Efficient Pyridinylmethyl Functionalization: Synthesis of 10,10-Bis[(2-fluoro-4-pyridinyl)methyl]-9(10*H*)-anthracenone (DMP 543), an Acetylcholine Release Enhancing Agent†

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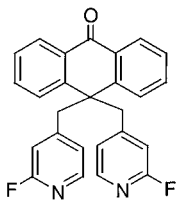
Received March 9, 1998

2-Fluoro-4-methylpyridine (**3**) is efficiently functionalized by chlorination, hydrolysis and methanesulfonylation into the novel alkylating agent **7**. This mesylate is used for the bisalkylation of anthrone under carefully defined conditions to prepare the cognition enhancer drug candidate **1**. This process proceeds in up to 37% overall yield and is adaptable for large scale synthesis.

Alzheimer's disease is the most frequently encountered age-associated dementia, striking about 10% of those over 65 and rising to about 50% for those over 85.[1,2] It is a particularly distressing affliction for both victims and their families, as symptoms usually progress through memory impairment, loss of motor coordination, and eventually death. Currently approved therapeutic agents are limited to tacrine, whose benefit-to-risk ratio is not high,[3] and the recently approved donepezil.[4] The need for more effective treatments continues to drive intense research in this direction.[5] In this paper, we present an efficient and practical synthesis for DuPont's lead compound in this area: DMP 543 (**1**). Our objective was the development of a safe, inexpensive and environmentally cognizant synthesis that would permit the preparation of kilogram lots of this drug candidate. This would allow timely preparation of drug substance for safety assessment, formulation development, and clinical studies. The potentiality to adapt this synthesis for eventual commercial production was also desirable.

As part of a program to develop compounds that might reduce cholinergic system dysfunction by acetylcholine release enhancement, DuP 996 (**2**, linopirdine) was found to be active both in vivo and in vitro.[6−8] Further variation



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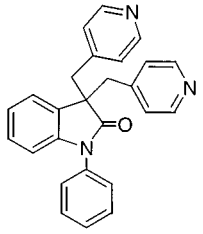

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of both core and pendant groups led to an analogue possessing an anthrone core approximately 10 times as potent.[9] However, DuP 996 was readily metabolized by *N*-oxidation of the pyridinylmethyl pendant groups, leading to short plasma residence times of the parent drug. Attenuation of the process was necessary to increase in vivo duration of these neurotransmitter release enhancing agents. It seemed likely that fluoro substituents in the ortho position of the pyridine rings would reduce both the nitrogen's basicity and susceptibility to *N*-oxidation. This hypothesis led to the design of **1**.[10]

The most expeditious synthesis of **1** would be the bisalkylation of anthrone with a properly functionalized 2-fluoropyridine. 2-Fluoro-4-methylpyridine (**3**), the only

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† Reported in part at the 216th National Meeting of the American Chemical Society, Boston, MA, August 23−27, 1998.

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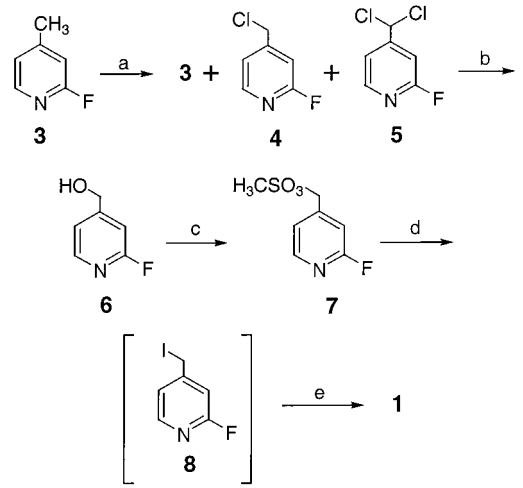
10.1021/jo9804339 CCC: $19.00
Published on Web 10/21/2000

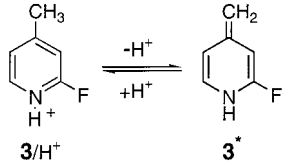
Scheme 1[a]



