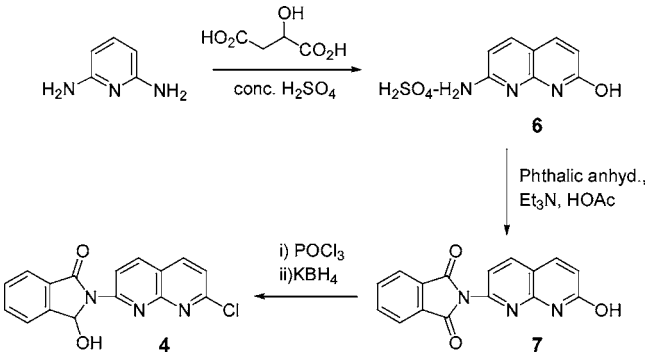
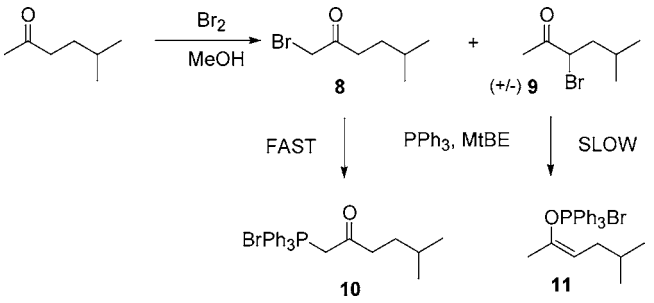
Scheme 2



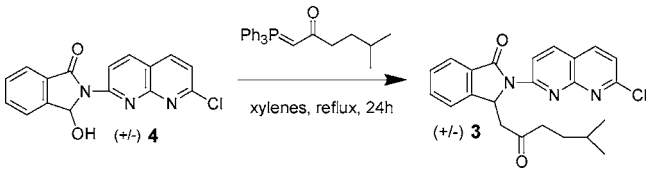
Scheme 3



Scheme 4



Scheme 5



hoped. With common brominating agents the preferred position of bromination is known to be the more substituted carbon.[5] An alternative is to brominate the silyl enol ether of the kinetic enolate,[6] but we chose not to pursue this at large scale because of the cost it would impart to this potentially inexpensive component. Instead, we experimented with brominating methyl iso-amyl ketone in methanol, a solvent which is known[7] to give decent levels of bromination at the primary carbon. The best result obtained for our substrate was a 63:37 ratio of C-1 (**8**) to C-3 (**9**) bromination (Scheme 4), with a small amount (<5%) of 1,3-dibromination.[7] We initially attempted to purify the resulting α-bromoketones by fractional distillation, but their similar boiling points (207 and 200 °C for **8** and **9**, respectively) and their flagrantly lachrymose nature encouraged us to rapidly seek other avenues. The solution was to take advantage of the reactivity differences of the C-1 and C-3 bromides with triphenylphosphine. It is known[8] that secondary and tertiary α-bromoketones tend, instead of a normal S_n2 displacement of the halide, to form an enolphosphonium compound by an S_N2' mechanism (Scheme 4). By running the displacement in a nonpolar solvent, such as *tert*-butyl methyl ether, we have found that the undesired pathway is extremely slow and the desired product (**10**) can be isolated almost exclusively. A small amount (1−3%) of triphenylphosphine oxide is evident in the product and is the result of either traces of oxygen in the reaction or, more likely, the formation of small amounts of **11** which is hydrolyzed during analysis. Because **11** is simply converted back to the original ketone during ylide formation, it did not serve as a source of concern. The conversion to the phosphonium salt is very efficient, giving a two-step yield of 57%.

