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A Rapid, Large-Scale Synthesis of a Potent Cholecystokinin (CCK) 1R Receptor Agonist

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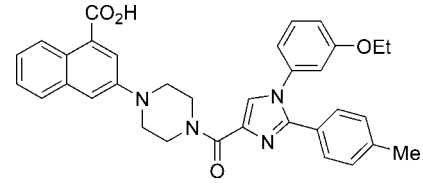
Abstract:

The development of a scalable synthesis of a potent cholecystokinin (CCK) 1R receptor agonist is described. The focus on a rapid short-term delivery rather than longer-term development allowed for the preparation of multihundred gram quantities to support aggressive timelines and evaluate safety and pharmacological studies. Key improvements involved streamlining the preparation of imidazole acid 7 and discovery of a more efficient preparation of naphthyl piperazine fragment 23, including an improved preparation of 3-bromonaphthallic anhydride 16.

Introduction

Cholecystokinin (CCK) is a gastrointestinal hormone and neurotransmitter that induces satiety by direct stimulation of vagal afferents that signal to feeding centers in the brain. There are two G-protein-coupled seven transmembrane receptors associated with the physiological actions of CCK: CCK1R and CCK2R (also known as CCKA and CCKB receptors, respectively). CCK1R is predominately located in the periphery and is believed to be the primary mediator of satiety, while CCK2R is mostly expressed in the brain. Shown to inhibit food intake in many species including humans,[1] CCK1R agonists have been studied as satiety agents for the treatment of obesity.[2] Recently, Merck & Co., Inc. identified a number of potent and selective CCK1R agonists for the potential treatment of obesity, and compound **1** was selected for preclinical development to fully define safety and pharmacological properties.[3] In recent years, the increased pace of drug discovery has led to a corresponding increase in the pace of preclinical development. Key to the successful initiation of preclinical programs with well-defined and accelerated timelines is the ability of process chemists to deliver required amounts of development candidates in a timely manner. In the fast-paced environment of drug development, the development of a long-term manufacturing route is typically not required in the initial stages of a program, and rapid first deliveries of API that support safety assessment and pharmacological studies may rely upon modifications to the existing route. Modifications that address liabilities such as low-yielding transformations, the use of potentially dangerous reagents and reaction conditions, and elimination of chromatography are examined and then implemented. The rapid development of a scalable synthesis of **1** aptly illustrates this approach.



1

The original synthesis of **1** employed by the Medicinal chemistry group involved 13 chemical steps (longest linear sequence 10 steps) and required 6 chromatographic purifications including reverse phase chromatography of **1** (Schemes 1−3).[3] Fortunately, the synthesis was convergent and **1** was obtained from two key intermediates: imidazole acid **7** (Scheme 1) and naphthyl piperazine **13** (Scheme 2). The preparation of **7** began with the condensation of **2** with **3** in the presence of NaHMDS to give benzamidine **4**. Direct reaction of **4** with ethyl bromopyruvate **5** in refluxing 1,4-dioxane afforded imidazole ester **6**, which was purified by chromatography. Saponification of the ester then gave imidazole acid **7** in 50% overall yield. The synthesis of **13** started with 3-nitro-1,8-naphthoic anhydride **8** and involved the use of stoichiometric HgO to provide 3-nitronaphthoic acid **9** in 59% yield (Scheme 2). Conversion of **9** to the corresponding ester (95%) was followed by reduction of the nitro group to give naphthyl amine **10** (95%) as an unstable intermediate. Treatment of **10** with sodium nitrite in 48% HBr and subsequent heating to 95 °C in the presence of CuBr under standard Sandmeyer reaction conditions furnished bromide **11** in 70% yield. Cross-coupling of **11** with *N*-Boc-piperazine **12** under standard Buchwald cross-coupling conditions[4] and deprotection of the product with TFA gave **13** in 50% yield. The overall yield of **13** was 19% from commercially available **8**.

The preparation of **1** from intermediates **7** and **13** in the initial route involved activation of **7** with MsCl in the presence of 1-methyl-imidazole followed by reaction with **12** to give **14**, which was purified by silica gel chromatography.[5] Saponification of the methyl ester with LiOH provided **1** in 70% yield after purification by reverse phase chromatography. The initial

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(1) For leading references, see: (a) Little, T. J.; Horowitz, M.; Feinle-Bisset, C. *Obes. Rev.* **2005**, *6*, 297. (b) Moran, T. H.; Kinzig, K. P. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2004**, *286*, G183. (c) Chandra, R.; Little, T. J. *Curr. Opin. Endocrinol. Diabetes Obes.* **2007**, *14*, 63. (d) Dufresne, M.; Seva, C.; Fourmy, D. *Physiol. Rev.* **2006**, *86*, 805.

(2) For leading references, see:(a) Szewczyk, J. R.; Laudeman, C. *Curr. Top. Med. Chem.* **2003**, *3*, 837. (b) García-López, M. T.; González-Muñiz, R.; Martín-Martínez, M.; Herranz, R. *Curr. Top. Med. Chem.* **2007**, *7*, 1180.

(3) Berger, R.; Zhu, C.; Hansen, A. R.; Harper, B.; Chen, Z.; Holt, T. G.; Hubert, J. A.; Lee, S. J.; Pan, J.; Qian, S.; Reitman, M. L.; Strack, A. M.; Weingarth, D. T.; Wolff, M. S.; MacNeil, D. J.; Weber, A. W.; Edmondson, S. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4833.

(4) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

(5) Ueki, H.; Ellis, T. K.; Martin, C. H.; Boettiger, T. U.; Bolene, S. B.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7104.

