Organic Process Research & Development

ARTICLE

pubs.acs.org/OPRD

# Convergent Kilo-Scale Synthesis of a Potent Renin Inhibitor for the Treatment of Hypertension

Louis-Charles Campeau,*[,†] Sarah J. Dolman,[†] Danny Gauvreau,[†] Ed Corley,[‡] Jinchu Liu,[‡] Erin N. Guidry,[‡] Stéphane G. Ouellet,[†] Dietrich Steinhuebel,[‡] Mark Weisel,[‡] and Paul D. O'Shea[†]

[†]Global Process Chemistry, Merck-Frosst, 16711 Trans Canada Highway, Kirkland, Québec H9H 3L1, Canada

[‡]Global Process Chemistry, Merck, P.O. Box 2000, Rahway, New Jersey 07065, United States

Supporting Information

**ABSTRACT:** Process research and development of a synthetic route towards a novel renin inhibitor (**1**) is described. The highly convergent synthetic route provided **1** in 15% yield on multikilogram scale with a longest linear sequence of 11 steps. The use of catalytic hydrogenation features prominently in our design. The proper choice of *N*-methylpyridone surrogate was also important, and we describe a method for the easy conversion of 2-methoxypyridines to *N*-methylpyridones using cheap and readily available reagents.

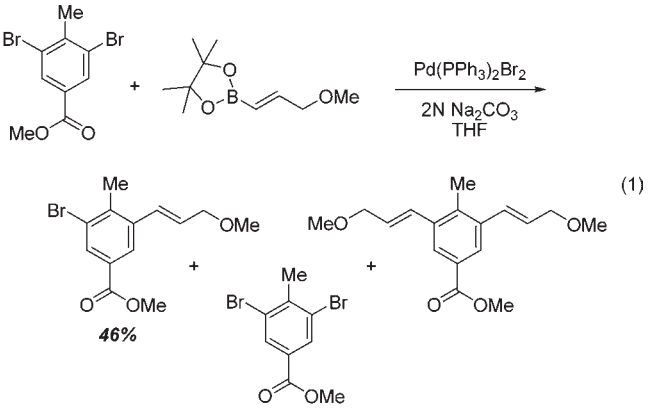
## INTRODUCTION

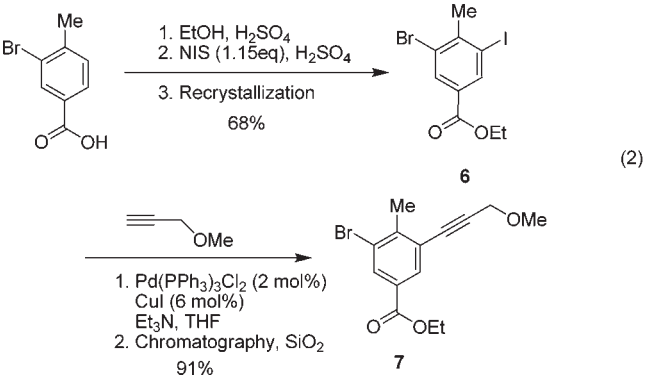
Essential hypertension is known to affect over a billion people worldwide.[1] If left untreated, hypertension can lead to failure of a host of biological functions in the brain, kidney, and heart.[2] The renin−angiotensin−aldosterone system[3] is a tightly regulated biological cascade known to play a role in the control of blood pressure. Consequently, its various steps have been targets of novel agents for relief of hypertension as well as end-organ protection.[4,5] As part of a drug discovery program in our laboratories, **1**·**HCl** was identified as a potent and selective inhibitor of renin with a suitable profile for further clinical development.[6] In order to do so, we developed a synthesis which would allow for its production on kilogram scale. Herein, we report our efforts to develop an enantioselective, practical, and convergent approach to **1** which was demonstrated on multikilogram scale for the first GMP delivery.

## RESULTS AND DISCUSSION

Our retrosynthetic analysis is shown in Figure 1. We envisioned that **1** could be assembled in a convergent manner with final amidation step between the key acid (**2**) and amine fragments (**3**). The chirality in **2** would be installed via asymmetric hydrogenation of the tetrasubstituted olefin which could be readily obtained from commercially available piperidine (**4**). The choice of pyridone surrogate was crucial to the success of this strategy. We envisaged the amine fragment (**3**) as accessible from amidation and reduction of the corresponding 3-bromo-4-toluic acid (**5**), while the alkyne moiety could be installed on an appropriately substituted halogenated arene.

**Amine Fragment (3) Synthesis.** Previously, gram-scale synthesis of amine (**3**) was achieved via a nonselective Suzuki coupling between a 3,5-dibromo aryl and the appropriate alkenyl-boronic acid (eq 1).[6a] The resulting mixture of mono- and bis-coupled products required column chromatography in order to isolate the desired intermediate and afforded low yield (46%).