[a] Reagents: (a) NCS, benzoyl peroxide, CH_3COOH, CH_3CN, 65−75%; (b) K_2CO_3, H_2O, 65−70%; (c) CH_3SO_2Cl, $(CH_3CH_2)_3N$, EtOAc, 90−95%; (d) NaI, THF; (e) anthrone, lithium *tert*-butoxide, THF, 65−75%.

suitably commercially available starting material, seemed to be a good candidate for functionalization of the benzylic position. The optimized process is described in Scheme 1. Our initial research was directed toward chloride **4**, which would be a precursor to the alkylating agent, iodide **8**.[11] There are a variety of potential short routes to α-chloropicolines from picolines;[12] however, the majority of these feature *N*-oxides as prominent intermediates and were unlikely to form efficiently from electron-deficient rings such as **3**. Most of the remaining one-step procedures require chlorine gas,[13] presenting operational hazards in our scale-up facilities that we decided to forego. Ultimately, the answer arose from classical radical-catalyzed chlorination, namely *N*-chlorosuccinimide (NCS)/benzoyl peroxide/carbon tetrachloride/heat/light[14] which produced an acceptable product mixture of **3**, **4**, and **5** (60−65% yield of **4**) if halted once **4** had attained its maximum concentration at 85−90% reaction. However, since chlorinated solvents are generally unacceptable in commercial processes, we were pleased to discover that acetonitrile could be substituted for carbon tetrachloride using the reaction conditions described above. A literature search revealed that non-chlorinated solvents are rarely used for benzylic or allylic chlorination with NCS.[15] Acetonitrile turns out to be a superior solvent in this system, particularly with regard to reaction efficiency, safety, cost, and environmental issues.

Scheme 2



Intriguingly, the presence of water increased the chlorination rate, as did increasing the flux of incandescent light but with less effect. Assuming that water reacted with either NCS or chlorine originating from NCS to produce traces of acid,[16] which was hypothesized to be catalyzing the chlorination, we added 3 mol % of acetic acid. Gratifyingly, the optimum reaction time dropped from 8 to 2 h and the solution yields increased to ≥70%.[17] There were fewer side-products, and light was no longer necessary. The process was optimized further to lead to large scale production; however, the use of acetonitrile as solvent[18] and acid-catalyzed rate enhancement remained the key improvements.

The role of acid catalysis in this radical-initiated reaction (benzoyl peroxide is still required) is worth discussing. Two possible initial reactions would be protonation of either NCS or **3**. Pyridinium ion formation could lead via a formal prototropic rearrangement to equilibrium with the unstable tautomer **3*** which should be quickly chlorinated,[19] (Scheme 2). Similar mechanisms are proposed for other heterocycles with benzylic methyl groups.[20] Alternatively, the presence of traces of acid or water in solutions of NCS will result in the formation of hydrogen chloride and then molecular chlorine,[16,21] and such conditions are known to accelerate the benzylic chlorination of toluene.[21]

However, further experiments suggested the tautomer **3*** was not involved. Since **3** is very weakly basic, any pyridinium ion would be in extremely low concentration in the presence of acetic acid.[22] Indeed, no signal shifts occurred in the ^1H or ^{13}CNMR spectra of **3** upon the addition of either acetic acid-d_4 to acetonitrile-d_3 solutions or deuterium chloride/deuterium oxide to chloroform-d_3 solutions.[23] Furthermore, as cited before, since the chlo-

(11) The corresponding bromide was a similarly poor alkylating agent of anthrone; Earl, R. A. unpublished research.

(12) (a) For a review, see: Mathes, W.; Schuly, H. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 144−149. (b) Newkome, G. R.; Puckett, W. E.; Kiefer, G. E.; Gupta, V. K.; Xia, Y.; Coreil, M.; Hackney, M. A. *J. Org. Chem.* **1982**, *47*, 4116−4120, ref 8 therein.

(13) (a) By chlorine in water: Nishimura, Y.; Itou, Y.; Morino, A.; Nishihara, K.; Kawamura, S. Eur. Pat. Appl. 557 967 A1; *Chem. Abstr.* **1994**, *120*, 30680. (b) By chlorine in acetic acid/sodium acetate but forms the trichloride: Brown, B. R.; Hammick, D. L.; Thewlis, B. H. *J. Chem. Soc.* **1951**, 1145−1149. (c) by chlorine in acetonitrile: Gunther, A. US Pat. **1993** 5,198,549. *Chem. Abstr.* **1992**, *116*, 83696.

