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# Bio- and Chemocatalysis for the Synthesis of Late Stage SAR-Enabling Intermediates for ROMK Inhibitors and MK-7145 for the Treatment of Hypertension and Heart Failure

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**ABSTRACT:** A synthetic strategy to provide two late-stage intermediates for the synthesis of diverse analogues of ROMK inhibitors for the treatment of hypertension and heart failure is described. Key transformations include carbonylation of a bromoarene, regioselective vinyl ether Heck coupling and bromination, and asymmetric enzyme-mediated ketone reduction and epoxide ring closure. On selection of MK-7145 (1) as clinical candidate, conditions were developed to convert 2 equiv of the epoxide intermediates to the  $C_2$ -symmetric active pharmaceutical ingredient.

KEYWORDS: carbonylation, Heck, ketoreductase, epoxide

T he renal outer medullary potassium channel (ROMK) was recently reported as a potential target for the treatment of hypertension and heart failure.<sup>1</sup> As a result, a drug discovery program was established to pursue the synthesis and evaluation of a series of oral small molecule ROMK inhibitors that would function as diuretics.<sup>2</sup> Additional development identified the  $\beta$ -dialkylaminoalcohol framework 2 (Figure 1a)



Figure 1. (a) Key pharmacophore; (b) Synthetic intermediates for ROMK program; (c) MK-7145.

as critical to improved hERG (human *Ether-à-go-go*-Related Gene) selectivity and improved pharmacokinetic profile.<sup>3</sup> An efficient synthesis of late-stage intermediates **3** and **4** was critical for rapid interrogation of this series of novel ROMK inhibitors (Figure 1b). From bromoketone **3**,  $\beta$ -aminoalcohol analogues could be accessed through a two-step sequence involving  $S_N 2$  displacement with an amine followed by reduction; similarly, direct epoxide opening of styrene oxide **4** would provide a complementary approach depending on the identity of the amine nucleophile. We envisioned that the ideal approach to these intermediates would be directly applicable to

the kilogram-scale synthesis of an identified clinical candidate. Herein, we present the synthesis of  $\alpha$ -bromoketone **3** and styrene oxide **4** as late-stage SAR-enabling intermediates and direct translation of this strategy to the multikilogram scale preparation and rapid progression of C<sub>2</sub>-symmetric clinical candidate, MK-7145<sup>3b</sup> (**1**, Figure 1c).

We envisioned that styrene oxide 4 would be directly accessible from bromoketone 3 via enzymatic reduction and cyclization of the resulting bromohydrin to the corresponding epoxide. As a result, we initially targeted an efficient synthesis of compound 3 as the key intermediate in this SAR-enabling strategy. Given the ultimate goal of translating this chemistry to the multikilogram scale, additional requirements included the use of readily available, inexpensive starting materials, minimization of the number of steps, and scalability of all transformations. To that end, we identified 3-hydroxy-2-methylbenzoic acid (5), known to be widely available on scale for \$80/kilogram, as an ideal starting material for this synthetic sequence. Our proposed retrosynthesis is shown in Scheme 1.

In a forward sense, the first two steps of the synthetic sequence involved classical organic chemistry reactions (Scheme 2). Benzoic acid 5 underwent smooth reduction with in situ generated borane<sup>4</sup> in tetrahydrofuran to afford benzyl alcohol 6. Careful control of the stoichiometry of sodium borohydride and boron trifluoride diethyl etherate, as well as aqueous workup to remove borate salts before product

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# Scheme 1. Retrosynthesis for Synthetic Intermediates 3 and 4



isolation, allowed for isolation of the desired product in 93% yield. Bromination of benzyl alcohol **6** was carried out with *N*-bromosuccinimide (NBS) in a mixture of trifluoroacetic acid and acetonitrile to afford *p*-bromophenol 7. The yield of this transformation proved highly temperature-dependent. At -30 °C, *o*-bromophenol regioisomer **8** (9%), dibromide **9** (3%), and TFA ester **10** (5%) impurities were observed, and desired bromophenol 7 was isolated in only 74% yield. Formation of these impurities was suppressed at -45 °C, and a 10% increase in isolated yield to 84% was obtained.<sup>5</sup>