**Special Issue:** Asymmetric Synthesis on Large Scale 2011

**Received:** April 18, 2011
**Published:** June 24, 2011





dx.doi.org/10.1021/op2001063 | *Org. Process Res. Dev.* 2011, 15, 1138–1148

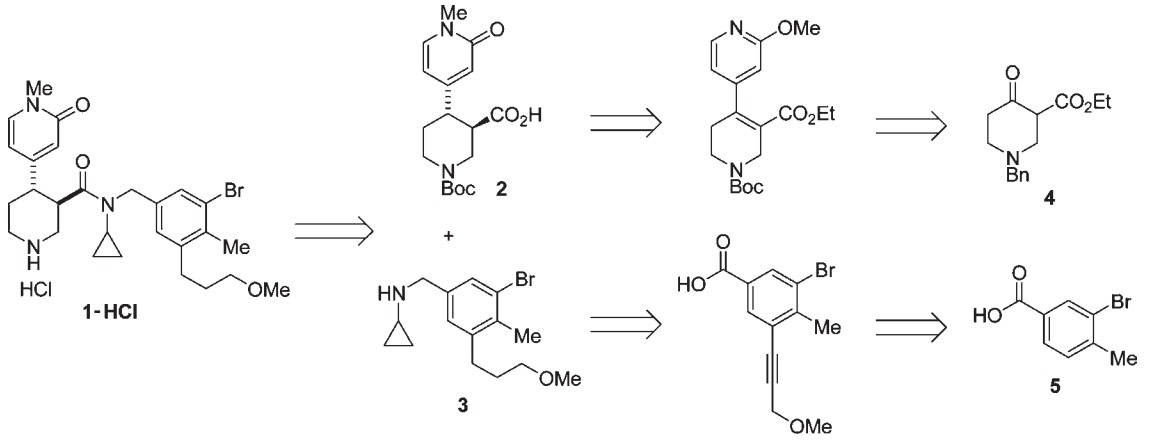
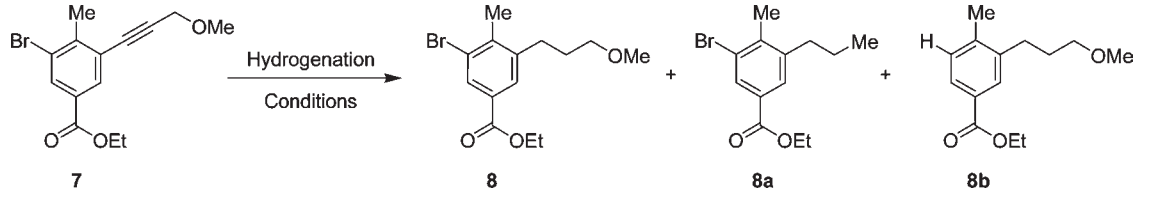



**Figure 1.** Retrosynthetic approach to **1**.

**Table 1. Hydrogenation of alkyne 7**




| entry | catalyst[a] | solvent | additive[b] | conversion[c] (%) | 8:8a[c] | 8b[c] (%) |
|---|---|---|---|---|---|---|
| 1 | $RhCl(PPh_3)_3$ | EtOAc | none | 0 | – | – |
| 2 | Pd/C | EtOH | none | 0 | – | – |
| 3 | Pd/C | EtOH | $MgBr_2$ | 100 | 9:1 | 3.3 |
| 4 | $PtO_2$ | EtOH | none | 100 | 1:1 | – |
| 5 | $PtO_2$ | PhMe | none | 100 | 13:1 | <3 |
| 6 | $PtO_2$ | PhMe | AcOH | 100 | 19:1 | – |
| 7 | $PtO_2$ | PhMe | $Cs_2CO_3$ | 100 | >50:1 | 1.8 |

[a] 5 mol % catalyst loading. [b] 20 mol % additive. [c] Determined by HPLC.

To circumvent this problem, we employed arene (**6**) which could be subjected to monoselective cross-coupling due to the differentially activated halides.[7] Additionally, by moving from a Suzuki to a Sonagashira coupling, we were able to replace the expensive vinyl-boronic ester with a propargyl ether (eq 2). Alkyne **7** was obtained from successful cross-coupling, and then studied under a variety of hydrogenation conditions.