(14) Newkome, G. R.; Kiefer, G. E.; Xia, Y.-J. *Synthesis* **1984**, 676−679.

(15) Literature searches using the Beilstein and Chemical Abstracts online databases only located three examples of NCS benzylic/allylic chlorination in unchlorinated solvents (the first two references feature substrates wherein the chlorinated position possessed additional activation toward chloride): (a) Vaz, A. D. N.; Schoellmann, G. *J. Org. Chem.* **1984**, *49*, 1286−1288. (b) Vilsmaier, E.; Dörrenbächer, R.; Müller, L. *Tetrahedron* **1990**, *46*, 8103−8116. (c) Hebbelynck, M. F.; Martin, R. H. *Bull. Soc. Chem. Belg.* **1959**, *59*, 193−207.

(16) Adam, J.; Gosselain, P. A.; Goldfinger, P. *Nature* **1953**, *171*, 704−705.

(17) In contrast, ring halogenation by *N*-halosuccinimides by a broad range of acid catalysts is known: Bovonsombat, P.; McNelis, E. *Synthesis* **1993**, 237−241 and references within.

(18) Acetonitrile is also an infrequently cited but useful solvent for ring brominations by *N*-bromosuccinimide: (a) Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328−5331. (b) Oberhauser, T. *J. Org. Chem.* **1997**, *62*, 4504−4506.

(19) Hyperconjugative effects have been correlated with unexpected pK_a values of some picolines: Brown, H. C.; Mihm, X. R. *J. Am. Chem. Soc.* **1955**, *77*, 1723−1726.

(20) Such a mechanism would be analogous to that reported for the bromination of 2-(dibromomethyl)quinoline in acetic acid/sodium acetate: (a) Brown, B. R.; Hammick, D. L.; Thewlis, B. H.; Walbridge, D. J. *J. Chem. Soc.* **1953**, 1369−1372. (b) Smalley, R. K. In *Quinolines Part 1*; Jones, G., Ed.; J. Wiley and Sons: New York, 1977, pp 622−623. The condensation of 2-methylthiazole with benzaldehydes in acetic acid: (c) Van Arnum, S. D.; Ramig, K.; Stepsus, N. A.; Dong, Y.; Outten, R. A. *Tetrahedron Lett.* **1996**, *37*, 8659−8662.

(21) Adam, J.; Gosselain, P. A.; Goldfinger, P. *Bull. Soc. Chem. Belg.* **1956**, *65*, 523−532.

(22) Compared to 4-picoline, an ortho fluorine atom decreases the basicity of **3** by ~6 pK_a units to ~0.2.[35,36] The pK_a of acetic acid is only 4.8.[37]

(23) Chemical shifts have been recorded for other pyridines under such conditions as an indicator of protonation: Corey, E. J.; Zheng, G. Z. *Tetrahedron Lett.* **1998**, *39*, 6165−6154.

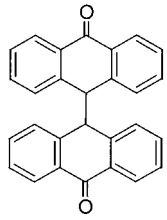
rination of toluene is accelerated by acid, the presence of a pyridine ring for the purposes of tautomerization is not required for acid induced rate increase. Our examination of the generality of this reaction toward other picolines led to similar conclusions regarding the choice of mechanism. All of the isomers of 2-fluoropicoline reacted at similar rates, including those that cannot achieve an intermediate analogous to **3***. The effect of acid seemed to be exclusive of the positional substitution of the substrate. In general, the acid induced effect on rate was remarkably similar for methyl-substituted ortho-halo picolines but was not noted for more basic picolines or quinolines. The selective nature of the effect of acid may be due to additional activation toward either chlorination or radical formation that the ortho-halo picolines may possess under these specific conditions, as compared to other nitrogen heterocycles that may be protonated under the reaction conditions. However, the principal role of the acid seems to be reaction with NCS, not **3**. Further discussion expanding the prototrophic rearrangement mechanism and the effect on other molecules is relegated to the Supporting Information along with additional chlorination data and experimental results.