With bromoarene 7 in hand, we sought next to form the lactone moiety present in both desired intermediates. We envisioned two approaches for installation of the requisite carbon. Initial efforts centered on cyanation of the arene with copper(I) cyanide (CuCN).<sup>6</sup> This transformation proceeded via the cyano intermediate 11 at 145 °C. Continued heating at 95 °C, with addition of 5.0 equiv of water, afforded the lactone 12 after 20 h (Scheme 3a). Unfortunately, while the reaction profile under these conditions appeared very clean, the isolated yield was only 62%. We attributed this result to entrainment of the product in the solids that formed during the reaction. Additionally, an excess of CuCN was required to achieve high conversion, which was undesirable for future large-scale syntheses. As a result, we turned our attention to palladiumcatalyzed carbonylation<sup>7</sup> to form the requisite lactone. At high pressure (85-90 psi CO) and temperature (130 °C), in the presence of 2.0 mol % Pd(OAc)<sub>2</sub> and 2.4 mol % diphenylphosphinopropane (dppp), bromoarene starting material 7 underwent clean carbonylation to form lactone 12 in 80% isolated yield (Scheme 3b).8 These arene core manipulations collectively positioned the synthesis for subsequent modification of the substrate to install the necessary bromoketone and epoxide functionalities.

In order to transform the phenol 12 to the desired bromoketone 3, a sequence of phenol activation, regioselective Heck reaction with *n*-butyl vinyl ether,<sup>9</sup> and treatment of the resultant vinyl ether with NBS was designed (Scheme 4). We prepared a series of aryl sulfonates in an effort to assess the

regioselectivity of the subsequent Heck reaction. Most aryl sulfonates (-Ms, -Ts, -4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, -2,4-di-NO<sub>2</sub>C<sub>6</sub>H<sub>3</sub>) provided low conversions to product, with regioselectivities ranging from 1:1 to 2:1 in favor of the desired  $\alpha$ -branched vinyl ether over its terminal regioisomer. On switching to the aryl triflate 13,10 we observed high conversion and regioselectivity in the Heck reaction to the desired product as a result of the triflate favoring an electronically controlled cationic Heck oxidative addition Pd complex mechanism.<sup>10c</sup> The crude reaction stream was used directly in the bromination, affording bromoketone 3 in 72% yield over the three-step sequence. Ultimately, we successfully developed a six-step, 45% yielding sequence from a readily available commercial starting material to provide the first of two valuable late-stage synthetic intermediates for further elaboration to ROMK inhibitors.

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The second intermediate of interest was styrene oxide 4. We quickly demonstrated that sodium borohydride reduction and treatment with base provided racemic access to this compound. Nonetheless, with the desired epoxide enantiomer defined, we sought to develop an asymmetric reduction of bromoketone 3 to insert into this sequence and focused our efforts on the use of a ketoreductase enzyme.<sup>11</sup> We rapidly identified commercial Codexis KRED MIF-20 as providing smooth reduction of the bromoketone to the corresponding bromohydrin in >99% ee. After conclusion of the enzymatic reaction,  $K_2CO_3$  was added to effect cyclization to the epoxide 4.

With these syntheses in hand, tens of grams of each of bromoketone 3 and epoxide 4 were then available to the medicinal chemistry team to react with amines to prepare the corresponding  $\beta$ -aminoalcohols. In turn, the team evaluated the potency, physical properties, and toxicities of a wide variety of structural analogues and identified MK-7145 (1) as its clinical candidate possessing the desired balance of these features.<sup>3</sup> Our defined strategy to develop an efficient, scalable synthesis of epoxide 4 proved beneficial for the large-scale preparation of MK-7145. In particular, we envisioned that treatment of 2 equiv of the epoxide with 1 equiv of piperazine would provide direct access to the desired compound.<sup>12</sup> We examined a series of solvents at elevated temperatures for the bis-epoxide opening. While running the reaction in tert-amyl alcohol provided the appropriate polarity to enable the fastest rate, the best ratio of the desired product observed relative to its monoterminal epoxide opening, mono-internal opening regioisomer 14 was only 2:1. Changing to N,N-dimethylacetamide (DMAc) as solvent led to similar mixtures at higher





#### Scheme 3. Lactone 12 Formation: (a) CuCN Conditions; (b) Carbonylation Conditions



Scheme 4. Conversion to Desired Synthetic Intermediates 3 and 4



# Scheme 5. End-Game for MK-7145



temperatures. The best ratio (close to 5:1) was observed in toluene, but the rate of reaction was severely compromised, and the monoepoxide opening **15** was the major product. Ultimately, use of a 1:1 mixture of toluene and DMAc at 140 °C allowed for complete conversion of the epoxide to MK-7145:14 in a 4.2:1 ratio (Scheme 5). Cooling the reaction mixture and adding water led to complete rejection of the undesired regioisomer and allowed for isolation of MK-7145 in 75% yield. Recrystallization from the same solvent system afforded the API in 92% yield and high purity with only 5 ppm residual palladium. This sequence was ultimately run on scale to afford >50 kg of MK-7145 and supply sufficient quantities of active pharmaceutical ingredient to carry out all preclinical and Phase I testing.

