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A Practical Synthesis of *m*-Prostaglandin E Synthase-1 Inhibitor MK-7285

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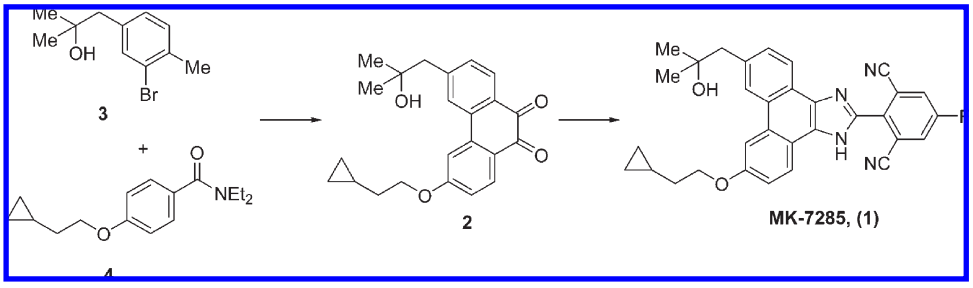

A practical, kilogram-scale chromatography-free synthesis of mPGE synthase I inhibitor MK-7285 is described. The route features a convergent assembly of the core phenanthrene unit via amide-directed *ortho*-metalation and proximity-induced anionic cyclization, followed by imidazole synthesis and late-stage cyanation.

Introduction

The modulation of prostaglandin metabolism is at the center of current anti-inflammatory therapies.[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors block the activity of cyclooxygenases and their ability to convert arachidonic acid into prostaglandin H_2 (PGH_2). PGH_2 can be subsequently metabolized by terminal prostaglandin synthases to the corresponding biologically active prostaglandins: prostacyclin (PGI_2), thromboxane TxA_2, PGD_2, $PGF_{2\alpha}$, and PGE_2. The transformation of PGH_2 to PGE_2 by prostaglandin E synthases (PGES) may represent a key step in the propagation of inflammatory stimuli. In particular, the microsomal enzyme prostaglandin E synthase-1 (mPGES-1) is inducible after exposure to pro-inflammatory stimuli.[2] Selective inhibitors of mPGES-1 are currently considered as potential anti-inflammatory therapeutics for the treatment of diseases such as osteoarthritis, rheumatoid arthritis, and acute or chronic pain.[3]

MK-7285, a structurally complex substituted phenanthrobis(cyano)phenylimidazole, is a potent and selective mPGES-1 inhibitor discovered at Merck Frosst (Figure 1).[4] As part of an ongoing drug development program in our laboratories, we required multikilogram amounts of MK-7285 (**1**). Herein we wish to report a practical synthesis of MK-7285 suitable for preparation of multikilogram amounts of the active pharmaceutical ingredient.

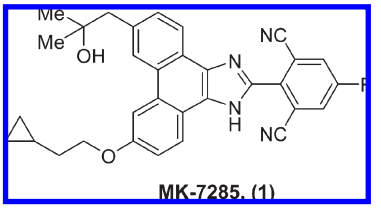

FIGURE 1. Structure of mPGES-1 inhibitor MK-7285.

Our synthetic strategy was based on disconnection of the phenanthroimidazole ring in **1** leading to phenanthrene dione **2** (Scheme 1). The substituted phenanthrene core would then be

(1) Funk, C. D. *Science* **2001**, *294*, 1871.
(2) (a) Jakobsson, P. J.; Thoren, S.; Morgenstern, R.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 7220. (b) Murakami, M.; Naraba, H.; Tanioka, T.; Semmyo, N.; Nakatani, Y.; Kojima, F.; Ikeda, T.; Fueki, M.; Ueno, A.; Oh, S.; Kudo, I. *J. Biol. Chem.* **2000**, *275*, 32783. (c) Murakami, M.; Kudo, I. *Prog. Lipid Res.* **2004**, *43*, 3.
(3) Kojima, F.; Kato, S.; Kawai, S. *Fund. Clin. Pharmacol.* **2005**, *19*, 255–261.
(4) (a) Giroux, A.; Boulet, L.; Brideau, C.; Chau, A.; Claveau, D.; Côté, B.; Ethier, D.; Frenette, R.; Gagnon, M.; Guay, J.; Guiral, S.; Mancini, J.; Martins, E.; Massé, F.; Méthot, N.; Riendeau, D.; Rubin, J.; Xu, D.; Yu, H.; Ducharme, Y.; Friesen, R. W. *Bioorg. Med. Chem. Lett.* **2009**, in press. (b) Côté, B.; Boulet, L.; Brideau, C.; Claveau, D.; Ethier, D.; Frenette, R.; Gagnon, M.; Giroux, A.; Guay, J.; Guiral, S.; Mancini, J.; Martins, E.; Massé, F.; Méthot, N.; Riendeau, D.; Rubin, J.; Xu, D.; Yu, H.; Ducharme, Y.; Friesen, R. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6816.

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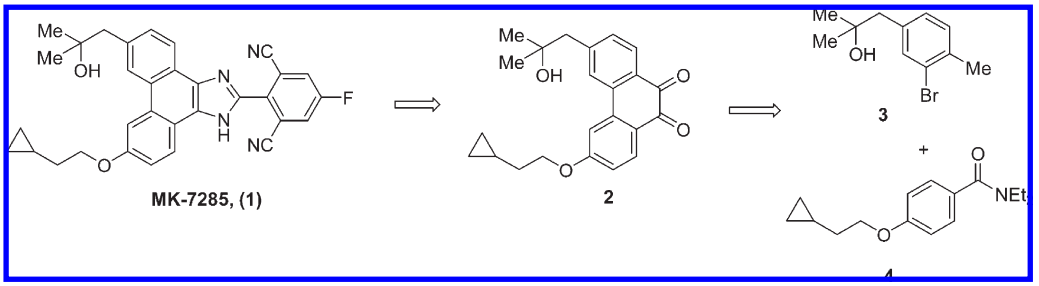
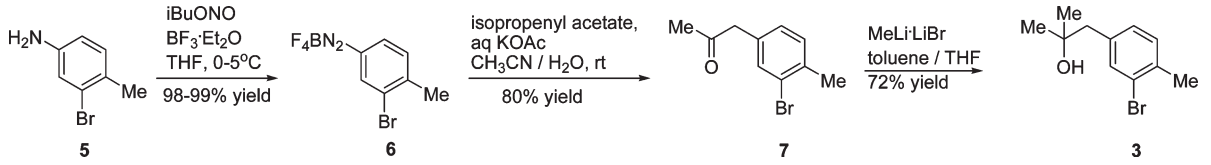
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Synthesis of Bromide 3

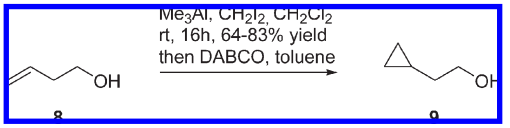


elaborated through a convergent assembly of bromide **3** and amide **4** via directed ortho-metalation (DoM)/in situ Suzuki cross-coupling,[5] followed by a proximity-induced anionic cyclization (i.e., directed remote metalation, DreM).[6]

Results and Discussion

The synthesis of bromide **3** began with diazotization of commercially available 3-bromo-4-methylaniline **5** with isobutyl nitrite in the presence of $BF_3 \cdot Et_2O$ to afford arenediazonium tetrafluoroborate salt **6** as a bench-stable solid in >98−99% isolated yield (Scheme 2).[7] We recently reported conditions for metal-free Meerwein arylation of olefins to provide α-aryl methyl ketones.[8] We applied these conditions toward preparation of ketone **7**. The Meerwein arylation was performed by slow addition of aqueous KOAc to a stirred slurry of arenediazonium tetrafluoroborate salt **6** in isopropenyl acetate/CH_3CN/H_2O at rt to afford the desired crude ketone **7** in 80% HPLC assay yield.[9] Slow addition of aqueous KOAc was required to control the rate of N_2 evolution from the reaction. Formation of the tertiary alcohol initially proved problematic due to competing ketone enolization and moderate conversion to **3**. Addition of MeLi·LiBr gave tertiary alcohol **3** in 72% assay yield at 85% conversion (15% ketone remaining). Other conditions (Me_3Al, MeMgCl, MeMgBr, MeLi, etc.) led to decreased conversion to the desired tertiary alcohol. In smaller scale experiments this reaction reproducibly afforded >95% conversion to the desired alcohol **3**. The difference in conversion was attributed to slightly higher internal temperature on a kilogram scale.