Despite improved chlorination conditions, **4** was still produced as a mixture with **3** and **5**. The mixture was carried forward without further purification as only **4** reacts with the anion of anthrone after in situ conversion to the iodide with sodium iodide (alkylation as the chloride provided much lower yields of the product). However this reaction produced numerous impurities that were laborious to remove. An analogue of **4** of improved alkylating characteristics and greater stability (**4** decomposed upon storage) was required. This led to the evaluation of the mesylate **7**, readily prepared from the benzylic alcohol **6**.

Hydrolysis of the chlorination mixture of **3**, **4**, and **5** in aqueous potassium carbonate at reflux selectively and completely converted **4** into **6** in 1 h while **3** and **5** remained unaffected. Isolation was expedient: **6** remained in the aqueous solution, permitting complete separation of **3** and **5** as an oily layer. Extraction of the heptane-washed aqueous solution with ethyl acetate isolated **6** in 65−70% yield. Considering the highly impure chlorinated starting mixture and the simple workup, the product is remarkably pure (≥98% LC area). This method is a considerable improvement over the existing procedure for the preparation of **6**[24] and may provide a general method for the preparation of hydroxyalkylpyridines from alkylpyridines.

Reaction of **6** with methanesulfonyl chloride/triethylamine in ethyl acetate produced the mesylate **7** in 88−95% yield. This compound was cleanly and nearly quantitatively converted to the iodide **8** upon treatment with sodium iodide in acetone. Unlike the corresponding tosylate,[25] **7** was crystalline, easy to purify and stable. More importantly, as we found later, mesylate **7** improved the subsequent conversion to **1**.

Besides **7**, a variety of alkylating agent candidates for anthrone were available to us for the preparation of **1**, namely chloride **4**, iodide **8**, and the corresponding bromide and tosylate. Care in the selection of the reaction conditions was required since the dialkylation of anthrone is often accompanied by *O*-alkylation.[26] The initial samples of **1** destined for safety assessment studies were made from **4** and anthrone under phase transfer conditions.[26b,c,27] Unfortunately, these alkylations proceeded in variable yields and purities. An improved process consisted of prior treatment of the crude chlorination mixture (**3**/**4**/**5**) with sodium iodide in acetone.[10c] Only monochloride **4** reacted to form iodide **8**. Subsequent reaction of this halogenated mixture with the anion of anthrone prepared with sodium hydride in THF formed crude **1** on a several hundred gram scale (neither **3** or **5** reacted under these conditions). However, purification required tedious chromatography and repeated recrystallization to achieve >99% purity. The use of **8** for bisalkylation, prepared from **7** rather than **4**, led to a cleaner reaction profile and improved overall yield. Alternatively, the addition of catalytic or stoichiometric NaI to a mixture of anthrone anion and the chlorination mixture produced **8** in situ from **4**, but as was detected later, this also catalyzed the formation of impurities. All of these reactions formed a mixture of **1**, *O*,*C* -dialkylated, and mono *O*-alkylated side-products, as determined by mass, ^{13}C NMR, and ^{1}H NMR spectroscopies. However, particularly difficult to remove were the two largest impurities: 10,10′-bianthrone (**9**) and 1,2-di(2-fluoro-4-pyridyl)ethylene (**10**).



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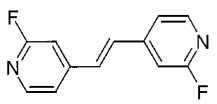

10

While bianthrone is a trace contaminant of commercial anthrone, we found that the presence of sodium iodide also promoted its formation, possibly via a radical coupling of the enolates induced by iodine oxidation.[28,29] The olefin **10** could arise from deprotonation of either **7** or **8**, followed by S_N2 alkylation onto another molecule of **7** or **8** and elimination of HX.[30] We found that **10** formed in 43% crystallized yield by the reaction of **7**, sodium iodide and potassium *tert*-butoxide in THF. These observations suggested we minimize the exposure of the alkylating agent to base and of anthrone anion to sodium iodide to suppress formation of sideproducts. Implementation of these conditions directly led to our optimized process.