We have described a strategy that has enabled the rapid preparation of a variety of structural analogues for interrogation by our ROMK discovery team and subsequent largescale synthesis of a clinical candidate. Specifically, intermediates **3** and **4** were prepared via 6- and 7-step sequences, respectively. Key transformations along the route included a palladium-catalyzed carbonylation of a bromoarene, a highly regioselective enol ether Heck reaction between an aryl triflate and *n*-butyl vinyl ether, followed by NBS treatment to afford the corresponding bromoketone, and highly enantioselective ketoreductase-mediated reduction of the bromoketone and subsequent cyclization to form the desired epoxide. Reaction of 2 equiv of the epoxide intermediate with piperazine, followed by crystallization from a ternary solvent system, afforded the clinical candidate MK-7145, which we have

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synthesized on >50 kg scale. Future studies will describe investigation of an alternative approach to the API to establish a process that provides MK-7145 in high regio-, enantio-, and diastereopurity prior to crystallization.

#### EXPERIMENTAL SECTION

**General.** All reagents were used without further purification. Products were authenticated against commercially available or previously described reagents.<sup>3b,c</sup> HPLC area percent was established on an Agilent 1100 liquid chromatography system with a Zorbax Eclipse Plus C18 column (50 mm × 4.60 mm, 1.8  $\mu$ m) at 25 °C and flow rate of 1.5 mL/min and  $\lambda$  = 210 nm. A = 0.1% phosphoric acid in HPLC water; B = acetonitrile: gradient 90% A, 10% B to 5% A, 95% B over 5 min. wt% was calculated via sample of unknown purity standard concentration HPLC peak area comparison against a pure reference of known concentration.

3-Hydroxy-2-methylbenzenemethanol (6) [54874-26-9]. THF (560 kg) and 3-hydroxy-2-methylbenzoic acid (5, 80.0 kg, 526 mol, 1 equiv) were charged into a vessel under nitrogen. The vessel was cooled to 10–15 °C. THF (1040 kg) and sodium borohydride (30.1 kg, 796 mol, 1.51 equiv) were charged to a second vessel, which was cooled to 8–10 °C. The solution of compound 5 was added dropwise to the sodium borohydride solution at 10-17 °C and stirred for an additional 2.0 h at 10-15 °C. Boron trifluoride diethyl etherate (129.7 kg, 914 mol, 1.74 equiv) was added to the mixture slowly over 8 h. The reaction mixture was stirred for an additional 18 h at 10-15 °C before cooling to 5-10 °C. Methanol (54.6 kg) was then added at 5-10 °C, and the mixture stirred for 3 h at 5-10 $^{\circ}$ C. 2% Na<sub>2</sub>CO<sub>3</sub> solution (1045 kg) was added slowly at 5–15  $^{\circ}C$  to achieve pH = 7, and the mixture was stirred for an additional 2 h at 10-20 °C. The mixture was then concentrated under vacuum below 45 °C to 800-960 L  $(10.0-12.0\times)$ . The aqueous layer was extracted  $3\times$  MTBE (650 kg, 350 kg, 300 kg). The combined organic layer was washed with 10% brine (322 kg). The organic layer was filtered through a pad of  $Na_2SO_4$  (16 kg) and concentrated to 300-350 L (3.5–4.5×) under vacuum below 45 °C. 400 kg (4.0–  $5.0\times$ ) *n*-heptane was added and the mixture was concentrated to 320-400 L (4.0-5.0 $\times$ ) under vacuum below 45 °C. The vessel was cooled to 0-10 °C and stirred for 2 h. The suspension was filtered, and the resultant cake was washed with 60 kg of *n*-heptane. 3-Hydroxy-2-methylbenzenemethanol (6) was isolated as a white solid (65.75 kg, 99.7 LCAP, 98.5 wt %, 90.5% corrected yield).