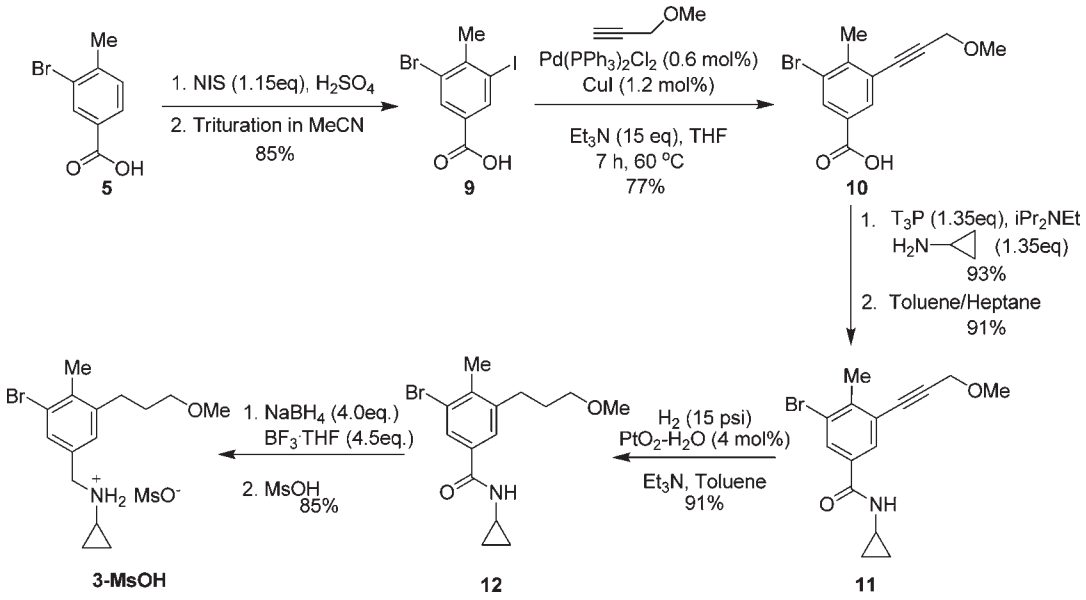
We found that the major issue associated with this hydrogenation step was the formation of two side products, **8a** and **8b**, resulting respectively from reduction of C-OMe and C−Br bonds. Formation of **8b** could be minimized by switching from Pd- to Pt-based catalysts. For example, Adam's catalyst afforded <3% **8b**; however, concomitantly high amounts of **8a** were observed (Table 1, entry 4). Screening revealed that **8a** levels could be reduced by switching the solvent from EtOH to PhMe (Table 1, entries 4−5) and that various additives could improve that ratio further (Table 1, entries 6−7).[8] It was also noted that higher levels of residual palladium, from the previous Sonogashira coupling, resulted in greater levels of impurity **8b**. In order to avoid this byproduct, we required palladium levels to be <100 ppm. We therefore chose to reorganize the synthesis around opportunities for purification via crystallization. Since amides **11** and **12** are highly crystalline,[9] we opted to run the amidation step first, followed by crystallization and finally reduction (Scheme 1). Moreover, this sequence allowed for elimination of one step from our synthesis as esterification would not be required.

Synthesis of the amine fragment is summarized in Scheme 1. Iodination of commercially available 3-bromo-4-methylbenzoic acid with *N*-iodosuccinimide (NIS) proved to be highly selective for the 5-position.[10] Excess NIS (1.15 equiv) allowed complete conversion and did not form any bis-iodo impurities after 2 h at 20 °C. Upon completion of the reaction, the mixture was slowly poured into cold 1 N HCl to precipitate product **9**. The solid was then triturated in ACN to recover benzoic acid **9** in high purity. Sonogashira coupling with methyl propynolate was performed directly on benzoic acid **9**. Gratifyingly, this reaction was highly selective for coupling of the iodide over the bromide with no bis-coupling observed.[7] By performing the coupling at 60 °C and with a large excess (15 equiv) of triethylamine, the palladium loading could be reduced below 1 mol %. Use of excess base allowed for complete conversion after 7 h, whereas longer reaction times were needed with less $Et_3N$. At the end of the reaction, a simple extractive workup[11] permitted rejection of impurities and isolation of acid-alkyne **10** in 77% yield.

Tripropylphosphonic acid anhydride ($T_3P$)-mediated[12] amidation between acid **10** and cyclopropyl amine afforded amide **11**


dx.doi.org/10.1021/op2001063 |*Org. Process Res. Dev.* 2011, 15, 1138–1148

**Scheme 1. Synthesis of amine fragment 3-MsOH**

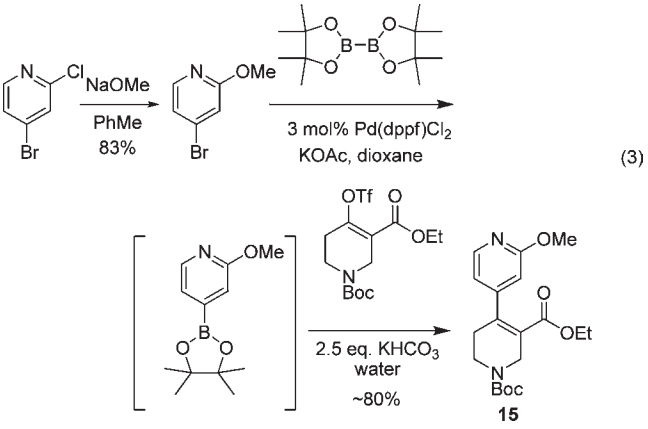



in 93% yield. Crystallization of this intermediate from toluene/heptane proceeded with high recovery (91%) to provide a purity upgrade with low metal content.[13] Hydrogenation with Adam's catalyst in PhMe with basic additives which had previously shown to be beneficial[14] showed high yield, with $Et_3N$ affording the best purity profile for production of amide **12**.