(24) A less convenient preparation of **6** is the reduction of 2-fluoro isonicotinic acid: Atsuyuki, A.; Ono, T.; Uchida, T.; Ohtaki, Y.; Fukaya, C.; Watanabe, M.; Yokoyama, K. *Chem. Pharm. Bull.* **1990**, *38*, 2446−2458.

(25) Prepared in a manner similar to the mesylate **7** using tosyl chloride in 90% yield.

(26) (a) Branz, S. E.; Carr, J. A. *Synth. Commun.* **1986**, *16*, 441−451 and references therein. (b) Majumdar, K. C.; Chattopadhyay, S. K. *Synthesis* **1988**, 552−553 and references therein. (c) Majumdar, K. C.; Khan, A. T.; Chattopadhyay, S. K. *J. Chem. Soc., Perkins Trans.* **1990**, 2219−2223.

(27) Willner, I.; Halpern, M. *Synthesis* **1979**, 177.

(28) Anthrone will dimerize in the presence of oxidants: (a) Bradley, W.; Watkinson, J. *J. Chem. Soc.* **1956**, 319−323. (b) Arndt, F.; Schlatter, J. M. *Chem. Ber.* **1954**, *87*, 1336−1339.

(29) Iodine catalyzes the cross-coupling of enolates via a radical mechanism: Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969−5972.

(30) This finding is analogous to the reaction of 4-(chloromethyl)-pyridine with sodium hydride: Crispino, G. A.; Breslow, R. *J. Org. Chem.* **1992**, *57*, 1849−1855.

When a solution of anthrone with 3 equiv of lithium *tert*-butoxide[31] in THF was mixed with a solution of mesylate **7** plus 0.5 equiv of sodium iodide in THF, 87−92% solution yields of **1** were achieved after 1−2 h. Significantly, the formation of **9** and **10** were now largely suppressed (<1% LC area %), and a subsequent cyclohexane reslurry of the isolated solids removed nearly all of both contaminants. An aqueous workup produced **1** of ~90% purity which was further refined by treatments with absorbents and 2-propanol recrystallizations, without chromatography, to yield **1** of >99.9% purity.

A final hurdle arose from the various polymorphic forms of **1**.[32] Currently, 14 polymorphs have been characterized by X-ray diffraction powder pattern spectroscopy.[33] The appearance of a new, crystalline form during a late stage campaign was unexpected. Furthermore, we were no longer able to prepare the other crystalline forms, even though the appearance of this new high melting form occurred over 300 miles from our developmental laboratories! This is an example of the phenomenon of "disappearing polymorphs".[34] We have subsequently accepted this new crystal as our preferred formulation form as thermal analysis indicates it to be the most stable identified polymorph to date.[33] This process is producing bulk drug in support of our ongoing program needs.

In summary, we have described a practical preparation of the acetylcholine release enhancing agent **1**. Of particular note is an acid-catalyzed benzylic chlorination with NCS conducted in acetonitrile rather than the usual chlorinated solvents, the hydrolysis of the ensuing mixture of picolines which also results in an efficient purification, the use of a mesylate as a convenient and stable precursor to the iodide, and much improved yields/selectivities in the bis-alkylation of anthrone enolates by the consideration of reaction parameters. The overall process is concise and permits progression to commercial manufacture.

Experimental Section

General. ^{1}H NMR spectra were determined at 300 MHz, ^{13}C NMR at 75.4 MHz, and ^{19}F NMR at 282 MHz, all in $CDCl_3$, unless otherwise specified. ^{19}F NMR spectra were recorded using $CFCl_3$ as an internal reference. Mass spectra (MS) were obtained by ammonia chemical ionization. High-resolution mass spectral (HRMS) data possess an uncertainty of ±0.1 mDa. Elemental analyses were performed at Quantitative Technologies Inc., Whitehouse, NJ. Melting points are uncorrected. Solvent mixtures are defined by volume (v/v). All solvents except for tetrahydrofuran (anhydrous) were reagent grade and were not further purified. All reactions were carried out under a positive pressure of nitrogen unless otherwise specified. Reagents and solvents were used as received unless otherwise noted. Reagent and intermediate quantities and yields are all corrected for purity. If a weight % purity was not obtained, the area % purity was assumed to be equivalent for the purposes of calculations. 2-Fluoro-4-methylpyridine was purchased from Lancaster Chem. Co. HPLC conditions: Zorbax 4.6 mm × 15 cm RX C18 column at 1.00 mL/min at 40 °C and 260 nm. Solvent A: water. Solvent B: CH_3CN. Solvent program: A/B 60/40 at $t = 0$ min, 40/60 at $t = 10$ min, 15/85 at $t = 15$ min, 40/60 at $t = 18$ min, 60/40 at $t = 20$ min. Retention times (min): **1**, $t_R = 8.2$; **3**, $t_R = 3.5$; **4**, $t_R = 4.1$; **5**, $t_R = 6.1$; **6**, $t_R = 1.7$; **7**, $t_R = 2.6$; **8**, $t_R = 5.2$.