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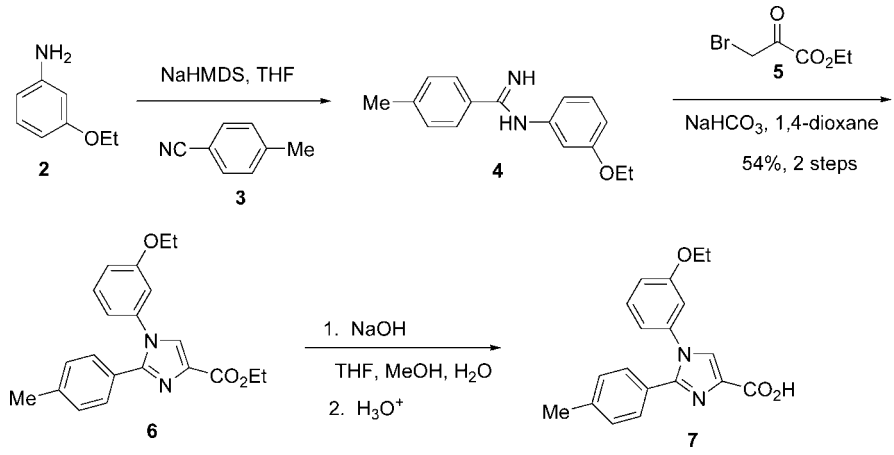
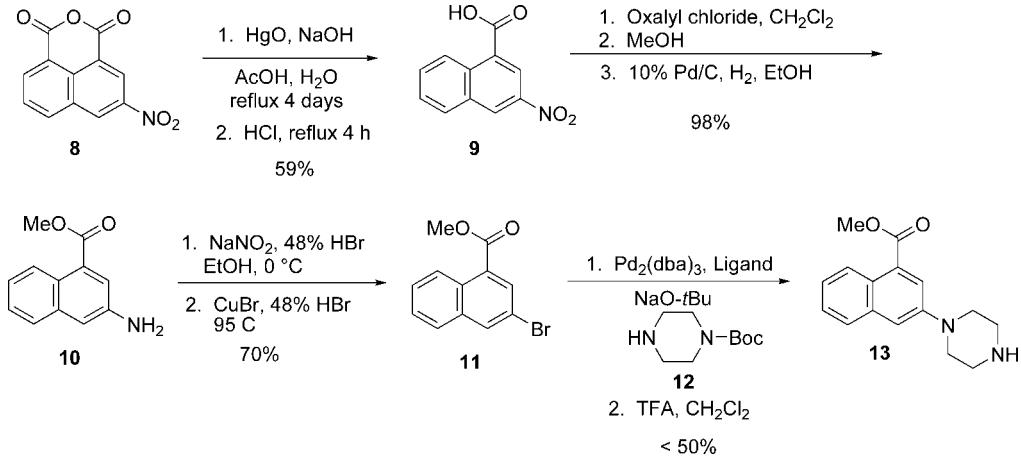
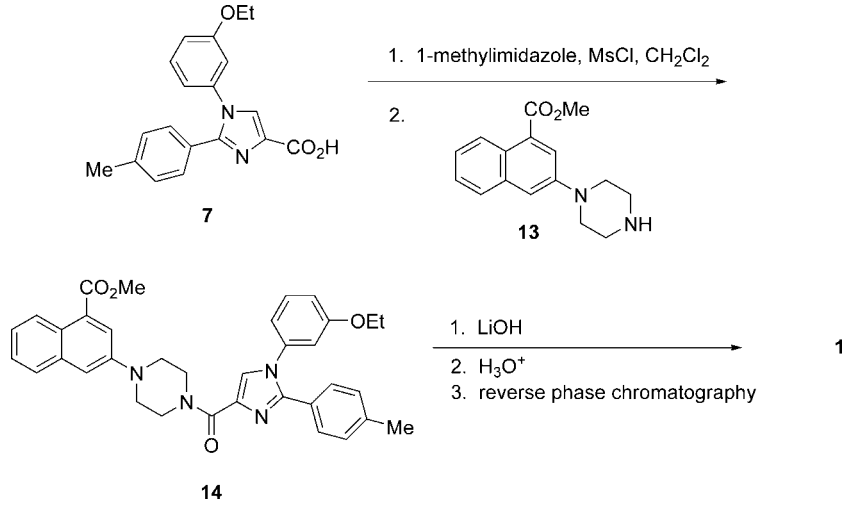
Scheme 1. **Initial synthesis of imidazole acid 7**