6-Bromo-3-hydroxy-2-methylbenzenemethanol (7) [1255206-72-4]. To a vessel containing acetonitrile (474 kg) were added compound 6 (68.8 kg, 498 mol, 1.0 equiv) and trifluoroacetic acid (439.4 kg) The vessel was cooled to -45.5  $^{\circ}$ C under nitrogen and N-bromosuccinimide (NBS) (3 × 27.5 kg,  $1 \times 6.2$  kg, 88.7 kg, 478 mol, 0.96 equiv) was added in 4 portions over 2 h at -45 °C. The mixture was stirred for an additional 40 min at -43 to -30 °C. 26% NaOH solution (611 kg) was added to the reaction mixture via vacuum between -5.1 and -19 °C to achieve pH 8.0. The mixture was stirred at -10 to -20 °C for an additional 30 min, then concentrated to 756-825 L (11-12x) below 45 °C. The temperature was adjusted to 15-25 °C, and MTBE (330 kg) and water (277 kg) were added to the vessel. Stirring was continued at 15-25 °C for 30-60 min until the solids dissolved. The phases were separated, and the aqueous layer was extracted with MTBE  $(2 \times 166 \text{ kg})$ . The combined

organic layers were washed with 10% NaCl solution  $(2 \times 200 \text{ kg})$ . The organic layer was filtered through Na<sub>2</sub>SO<sub>4</sub> (47.6 kg) and washed with additional MTBE (20 kg). The resulting solution was concentrated to (~3 V) below 30 °C, and the temperature was adjusted to 55–59 °C to afford a homogeneous solution. *n*-Heptane (62.4 kg) was added dropwise at 55–59 °C and the mixture was stirred at 55–59 °C for 2 h. The reaction mixture was cooled to 30–35 °C, and *n*-heptane (130.6 kg) was added dropwise over 6 h. After stirring at 30–35 °C for an additional 1 h, the reaction mixture was cooled to 5–10 °C and stirred for an additional 2 h. The solids were filtered, washed with heptane (70 kg), and dried to afford 6-bromo-3-hydroxy-2-methylbenzenemethanol (7) as a white solid (87.06 kg, 96.2 wt %, 80.5% corrected yield).

6-Hydroxy-7-methyl-1(3H)-isobenzofuranone (12) [6553-26-0]. THF (1380 kg) and compound 7 (140 kg, 645 mol, 1.0 equiv) were charged to a vessel under nitrogen at 15-25 °C and stirred 30 min until all solids dissolved. Pd(OAc)<sub>2</sub> (3 kg, 13.4 mol, 2.0 mol %), dppp (6.5 kg, 15.8 mol, 2.4 mol %), and NaOAc (106 kg, 1290 mol, 2.0 equiv) were subsequently charged to the same vessel. The batch was heated to 128-132 °C and pressurized with carbon monoxide to 0.55-0.65 MPa for 24 h. The temperature was cooled to 30-40 °C and active carbon (14 kg) was added. The mixture was warmed to 50–60  $^{\circ}\mathrm{C}$  for 1.5 h. After filtration, the mixture was concentrated to 400–500 L (3.0×) below 40 °C. Ethyl acetate (568 kg) was added, and the mixture was concentrated to 257 L  $(3.0\times)$  below 40 °C. Ethyl acetate (2322 kg) was added, the temperature was adjusted to 20-30 °C and the reaction mixture was stirred for 60 min. The organic layer was washed with water (825 kg). The aqueous layer was then extracted with ethyl acetate (928 kg). The combined organic layers were washed with 7% aqueous sodium bicarbonate (403 kg) and 10% brine (840 kg). The organic layer was filtered through  $Na_2SO_4$  (30 kg), and the filtrate was concentrated to 400–500 L (4.0 $\times$ ) below 50 °C. The temperature was adjusted to 30– 35 °C, and *n*-heptane (678 kg) was added slowly. The reaction mixture was cooled to 10-15 °C and stirred for 3-3.5 h. The solids were filtered, washed with heptane (120 kg), and dried to afford 6-hydroxy-7-methyl-1(3H)-isobenzofuranone (12) as a white solid (85 kg, 95.5 wt %, 80.3% corrected yield).