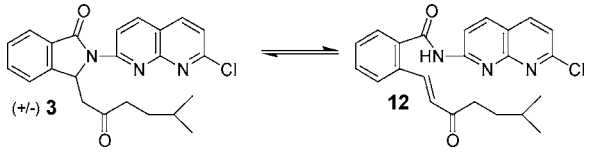
The ylide formed rapidly in a biphasic system of aqueous carbonate and xylenes; the phosphonium salt is initially insoluble in both phases, but after 15 min the ylide is formed and two clear phases are achieved. After removing the aqueous layer and refluxing the ylide with hydroxy-isoindolinone **4** in xylenes (ca. 136 °C) for 24 h (Scheme 5), an 85% yield of the desired adduct **3** was realized. A screen of alternate reaction solvents showed that only nonpolar aprotic solvents gave acceptable yields and that addition of polar cosolvents (e.g., DMSO, DMF, DMI, DMP, and the like) greatly decreased the conversion. The reaction proceeds at temperatures as low as 110 °C, but this is impractical because the rate of ylide decomposition is competitive with the desired reaction at this temperature. After the reaction is complete, a solvent switch to 2-propanol allows for the isolation of racemic pagoclone (**3**) as a white crystalline solid with >99% chemical purity.

A key difficulty in this synthesis was the resolution of the enantiomers of **3**; the molecule is not susceptible to salt formation, and we could find no practical enzymatic resolution. (Lactam hydrolysis was investigated, for example.) We also looked briefly at making diastereomeric derivatives of the ketone functionality, but found that the ketone was very sterically crowded, making derivatization inefficient at best. A complicating factor was the ease with which the resolved ketone will racemize under basic, acidic, and thermal conditions. Deuterium labeling studies showed that the mechanism for racemization was a retro-Michael/Michael reaction, as shown in Scheme 6. The low activation energy of this racemization pathway made deprotection of the ketone derivatives almost impossible.

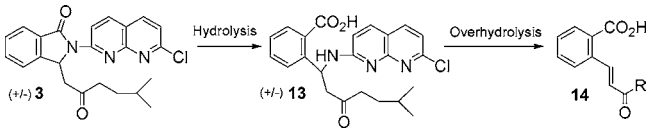
The method used for the initial deliveries of drug substance was to open the lactam under hydrolytic conditions to afford carboxylic acid **13** which can be resolved via

(5) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons: New York, 1985; pp 529−530.
(6) Blanco, L.; Amice, P.; Conia, J. *Synthesis* **1976**, 194.
(7) Ha, H.-J.; Lee, S.-K.; Ha, Y.-J.; Park, J.-W. *Synth. Commun.* **1994**, *24*(18), 2557.
(8) Further dilution of the reaction will give an increasing ratio, but the cost of decreased throughput negates this benefit. Bromine was used as the limiting reagent in order to minimize the amount of 1,3-dibromo product.

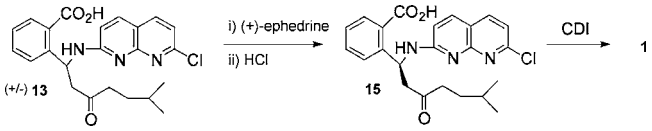
Scheme 6



Scheme 7



Scheme 8



diastereomeric salt formation. As shown in Scheme 7, the challenge in this ring-opening reaction was to avoid overhydrolysis to the enone **14** which, under most reaction conditions tried, was a competitive or even dominant reaction. The conditions employed for pilot runs involved hydrolysis with aqueous hydroxide in a two-phase mixture of *1,2*-dimethoxyethane and THF at 34 °C for at least 24 h. Even with these highly optimized conditions, the reaction could only be run to about 98% completion and the amount of byproduct **14** was in the 5−8% range.

After removal of the residual racemic pagoclone (**3**) by precipitation, the carboxylic acid **13** could be isolated as a stable white powder in 85% yield by precipitation from aqueous methanol. The acid was resolved using the known[9] ephedrine salt formation (Scheme 8) to provide the acid **15** in >98% ee and 80% theoretical yield. The salt can then be neutralized and the lactam reformed with carbonyldiimidazole (CDI) or acetic anhydride/imidazole to produce (+)-pagoclone (**1**) in 95% yield. The (−)-enantiomer of the acid can be recovered from the resolution step and recycled. We were unsuccessful in scrambling the stereocenter in the open form (**13**) because β-elimination of the amine to **14** was rapid and irreversible, but once the lactam was reformed with CDI the material racemized rapidly in the ring-opening step. (Scheme 7).