Scheme 2. **Initial synthesis of naphthyl piperazine 13**

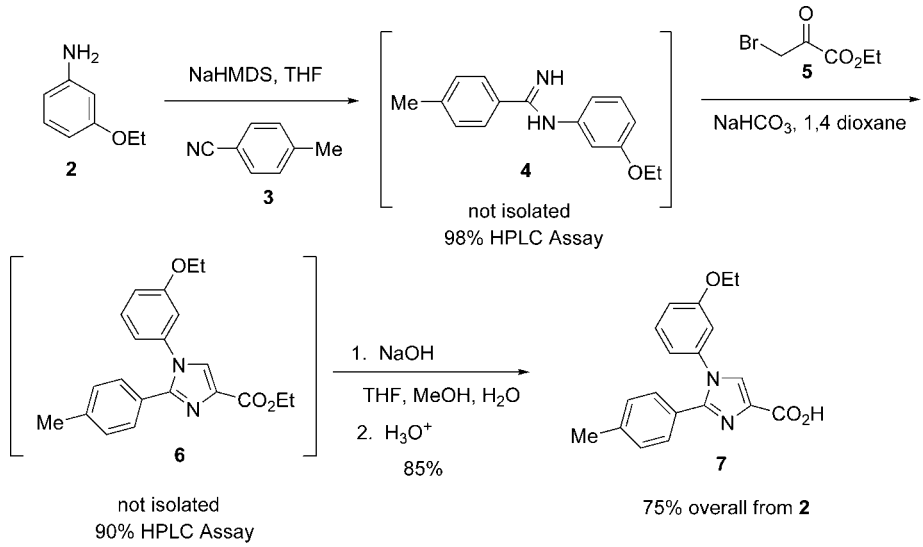


Scheme 3. **Final steps in initial synthesis of 1**

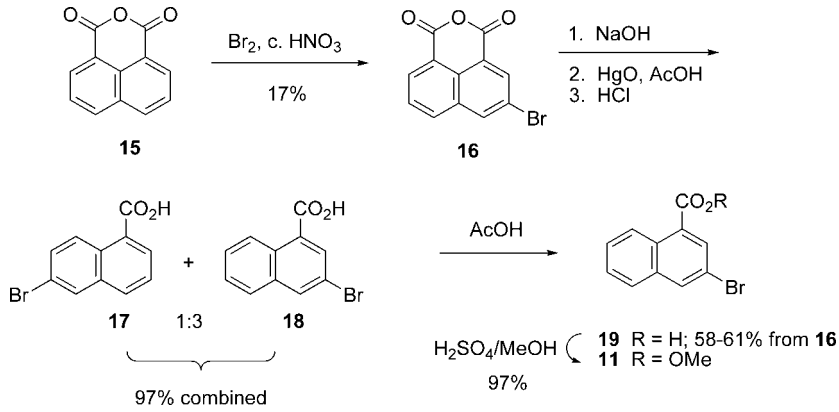


synthesis involved 10 linear steps and proceeded in 13% overall yield. Although the chemistry utilized in Schemes 1−3 for the synthesis of **1** appeared to be straightforward, several liabilities needed to be addressed prior to scale-up. The preparation of imidazole acid **7** was in reasonable shape, and only process improvements including elimination of chromatography and finding suitable conditions to improve the yields and efficiency were required. On the other hand, the preparation of naphthyl piperazine **13** required more attention due to the length of the synthesis and the reported instability of **10**. Specific problems that needed to be addressed in the short term also included the long reaction times with HgO (4 days) for the preparation of **9**, insertion of the bromide via diazonium chemistry in the preparation of **11**, and the extremely unreliable cross-coupling of **11** with **12**, where yields were reported to fluctuate between 10−50%. Finally, the coupling of **7** and **13** at the final stages of the synthesis needed to be improved to streamline the process and allow for the isolation of **1** without recourse to chromato-

Scheme 4



Scheme 5



graphic purification. To meet the aggressive delivery timelines, a strategy was rapidly developed that allowed for the preparation of **1** on multihundred gram scale. In this manuscript we outline an improved preparation of **1** that was utilized for the short-term delivery.

Imidazole Acid. The preparation of **7** followed the initial synthesis outlined in Scheme 1; however, the process was completely optimized as a through-process where **7** was the only isolated product (Scheme 4). For example, reaction of *m*-phenetidine **2** (1.0 equiv) with NaHMDS (1.1 equiv) in THF at 3−5 °C followed by the addition of *p*-tolunitrile **3** and warming to room temperature resulted in quantitative conversion to **4** in <1 h. After dilution with MTBE and water, the layers were separated, and the MTBE stream was carried forward without further purification. The HPLC assay yield of **4** was 98% after workup. The crude MTBE stream containing **4** was then solvent switched from MTBE to 1,4-dioxane, ethyl bromopyruvate **5** (1.2 equiv) and solid $NaHCO_3$ (2.5 equiv) were added, and the mixture was heated to an internal temperature of 95−97 °C for 2 h.[6] After dilution of the crude reaction mixture with MTBE and water, the layers were separated, and the MTBE stream was carried forward without further purification. The HPLC assay yield of **6** was 90% after aqueous workup. The MTBE stream containing **6** was solvent switched to THF, and MeOH and NaOH (2 equiv) were added. After stirring for 2 h, the reaction was made acidic with 2 N HCl and extracted with IPAc, and the product **7** was crystallized from IPAc/heptane in analytically pure form and in 75% overall yield from **2**.

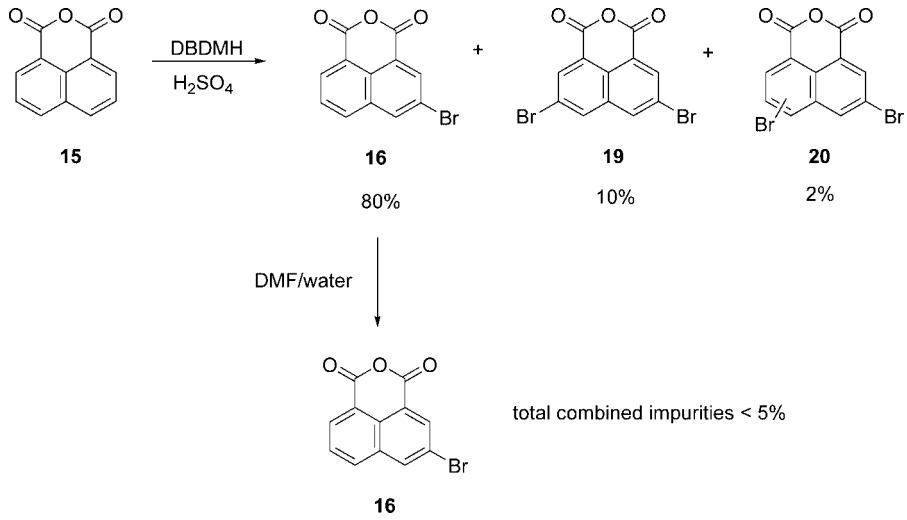
Naphthyl Piperazine. Given the liabilities mentioned above regarding the initial synthesis of **13**, our efforts were focused on overhauling this route. To avoid the low-yielding and potentially hazardous diazonium chemistry of the unstable aniline intermediate **10**, a new synthesis of bromide **11** was required. The deceptively simple structure of **11** masks the fact that 1,3-disubstituted naphthalenes are difficult to prepare via standard directing rules for naphthalenes. Fortunately recent reports by Moseley and co-workers[7] appeared outlining the preparation of bromo ester **11** that closely followed an earlier synthesis (Scheme 5).[8] Bromination of readily available naphthalic anhydride **15** with 0.75 equiv of bromine in 70% concentrated nitric acid occurred regioselectively in the 3-position of the naphthalene ring to give **16** in 17% yield. Any

(6) 1,4-Dioxane proved to be the superior solvent for this reaction and was selected for use in the short term despite its toxicological properties.

(7) (a) Moseley, J. D.; Moss, W. O. *Org. Process Res. Dev.* **2003**, *7*, 53. (b) Moseley, J. D.; Moss, W. O.; Welham, M. J.; Ancell, C. L.; Banister, J.; Bowden, S. A.; Norton, G.; Young, M. *Org. Process Res. Dev.* **2003**, *7*, 58.

(8) (a) Rule, H. G.; Thompson, S. B. *J. Chem. Soc.* **1937**, 1764. (b) Whitmore, F. C.; Fox, A. L. *J. Am. Chem. Soc.* **1929**, *51*, 3363.