SCHEME 3. Synthesis of 2-Cyclopropylethanol 9



Synthesis of Amide Intermediate. The 2-cyclopropylethanol side chain **9** was prepared via cyclopropanation of 3-buten-1-ol **8** with Me_3Al and CH_2I_2 in dichloromethane (Scheme 3).[10] After an exothermic and methane-generating quench, careful concentration afforded the iodomethane-free desired alcohol that was fractionally distilled at atmospheric pressure to provide 2-cyclopropylethanol **9** in 64−83% yield. We found that residual CH_2I_2 led to competing alkylation of 2-cyclopropylethanol. Residual CH_2I_2 was destroyed by treatment of the crude alcohol with 1,4-diazabicyclo[2.2.2]octane (DABCO, 200 mol %) prior to performing the S_NAr step. Simple filtration of the resulting DABCO ammonium salt afforded a solution of 2-cyclopropylethanol **9** in toluene ready for the S_NAr step.

Treatment of 4-fluorobenzoyl chloride **10** with diethylamine under Schotten−Bauman conditions in the presence of aqueous K_2CO_3 as base cleanly afforded the corresponding amide **11** that was 99.4A% by HPLC (Scheme 4). While the reaction could be performed in other solvents such as MTBE, we opted for toluene in order to avoid a solvent-switch for the subsequent S_NAr reaction. The S_NAr reaction was performed in toluene, and potassium *tert*-pentoxide was used as base since it led to better conversions than *t*-BuOK (33%) and $KN(SiMe_3)_2$ (95%).[11] Thus, reaction of **11** with 120 mol % of 2-cyclopropylethanol **9** led to complete conversion after 16 h at 90 °C and afforded amide **4** in 94% yield.

Synthesis of Phenanthrene Dione Intermediate. We envisaged two complementary approaches for the formation of

(5) (a) de Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett*. **1978**, *19*, 5099. (b) Cheng, W.; Snieckus, V. *Tetrahedron Lett*. **1987**, *28*, 5097. (c) Reviewed in: Anctil, E. J.-G.; Snieckus, V. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: New York, 2004; Vol. 2, pp 761−813.

(6) (a) Wang, X.; Snieckus, V. *Tetrahedron Lett*. **1991**, *32*, 4879. (b) Wang, X.; Snieckus, V. *Tetrahedron Lett*. **1991**, *32*, 4883. (c) Cai, X.; Brown, S.; Hodson, P.; Snieckus, V. *Can. J. Chem*. **2004**, *82*, 195. (d) A related approach has been reported recently: Limanto, J.; Dorner, B. T.; Hartner, F. W.; Tan, L. *Org. Proc. Res. Dev*. **2008**, *12*, 1269.

(7) Doyle, M. P.; Bryker, W. J. *J. Org. Chem*. **1979**, *44*, 1572.

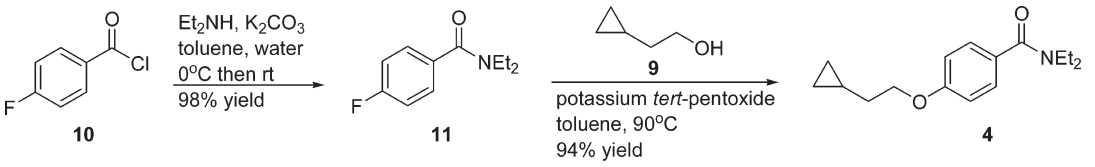
(8) Molinaro, C.; Mowat, J.; Gosselin, F.; O'Shea, P. D.; Marcoux, J.-F.; Angelaud, R.; Davies, I. W. *J. Org. Chem*. **2007**, *72*, 1856.

(9) Diazonium tetrafluoroborate salt **6** was deemed bench-stable as it exhibited an exotherm of 35.8 cal/g initiating at 100 °C and a smaller exotherm of 3.5 cal/g initiating at 175 °C as measured by differential scanning calorimetry.

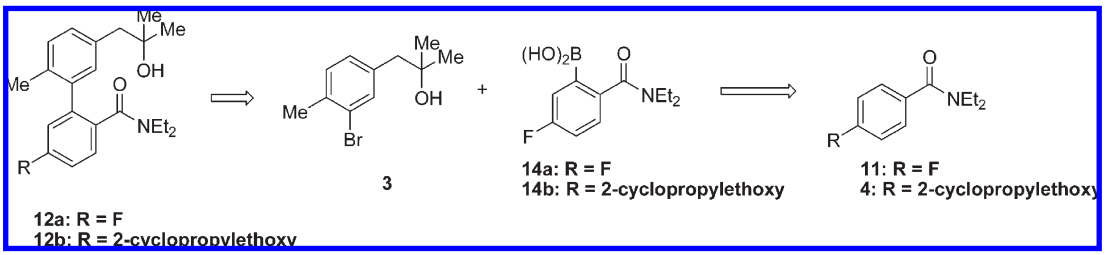
(10) (a) Maruoka, K.; Fukutani, Y.; Yamamoto, H. *J. Org. Chem*. **1985**, *50*, 4412. (b) Russo, J. M.; Price, W. A. *J. Org. Chem*. **1993**, *58*, 3589. (c) For a review, see: Charette, A. B.; Beauchemin, A. *Org. React*. **2001**, *58*, 1.

(11) (a) Kim, A.; Powers, J. D.; Toczko, J. F. *J. Org. Chem*. **2006**, *71*, 2170. (b) Rodriguez, J. R.; Agejas, J.; Bueno, A. B. *Tetrahedron Lett*. **2006**, *47*, 5661. (c) Woiwode, T. F.; Rose, C.; Wandless, T. J. *J. Org. Chem*. **1998**, *63*, 9594.