Until the final batch of pagoclone was produced, we operated under the assumption that it was critical to obtain high ee in the resolution step because crystallization of the final drug substance did not improve enantiometric purity. However, the final batch was partially racemized[10] in the final isolation step to 88% ee, and an alternate purification had to be devised out of necessity. It was known that the racemic crystal of pagoclone is less soluble and higher-melting than the pure enantiomer (174 vs 165 °C), and this fact was used to our advantage. We found that after stirring the batch in a mixture of acetone (25 vol) and absolute ethanol (15 vol) at 20 °C for several hours, a small amount of racemic material could be removed by filtration, and the material in solution was >98% ee. After concentration and recrystallization from ethanol, ca. 90% of the material was salvaged.

The above-described resolution process had an undesirable number of steps, was the bottleneck in the plant, and was responsible for 80% of the cost of goods. Therefore, an alternate means of resolution was pursued. It was found that the enantiomers of pagoclone separate well on a number of chiral HPLC stationary phases, and this led us to investigate chiral multicolumn chromatography[11] as a means to a cost-effective resolution. The process (see Experimental Section for details) was tested on a 26 kg batch of racemic feed and produced a 95% yield of >99% ee (+)-pagoclone in the raffinate. The (−)-enatiomer could be racemized by heating the extract stream with a solution of aqueous base (KOH, for example). This recycling of the extract would allow for an almost quantitative yield on the resolution, and the estimated throughput would be 25 kg of (+)-pagoclone per day using 30-cm columns. This translates to about 2.0 kg of pure enantiomer per kg of stationary phase per day. We could have expected even greater productivity, except that in our case the throughput was limited by the low solubility of the racemic material in the mobile phase (17 g/L).

Although there would be capital expenses incurred in the commission of a chromatography unit, the cost savings gained by using this chromatography as a continuous process are substantial. The cost of the final drug substance would be decreased by >60%.

Conclusion

Starting from inexpensive raw materials, we have developed a practical, scalable, and cost-effective commercial synthesis of pagoclone. Use of asymmetric multicolumn chromatography for the resolution of the enantiomers was demonstrated as an alternative to classical resolution.

Experimental Section

2-Amino-7-hydroxy-1,8-naphthyridine Sulfuric Acid Salt (6). 2,6-Diaminopyridine (150 kg, 1375 mol) was added in six portions to concd sulfuric acid (1030 kg) at 40−50 °C. The solution was allowed to exotherm, and the next portion was not added until the temperature was within range. After the solution became homogeneous, the reaction was cooled to 25 °C and D,L-malic acid (185 kg, 1380 mol) was added in one portion. The reaction was heated to 110−120 °C over 1 h. CAUTION: Carbon monoxide is evolved during this time. After 1 h, the reaction was cooled to 25 °C and transferred into a cold aqueous sodium chloride solution (10 °C, 150 kg in 1125 L of water), maintaining the temperature below 50 °C. The slurry was stirred for 2 h at 20 °C and then filtered. The filter cake was washed with hexanes (270 L) to drive out residual water. The solid was dried under vacuum at 60 °C to afford 303 kg (85% yield) of a pale yellow powder. MS (DCI) M + 1 at 162, 100%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.32 (br s, 5H, −O**H**, −N**H**$_2$,

(9) David-Comte et al. (Rhone-Poulenc Rorer). U.S Patent 5,498,716, March, 1996.

(10) The racemization was most likely due to contamination of the crystallization solution with traces of base, although this could not be confirmed in retrospect.

(11) This process is similar to simulated moving bed chromatography.

H_2SO_4), 6.41 (d, $J = 9.0$ Hz, 1H), 6.56 (d, $J = 9.0$ Hz, 1H), 7.85 (d, $J = 6.6$ Hz, 1H), 7.91 (d, $J = 6.6$ Hz, 1H); mp >350 °C.