Scheme 6



attempts by the authors to improve the yield of **16** were unsuccessful. Mercury acetate-mediated decarboxylation in the presence of NaOH/HgO/AcOH gave predominately the desired 1,3-isomer **18** but also produced significant amounts of the corresponding 1,6-isomer **17**. After an acidic quench to liberate the organo-mercury intermediates, **17** and **18** were isolated as a 3:1 mixture in 97% combined yield. Recrystallization from acetic acid gave pure **18** in 58−61% overall yield from **16**. Conversion of acid **18** to bromo ester **11** was accomplished in 97% yield by esterification in MeOH with 0.5 equiv of concentrated sulfuric acid.

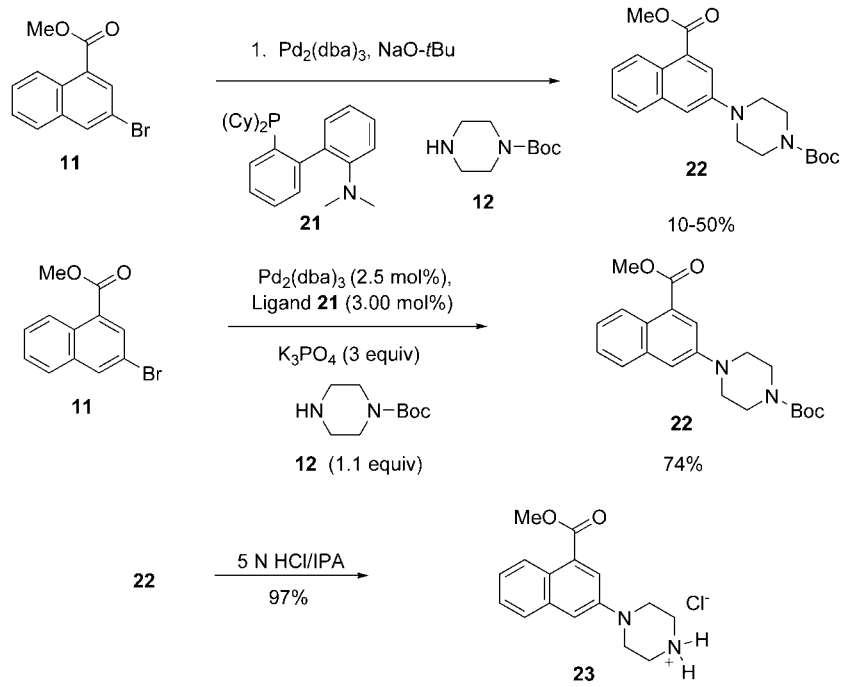
In evaluation of this reported route, our primary concern was the low-yielding bromination of **15**, and our first goal was to examine alternative methods for the preparation of 3-bromonaphthalic anhydride **16**. The bromination procedure described in the literature was never seriously considered because of extremely low yields and reported instability of waste streams that were prone to gassing.[6] A number of conditions were rapidly investigated for the conversion of **15** to **16** that involved numerous solvent systems and brominating agents (Br_2, NBS, dibromodimethylhydantoin). After extensive experimentation, it was discovered that optimal conditions involved reacting **15** with dibromodimethylhydantoin (DBDMH) in concentrated sulfuric acid between −5 and 0 °C for 1 h and allowing the reaction mixture to warm to room temperature overnight (Scheme 6).[9] The resulting reaction mixture was inversely quenched into water, and the resulting slurry was filtered to provide **16** consistently in 80% HPLC assay yield. Also detected in the crude isolated solid were unreacted starting material **15** (7%), dibromide **19** (10%), and an unidentified dibromoisomer **20** (2%). Recrystallization of the crude mixture from DMF/water (10:1) furnished **16** in 70% overall yield from **15** while also reducing the overbrominated byproduct **19/20** to <5%. The level of these impurities was subsequently demonstrated not to be detrimental to the downstream chemistry as they were effectively removed.

With an effective method for the preparation of **16** in hand, conversion of **16** to bromo ester **18** was conducted as described in Scheme 5 with only slight modifications. While the use of stoichiometric mercury presented environmental concerns, we accepted the fact that disposal of mercury waste was reliable on the scale intended for the first delivery. Since the first delivery required only several hundred grams of **1**, the controversial decision was made to use mercury for the preparation of **11**, while recognizing that this would never be considered for pilot-plant scale or for full-scale manufacturing. Mercury acetate mediated decarboxylation of **16** in the presence of NaOH/HgO/AcOH gave a mixture of organo-mercury intermediates that were hydrolyzed with concentrated HCl in a one-pot process to provide a 3:1 mixture of **18/17** in near quantitative yield. The bromo acid mixture at this point was found to be contaminated with 5500−8500 ppm Hg. Recrystallization from acetic acid provided **18** in 56% overall yield from **16**. The recrystallization of **18** lowered the Hg level to ∼1200 ppm Hg. The presence of Hg at this level required careful control in subsequent transformations and was carefully tracked (vida infra) to provide API with acceptable levels of heavy metals. The esterification of **18** was conducted in MeOH at 65 °C for 18 h in the presence of 0.5 equiv of sulfuric acid and was followed by an aqueous workup and extraction of the product into EtOAc/hexane. The crude organic stream containing **11** was treated with Darco G60 to further lower the Hg level, filtered, and concentrated to provide **11** in 89% yield (99 wt %, 742 ppm Hg).

The coupling of **11** and Boc-piperazine **12** in the original synthesis was extremely unreliable with yields never exceeding 50%, and this reaction required extensive optimization of all the reaction parameters to enable the reaction to be carried out in a reproducible manner. The original coupling was carried out in the presence of $Pd_2(dba)_2$ and ligand **21** in the presence of NaO-*t*Bu as the base in toluene or dioxane at 85 °C for 18 h. Efforts aimed at identifying other catalyst/ligand systems in the short time frame in which this research was conducted proved unfruitful. Therefore, we elected to optimize this reaction in terms of catalyst/ligand loading, base, solvent, and temperature. Initial experiments rapidly identified that when all of the reagents were added together and heated to 75−85 °C, variable results were obtained and conversions were typically low

(9) Leazer, J. L., Jr.; Cvetovich, R.; Tsay, F.-R.; Dolling, U.; Vickery, T.; Bachert, D. *J. Org. Chem.* **2003**, *68*, 3695.