Amide reduction was performed using borane prepared in situ from $NaBH_4$ and $BF_3 \cdot THF$.[15] Slow addition of $BF_3 \cdot THF$ (4.5 equiv) to a mixture of amide and sodium borohydride (4 equiv) was needed to control the heat and gas evolution associated with this transformation. The resulting amine was an oil. To facilitate handling and storage, as well as guarantee high purity, its MsOH salt was prepared. **3**-MsOH was prepared via slow addition of MsOH to a solution of the amine in MTBE/i-PrOAc in the presence of 2 wt % seeds. Using this procedure, **3**-MsOH was obtained in 85% yield over the two steps with a purity profile suitable for the final amidation step and end-game (HPLC 97.8 A%). The MsOH salt is air stable, and no degradation was observed over >2 months at room temperature.

**Acid Fragment (2) Synthesis.** Synthesis of the acid fragment (**2**) centered around asymmetric hydrogenation of a highly substituted tetrahydropyridine.[16,17] Success of this strategy would be highly dependent on the nature of the protecting group as well as the nature of the aryl substituent. Early screening revealed liabilities associated with over-reduction of the pyridone-ring during high-pressure hydrogenation of substrates derived from the requisite methylpyridone. Various pyridine derivates as well as pyridine *N*-oxides were investigated as potential alternative substrates for hydrogenation. Any surrogate would have to be amenable to facile, high-yielding and scalable pyridine-to-pyridone rearrangement. Substrates derived from pyridine *N*-oxide also suffered from various side reactions associated with N−O bond reduction which ultimately led to catalyst deactivation. Installation of a 2-methoxy pyridine appendage was selected due to a superior performance in the asymmetric hydrogenation (vide infra), as well as precedence for conversion to the requisite *N*-methylpyridone.[18]

With our strategy firmly established we undertook the synthesis of acid (**2**) (Figure 2). The piperidine core could be conveniently constructed from commercially available benzyl-protected $\beta$-keto ester (**4**). The benzyl protecting group was switched for a Boc followed by activation of the ketone as a triflate as previously described.[16,19] With the triflate in hand, the stage was set for the installation of the required methylpyridone in **1**. The choice of coupling partner for this Suzuki reaction was largely guided by the availability of the desired starting materials in the appropriate timelines. While 4-bromo-2-methoxy pyridine was shown to be a viable coupling partner in a one-pot borylation−Suzuki sequence to provide **15** on gram-scale, it was not available on kilogram scale within reasonable timelines. An alternative preparation of this building block using 4-bromo-2-chloropyridine was developed. Unfortunately, we were still faced with unacceptable lead times for the raw material, and another route had to be designed. Nonetheless, this sequence could be used in future deliveries of **1** (eq 3).




(3)

For the first GMP delivery of **1** we opted for the use of readily available 2,4-dichloropyridine. $S_NAr$ reaction with sodium methoxide afforded the 4-chloro-2-methoxypyridine as the major


dx.doi.org/10.1021/op2001063 |*Org. Process Res. Dev.* 2011, 15, 1138–1148

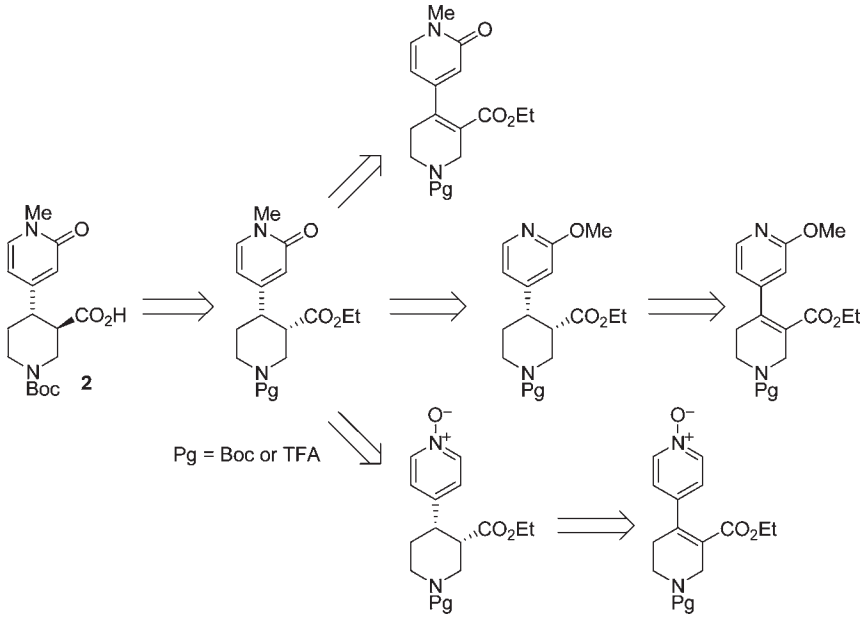
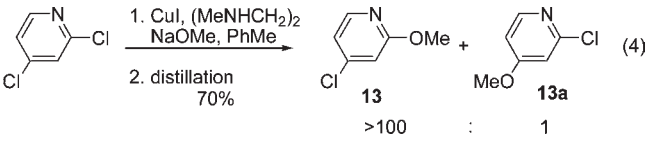