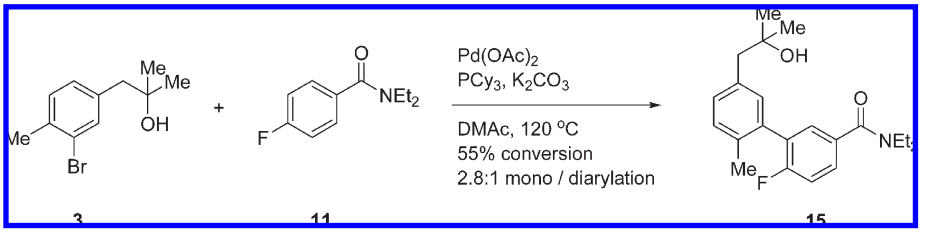
SCHEME 4. Synthesis of Amide 4



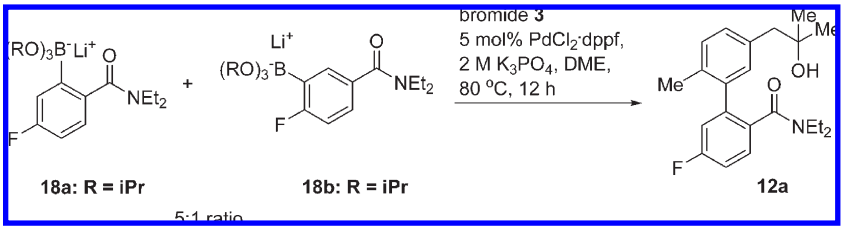
SCHEME 5. Arylation Approaches to Biaryl 12a/12b



SCHEME 6. Palladium-Catalyzed Direct Arylation Approach



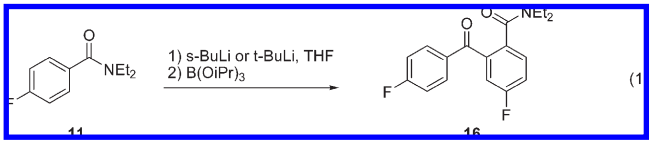
SCHEME 7. In Situ Cross-Coupling



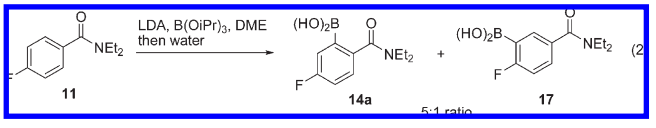
biaryl **12a**/**12b**. In a first approach, we envisioned a direct metal-catalyzed arylation between amide **11** and bromide **3** (Scheme 5).[12] In a second approach, we expected that appropriate functionalization of amides **4** or **11** could be accomplished through a directed ortho-metalation (DoM) and boronation sequence to afford boronic acids **14a**/**14b**. Subsequent cross-coupling with bromide **3** would lead to the desired biaryl intermediate **12a**/**12b**.

Direct arylation of 4-fluoroamide **11** with bromide **3** afforded promising conversion and selectivity of mono vs diarylation in Pd-catalyzed reactions (Scheme 6).[12c,d] However careful ^{1}H NMR spectroscopic analysis showed that arylation occurred at the *ortho* position to the 4-fluoro substituent to yield undesired biaryl **15**.

In light of these results, we next turned our attention to a DoM/cross-coupling route to the biaryl intermediate. Initial studies involving the stepwise DoM/boronation sequence on amide **11** using *s*-BuLi or *t*-BuLi as the base led only to the formation of benzophenone condensation product **16** (eq 1).



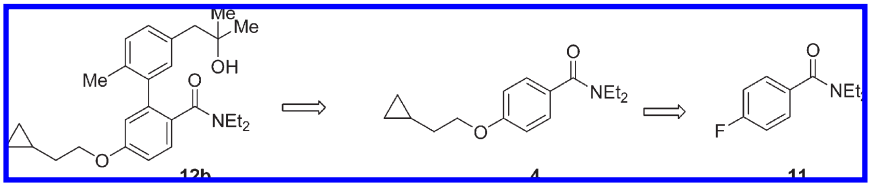
Boronation could be achieved by performing the DoM in presence of triisopropylborate, leading to a mixture of boronic acids **14a**/**17** with a maximum 5:1 ratio of *ortho*/*meta* regioisomers using LDA as the base in DME (eq 2). Unfortunately, after workup the mixture of boronic acids **14a**/**17** was water-soluble across the pH range and the isomers could not be easily separated by nonchromatographic means.



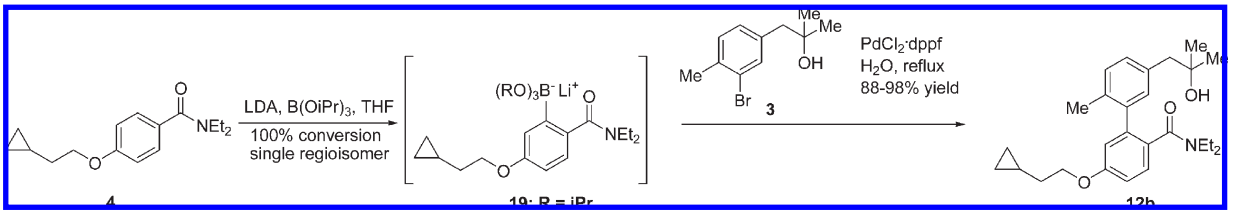
Nevertheless, we found that the corresponding mixture of lithium boronate esters **18a**/**18b** underwent in situ Suzuki

(12) (a) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (d) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097.

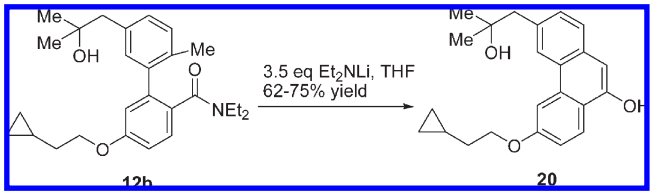
SCHEME 8. Potential Alternative Sequence of Steps to Biaryl 12b



SCHEME 9. Improved DoM/Cross-Coupling to Biaryl 12b



SCHEME 10. Intramolecular Anionic Cyclization to 20



cross-coupling with bromide **3** using 5 mol % $PdCl_2$·dppf as the catalyst with aqueous K_3PO_4 in DME to provide the desired biaryl **12a** along with the corresponding *meta*-regioisomer as a ~5:1 mixture of regioisomers (Scheme 7).

The undesired boronate regioisomer was hypothesized to arise from the influence of the electron-withdrawing fluorine atom on the aromatic ring in **11** which renders the protons *ortho* to the fluorine more acidic.[13] We considered that we could potentially override the *ortho* effect by simply changing the synthetic sequence of reactions and performing the S_NAr displacement first to form 4-(2-cyclopropylethoxy)-benzamide **4** (Scheme 8). The ether side chain should be a weaker *ortho*-director than the amide, thus resulting in increased regioselectivity of metalation/boronation.[14]

When we subjected amide **4** to the DoM/boronation conditions (LDA, $B(OiPr)_3$, DME or THF) only the desired lithium boronate regioisomer **19** was obtained (Scheme 9). Once again, the high solubility of the corresponding boronic acid (not shown) in water precluded its isolation. Gratifyingly, in situ Suzuki cross-coupling between bromide **3** and lithium boronate **19** using $PdCl_2$·dppf as catalyst afforded the desired biaryl **12b** in high yield. Optimization showed that additional base was not required and that simple addition of H_2O (2 mL/g) was sufficient. Furthermore, catalyst levels could be lowered from 5 to 1 mol % using purified bromide **3** without affecting conversion or yield. Unfortunately, the reaction stalled at 30−50% conversion when the cross-coupling was performed using crude bromide **3** even at >5 mol % catalyst loading. Treatment of crude **3** with Darco KB carbon (50 wt %) restored the performance of the cross-coupling, allowing the reaction to proceed to completion at catalyst loadings between 2.5 and 5 mol %. The DoM/boronation/in situ Suzuki cross-coupling protocol routinely produced biaryl **12b** in the range of 88−98% yield.