Scheme 7



(35−75%). However, when the catalyst and ligand were premixed prior to the addition of **11** and **12**, more consistent results were obtained. The optimal conditions for the coupling of **11** and **12** involved premixing the catalyst ($Pd_2(dba)_3$, 2.5 mol %), ligand **21** (3 mol%), and powdered anhydrous K_3PO_4 (3.00 equiv) in 2-methyltetrahydrofuran (2-MeTHF) at 78 °C (Scheme 7).[10] This resulted in the formation of a beige-green slurry of the active catalyst. A solution containing a mixture of **11** and **12** (1.1 equiv) in 2-MeTHF was then added dropwise over 2 h, and the reaction mixture was stirred at 78 °C for 18−24 h. Although these reaction conditions were effective on small scale employing a stir-bar, mechanical stirring of the reaction mixture resulted in increased reaction times. This observation was attributed to a "grinding" effect of the stir-bar.[11,12] When the reaction was scaled to >100 g, the reaction required heating at 78 °C for 5 days to give complete conversion of the starting material. There did not appear to be any adverse affects after prolonged heating as the reaction profile remained clean. In addition, the reaction appeared to be insensitive to the presence of residual mercury present from the previous steps. Upon completion of the reaction, the reaction mixture was cooled to room temperature and filtered. At this stage of the synthesis, removal of both Pd and Hg to acceptable levels was actively investigated employing the absorbent screening protocol previously described from these laboratories.[13] From the initial screen, the polystyrene-based resin MP-TMT that contains trimercaptotriazine was found to exhibit the highest selectivity in removal of both Pd and Hg.[14] The filtrate from the coupling reaction was treated with MP-TMT resin, resulting in the reduction in the level of residual Pd to 37 ppm and Hg to <3 ppm. The resin was filtered, and the product was crystallized from IPAc/heptane to give **22** in 74% overall yield. Removal of the Boc protecting group was accomplished with 5 N HCl in IPA at 50 °C. No detectable amounts of isopropyl esters resulting from trans esterification of either the starting material **22** or the product **23** were observed by either HPLC or NMR of the crude reaction mixture. The product **23** began to crystallize from the reaction mixture during the course of the reaction, and upon cooling to room temperature, compound **23** was isolated in analytically pure form in 97% isolated yield.

Amide Bond Formation and Completion of the Synthesis. The end game preparation of compound **1** involved amide bond formation between imidazole acid **7** and naphthyl piperazine **23** (Scheme 8). To eliminate chromatography and facilitate isolation of ester intermediate **14**, a one-pot amide formation, ester hydrolysis, acidification protocol was investigated. Our investigations were first focused on appropriate activation of **7** and subsequent reaction with HCl salt **23**. It was rapidly established that activation with 1,1′-carbonyldiimidazole (CDI) (1 equiv) in DMAc at room temperature for 1 h furnished the intermediate acyl imidazole quantitatively.[15] It was reasoned that the liberated imidazole would also serve as an effective

(10) For a leading reference on the use of anhydrous K_3PO_4 in palladium-catalyzed amininations, see: Wolf, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(11) For a detailed discussion on the effect of partical size and rate increase on palladium-catalyzed aminations, see: Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemière, G. L. F.; Dommisse, R. A. *J. Org. Chem.* **2004**, *69*, 6010.

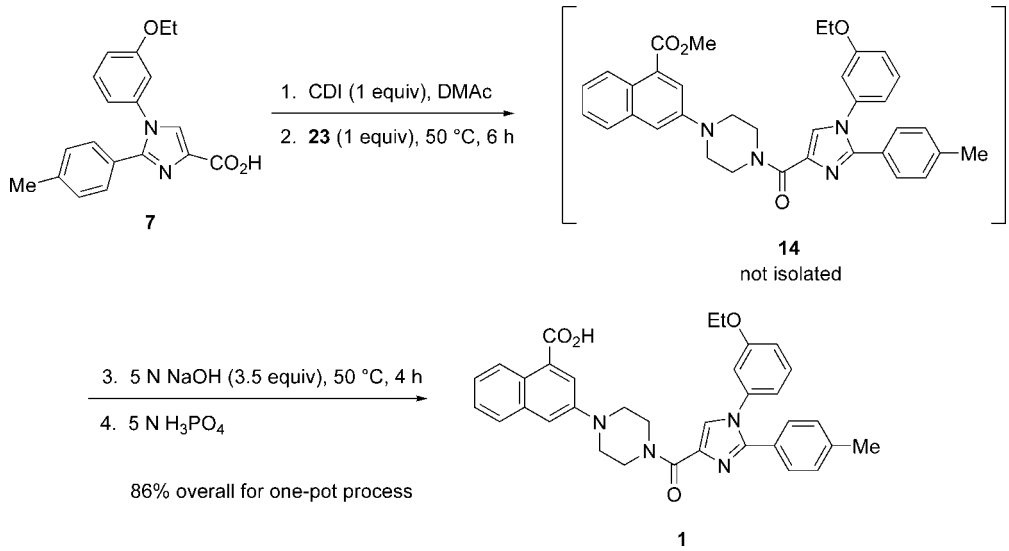
(12) For other recent references on the importance of particle size for successful scale-up, see: (a) Wilk, B. K.; Mwisiya, N.; Helom, J. L. *Org. Process Res. Dev.* **2008**, *12*, 785. (b) Qafisheh, N.; Mukhopadhyay, S.; Joshi, A. V.; Sasson, Y.; Chauh, G.-K.; Jaenicke, S. *Ind. Eng. Chem. Res.* **2007**, *46*, 3016.

(13) Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; Dasilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. *Org. Process Res. Dev.* **2005**, *9*, 198.

(14) MP-TMP is commercially available from Argonaut, Inc. and Biotage.

(15) For leading references using CDI for the preparation of amides on scale, see: (a) Dunn, P. J.; Hughes, M. L.; Searle, P. M.; Wood, A. S. *Org. Process Res. Dev.* **1993**, *7*, 244. (b) Vaidyanathan, R.; Kalthod, V. G.; Ngo, D. P.; Manley, J. M.; Lapekas, S. P. *J. Org. Chem.* **2004**, *69*, 2565.