**Figure 2.** Different strategies for synthesis of acid fragment **2**.

product with solvent showing the greatest effect on product ratios.[20] Reaction run in toluene afforded a good ratio of **13**:**13a**, albeit with low conversion. Inspired by a recent report that copper salts catalyze this type of displacement whilst improving the isomeric ratio,[21] we screened various copper catalysts and identified CuI and *N*,*N*′-dimethylethylenediamine as an effective catalyst/ligand combination to improve the rate of reaction. We found that complete conversion could be achieved within 20 h with reduced catalyst loading (2 mol %) if the reaction was run more concentrated (1.0 M) and with a larger excess of sodium methoxide (1.7 equiv). These optimized conditions maintained a good ratio (100:1) of **13**:**13a** and afforded good isolated yield (70%) of the desired regioisomer after distillation (eq 4).[21]




(4)

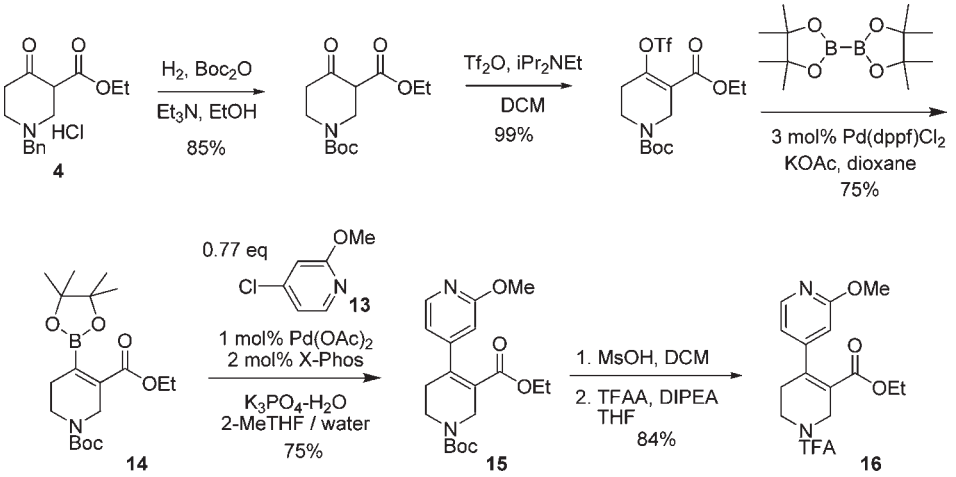
4-Chloro-2-methoxypyridine was then used in the Suzuki reaction with vinyl boron−pinacol ester **14**. Optimization of the Suzuki-coupling conditions revealed that a combination of 1 mol % $Pd(OAc)_2$, 2 mol % X-Phos,[22] and aqueous $K_3PO_4$ in 2-methyltetrahydrofuran (2-MeTHF) at 50 °C afforded complete conversion of the chloropyridine starting material to the desired product **15** in a 75% assay yield. All attempts at immediately performing hydrogenation on Boc protected **15** resulted in partial deprotection and catalyst poisoning.[23] Thus, it was necessary to perform a protecting group switch from Boc to TFA. Fortunately, this protecting group switch, while inelegant, could be performed as a through process without isolation of the free piperidine (Scheme 2).

Olefin **16** was subjected to chiral hydrogenation previously developed in our laboratories.[16,24] Initial conditions were Ru(cod)(methallyl)$_2$/SL-J212-1 (10 mol % preformed catalyst) at room temperature, 500 psig, in 2-MeTHF, with 1.2 equiv of $HBF_4 \cdot OEt_2$. Tetrafluoroboric acid was required to protonate the pyridyl-nitrogen, which otherwise acts as a catalyst poison. High enantioselectivity (98% ee) and complete conversion were obtained using the above reaction conditions. Further pressure and temperature optimization showed the reaction can proceed within 16 h at 350 psi of $H_2$ at 50 °C with reduced catalyst loadings (1.5 mol %), with no erosion of enantioselectivity. Using these optimized conditions, the catalyst loading could be further reduced to 1 mol % without effect on conversion or rate.[25] Following hydrogenation, charcoal treatment was performed to reduce transition metal levels, and chiral ester **17** was afforded in 85% yield and >98.5% ee.