Bromoketone 3 via Triflate 13. Dichloromethane (1298 kg) and compound 12 (85 kg, 518 mol, 1.0 equiv) were charged to a vessel under nitrogen and stirred for 30 min at 15-25 °C. Triethylamine (84 kg, 830 mol, 1.6 equiv) was added in one portion, and the reaction mixture was cooled to 3-8 °C. Tf<sub>2</sub>O (162 kg, 574 mol, 1.1 equiv) was added dropwise while maintaining the temperature at 3-8 °C. The mixture was stirred for an additional 20 min at 3-8 °C, and water (380 kg) was added. The reaction mixture was warmed to 20-30 °C and stirred for an additional 20 min. The phases were separated, and the organic layer was washed with water three times (456 kg, 404 kg, 454 kg). The organic layer was filtered through Na<sub>2</sub>SO<sub>4</sub> (56 kg), and the solids were washed with dichloromethane (243 kg). The combined organic liquors were concentrated to 127-212 L (1.5-2.5×) below 40 °C, and the KF value was measured ( $\leq 0.2\%$ ). DMF was added (780 kg), and the solution, containing triflate 13, was concentrated to 722-765 L (8.5-9.0x) below 40 °C. Pd(OAc)<sub>2</sub> (2.36 kg, 11 mol, 2.0 mol %) and dppp (5.05 kg, 12.2 mol, 2.4 mol %) were added, and the mixture was stirred for 20 min at 20–30 °C. Triethylamine (59.8 kg, 591 mol, 1.14 equiv) and *n*-butyl vinyl ether (261 kg, 2610 mol, 5.0 equiv)

were added to the reaction mixture, and the batch was heated to 80-85 °C for 3 h. The reaction mixture was cooled to 10-15 °C. Ethyl acetate (912 kg) and water (460 kg) were added to the vessel, and the temperature was cooled to 10–15  $^{\circ}$ C. The layers were separated, and the aqueous layer was extracted with ethyl acetate (858 kg). The combined organic layers were washed twice with water (400 kg, 423 kg), and the organic layer was concentrated to 127-212 L (1.5-2.5×) below 40 °C. THF was added (936 kg), and the mixture was concentrated to about 383–425  $\rm \tilde{L}$  (4.5–5.0×) below 40  $^{\circ}\rm C$ under vacuum. Water (104 kg) was added, and the mixture was cooled to 0-5 °C. NBS (103 kg, 579 mol, 1.1 equiv) was added in portions slowly, with the inner temperature maintained below 15 °C during the addition and 30 min thereafter. 48% HBr (1.0 kg) was added to adjust the pH value to 3-4. Water (530 kg) was added slowly, and the reaction mixture stirred at 15-20 °C for 20 min. Additional water (700 kg) was added slowly, and the mixture was cooled to 5-10 °C for 30 min. The suspension was filtered, and the cake was washed with cooled water (170 kg). The wet cake was dissolved in ethyl acetate (1550 kg), and the mixture was heated to 50-60 °C for 30 min. Active carbon (9.2 kg) was added, and the mixture was heated to 60-70 °C for 30 min. The suspension was filtered, and the cake was washed with ethyl acetate (96.2 kg) through Celite (8.8 kg). The filtrate was concentrated to 467-552 L (5.5-6.5×) below 40 °C. The mixture was then heated to 60–70  $^{\circ}\mathrm{C}$  to dissolve all the solids. *n*-Heptane (330 kg) was added dropwise at 60-70 °C until there was solid precipitated, and the mixture was cooled slowly to 25-30 °C over 5 h. Additional *n*-heptane (706.6 kg) was added dropwise, after which the mixture was cooled to 0-10°C over 3 h. After stirring for an additional 2 h, the solids were filtered and washed with n-heptane (138 kg). The cake was dried at 20-26 °C for 12-14 h in vacuum to give active bromoketone 3 as a white solid (98.9 kg, 98.2 wt %, 71% vield).