Scheme 8



base for neutralizing the HCl salt of **23** and facilitate amide bond formation. Treatment of the preformed acyl imidazole of **7** with **23** (1 equiv) at room temperature resulted in incomplete conversion to intermediate **14**. However, upon heating to 50 °C complete conversion to **14** was observed after 6 h. Saponification of methyl ester **14** was accomplished by the direct addition of 3.5 equiv of 5 N NaOH to the reaction mixture and heating for 4 h at 50 °C. The exact amount of NaOH used in the saponification was found to be crucial. When increased amounts of NaOH were employed, hydrolysis of the amide bond resulted leading to the formation of **7** and **23**, and decreased amounts of NaOH led to incomplete ester hydrolysis. After cooling the reaction mixture to room temperature, the pH of the reaction mixture was adjusted to 5 by the addition of 5 N H_3PO_4. During the pH adjustment, the desired product **1** crystallized from the reaction mixture and was isolated in analytically pure form in 86% overall yield.

In conclusion, we have outlined a rapid and efficient multihundred gram synthesis of the potent CCK1R agonist **1**. The streamlined, chromatography-free approach to **1** involved key process improvements in the preparation of imidazole acid **7**, a complete overhaul in the preparation of the naphthyl piperazine fragment **23** including an improved synthesis of bromoanhydride **16**, and increased productivity in the end game coupling. The longest linear sequence was 7 steps starting from **18** and provided **1** in 23% overall yield.

Experimental Section

All reagents were purchased from commercial sources and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer at 400 and 100 MHz, respectively, with chemical shifts given in ppm relative to TMS at $\delta = 0$. Reaction mixtures and products were analyzed by reverse phase HPLC on a Hewlett-Packard 1100 instrument using a 4.6 × 250 mm Symmetry Shield RP18 column. Solvent compositions consisted of 0.1% H_3PO_4 and acetonitrile with a flow rate of 1.5 mL/min.

Preparation of 1-(3-Ethoxyphenyl)-2-(4-methylphenyl)-1*H*-imidazole-4-carboxylic Acid (7). To a 2-L flask 3-neck flask was charged 150 mL of THF (150 mL) and 51.7 g (376 mmol) of *m*-phenetidine **2**, and the solution was cooled to an internal temperature of 0−3 °C. To the cooled solution was added 414 mL (414 mmol) of 1 M NaHMDS in THF over 20 min, during which time the internal temperature increased to 8 °C. After 20 min of stirring at 3−5 °C, a solution of 45.4 g (387 mmol) of *p*-tolunitrile **9** in 50 mL of THF was added to the dark solution over a period of 20 min. The reaction mixture was then allowed to warm to room temperature and was stirred at this temperature for 1 h. The reaction mixture was then diluted with 500 mL of water and 500 mL of MTBE, and the layers were separated. The organic layer was washed with 500 mL of water and was used in the next reaction without further purification. HPLC assay indicated 93.3 g (98%) of *N*-(3-ethoxyphenyl)-4-methylbenzamidine **4**. An analytical sample was obtained by chromatography on silica gel, giving **4** as a colorless solid: mp 95−96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (t, 3H, $J = 7.0$ Hz), 2.40 (s, 3H), 4.01 (q, 2H, $J = 7.0$ Hz), 4.89 (br s, 2H), 6.54−6.62 (m, 3H), 7.23 (m, 3H), 7.73 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 21.3, 63.2, 107.6, 109.5, 113.8, 126.6, 129.1, 130.1, 132.7, 140.7, 150.9, 154.1, 160.0. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.44; H, 6.99; N, 10.98.

The above MTBE solution containing 93.3 g (367 mmol) of crude **4** was concentrated under reduced pressure, and the solvent was switched to a final volume of 900 mL of 1,4-dioxane. To the resulting 1,4-dioxane solution of **4** were added 95.4 g (440 mmol) of 90% technical grade ethyl bromopyruvate **5** and 80.0 g (917 mmol) of sodium bicarbonate. The mixture was heated to 95−97 °C for 2 h and allowed to cool to room temperature. The reaction mixture was diluted with 1 L of water and 1 L of MTBE, and the layers were separated. The organic layer was washed with 500 mL of water and concentrated under reduced pressure while solvent switching to THF and a final volume of 450 mL. To the THF solution containing crude **6** were added 330 mL of MeOH and 330 mL (660 mmol) of a 2 N solution of NaOH. The mixture was stirred at room temperature for 2−3 h, and 330 mL of 2 N HCl was added until a final pH ~3.0−3.5 was obtained. To the solution was added 800 mL of IPAc, and the layers were separated. The organic layer was washed with 600 mL of water. The

solvent was removed under reduced pressure with feeding of IPAc (constant volume of ~1.2 L, ca. 2 L of IPAc needed) to remove residual THF and MeOH. During the course of the distillation the product began to crystallize. The slurry was heated to 70 °C, and 800 mL of heptane was added over 1 h. The slurry was allowed to cool to room temperature, stirred for 2 h, and filtered. The wet cake was washed with 100 mL of heptane, and the product was dried in a vacuum oven at 40 °C for 8 h under a stream of nitrogen to give 91 g (75% overall yield from **2**) of **7** as a colorless solid: mp 162−163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, 3H, J = 7.0 Hz), 2.32 (s, 3H), 3.96 (q, 2H, J = 7.0 Hz), 6.76 (m, 2H), 6.95 (dd, 1H, J = 8.4 and 1.8 Hz), 7.08 (d, 2H, J = 8.0 Hz), 7.30 (m, 3H), 7.88 (s, 1H), 10.12 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 21.4, 64.0, 112.0, 115.5, 117.9, 125.8, 128.8, 128.9, 129.1, 130.5, 132.3, 138.5, 139.6, 147.9, 159.8, 165.7. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.66; H, 5.36; N, 8.51.

Preparation of 3-Bromonaphthallic Anhydride (16). A 50-L round-bottomed flask equipped with a mechanical stirrer, a thermocouple, and a nitrogen inlet was charged with 5.11 kg (25 mol) of naphthalic anhydride **15** and 25 L of 95−98% sulfuric acid (25 L) at 20 °C. The mixture was stirred at 20−25 °C for 30 min to obtain complete dissolution and was cooled to −5 to −10 °C. To the solution was added portion-wise 3.93 kg (13.8 mol) of dibromodimethylhydantoin over 1 h while maintaining the internal reaction temperature was maintained between −10 to −5 °C, and the mixture was stirred at this temperature for 1 h and allowed to warm slowly to room temperature overnight.