2-Hydroxy-7-*N*-phthalimidyl-1,8-naphthyridine (7). A reactor was charged with naphthyridine salt (**6**) (165 kg, 636 mol), phthalic anhydride (246 kg, 1660 mol), and glacial acetic acid (850 kg) and cooled to 20 °C. Triethylamine was added (257 kg, 2540 mol) while maintaining the temperature below 30 °C. The reaction was heated to 115 °C and held for 5 h. After cooling to below 30 °C, methanol (900 L) was added, and the slurry was stirred for 30 min. The solids were filtered and rinsed with methanol (440 L). The product was dried under vacuum at 60 °C to afford 176 kg (95%) of a tan powder. ^{1}H NMR: 12.45 (s, 1H), 8.43 (d, $J = 8.1$ Hz, 1H), 8.09 (m, 5H), 7.49 (d, $J = 8.1$, 1H), 6.74 (d, $J = 9.5$, 1H); CI (MS) M + 1 at 292, 100%.

(±)-2-(7-Chloro-1,8-naphthyridin-2-yl)-3-hydroxy-1-isoindolinone (4). A reactor was charged with hydroxyphthalimide (**7**) (120 kg, 412 mol), sodium chloride[12] (1.2 kg), acetonitrile (755 kg), and dimethylformamide (1.5 kg). The mixture was heated to reflux (ca. 83 °C), and a solution of phosphorus oxychloride (69.1 kg, 450 mol) in acetonitrile (5 kg) was added. After 4 h at reflux, the mixture was cooled to 5 °C, and acetonitrile (240 kg) and potassium hydroxide (201 kg of a 45% aqueous solution) were added. After the mixture was stirred for 15 min, the pH was adjusted to 8 with additional potassium hydroxide if necessary. A solution of potassium borohydride (83.3 kg, 1544 mol) in water (900 L) was added to the reaction at 0−15 °C. After the mixture was stirred for 1 h at 20−30 °C, the reaction was quenched by addition of glacial acetic acid (630 kg) and water (5 L). After the mixture was stirred for 15 min, the solids were collected by filtration and washed with water (2 × 300 L) and methanol (2 × 300 L). The solids were dried under vacuum at 75 °C to afford 109 kg (85%) of a tan solid. MS (DCI) M + 1 at 312, 100%; ^{1}H NMR (400 MHz, DMSO-d_6): 8.58 (d, $J = 10.5$ Hz, 1H), 8.52 (d, $J = 10.5$ Hz), 8.45 (d, $J = 8.7$ Hz, 1H), 7.83 (ddd, $J = 7.7$, 1.0, 1.0 Hz, 1H), 7.77 (ddd, $J = 7.7$, 7.7, 1.4 Hz, 1H), 7.72 (ddd, $J = 7.7$, 1.4, 1.4 Hz, 1H), 7.63 (dd, $J = 7.7$, 1.4 Hz), 7.60 (d, $J = 8.7$ Hz, 1H), 7.05 (s, 1H), 6.95 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 166, 154, 153, 153, 144, 141, 139, 134, 130, 130, 124, 123, 122, 119, 116.