Several issues arose during the optimization of the intramolecular anionic cyclization of biaryl **12b** to phenanthren-9-ol **20** (Scheme 10). The outcome of the cyclization reaction was sensitive to substrate concentration. At concentrations above 10 mL/g (0.24 M), byproducts arising from intermolecular condensation of **12b** were observed as ascertained by LC−MS analysis of the crude reaction mixture (5−10A% HPLC). We found that treatment of crude biaryl **12b** with Darco KB carbon prior to cyclization was required in order to minimize both the charge of lithium diethylamide for cyclization of **12b** and the observed emulsification in the aqueous workup of phenanthren-9-ol **20**. We also found that extractive workup of crude **20** with aqueous LiOH followed by carbon treatment of the wet organic stream with 50 wt % Darco KB carbon were required to reject a number of unidentified impurities and to provide material of sufficient purity for the subsequent oxidation step. This protocol afforded phenanthren-9-ol **20** in yields ranging from 62 to 75% yield.

Oxidation of phenantren-9-ol **20** to diketone **2** was performed through a dibromination/hydrolysis sequence as described in Scheme 11.[15] Various brominating agents (HBr, Br_2, NBS) and reaction solvents were investigated for this transformation but only low to moderate conversions (40−78%) and/or decomposition were observed. Addition of *N*,*N*-diisopropylethylamine only led to minor improvement (83% conversion). Better conversion was observed with *tert*-butylamine as base, but competing formation of the *tert*-butyl hemiaminal of diketone **2** afforded lower isolated yields (61%) from chromatographed biaryl **12b**.[16] The reagent

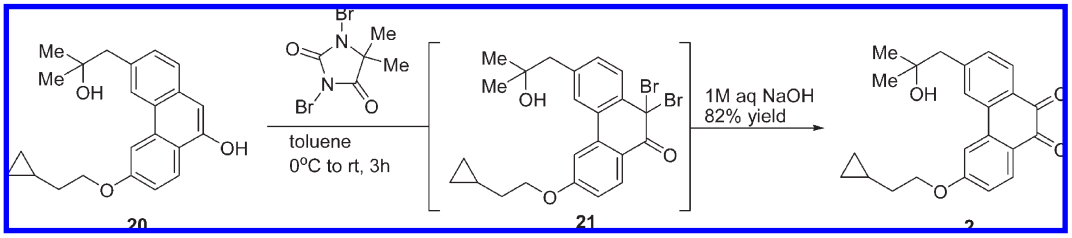
(13) (a) Streitweiser, A; Mares, F. *J. Am. Chem. Soc.* **1968**, *90*, 644. (b) Streitweiser, A.; Scannon, P. J.; Niemeyer, H. M. *J. Am. Chem. Soc.* **1975**, *97*, 7936. (c) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33*, 7495.

(14) (a) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. (b) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790.

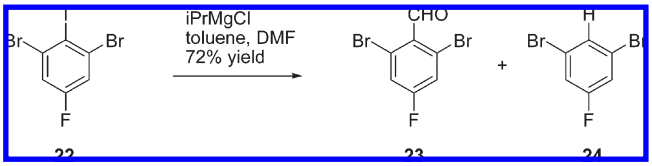
(15) (a) Nagano, T. *J. Org. Chem.* **1957**, *22*, 817. (b) Cushman, M.; Patel, H. H.; Scheuring, J.; Bacher, A. *J. Org. Chem.* **1992**, *57*, 5630.

(16) LCMS analysis of the reaction mixtures showed a peak with [M + H] 438 which corresponds to the hemiaminal. ^1H NMR spectroscopic analysis of crude reaction mixture in acetone-d_6 showed multiple signals in the aromatic region as well as large singlet at 1.45 ppm which account for the *t*-Bu group.

SCHEME 11. Synthesis of Diketone 2



SCHEME 12. Synthesis of Aldehyde 23



of choice for this reaction proved to be 1,3-dibromo-5,5-dimethylhydantoin because it did not require the addition of base and led to similar yields (60%) of diketone **2** without purification of biaryl **12b** and phenanthren-9-ol **20**.[17] The reaction could be performed in a variety of solvents (DME, DMF, iPAc, MeCN) but showed some sensitivity to oxygen since degassing the solution of **20** prior to the reaction increased the yield by 5%. Hydrolysis of dibromoketone **21** to the diketone **2** required treatment with 1 M aqueous NaOH and heating at 50 °C for 16 h to reach complete conversion. Milder bases and lower temperatures led to lower conversion. The yield of the oxidation of **20** to diketone **2** increased to 82% after implementing the extractive workup with LiOH and carbon treatment of **20**. The crude product (87.8A% HPLC) was recrystallized in iPAc/heptane to afford phenanthrene dione **2** as a brown solid in 84% yield.

Synthesis of Aldehyde Intermediate. 2,6-Dibromo-4-fluorobenzaldehyde **23** was obtained by halogen−metal exchange of 1,3-dibromo-5-fluoro-2-iodobenzene **22** with isopropylmagnesium chloride, followed by formylation of the resulting arylmagnesium chloride with DMF. In THF as solvent, competing reduction of **22** by *i*-PrMgCl afforded **23**/**24** ratios of 85:15. In comparison, switching to toluene as solvent improved the ratio of **23**/**24** to 95:5 (Scheme 12) and afforded aldehyde **23** in 72% yield after recrystallization from 2-propanol/water.

End-Game Chemistry. Condensation of phenanthrene diketone **2** with 2,6-dibromo-4-fluorobenzaldehyde **23** in the presence of ammonium acetate in AcOH for 1 h at 90 °C afforded dibromoimidazole **25** in 85% yield (Scheme 13). When crude aldehyde **23** was used, we observed late-running impurities (unidentified) in the HPLC chromatogram of crude imidazole **25**. Fortunately, we found that simple recrystallization of aldehyde **23** from 2-propanol/water eliminated these impurities.

Preliminary attempts at the cyanation of **25** using 250 mol % of CuCN in DMF at 90 °C for 16 h afforded >95% conversion to MK-7285 free base **26a** along with significant monocyanation and reduction products **26b**/**26c** (4−6A% and 2−6A%, respectively). Not surprisingly, rejection of these impurities proved to be extremely problematic at the API tosylate salt stage. The cyanation reaction conditions were then investigated further in order to avoid formation of **26b** and **26c**. Increasing the amount of CuCN to 400 mol % afforded higher conversion (>99%) but had no significant effect on the impurity profile as ascertained by HPLC. Slow addition of reagents was then investigated but showed no major improvement in terms of impurities generation. Various cyanide sources [including KCN, NaCN, $Zn(CN)_2$, and $K_4Fe(CN)_6$][18] as well as Pd-catalyzed cyanations[19] gave low or no conversion toward the desired bis(nitrile)imidazole **26a**. Solvent investigation showed that reduction product **26c** was not observed in DMAc at 120 °C. However the reaction suffered from lower conversion (≤95%) and significant hydrolysis of both nitriles to afford bis(amide)imidazole **26f** (5−10A%). We found that addition of imidazole (100 mol %) greatly increased the reaction rate in DMAc at 120 °C and led to higher conversions presumably due to stabilization of CuCN. A screen of nitrogen base additives showed that 1-methylimidazole (200 mol %) led to highest increases in both reaction rates and conversions (>99%) and minimized the formation of byproduct at 90 °C (Scheme 14).[20]

These conditions also allowed reduction of the CuCN charge to 250 mol % instead of the 400 mol % usually required to reach ≥99% conversion. The reaction showed 1.3A% residual **26b** after 18 h but then required an additional 6 h to reduce the level down to 0.3−0.8A%. Careful LC−MS analysis showed that the residual **26b** was in fact the chloro analogue **26d** that came from aldehyde **23**.[21] The level of **26d** was then conveniently controlled with extended reaction time without adverse effect on reaction yield or purity profile. Workup of the reaction required the use of 2-methyl-THF in order to avoid problematic tar formation.[22] The desired MK-7285 free base was obtained as a THF solution (3.02 kg, 99%

(17) (a) Alam, A. *Synlett* **2005**, 2403. (b) Chassaing, C.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett*. **1997**, *38*, 4415.