4-(Chloromethyl)-2-fluoropyridine (4). A mixture of **3** (50.0 g, 0.441 mol), acetonitrile (250 mL), *N*-chlorosuccinimide (88.4 g, 0.662 mol), benzoyl peroxide (2.15 g, 8.9 mmol), and acetic acid (1.50 mL, 26.2 mmol) were heated at reflux for 90 min. LC and ^{1}H NMR analysis indicated a 69% yield of **4**, 17% of **5**, and 12% of remaining unreacted **3** (the yield of **4** peaked at 71% after 80 min at reflux). The mixture was poured into water (200 mL) and extracted with EtOAc. The organic layer was separated, washed with 5% aqueous NaCl solution, and concentrated in vacuo at 35 °C to 62.2 g of red oil. This mixture was hydrolyzed as described in the next step without further purification.

An analytical sample was prepared by the chlorination of **7** as follows. A solution of **7** (3.00 g, 14.6 mmol), NaCl (9.00 g, 154 mmol), 2 N HCl (6.0 mL), water (15 mL), and acetone (150 mL) was heated at reflux for 3 h. The cooled mixture was diluted with water (200 mL) and EtOAc (100 mL). The organic phase was separated, washed with water, and dried over $MgSO_4$. The solution was concentrated in vacuo and distilled, and the fraction boiling at 70−72 °C (3.5 mmHg) was collected to yield 1.30 g (61%) of colorless oil. ^{1}H NMR: 8.22 (d, $J = 5.1$ Hz, 1H), 7.21 (d, $J = 5.1$ Hz, 1H), 6.99 (s, 1H), 4.57 (s, 2H). ^{13}C NMR: 164.0 (d, $J = 239.2$ Hz), 151.5 (d, $J = 8.1$ Hz), 148.0 (d, $J = 15.1$ Hz), 120.6 (d, $J = 4.5$ Hz), 108.8 (d, $J = 38.8$ Hz), 43.2 (d, $J = 3.5$ Hz). ^{19}F NMR: −67.8. MS: *m/e* 146 (M + 1). Anal. Calcd for C_6H_5ClFN: C, 49.51; H, 3.46; N, 9.62; F, 13.05. Found: C, 49.31; H, 3.56; N, 9.32; F, 12.84.

2-Fluoro-4-pyridinemethanol (6). Impure **4** (62.2 g, contains 0.31 mol), water (700 mL), and potassium carbonate (56.0 g, 0.41 mol) were heated as a stirred oily suspension for 2 h (LC indicated <1% **4** remained). The mixture was cooled, the layers were separated, and the lower, organic phase was further extracted with water. The combined aqueous extracts were washed with heptane and extracted with EtOAc. The extracts were dried over $MgSO_4$ and concentrated in vacuo to 24.8 g (62%) of white solids (98 LC area %). An analytical sample was prepared by recrystallization from 1:1 EtOAc/heptane (5 mL/g) to produce colorless needles, mp 59.3−60.4 °C. ^{1}H NMR: 8.07 (d, $J = 5.1$ Hz, 1H), 7.15 (d, $J = 5.1$ Hz, 1H), 6.98 (s, 1H), 4.77 (d, $J = 5.4$ Hz, 2H), 4.26 (br s, 1H). ^{13}C NMR: 164.0 (d, $J = 239.6$ Hz), 157.1 (d, $J = 7.6$ Hz), 146.9 (d, $J = 14.1$ Hz), 118.7 (d, $J = 4.0$ Hz), 106.5 (d, $J = 37.2$ Hz), 62.5 (d, $J = 3.0$ Hz). ^{19}F NMR: −68.8. MS: *m/e* 128 (M + 1). Anal. Calcd for C_6H_6FNO: C, 56.69; H, 4.76; F, 14.95; N, 11.01. Found: C, 56.66; H, 4.63; F, 14.74; N, 11.03.