(±)-2-(7-Chloro-1,8-naphthyridin-2-yl)-3-(5-methyl-2-oxo-hexyl)-1-isoindolinone (3). While being stirred, the following were charged to a reactor in this order: water (1185 L), sodium carbonate (120 kg, 1700 mol), phosphonium salt (**10**) (370 kg, 813 mol), and xylenes (1350 kg). After the mixture was stirred for 30 min, the reaction became clear, and the lower aqueous layer was removed. The organics were then washed[13] with a sodium carbonate solution (60 kg in 1185 L of water). To the organics was added the hydroxy compound (**4**) (158 kg, 507 mol). The reaction mixture was heated to 136 °C for 24 h (initially under distillation conditions to remove residual water, then under reflux). The reaction mixture was cooled to 80 °C and then vacuum distilled to remove the majority of the xylenes. To the resulting slurry was charged 2-propanol (2284 L). The slurry was heated to reflux and then cooled to 20 °C. The solids were collected by filtration, washed with 2-propanol (600 L) and methanol (300 L), and dried under vacuum at 60 °C to afford 170 kg (82%) of the title compound as an off-white solid. APCI/MS: M + H$^+$ at 408, 100%; ^{1}H NMR (200 MHz, DMSO-d_6): 8.87 (d, $J = 8.8$, 1H), 8.61 (m, 2H), 7.93 (d, $J = 7.0$, 1H), 7.74 (m, 4H), 6.05 (m, 1H), 3.62 (m, 1H), 3.28 (dd, $J = 7.0$, 17.2, 1H), 2.42 (m, 2H), 1.35 (m, 3H), 0.79 (d, $J = 6.2$, 6H); mp 173−174 °C.

[(5-Methyl-2-oxo)-hexyl]-triphenylphosphonium Bromide (8). To a solution of methanol (850 L) and 5-methyl-2-hexanone (152 kg, 1330 mol) at 0 °C was added bromine (185 kg, 1156 mol) such that the temperature remained below 15 °C. The solution was stirred at 10 °C for about 2 h. An exotherm (ca. 10 °C) occurs when the reaction is about 80% complete; after this subsides, the reaction is complete. The reaction was quenched with water (148 L). After the mixture was stirred for 30 min, *tert*-butyl methyl ether (1100 kg) was added, followed by a sodium chloride solution (133 kg in 740 L of water). After the mixture was stirred for 15 min,[14] the aqueous layer was discarded. The organics were further washed with a sodium bicarbonate solution (36 kg in 744 L of water) and a sodium chloride solution (as above). The solvent was vacuum distilled, replaced with *tert*-butyl methyl ether (550 kg), and redistilled. To the cooled bromoketone product in *tert*-butyl methyl ether (281 kg, 10 °C) was added a solution of triphenylphosphine (303 kg, 1156 mol) in *tert*-butyl methyl ether (281 kg). After 12 h at 20 °C, the solids were filtered and washed with *tert*-butyl methyl ether (115 kg). The material was dried under vacuum for at least 12 h at 40 °C to afford 300 kg (57%) of white crystals. ^{1}H NMR: 7.87 (m, 15H), 5.66 (dd, $J = 2.9$, 12.8, 2H), 2.71 (m, 2H), 1.35 (m, 3H), 0.80 (d, $J = 6.2$, 6H); CI (MS) M at 455, 100%.

(±)-2-[1-(7-Chloro-1,8-naphthyridin-2-ylamino)-6-methyl-3-oxo-heptyl]-benzoic Acid (13). A reactor was charged with racemic pagoclone (**3**) (111 kg, 272 mol), 1,2-dimethoxyethane (404 kg), and tetrahydrofuran (633 L), followed by addition of a potassium hydroxide solution (85 kg in 1100 L of water). The solution was stirred at 34 °C for at least 30 h. The reaction was cooled to 20 °C, and the lower aqueous layer was discarded. Water (610 L) was added, and the pH was adjusted to 9 with aqueous hydrochloric acid (4N). The tetrahydrofuran was removed by vacuum distillation. Water (350 L) was added, and the pH was adjusted to 11.5 with aqueous potassium hydroxide (1.4N). The precipitate (residual racemic pagoclone) was removed by filtration. After adding dichloromethane (1027 kg), the aqueous layer was acidified to less than pH 1.4. The organic layer was washed with water (450 L) and concentrated under vacuum. The residue was precipitated from methanol (300 L) and water (320 L), filtered, and dried

(12) The product was very fine and difficult to isolate by centrifuge unless sodium chloride was added to the reaction mixture.

(13) The purpose of this additional wash is to remove residual bromide. If this is not done, up to 0.5% of the resulting product will have bromo rather than chloro-naphthyridine.