(18) (a) For a review, see: Ellis, G. P.; Romney-Alexander, T. *Chem. Rev*. **1987**, *87*, 779–794. (b) Merz, V.; Weith, W. *Ber*. **1877**, *10*, 746.

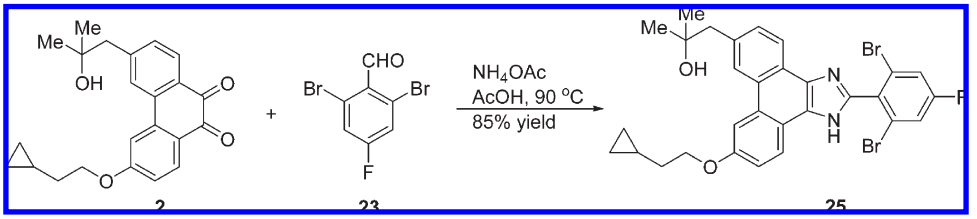
(19) For a review, see: (a) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem*. **2003**, 3513. For several examples, see: (b) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem*. **1998**, *63*, 8224. (c) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun*. **1994**, *24*, 887. (d) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem*. **2005**, *70*, 1508.

(20) (a) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Synlett* **2007**, 555. (b) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Chem.—Eur. J*. **2007**, *13*, 6249.

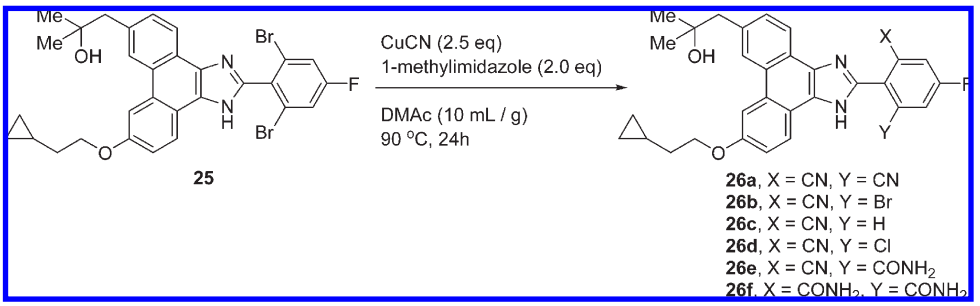
(21) We presume that the formation of the chloroaldehyde analogue occurs during the halogen−metal exchange reaction via benzyne formation. Careful GC−MS analysis of starting material **22** did not show any *chloro*-**22**. (a) Villieras, J. *Bull. Soc. Chim. Fr*. **1967**, *5*, 1520. (b) Villieras, J.; Kirschleger, B.; Tarhouni, R.; Rambaud, M. *Bull. Soc. Chim. Fr*. **1986**, 470. (c) Reviewed in: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed*. **2003**, *42*, 4302-4320. (d) Wang, X.-J.; Sun, X.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett*. **2006**, *8*, 305–307.

(22) Aycock, D. F. *Org. Proc. Res. Dev*. **2007**, *11*, 156.

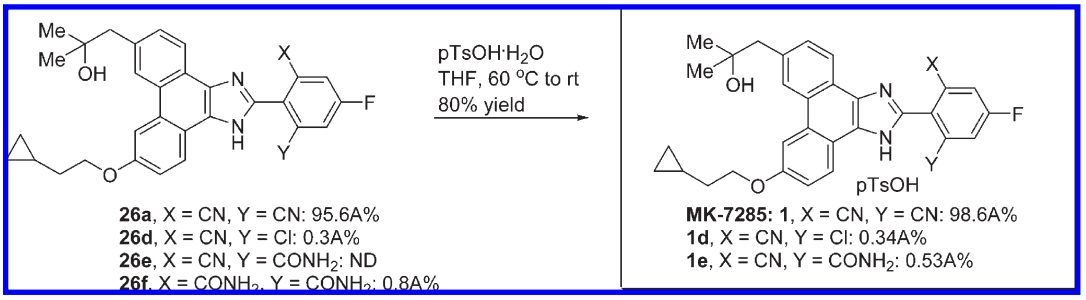
SCHEME 13. Synthesis of Imidazole 25



SCHEME 14. Cyanation of Imidazole 25



SCHEME 15. Formation of MK-7285 Tosylate



yield, HPLC: 95.6A%, 0.3A% **26d**, 0.8A% **26f**, ion chromatography: < 1.3 ppm residual cyanide).

MK-7285 tosylate was identified as a stable crystalline and bioavailable form. Tosylate salt formation was performed by heating a solution of MK-7285 crude free base **26a** in THF at 60 °C and adding a solution of *p*-TsOH·H_2O in THF over 30 min (Scheme 15). Residual THF levels in the API proved problematic (1.9 wt %). Heating the API (**1**) under high vacuum/dry N_2 sweep at temperatures up to 60 °C failed to reduce substantially the levels of residual THF (1.6 wt %). A reslurry of MK-7285 tosylate in heptane eliminated completely THF and left 0.07 wt % heptane. However, we found that simply drying the batch on the frit under low vacuum under atmospheric moisture reduced THF levels to 0.08 wt % in only 2−3 h at rt. The desired MK-7285 tosylate salt (**1**) was obtained as a bright yellow solid in 80% yield, HPLC: 98.6A% **1**, 0.34A%, **1d**, 0.53A% "mono-amide" **1e**, 2.2 wt % water, ICPMS analysis: residual Fe, Pd, Cu < 10 ppm.

Conclusion. In conclusion, we have reported a robust and practical chromatography-free synthesis of mPGES-1 inhibitor MK-7285 tosylate that is suitable for preparation of multikilogram amounts of API.

Experimental Section

5-(2-Cyclopropylethoxy)-5′-(2-hydroxy-2-methylpropyl)-2′-methylbiphenyl-2-carboxylic Acid Diethyl Amide (12b). A visually clean 50 L round-bottom flask equipped with an N_2 inlet, thermocouple, addition funnel, and mechanical stirrer was charged with diisopropylamine (3.64 L, 25.6 mol) and THF (13 L) and cooled to an internal temperature of −5 °C. *n*-Butyllithium (10.23 L, 25.6 mol, 2.5 M in hexane) was added over 1−2 h, keeping the internal temperature below 0 °C. The mixture was then stirred for 30 min at −5 °C. A visually clean 100 L round-bottom flask equipped with an N_2 inlet, thermocouple, addition funnel, and mechanical stirrer was charged with *N*,*N*-diethylbenzamide **4** (3.75 kg, 89.07 wt %, 12.78 mol), THF (25 L), and triisopropyl borate (5.94 L, 25.6 mol). The mixture was cooled to an internal temperature of −25 °C. The LDA solution formed in the 50 L reactor was added to the amide solution over 2 h, keeping the internal temperature below −20 °C. The batch was stirred for 2 h for complete consumption of amide. Water (8 L) was then added rapidly, and the reaction mixture was warmed to 20 °C. The mixture was degassed with N_2 for 10 min. A solution of aryl bromide **3** (7.4 kg, 30 wt % in toluene, 9.13 mol) was added, and the mixture was continued to be degassed for an additional 10 min. Solid $PdCl_2$·dppf (250 g, 0.342 mol) was added while the solution continued to be degassed for an additional 15 min. A reflux condenser was fitted, and the mixture was very slowly brought to an internal temperature of 65 °C over 1−2 h in order to control the rate of reflux, refluxing for a total of 12 h under N_2. The reaction mixture was then cooled to 30 °C and transferred to a visually clean 160 L extractor, and the reaction vessel was rinsed with 2 L of toluene. The remaining residue in the flask was rinsed with water (24 L) and added to the extractor. The layers were cut, and