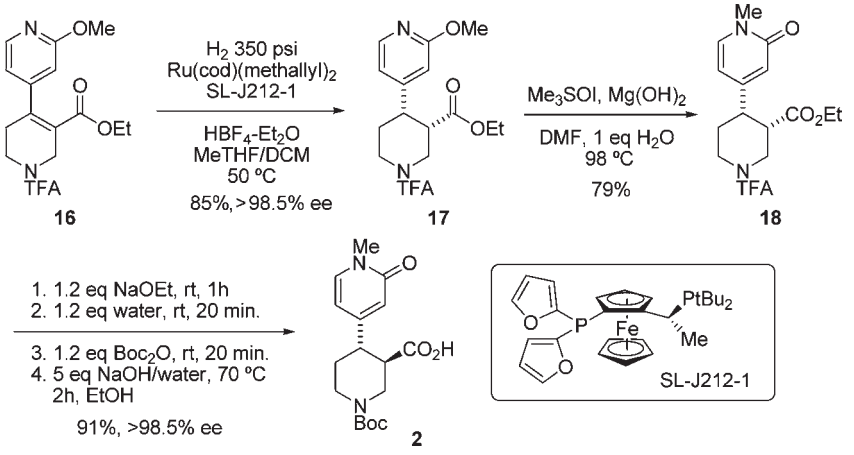
The crude stream from hydrogenation was then used directly in the pyridine/pyridone conversion. Early studies showed it was possible to effect this transformation with a large excess of iodomethane at high temperature. This approach was viable and was successfully performed on small scale in sealed vessels. However, the low boiling point and high toxicity associated with MeI prevented scale-up of this process. Therefore, a superior alternative would have to be devised. Drawing from previous experience with selective *N*-alkylation of heterocycles,[26] we were pleased to find that treatment of crude **17** with trimethylsulfoxonium iodide and magnesium hydroxide in DMF at 98 °C afforded clean conversion to the *N*-methylpyridone within 2 h (Scheme 3). The use of wet DMF was crucial to achieve high conversion; therefore, one equivalent of water was added to the reaction.[27] The crystalline pyridone was isolated as a solid after a trituration in MTBE/i-PrOAc in 79% yield. The final four-step sequence for the preparation of acid **2** was carried out in one-pot (eq 5).[16] Treatment of **18** with sodium ethoxide afforded a ratio of *trans:cis* (**18a**:**18**) of approximately 6:1. Despite this modest ratio, after TFA removal by addition of water and reprotection with *tert*-butyl carbamate (**18c**), the ratio continued to upgrade to ∼22:1; after hydrolysis with 5 N NaOH the ratio had improved to >100:1 for crude acid **2**. Trituration of the acid in


dx.doi.org/10.1021/op2001063 |*Org. Process Res. Dev.* 2011, 15, 1138–1148

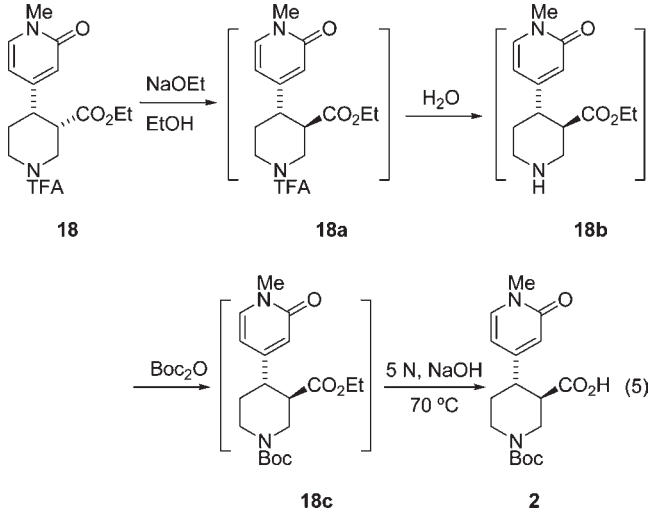
**Scheme 2. Synthesis of hydrogenation precursor 16**




**Scheme 3. Chiral hydrogenation and pyridone rearragement in the synthesis of acid 2**



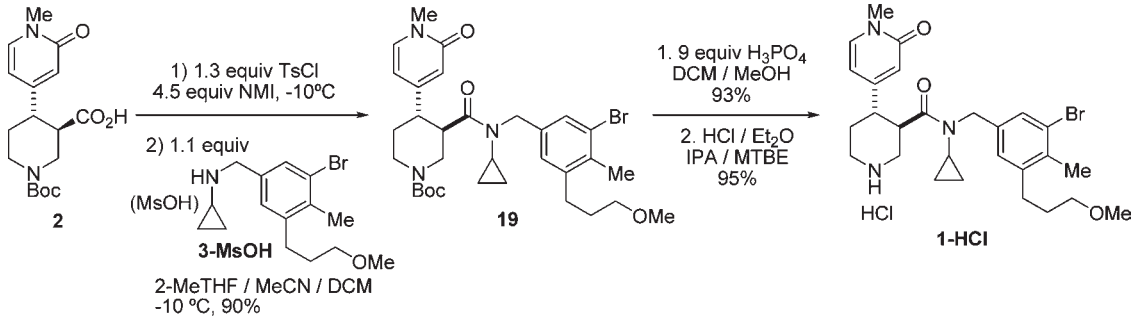

MTBE/2-MeTHF afforded complete rejection of the undesired *epi*-**2** affording **2** in 91% yield and >98.5% ee.