(14) The reaction was initially monitored for completion by GC and was complicated by some methyl ketal formation during the reaction. This stir allows adequate time for the ketals to be converted to ketone.

at 50 °C under vacuum to afford 99.7 kg (86%) of a white powder. DCI/MS: M + H^+ at 426, 100%; ^{1}H NMR (200 MHz, DMSO-d_6): δ 13.5 (br s, 1H), 8.25 (d, J = 8 Hz, 1H), 8.04 (d, J = 9 Hz, 1H), 7.85 (d, J = 9 Hz, 1H), 7.80 (d, J = 9 Hz, 1H), 7.60 (dd, J = 8, 8 Hz, 1H), 7.45 (dd, J = 8, 8 Hz, 1H), 7.30 (dd, J = 8, 8 Hz, 1H), 7.15 (d, J = 9 Hz), 6.90 (d, J = 9 Hz, 1H), 2.9 (m, 2H), 2.5 (m, 2H), 1.3 (m, 3H), 0.8 (d, 6H); mp 173−174 °C.

(+)-2-(7-Chloro-1,8-naphthyridin-2-yl)-3*S*-(5-methyl-2-oxohexyl)-1-isoindolinone (1). A reactor was charged with 100 kg of carboxylic acid (**13**) (234 mol), ethanol (385 kg), water (23 L), and (1*S*,2*R*)-ephedrine hemihydrate (42.8 kg, 246 mol). The reaction was heated at 40 °C until homogeneous, filtered, and cooled to 20 °C until onset of crystallization and then to 0 °C for 2 h. The precipitate was filtered and washed with a solution of ethanol (221 kg) and water (11 L). This solid was added to a solution of concd hydrochloric acid (12.8 kg), water (133 L), and dichloromethane (535 kg). After 15 min, the aqueous layer was removed, and the organics were washed with water (135 L). The dichloromethane was distilled at atmospheric pressure to a volume of 250 L, and then a solution of *N*,*N*-carbonyldiimidazole (30.3 kg) in dichloromethane (234 kg) was added. After 15 min, water (256 L) was added. The aqueous layer was removed, and the organics were washed with additional water (256 L). The organics were concentrated by distillation and replaced with ethanol (530 kg). The slurry was cooled to 5 °C for 3 h and filtered. The solids were dried under vacuum at 60 °C to afford 35 kg (63% of theory, 32% yield) of a white crystalline material. ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.87 (d, J = 8.8, 1H), 8.61 (m, 2H), 7.93 (d, J = 7.0, 1H), 7.74 (m, 4H), 6.05 (m, 1H), 3.62 (m, 1H), 3.28 (dd, J = 7.0, 17.2, 1H), 2.42 (m, 2H), 1.35 (m, 3H), 0.79 (d, J = 6.2, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 80.74 (C2), 115.98 (C19), 119.068 (C17), 121.91 (C15), 123.39 (C9), 124.10 (C6), 129.90 (C8), 130.23 (C4), 133.90 (C7), 139.40 (C18), 140.53 (C16), 144.45 (C3), 152.69 (C12), 153.06 (C10), 153.77 (C14), 166.43 (C5); CI (MS) M + 1 at 408, 100%; $[\alpha]^{20}_D$ = +135° (c = 1, dichloromethane); mp 169 °C.

Multicolumn Chromatography Conditions. A 26 kg lot of racemic material (**3**) was purified using a mobile phase of 90% toluene and 10% 2-propanol and a feed of 17 gm/L in the mobile phase. The chiral stationary phase was 720 gm of (*S*,*S*)-Whelk-O 1 available from Regis Technologies which was packed into 6 × 5 cmID columns. The feed flow rate was 59 mL/min, and the raffinate produced a stream of product with >99.5% optical purity. The product was isolated by concentration and crystallization from ethanol. The extract stream was racemized with 0.1% (v/v) of 0.5N potassium hydroxide at 50 °C for 2 h. Following racemization, the solution was washed with one volume 0.1N hydrochloric acid and 1 vol of water.

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