the organic layer was washed for with 1 N NaOH (17 L). MTBE (17 L) was then added to the organic layer and washed with 1 N aqueous HCl (17 L), followed by H_2O (2 × 17 L). The resulting organic layer was then combined with a second batch of the same size. The combined organic layers were then treated with Darco KB (4 kg, 50 wt % based on combined total mass of product) for 1 h at rt. The batch was filtered on Solka-floc, and the filter cake was washed with MTBE (2 × 17 L) and toluene (2 × 17 L). The filtrate was line-filtered, concentrated, and flushed with toluene (2 × 17 L) and THF (2 × 17 L) to afford 7.69 kg of biaryl amide **12b** (7.69 kg, 40 wt % in THF, 98.7% assay yield): ^{1}H NMR (400 MHz, acetone-d_6) δ 7.23 (d, 1H, J = 8.4 Hz), 7.16−7.04 (m, 3H), 6.97 (dd, 1H, J = 8.4, 2.6 Hz), 6.78 (s, 1H), 4.11 (t, 2H, J = 6.6 Hz), 3.24 (s, 1H), 3.02 (bs, 4H), 2.68 (s, 2H), 2.17 (s, 3H), 1.68 (q, 2H, J = 6.6 Hz), 1.13 (s, 6H), 0.92−0.86 (m, 4H), 0.71 (t, 3H, J = 7.1 Hz), 0.49−0.39 (m, 2 H), 0.16−0.10 (m, 2H); ^{13}C NMR (101 MHz, acetone-d_6) δ 169.3, 158.7, 140.3, 139.0, 135.5, 131.7, 130.2, 129.7, 129.2, 127.6, 115.7, 113.0, 111.5, 69.9, 67.9, 49.3, 42.3, 37.6, 34.2, 19.3, 13.3, 11.7, 7.6, 3.8; HRMS calcd for $C_{27}H_{37}NO_3$ [M + H] 424.2846, found 424.2861. HPLC analysis: column: Zorbax XDB C18, 4.6 × 30 mm, 1.8 μm; eluent: 0.1% aqueous H_3PO_4/0.1% H_3PO_4 in CH_3CN (85:15 to 10:90 over 7 min, hold 1 min); flow: 1.5 mL/min; det: 220 nm; temp: 20 °C; inj: 5 μL, post-time: 2.00 min. Diethyl benzamide **4**: 4.66 min; aryl bromide **3**: 4.30 min; biaryl amide **12b**: 5.63 min.

Note on Biaryl 12b NMR Spectroscopic Analysis. NEt_2 signals are unusual. In $CDCl_3$, the ethyl groups are not equivalent and difficult to assign. In acetone-d_6, one CH_3 (0.71) is well resolved while the other CH_3 (0.92−0.86) is not, and the methylenes (3.02) are similarly unresolved. This complicates the already complex ^{13}C NMR analysis, where some tertiary and quaternary carbons in the aromatic system either do not show up or are low, broad signals.

6-(2-Cyclopropylethoxy)-3,3-(2-hydroxy-2-methylpropyl)phenanthren-9-ol (20). A visually clean 50 L round-bottom flask equipped with an N_2 inlet, thermocouple, 5 L addition funnel, and mechanical stirrer was charged with diethylamine (6.64 L, 63.5 mol) and THF (24 L) and cooled to an internal temperature of −5 °C. *n*-Butyllithium (25.4 L, 63.5 mol, 2.5 M in hexane) was added over 1−2 h keeping internal temperature below 0 °C. The mixture was stirred for 30 min at −5 °C. A visually clean 160 L extractor equipped with an N_2 inlet, thermocouple, addition funnel, and glycol cooling lines was charged with biaryl amide **12b** (7.69 kg, 40 wt % in THF, 18.15 mol, contained 13 L of THF) and diluted with THF (67 L) to give a total THF volume of 80 L. The lithium diethylamide solution formed in the 50 L reactor was added to the biaryl amide **12b** solution over 2 h, keeping the internal temperature below 0 °C. Half of the reaction mixture was then transferred into another visually clean 160 L extractor equipped with an N_2 inlet, thermocouple, and glycol cooling lines in order to ease stirring due to the large volume. The batch was very thick and became somewhat difficult to stir for 30−60 min. Both extractors were kept at −5 °C and stirred for 14 h for complete conversion of the biaryl amide. For each extractor: The reaction was quenched with 40 L of H_2O and diluted with 40 L of hexanes with mixing and warming to 20 °C. The layers were cut and the aqueous layers kept. The organic layer was then extracted with 1 N aqueous LiOH (5 × 20 L) for 15−20 min each. The combined aqueous layer was washed with hexanes (20 L) and then divided into two batches due to the large volume. For each batch: Toluene (10 L) was added to the aqueous layer with stirring, and the aqueous layer was acidified to pH 1−2 with 12 N HCl (~8 L). The layers were cut, and the aqueous layer was extracted with toluene (2 × 10 L). The combined toluene layers from both batches were washed with water (2 × 20 L). Darco KB (1 kg, 50 wt % based on mass of product) was added to the toluene solution and stirred for 1 h at rt. Solutions from both extractors were filtered over a single bed of Solka-floc, washing with 2 × 20 L of toluene. The filtrate was concentrated and flushed with toluene (2 × 20 L) to afford 4.03 kg of phenanthren-9-ol **20** (4.03 kg, 63.3% assay yield, 30 wt % in toluene). An analytical sample was isolated by chromatography on silica gel using hexanes/EtOAc (10:1) as eluent. Phenanthren-9-ol was isolated as an unstable 2:1 mixture of enol/keto form. Enol form: ^{1}H NMR (400 MHz, acetone-d_6) δ 9.08 (bs, 1H), 8.51 (s, 1H), 8.36−8.28 (m, 1H), 8.19 (d, 1H, J = 2.4), 7.57 (d, 1H, J = 8.1), 7.43 (dd, 1H, J = 8.1, 1.52), 7.28 (dd, 1H, J = 9.0, 2.4), 7.00 (s, 1H), 4.25 (t, 2H, J = 6.5), 2.99 (s, 2H), 1.77−1.69 (m, 2H), 1.26 (s, 6H), 0.98−0.90 (m, 1H), 0.56−0.42 (m, 3H), 0.21−0.12 (m, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 4.7, 8.5, 29.7, 35.1, 50.7, 68.7, 71.0, 103.7, 105.8, 107.5, 116.7, 121.6, 125.0, 125.1, 126.6, 130.7, 133.2, 134.0, 134.6, 151.5, 159.2. Keto form: ^{1}H NMR (400 MHz, acetone-d_6) δ 8.65 (s, 1H), 8.42 (d, 1H, J = 9.0), 8.09 (s, 1H), 7.35 (dd, 1H, J = 9.0, 2.3), 7.25 (d, 1H, J = 8.3), 7.12 (d, 1H, J = 8.3), 4.32 (t, 2H, J = 6.5), 3.50 (s, 2H), 2.97 (s, 2H), 1.81−1.75 (m, 2H), 1.25 (s, 3H), 0.98−0.90 (m, 1H), 0.56−0.42 (m, 2H), 0.21−0.12 (m, 2H); ^{13}C NMR (101 MHz, acetone-d_6) δ 4.7, 8.5, 29.7, 35.1, 50.5, 60.5, 68.9, 71.0, 105.9, 116.8, 121.7, 125.2, 125.3, 126.2, 126.8, 130.9, 133.1, 134.3, 134.8, 159.6, 170.9; HRMS calcd for $C_{23}H_{27}O_3$ [M + H] 351.1955, found 351.1952. HPLC analysis: Column: Zorbax XDB C18, 4.6 × 30 mm, 1.8 μm; eluent: 0.1% aqueous H_3PO_4/0.1% H_3PO_4 in CH_3CN (85:15 to 10:90 over 7 min, hold 1 min); flow: 1.5 mL/min; det: 220 nm; temp: 20 °C; inj: 5 μL, post-time: 2.00 min. Biaryl amide **12b**: 5.63 min; phenanthren-9-ol **20**: 5.14 min.