**Final Amidation and End-Game.** Work from the discovery group had shown that HATU effectively coupled amine **3** with acid **2**.[6] However, previous experience led us to consider the use of a *p*-toluenesulfonyl mixed anhydride as a more economic mode of activation.[28] In this procedure, the acid is first activated as an electrophile using *p*-toluenesulfonyl chloride and *N*-methylimidazole (NMI) in 2-MeTHF/MeCN. After addition of the requisite amine, the desired amide was obtained. We were pleased to find that we could directly use **3-MsOH** salt in this coupling reaction by simple modification: an additional equivalent of NMI was used to neutralize the salt (Scheme 4). To make the process more easily scalable, the salt was first dissolved in DCM and added as a solution which allowed complete control of the rate of addition. Careful optimization of this process with respect to temperature was performed in order to avoid any formation of the diastereomeric *cis*-**19**. Stress tests on the reaction revealed that performing the reaction at higher temperature increased the relative proportion of *cis*-diastereomer, with room temperature reaction yielding as much as 5%. Gratifyingly, by keeping the temperature below −5 °C during the acid activation and subsequent addition of the amine, the levels of *cis*-**19** were kept below 0.5%. The crude solution of amide **19** was directly used in the Boc deprotection step. Development on this step revealed that TFA, $H_3PO_4$, formic acid, and anhydrous HCl could potentially be used to perform


dx.doi.org/10.1021/op2001063 |*Org. Process Res. Dev.* 2011, 15, 1138–1148

**Scheme 4. Final amidation and end-game**




the reaction. The two acids which afforded the highest yields and cleanest conversion were $H_3PO_4$ and HCl. Mainly for its ease of manipulation, phosphoric acid was used for this step. Reactions could be run in DCM as solvent with 9 equiv of $H_3PO_4$. It was observed that the **1** phosphoric acid salt would gum out during the course of the reaction. To obviate this issue, 0.5 mL/g of MeOH was added to the reaction which provided a homogeneous solution. Extractive workup allowed for rejection of major impurities. The solution of the free base was then carried forward to the final salt formation and isolation.

**1**-HCl salt was identified as a stable crystalline and bioavailable form. The HCl salt formation was achieved by dissolving the free base in IPA (5 mL/g) with 0.1 mL/g of water and 2 wt % of seeds. Seeds were critical in order to obtain the desired crystalline polymorph. To this cooled solution is added HCl in diethyl ether (1.3 equiv). After ageing for 18 h at room temperature, MTBE is added, and the suspension is then cooled for maximum recovery (95%) after filtration. **1**-HCl was obtained as a white solid, HPLC 98.4 A%, >99.9% ee.

## CONCLUSION

In summary, a highly convergent and scalable route to a novel renin inhibitor was developed. The amine fragment (**3**) required six steps and the chiral acid (**2**) nine steps. The longest linear sequence is 11 steps starting from commercially available piperidine **4**. The key chiral center was installed via an enantioselective hydrogenation of a tetrasubstituted olefin and the amine fragment synthesis features a highly selective Sonogashira coupling and alkyne hydrogenation. This process was performed on multikilogram scale to provide >2.5 kg of **1**-HCl salt.

## EXPERIMENTAL SECTION

**3-Bromo-5-iodo-4-methylbenzoic Acid (5).** 3-Bromo-4-methyl benzoic acid (7.50 kg, 1.0 equiv) was dissolved in $H_2SO_4$ (22.5 L, 3 mL/g). The mixture was cooled to 5 °C. The *N*-iodosuccinimide (9.00 kg, 1.15 equiv) was added in six portions (1.5 kg each) over a period of 1 h to control the exotherm (internal temperature between 5 and 20 °C). Ten liters of $H_2SO_4$ was added to facilitate stirring. The mixture was warmed to 20 °C and aged for a period of 1 h. HPLC showed >98% conversion to the desired iodo-aryl. The mixture was poured onto a cold (2 °C) 1 N HCl solution (60 L, 8 mL/g) over a period of 1 h at <35 °C. The iodo-aryl precipitated out of solution. The mixture was stirred 20 min at 20 °C, then filtered, rinsed 2 × 2.5 mL/g 1 N HCl (2 × 20 L). The pink precipitate was triturated in acetonitrile (8 mL/g, 60 L). After stirring for 60 min at 20 °C, the mixture was filtered. The cake was rinsed with cold (2 °C) acetonitrile (2 × 2 mL/g, 2 × 15 L). The product was dried under nitrogen atmosphere for 15 h. Crude mass (dried): 10.05 kg, 85%, as a pale-pink solid (93.7 A% by HPLC). **$^1$H NMR (400 MHz, DMSO-$d_6$)**: $\delta$ 8.27 (s, 1 H); 8.02 (s, 1 H); 2.60 (s, 3 H). **$^{13}$C NMR (101 MHz, DMSO-$d_6$)**: $\delta$ 164.5, 144.4, 138.9, 132.9, 131.5, 122.9, 101.8, 29.1. **IR (neat)**: 3068, 2683, 2533, 1683, 1534, 1370, 1284, 1141, 902, 766, 718. **HRMS**: (ESI) *m*/*z* calcd for $C_8H_6BrIO_2$ (M + H) 340.8669, found 340.8666. **Melting point**: 152.5−154.2 °C.