2-Fluoro-4-pyridinemethanol, 4-Methylbenzenesulfonate (7). A solution of **6** (170.0 g, 1.311 mol), EtOAc (2.6 L), and triethylamine (270.0 mL, 1.937 mol) were cooled to 0−5 °C, and methanesulfonyl chloride (130.0 mL, 1.680 mol) was added over 100 min while the temperature was maintained at <20 °C. The reaction was aged for another 10 min (LC indicated the area % of **6** was <1%). The reaction was mixed with water (350 mL), and the phases were separated. The organic layer was washed with water and saturated brine. The solution was dried over Na_2SO_4, filtered, and concentrated in vacuo to approximately 900 mL. This solution was diluted with heptane (600 mL), cooled to 0−5 °C, and stirred for 2 h. The crystals were filtered and air-dried to 251.0 g (93%) of pale yellow crystals (>97 LC wt % purity). An analytical sample was prepared by recrystallization from 1:1 EtOAc/heptane (15 mL/g), mp = 58.3−59.1 °C. ^{1}H NMR: 8.27 (d, $J = 5.4$ Hz, 1H),

(31) Alternative bases examined included lithium diisopropylamide, *n*-butyllithium, lithium isopropoxide, lithium *tert*-butoxide, lithium methoxide, potassium *tert*-butoxide, and sodium hydride.

(32) For an excellent monograph of polymorphism and related crystalline species, see: Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Krieger Publishing Co.: Malabar, FL, 1994.

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7.20 (d, J = 5.1 Hz, 1H), 6.98 (s, 1H), 5.26 (s, 2H), 3.10 (s, 3H). ^{13}C NMR (DMSO-d_6): 163.2 (d, J = 235.2 Hz), 150.0 (d, J = 8.6 Hz), 148.0 (d, J = 15.6 Hz), 120.3 (d, J = 3.5 Hz), 107.7 (d, J = 38.2 Hz), 68.3 (d, J = 3.0 Hz), 37.0. ^{19}F NMR: −66.85. MS: *m*/*e* 206 (M + 1). Anal. Calcd for $C_7H_8FNO_3S$: C, 40.96; H, 3.93; F, 9.26; N, 6.82; S, 15.62. Found: C, 41.00; H, 3.81; F, 9.47; N, 6.70; S, 15.76.

10,10-Bis[(2-fluoro-4-pyridinyl)methyl]-9(10*H*)-anthracenone (1). Two solutions are prepared. For one, 1.0 M lithium *tert*-butoxide in THF (1.00 L, 1.00 mol) was added to a solution of anthrone (70.0 g, 0.357 mol) in THF (0.70 L) at 15−30 °C to form lithio anthrone. The second solution was prepared by mixing sodium iodide (45.0 g, 0.300 mol), **7** (150.0 g, 0.731 mol), and THF (1.60 L) at 40 °C for 3 h to form a mixture of **7**/**8**. The lithio anthrone solution was added dropwise over 100 min at 40−50 °C to the iodide/mesylate solution. The reaction was aged for 1 h (the LC peak area for **8** was <1%). The solution was washed with saturated aqueous brine. Volatiles were removed in vacuo, and the residue was diluted with toluene (1.3 L). The solution was heated to 100 °C, cooled to 90 °C, and stirred with basic alumina (120 g) for 30 min. The solution was filtered through a Celite pad, concentrated by atmospheric distillation to 500 mL, and cooled to 25 °C to crystallize **1**. Further crystallization was induced by the dropwise addition of *n*-heptane (0.60 L) followed by cooling to 0 °C for 2 h. The crystals were filtered, washed with *n*-heptane and dried at 60 °C in vacuo to yield 121 g of **1** (92 LC wt %, 75% yield from anthrone).