3-(2-Cyclopropylethoxy)-6-(2-hydroxy-2-methylpropyl)phenanthrene-9,10-dione (2). Crude phenanthren-9-ol **20** (27.73 kg at 13.5 wt %; 3.74 kg, 10.67 mol) that already contained 27.8 L of toluene was diluted with toluene (9.6 L). The solution was degassed for 30 min with subsurface nitrogen sparge, cooled to −5 °C, and protected from light. Solid 1,3-dibromo-5,5-dimethylhydantoin (4.58 kg, 16.01 mol) was added portionwise over 1 h, and the internal reaction temperature was maintained under 9 °C. The reaction mixture was warmed to rt over 30 min and kept at this temperature for 2.5 h. Aqueous NaOH (56 L, 1 M) was added, and the mixture was stirred vigorously at 50 °C for 16 h. The reaction mixture was cooled to rt, and the layers were cut. The aqueous layer was back-extracted with toluene (18.7 L), and the combined organic layers were washed with 1 M aqueous NaOH (2 × 37.4 L) and 1% aqueous NaCl (2 × 37.4 L). HPLC assay of the toluene solution indicated 53.41 kg, 5.95 wt % in toluene for a total mass 3.18 kg of diketone **2** (81.7% yield). The organic layer was concentrated and flushed with toluene (20 L) and then with iPAc (2 × 40 L). The slurry was warmed to 80 °C until a homogeneous solution was obtained. ^{1}H NMR analysis of the solution showed a 1:25.1:0.15 mol ratio of diketone/iPAc/toluene (87 wt % iPAc; 0.5 wt % toluene). The diketone solution already contained 22.3 kg (25.6 L) of iPAc. Fresh iPAc (4.6 L) was added, and the solution was heated to 80 °C. The solution was cooled to rt over 2 h, and heptane (90.6 L) was added over 1 h. The resulting slurry was stirred at rt for 16 h and then filtered. The filter cake was washed with iPAc/heptane (1:3, 2 × 31.8 L, 1 × 10 L). The batch was dried under low vacuum on the frit for 64 h. Diketone **2** was obtained as a brown solid (3.5 kg, 76.7 wt % for a total mass 2.68 kg, 84% yield, 69% yield over oxidation/recrystallization): mp = 127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (1 H, d, J = 8.7 Hz), 8.09 (1 H, d, J = 7.9 Hz), 7.80 (1 H, s), 7.43 (1 H, d, J = 2.3 Hz), 7.32 (1 H, d, J = 8.0 Hz), 6.91 (1 H, dd, J = 8.7, 2.3 Hz), 4.19 (2 H, t, J = 6.6 Hz), 2.90 (2 H, s), 1.75 (2 H, q, J = 6.7 Hz), 1.32 (6 H, s), 0.94−0.85 (1 H, m), 0.56−0.51 (2 H, m), 0.19−0.14 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 178.6, 165.5, 146.9, 138.0, 135.1, 133.6, 131.9, 130.0, 129.8, 125.9, 124.7, 114.5, 110.5, 70.9, 68.8, 50.0, 34.2, 29.6, 7.7, 4.4; IR (cm^{-1}, NaCl thin film): 3583,

3475, 3077, 3001, 2970, 2875, 1672, 1659, 1592, 1311, 1240, 1223; HRMS calcd for $C_{23}H_{25}O_4$ [M + H] 365.1753; found 365.1750. Conversion and wt % were determined by HPLC with a 4.6 mm × 25 cm ACE C18 column (0.1% aq H_3PO_4/CH_3CN 70:30 to 40:60 over 10 min, to 35:65 over 5 min, to 5:95 over 10 min, hold 5 min, 1.5 mL/min, 220 nm, 35 °C); diketone **2**, t_R = 14.17 min.

1-[9-(2-Cyclopropylethoxy)-2-(2,6-dibromo-4-fluorophenyl)-1*H*-phenanthro[9,10-*d*]imidazol-9-yl]-2-methylpropan-2-ol (25). A visually clean 160 L extractor equipped with a dropping funnel and a N_2 inlet was charged with glacial acetic acid (13.2 L). Solid diketone **2** (2.63 kg, 7.22 mol), solid aldehyde **23** (2.02 kg, 7.17 mol), and NH_4OAc (5.56 kg, 72.2 mol, 1000 mol %) were added. The resulting suspension was heated to an internal temperature 93.6−96.0 °C for 1 h. HPLC showed 98.0% conversion to imidazole **25**. The reaction mixture was cooled to 40 °C, diluted with iPAc (26.4 L), and washed with H_2O (26.4 L); the aqueous layer was pH 4. The extractor was charged with H_2O (26.4 L) and 1 N aqueous NaOH (20.0 L), and the layers were cut. The organic layer was washed with 1 N aqueous NaOH (20 L); the aqueous layer was pH 9.5. The layers were cut, and the organic layer was treated with Darco G-60 (5.26 kg, 200 wt %). The suspension was stirred at 23.4 °C for 1 h, and the solids were filtered through Solka-floc and rinsed with iPAc (2 × 13.2 L). The solution was concentrated, and the solids were dried under vacuum at 30 °C overnight. Imidazole **25** was obtained as light brown solid: 3.85 kg, 85.3% assay yield, 94.0 A% HPLC; an analytical sample was prepared by chromatography on silica gel using EtOAc/hexane (1:1) as eluent: mp = 225.5−226.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.85 (br s, 1 H), 8.64 (br s, 1H), 8.46 (s, 1 H), 8.16 (s, 1 H), 8.04 (br s, 1 H), 7.42−7.29 (br m, 3 H), 7.23−7.02 (br m, 1 H), 4.23 (t, 2H, J = 6.67 Hz), 3.00 (s, 1 H), 1.78 (q, 2H, J = 6.78 Hz), 1.29 (s, 6 H), 1.01−0.88 (m, 1 H), 0.58−0.52 (m, 2 H), 0.19 (q, 2H, J = 5.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.1 (d, J = 257.6 Hz), 157.1, 145.9, 134.4, 130.4 (d, J = 14.3 Hz), 129.9 (br), 129.4 (br), 128.0, 125.8 (d, J = 10.3 Hz), 125.0, 124.1, 122.5, 119.6 (d, J = 14.8 Hz), 116.1, 107.2, 71.0, 68.4, 50.0, 34.5, 29.1, 7.8, 4.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ −107.0 (reference −62.7); IR (cm^{-1}, $CHCl_3$) 2969, 1592, 1561, 1451, 1423, 1230, 908, 732; HRMS calcd for $C_{30}H_{28}Br_2FN_2O_2$ [M + H] 625.0502, found 625.0504. Conversion and yield were determined by HPLC with a 4.6 × 250 mm Zorbax RX-C8 column (0.1% aqueous H_3PO_4/CH_3CN 70:30 to 5:95 over 25 min, hold 5 min, 2 mL/min, 220 nm, 35 °C); t_R = 12.2 min.