In a separate 100-L round-bottomed flask equipped with a mechanical stirrer and thermocouple was added 50 L of water, and the solution was cooled in an ice−water bath. The above reaction mixture was added to the water with stirring over 1 h while maintaining the internal temperature below 75 °C. The resulting slurry was cooled to 30 °C and filtered. The reaction flask was rinsed with 10 L of water, and the cake was washed with 25 L of water and 25 L of 10% water in DMF. The wet cake was dried under nitrogen/vacuum overnight.

The crude wet cake was transferred to a 100-L round-bottomed flask equipped with a mechanical stirrer, nitrogen inlet, and addition funnel. To the crude product was added 50 L of DMF, and the slurry was warmed to 90 °C to give a homogeneous solution. The solution was allowed to cool to 70 °C and seeded with 1.00 g of pure **16**. The slurry was allowed to cool to room temperature overnight. To the slurry was added 5 L of water over 30 min, and the slurry was aged for 1 h and filtered. The wet cake was washed with 10 L of 10% water in DMF and then with 10 L of MeOH. The crude product was dried under a nitrogen flow for 3 h and then in vacuo at 70 °C overnight to give 5.10 kg (95 wt %, 70% yield from **15**) as a colorless solid which was identical in all regards to that published in the literature.[7b]

Preparation of 3-Bromonaphthalic Acid (18). In a 5-L 3-neck round-bottomed flask equipped with a thermocouple and reflux condenser was charged 250 g of bromo anhydride **16** and 2.0 L of 1 N NaOH solution. The resulting slurry was warmed to 60 °C. A separate 1-L round-bottomed flask was charged with 189 g of solid yellow HgO, 600 mL of water, and 200 mL of AcOH, and the mixture was warmed to ~ 50 °C to give a homogeneous, colorless solution. The freshly prepared mercury acetate solution was then added to the slurry of **16** in NaOH, and the reaction mixture was heated to 96−98 °C for 36−48 h. To the reaction mixture was then added 800 mL of concentrated HCl, and the mixture heated to 96−98 °C for 5 h, cooled to room temperature, and aged overnight at room temperature. The resulting solid was filtered, and the wet cake was slurry washed with water (3 × 1 L) and then dried under vacuum/N_2 sweep to give 211 g of crude bromo acids **17**:**18** as a 1:3 mixture of regioisomers.[16] NOTE: *The product at this point was contaminated with ~5500−8500 ppm Hg, and appropriate precautions should be taken to avoid exposure.*

In a 5-L round-bottomed flask were added 440 g of crude mixture of bromoacids **17**:**18** and 3.5 L of AcOH, and the slurry was heated to reflux to give a homogeneous solution. The solution was allowed to slowly cool to 65 °C, seeded with 1.00 g of pure **18**, allowed to slowly cool to room temperature, and aged overnight. The product was then collected by filtration, washed with heptane, and dried under vacuum/N_2 sweep at 50 °C for 24 h to give 268 g (92 wt %, 56%) of the desired regioisomeric product **18** as a colorless solid which was identical in all regards to that published in the literature.[7b] NOTE: *The product at this point was contaminated with ~1200 ppm Hg, and appropriate precautions should be taken to avoid exposure.*

Preparation of Methyl 3-Bromonaphthoate (11). A 5-L 3-neck flask equipped with a thermocouple and reflux condenser was charged with 251.08 g (0.982 mol) of bromoacid **18**, 1.85 L of MeOH, and 26.2 mL (0.49 mol) of concentrated H_2SO_4. The resulting slurry was heated to 60−65 °C for 18 h until complete consumption of **18** was observed by HPLC. The reaction mixture was cooled to room temperature and diluted with 1.0 L of 1:1 EtOAc/hexane and with 1.0 L of water. The layers were well mixed for 30 min and allowed to settle, and the bottom aqueous layer was separated. The organic layer was washed with 650 mL of brine and then treated with 259 g of Darco G60 for 1 h. The mixture was filtered through Solka Floc, rinsing the pad with 500 mL of 1:1 EtOAc/hexane and then 500 mL of EtOAc. The solvent was removed under reduced pressure, and the crude product was dried under vacuum/N_2 sweep to give 232.68 g of bromo ester **11** (99 wt %, 89%) as a colorless solid which was identical in all regards to that published in the literature.[7b]

Preparation of *tert*-Butyl 4-[4-(Methoxycarbonyl)-2-naphthyl]-1-piperazinecarboxylate (6). Two 140 g batches were set up side-by-side and conducted in the same manner. A 5-L 4-neck round-bottomed flask equipped with a mechanical stirrer, thermocouple, 250 mL addition

(16) Analysis of the crude product was carried out by HPLC as described in ref 7b.

funnel, and a nitrogen inlet was charged with 1.4 L of 2-Me-THF, and the solvent was degassed for ~2 min with a submerged nitrogen line. To the solvent was added sequentially 6.3 g (16.0 mmol) of ligand **21**,[17] 7.60 g (13.0 mmol) of $Pd(dba)_2$, and 336 g (1.58 mol) of powdered K_3PO_4,[18] and the system was evacuated under vacuum and then purged with nitrogen. The resulting red slurry was heated to 78 °C over ~30 min, at which point the color of the slurry changed to beige/light green.

In a separate 2-L round-bottomed flask was added 1.1 L of 2-Me-THF, and the solution was degassed for ~2 min. To the solution were added 140.0 g (0.528 mol) of ester **11** and 108.0 g (0.581 mol) of *N*-Boc-piperazine **12** followed by evacuation of the vessel under vacuum and purging with nitrogen, and the mixture was stirred for ~10 min at room temperature to fully dissolve the solids. The mixture was then transferred via cannula to the 250-mL addition funnel and was charged into the above mixture containing the catalyst/ligand in 125 mL portions over a 2 h period while maintaining the internal reaction temperature at 78 °C. The reaction mixture was aged at 78 °C for 5 days until full conversion was observed by HPLC. Upon completion, the dark greenish brown slurry was cooled to room temperature, and the solids were filtered through a pad of Solka Floc, slurry rinsing the pad with 2-Me-THF. The dark orange brown filtrate was stirred with MP-TMT resin[10] (140 g) at room temperature for 1 h under nitrogen. The solids were filtered, rinsing with 2-Me-THF, and then held overnight at ambient temperature.