Further manipulations were performed to attain the polymorphic form and purity desired to support human clinical dosing. Two such preparations were combined (238.0 g), dissolved in refluxing 2-propanol (IPA) (3.80 L), cooled slightly below reflux, and filtered through a Celite pad. The solution was concentrated by atmospheric distillation to 1.90 L and cooled to 0 °C over 3 h. The crystals were collected by filtration, washed with cold IPA (0 °C), and dried as above to give 208 g of crystals. To remove anthrone, biathrone, and **15**, part of this (178.4 g) was slurried with refluxing cyclohexane (4.5 L) for 6 h, cooled to 75 °C, and filtered. The cake was washed with cyclohexane (0.25 L) at 70 °C and dried at 60 °C in vacuo to 167.1 g. Material from multiple runs (327 g) derived from a total of 1.261 mol of anthrone was dissolved in IPA (3.50 L) at 75 °C, treated with Darco G-60 (52 g), and stirred for 30 min. The suspension was filtered through a pad of Celite, and the filtrate was concentrated to 2.60 L by atmospheric distillation and cooled to 0 °C. The crystals were filtered, washed with cold IPA (0 °C), dried in vacuo at 50 °C, and ground in a mortar and pestle to 283.8 g (yield 55%), LC peak area = 99.94%, LC wt % assay >99.9%, mp 169 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.42 (dd, J = 0.9, 7.7 Hz, 2H), 7.95 (dd, J = 1.5, 7.7 Hz, 2H), 7.93 (ddd, J = 1.5, 7.7, 7.7 Hz, 2H), 7.65 (d, J = 5.2 Hz, 2H), 7.53 (ddd, J = 0.9, 7.7, 7.7 Hz, 1H), 6.11 (ddd, J = 1.4, 2.3, 5.2 Hz, 2H), 5.92 (dd, J = 1.3, 1.4 Hz, 2H), 3.95 (s, 4H). ^{13}C NMR (100.6 MHz, DMSO-d_6): 181.7, 162.3 (d, J = 235.0 Hz), 152.1 (d, J = 7.6 Hz), 146.4 (d, J = 16.0 Hz), 144.1, 134.0, 131.7, 128.5, 128.0, 126.5, 122.6, 109.7 (d, J = 37.4 Hz), 47.9, 47.5 (d, J = 2.3 Hz). ^{19}F NMR (376.1 MHz, DMSO-d_6): −70.56. HRMS (ESI): 413.1446 (calcd 413.1465 for $C_{26}H_{19}F_2N_2O$). IR (KBr): 3060, 2946, 1665, 1602, 1556, 1475, 1452, 1407, 1321, 1269, 1149, 931, 839, 776, 702, 645 cm^{-1}. Anal. Calcd for $C_{26}H_{18}F_2N_2O$: C, 75.72; H, 4.40; F, 9.21; N, 6.79. Found: C, 75.70; H, 4.34; F, 9.21; N, 6.78.

Acknowledgment. The authors thank Drs. Robert E. Waltermire and Philip Ma for useful discussions, Ken Lynam for analytical assay development, Dr. Gregory A. Nemeth and Mr. Thomas Scholz for spectral interpetations, Dr. Michael B. Maurin for collaboration on the polymorph situation, Drs. Robert Chorvat, Joerg Deerberg, and Rafael Shapiro for reviewing this manuscript, Profs. William Berkowitz and Henry Rapoport for helpful suggestions, and Barbara N. Fisher for technical assistance.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for **1**, **4**−**8**, **10**, and 3-(chloromethyl)-2-fluoropyridine, a list of the significant IR spectral peaks of **4** and **7**, the preparation, purification, and a list of the ^{1}H and ^{13}C NMR spectral peaks for **5, 8, 10**, and the chlorinated and hydroxylated isomers of **3**, the assignments of the ^{1}H and ^{13}C NMR spectral peaks of **1**, an expanded discussion of the chlorination mechanism, and tables of chlorination data figures derived from them. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9804339