2-[9-(2-Cyclopropylethoxy)-6-(2-hydroxy-2-methylpropyl)-1*H*-phenanthro[9,10-*d*]imidazo-2-yl]-5-fluoroisophthalonitrile (26a). Crude dibromoimidazole **25** (3.673 kg, 5.86 mol) was flushed with DMAc (5.5 L) to remove any residual iPAc and was diluted in DMAc (29.2 L). 1-Methylimidazole (934.8 mL, 11.73 mol, 200 mol %) and CuCN (1.313 kg, 14.66 mol, 250 mol %) were added. DMAc (2 L) was added, and the reaction mixture was degassed using a subsurface nitrogen sparge for 20 min and then heated to 90 °C for 24 h. The batch was cooled to rt and transferred into an cylindrical extractor containing 2-methyltetrahydrofuran (36.7 L). Aqueous NH_4Cl/NH_4OH buffer [saturated aqueous NH_4Cl/30% aqueous NH_4OH/water (4:1:3), 36.7 L] was then added, the mixture was stirred vigorously for 10 min, the layers were cut, and the aqueous layer was back-extracted with iPAc (36.7 L). The combined organic layers were washed with NH_4Cl/NH_4OH buffer (3 × 36.7 L) with 10 min of vigorous stirring for each wash. The organic layer was then washed with water (36.7 L), concentrated, and flushed with iPAc (22 L) and then with THF (2 × 36.7 L). HPLC assay of the concentrated solution indicated 14.05 kg, 21.5 wt % in THF for a total mass 3.02 kg of MK-7285 free base **26a** (99% yield). ^{1}H NMR analysis showed a 1:20.75:0.545 mol ratio of MK-7285/THF/iPAc (9.7 wt % iPAc vs MK-7285). The MK-7285 solution already contained 9.815 L of THF. An analytical sample was obtained by salt-break of MK-7285 tosylate in iPAc and saturated aqueous $NaHCO_3$: mp = 178−180 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.21−13.84 (1 H, br), 8.65 (1 H, s), 8.56 (1 H, d, J = 8.2 Hz), 8.56 (1H, d, J = 8.2 Hz), 8.44−8.27 (2 H, br), 8.25 (1 H, s), 7.63 (1 H, d, J = 8.2 Hz), 7.42 (1 H, d, J = 8.7 Hz), 4.29 (2 H, t, J = 6.5 Hz), 2.97 (2 H, s), 1.74 (2 H, q, J = 6.6 Hz), 1.15 (6 H, s), 0.97−0.90 (1 H, m), 0.52−0.46 (2 H, m), 0.21−0.17 (2 H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.1 (d, J = 255.1 Hz), 157.1, 140.8, 136.6 (br), 134.3, 134.3, 130.3, 129.7 (br), 127.2, 126.0, 125.8, 125.7, 123.5, 121.0, 116.6, 115.6, 115.5, 115.4, 115.3, 107.2, 69.6, 68.0, 49.5, 33.8, 29.4, 7.8, 4.3; ^{19}F NMR (375 MHz, $CDCl_3$) δ − 108.9; IR (cm^{-1}, NaCl thin film) 3498, 3431, 3075, 2964, 2865, 2222, 1629, 1592, 1506, 1453, 1300, 1216; HRMS calcd for $C_{32}H_{27}FN_4O_2$ [M] 518.2196, found 518.2193. Conversion and yield were determined by HPLC with a 4.6 mm × 15 cm Waters Symmetry C18 column (pH 6.8 phosphate buffer/CH_3CN 47:53 hold 18 min, to 35:65 over 2 min, to 10:90 over 0.1 min, hold 2 min, to 47:53 over 0.1 min, hold 4 min, 1 mL/min, 220 nm, 35 °C); MK-7285 t_R = 10.21 min.

2-[9-(2-Cyclopropylethoxy)-6-(2-hydroxy-2-methylpropyl)-1*H*-phenanthro[9,10-*d*]imidazo-2-yl]-5-fluoroisophthalonitrile 4-Methylbenzenesulfonate (MK-7285 Tosylate, 1). A visually clean 50 L round-bottom flask equipped with a mechanical stirrer, a dropping funnel, a reflux condenser, and a N_2 inlet was charged with line-filtered MK-7285 crude free base **26a** (3.0 kg, 5.785 mol, 95.6A% HPLC, 21.5 wt % in THF, KF 364 ppm, 9.7 wt % residual iPAc, 0.3A% HPLC **26d**, 0.8A% HPLC t_R = 4.8 min **26f**). The flask was rinsed with line-filtered THF (2 × 625 mL). The dark brown solution was heated to 60 °C. A solution of line-filtered *p*-TsOH·H_2O (1.10 kg, 5.785 mol) in THF (7 L) was added over 30 min, and the batch was aged at 60 °C for 30 min. Crystallization began at 10−15 min to afford a light slurry. The batch was allowed to cool to rt and stirred at rt for 2−3 h. The slurry was filtered, and the filter cake was washed with line-filtered THF (2 × 10 L). The solids were dried on the filter pot overnight at rt and then under vacuum/N_2 sweep at 30 °C over the weekend and then dried on the frit for 5 h. MK-7285 tosylate **1** was obtained as a bright yellow solid: 3.2 kg, 80% yield, 98.6A% HPLC, 0.34A% HPLC **1d**, 0.53A% HPLC **1e**; HPLC analysis **1e** t_R = 5.26; **MK-7285** t_R = 12.27; **1d** t_R = 16.02; mp 174−176 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.70 (s, 1H), 8.59 (d, 2H, J = 8.5), 8.39 (d, 1H, J = 26.0), 8.38 (d, 1H, J = 25.0), 8.29 (d, 1H, J = 2.0), 7.68 (d, 1H, J = 8.0), 7.50 (d, 2H, J = 8.0), 7.47 (dd, 1H, J = 2.0, 9.0), 7.14 (d, 2H, J = 8.0), 4.31 (dd, 2H, J = 6.0, 6.5), 3.00 (s, 2H), 2.30 (s, 3H), 1.75 (dd, 2H, J = 6.5, 13.0), 1.17 (s, 6H), 0.96 (bm, 1H), 0.49 (m, 2H), 0.20 (dd, 2H, J = 5.0, 9.5); ^{13}C NMR (DMSO-d_6) δ 162.7, 160.7, 157.7, 144.8, 140.0, 138.3, 137.5, 132.3, 131.1, 130.7, 130.3, 130.2, 128.3, 127.5, 126.0 (J = 25.0), 125.9, 125.5, 123.7, 121.8, 121.2, 117.3, 116.9, 115.9 (J = 10.6), 115.3, 107.4, 69.6, 68.1, 49.5, 33.9, 29.4, 20.8, 7.9, 4.3; ^{19}F NMR (DMSO-d_6) δ −106.9; HRMS calcd for $C_{32}H_{28}FN_4O_2$ [M + H] 519.2191, found 519.2196.

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Supporting Information Available: Experimental procedures for compounds **3**, **4**, **6**, **7**, **11**, and **23**. Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of compounds **1**−**4**, **6**, **7**, **11**, **12b**, **20**, **23**, **25**, and **26a**. This material is available free of charge via the Internet at http://pubs.acs.org.