In a separate 5-L 4-neck round-bottomed flask equipped with a mechanical stirrer, thermometer probe, short path distillation head, and a vacuum line was transferred the above crude reaction mixture via in-line filtration (5 μm pore size). The solvent was removed under reduced pressure to a volume of ~ 980 mL while maintaining the internal temperature below 65 °C. The solvent was then switched to IPAc by concentration under reduced pressure, flushing with ~ 3 L of IPAc, and the volume was adjusted to a final volume of 1.1 L. The resulting slurry was then heated to an internal temperature of 70 °C to dissolve solids, allowed to slowly cool over 1 h to 50 °C, and then aged for 1 h at 50 °C, during which time the product began to crystallize. To the slurry was added dropwise 3.5 L of heptane over a 1 h period, and the slurry was stirred overnight at room temperature. The slurry was filtered, and the wet cake was washed with 500 mL of heptane. After drying for 3 h on the filter pot under vacuum/N_2 sweep, the solid was further dried in a vacuum oven at 30 °C under a flow of nitrogen for 36 h to give 280.0 g (97 wt %, 74%) of **22** as a yellow solid: mp 107−108 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 9H), 3.28 (m, 4H), 3.64 (m, 4H), 3.96 (s, 3H), 7.29 (d, 1H, J = 2.6 Hz), 7.44 (m, 2H), 7.72 (m, 1H), 7.98 (d, 1H, J = 2.6 Hz), 8.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 43.1, 49.4, 52.1, 79.7, 115.9, 123.8, 125.2, 125.5, 126.4, 126.6, 127.3, 128.0, 135.1, 147.5, 154.6, 167.8. Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.13; H, 7.23; N, 7.56.

Preparation of 4-[4-(Methoxycarbonyl)-2-naphthyl]-1-piperazine Hydrochloride 23. To a 5-L round-bottomed flask equipped with a mechanical stirrer and thermocouple were charged 1.5 L of IPA and 250 g (0.675 mol) of **22**. To the resulting slurry was added 675 mL of a 5 N hydrochloric acid solution in IPA. The homogeneous solution was heated to 50 °C for 2 h, at which point the HCl salt of **23** began to crystallize from solution. The slurry was cooled to room temperature and filtered, and the wet cake was washed with 500 mL of IPA. The wet cake was dried in a vacuum oven at 50 °C under a stream of nitrogen for 24 h to give 211 g (95 wt %, 97% yield) of **23** as a white solid: mp 242−243 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.23 (m, 4H), 3.52 (m, 4H), 3.92 (s, 3H), 7.42 (m, 1H), 7.48 9m, 1H), 7.55 (m, 1H), 7.84 (m, 1H), 7.93 (m, 1H), 8.50 (m, 1H), 8.73 (br s, 1H), 9.71 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.7, 45.9, 52.7, 115.7, 122.9, 125.2, 125.6, 125.7, 127.1, 128.0, 128.4, 135.1, 146.8, 167.6. Anal. Calcd for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13. Found: C, 63.00; H, 6.32; N, 9.05.

Preparation of 3-{4-[1-(3-Ethoxyphenyl)-2-*p*-tolyl-1*H*-imidazole-4-carbonyl]-piperazin-1-yl}-naphthalene-1-carboxylic Acid (1). In a 5-L round-bottomed flask equipped with a mechanical stirrer and thermocouple were charged 2.25 L of DMAc and 225.7 g (0.70 mol) of imidazole acid **7**. To the solution was added 113.5 g (0.70 mol) of CDI in one portion. The resulting mixture was aged at room temperature for 1 h, and 214.8 g (0.70 mol) of **23** was added as a solid in one portion. The resulting slurry was heated to 50 °C for 6 h. To the reaction mixture was then added 490 mL (2.45 mol) of 5 N NaOH, and the solution was stirred at 50 °C for 4 h. The reaction mixture was allowed to cool to room temperature and was neutralized to pH ~5 by the addition of 410 mL (2.05 mol) of 5 M aqueous phosphoric acid over 1 h. To the resulting thick slurry was added 450 mL of water, and the slurry was stirred for 2 h at room temperature and filtered. The wet cake was washed with 1 L of water and was dried in a vacuum oven at 55 °C under a stream of nitrogen for 48 h to give 340 g (86%) of **1** as a light yellow solid: mp 230.1 (DSC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.22 (t, 3H, J = 7.0 Hz), 2.24 (s, 3H), 3.33 (m, 4H), 3.65−3.95 (br m, 2H), 3.95 (q, 2H, J = 7.0 Hz), 4.21−4.55 (br m, 2H), 6.78 (dd, 1H, J = 7.7 and 1.4 Hz), 6.91 (t, 1H, J = 2.0 Hz), 6.95 (dd, 1H, J = 8.3 and 2.0 Hz), 7.09 (d, 2H, J = 8.1 Hz), 7.22 (d, 2H, J = 8.1 Hz), 7.27−7.35 (m, 2H), 7.38−7.43 (m, 2H), 7.76 (d, 1H, J = 8.3 Hz), 7.88 (s, 1H), 7.94 (d, 1H, J = 2.4 Hz), 8.60 (d, 1H, J = 8.3 Hz), 13.2 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.9, 21.3, 49.4, 63.9, 112.6, 114.8, 115.5, 118.5, 122.8, 124.9, 125.8, 125.9, 126.9, 127.4, 128.7, 128.8, 129.4, 130.8, 135.5, 136.9, 138.9, 139.0, 145.5, 147.8, 159.6, 162.2, 169.3. Anal. Calcd for $C_{34}H_{32}N_4O_4$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.79; H, 5.71; N, 10.01.

(17) Ligand **21** was purchased from Strem Chemicals, Inc. and was used as received.

(18) Commercially available anhydrous powdered K_3PO_4 from Riedel de Haen was employed.

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