4-Methyl-5-(2R)-2-oxiranyl-1(3H)-isobenzofuranone (4) [1255206-70-2]. Water (978 kg) and K<sub>2</sub>HPO<sub>4</sub>·3H<sub>2</sub>O (16.5 kg) were charged to a vessel and stirred until all the solids dissolved.  $H_3PO_4$  (2.1 kg) was added dropwise at 15–25 °C to adjust the pH to 7.0. This buffer solution (501 kg) was transferred to a new vessel, to which was also added compound 3 (97 kg, 361 mol, 1.0 equiv) under nitrogen. IPA (756 kg) was then charged followed by NADP+ (3.88 kg) and Codexis KRED-MIF-20 (3.88 kg), and the mixture was stirred for 1 h at 15-25 °C until all the solids were dissolved. The remaining buffer solution was transferred to the vessel, and the mixture was warmed to 28-33 °C and stirred for 6 h. The batch was cooled to 22  $\pm$  2 °C. and 36.3% aqueous K<sub>2</sub>CO<sub>3</sub> solution (162 kg) was added dropwise at 20-25 °C over 3 h, followed by stirring for an additional 3 h.  $Na_2SO_4$  (50 kg) was charged in portions, the mixture was stirred for 30 min and then cooled to 0-10 °C. H<sub>3</sub>PO<sub>4</sub> (31.7 kg) was added to the vessel, and the pH was measured as 7.33 after 30 min. Ethyl acetate (893 kg) was added, and the reaction mixture stirred for 30 min at 20-30 °C. The aqueous layer was removed. Ethyl acetate (1213 kg) was added to the emulsification layer in the original vessel. The reaction mixture was stirred for 40 min at 20–30 °C, and the aqueous layer was removed. The emulsification layers were combined, filtered, and centrifuged, and the aqueous layer was separated. 17% aqueous Na<sub>2</sub>SO<sub>4</sub> solution (340 kg, 180 kg) was added twice into the organic layer, stirred, and separated. The resultant organic layer was concentrated to 340-437 L (3.54.5×) below 40 °C. Ethyl acetate (862 kg) was added, and it was concentrated to 340-437 L (3.5-4.5×). GC analysis indicated assay of IPA%  $\leq$  10.9%. Ethyl acetate (862 kg) was added, and the organic layer was washed with water  $(2 \times 300$ kg). The organic layer was concentrated to 340-437 L (3.5-4.5×) under vacuum at  $T \leq 42$  °C, with addition of more ethyl acetate and subsequent concentration to azeotope off water and achieve KF = 0.2%. Ethyl acetate (715.2 kg) was added, the mixture was warmed to 28-32 °C, and Ecosorb C-941 (6.75 kg) was added. The mixture was stirred at 28-32 °C for 35 min, followed by filtration through Celite (20 kg) at 25-30°C and washing of the cake with ethyl acetate (110 kg). The filtrate was concentrated to 272-340 L (2.8-3.5×) below 42 °C. The mixture was warmed to 60–70 °C until all the solids were dissolved, and *n*-heptane (137 kg) was added dropwise to the mixture at 60–70 °C until the solid was precipitated. The mixture was cooled to 20–30 °C over 3 h, and *n*-heptane (634) kg) was added dropwise into the mixture over 4.3 h. The mixture was then cooled and stirred at 0-10 °C for 90 min. The suspension was filtered, and the cake was washed with *n*heptane (131 kg). The cake was dried at 35-40 °C under vacuum for 18 h to give 4-methyl-5-(2R)-2-oxiranyl-1(3H)isobenzofuranone (4) (56.6 kg, 99.7 LCAP, 82.3% yield).

MK-7145 (1).<sup>3c</sup> DMAc (242 kg) was charged to a vessel and degassed with nitrogen. Piperazine (12.43 kg, 144 mol, 1.0 equiv) and compound 4 (51.6 kg, 271 mol, 1.9 equiv) were added to the solution under nitrogen. The mixture was heated to 128-137 °C over 1 h under and stirred at temperature for 18 h. The reaction mixture was cooled to 50-60 °C, and water (129 kg) was added dropwise, followed by DMAc/water (wt/ wt = 1:4, 129 kg). The mixture was cooled to 10-25 °C over 1 h and stirred for an additional 1 h. The suspension was filtered, and the wet cake was washed with 140 kg of DMAc/water (1:4). The wet cake was dried in an oven at 45-50 °C until KF  $\leq$  1.0%, which has afforded compound 1 (47.2 kg, 99.7 wt %, 74.6% yield). The API (47.2 kg) was recrystallized from DMAc (512 kg), toluene (248 kg), and water (558 kg), with heating at 80-110 °C, followed by cooling to room temperature to obtain MK-7145 as an off-white solid (43.375 kg, 99.9 LCAP, 91.8% corrected yield). The <sup>1</sup>H NMR spectrum was consistent with the literature report.

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00314.

Full characterization of specified impurities is provided, along with MK-7145 HPLC and <sup>1</sup>H NMR spectral data (PDF)

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### Notes

The authors declare no competing financial interest.

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# ABBREVIATIONS

ROMK renal outer medullary potassium channel; hERG human *Ether-à-go-go*-Related Gene; SAR structure activity relationship; NBS *N*-bromosuccinimide; TFA trifluoroacetic acid; CuCN copper(I) cyanide; dppp diphenylphosphinopropane; KRED ketoreductase; DMAc *N*,*N*-dimethylacetamide; API active pharmaceutical ingredient; ppm parts per million; LCAP liquid chromatography area percent

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