**3-Bromo-5-(3-methoxyprop-1-yn-1-yl)-4-methylbenzoic Acid (9).** 3-Bromo-5-iodo-4-methylbenzoic acid (8.00 kg, 1.0 equiv) is dissolved in THF (16 L, 2 mL/g) and $Et_3N$ (49 L, 15 equiv). The mixture was degassed bubbling nitrogen in the solution for a period of 10 min. $PdCl_2(PPh_3)_2$ (82 g, 0.005 equiv) was added, followed by the CuI (45 g, 0.01 equiv) and methylpropargyl ether (2.97 L, 1.5 equiv). The mixture was warmed to 60 °C and aged for a period of 7 h. After 5 h, 0.1% $PdCl_2(PPh_3)_2$ (16 g) and 0.2% CuI (9 g) were added. After 7 h, HPLC showed >99% conversion. The volatiles were removed under reduced pressure. The residue was dissolved in 1N NaOH (8 mL/g, 64 L) and MTBE (4 mL/g, 32 L). The layers were separated, the aqueous layer was washed 1 × MTBE (1 × 4 mL/g, 32 L). The aqueous layer was acidified to pH 1 using 6 N HCl (9 L), then extracted with i-PrOAc (1 × 7 mL/g, 1 × 55 L, 1 × 5 mL/g, 1 × 40 L, 1 × 2.5 mL/g, 1 × 20 L). Combined organic layers were washed with brine (4 mL/g, 32 L). To the dark i-PrOAc solution was added Darco KB-G (25 wt %, 2.0 kg). The suspension was stirred for a period of 2 h. The suspension was filtered over Solka Floc, rinsed 2 × 2.5 mL/g i-PrOAc (2 × 20 L). The filtrate was treated with $Na_2SO_4$ (0.5 kg/20 L) for 16 h, then concentrated to dryness under reduced pressure. Assay yield: 5.11 kg, 77%, as an orange solid (91.3 A% by HPLC). **$^1$H NMR (400 MHz, acetone-$d_6$)**: $\delta$ 8.13 (s, 1 H); 8.00 (s, 1 H); 4.40 (s, 2 H); 3.41 (s, 3 H); 2.59 (s, 3 H). **$^{13}$C NMR (101 MHz, acetone-$d_6$)**: $\delta$ 165.6, 145.1, 134.1, 133.0, 130.8, 125.6, 125.5, 92.3, 84.0, 60.4, 57.7, 21.8. **IR (neat)**: 1692, 1548, 1421, 1304, 1099, 767. **HRMS**: (ESI) *m*/*z* calcd for $C_{12}H_{11}BrO_3$ (M + H) 280.9818, found 280.9821. **Melting point**: 134.2−135.2 °C.

**3-Bromo-*N*-cyclopropyl-5-(3-methoxyprop-1-yn-1-yl)-4-methylbenzamide (10).** 3-Bromo-5-(3-methoxyprop-1-yn-1-yl)-4-methylbenzoic acid (5.05 kg, 1.0 equiv) is dissolved in THF (30 L, 6 mL/g). DIPEA (6.84 L, 2.20 equiv) and the cyclopropyl amine (1.70 L, 1.35 equiv) are added. The mixture was cooled to 9 °C. Propylphosphonic anhydride ($T_3P$) (50 wt % in EtOAc, 14.4 L, 1.35 equiv) was added to the solution over a period of 90 min to control the exotherm (9 to 19 °C). The mixture was warmed to 19 °C and aged for a period of 15 min.


dx.doi.org/10.1021/op2001063 |*Org. Process Res. Dev.* 2011, 15, 1138–1148

HPLC showed >98% conversion. The reaction was quenched by pouring the solution on a cold (5 °C) saturated solution of $NH_4Cl$ (8 mL/g, 40 L). The mixture was allowed to warm to 20 °C and stirred 60 min. The mixture was diluted with i-PrOAc (8 mL/g, 40 L). The layers were separated, the aqueous layer was back extracted 1 × *i*-PrOAc (6 mL/g, 30 L). Combined organic layers were washed 1 × 1 N HCl (4 mL/g, 20 L), 1 × saturated $NaHCO_3$ (4 mL/g, 20 L), 1 × brine (4 mL/g, 20 L). The organic layer was dried with $Na_2SO_4$ (500 g/20 L) over 18 h, and concentrated under reduced pressure, then solvent switched to toluene. Assay yield: 5.34 kg, 93%. The crude 3-bromo-*N*-cyclopropyl-5-(3-methoxyprop-1-yn-1-yl)-4-methylbenzamide (5.33 kg, 1.0 equiv) was then suspended in toluene (36 L, 7 mL/g). The mixture was warmed to 50 °C to dissolve the solids. The solution was cooled to 25 °C. Seeds (0.5%, 25 g) were added, and the mixture was aged at 25 °C for 45 min. Heptane (7 mL/g, 36 L) was added over a period of 5 min. The mixture was aged at 20 °C for 1 h, then cooled to 5 °C, aged 10 min, then filtered. The cake was rinsed 2 × 3 mL/g cold (2 °C) toluene/heptane 1:2 (2 × 15 L), 1 × 3 mL/g heptane (15 L). The material was dried on frit under a nitrogen atmosphere for a period of 40 h. Yield: 4.84 kg, 91% as a beige solid (97.5 A% by HPLC). **$^1$H NMR (500 MHz, Acetone-$d_6$)**: $\delta$ 8.01 (s, 1 H); 7.92 (s, 1 H); 7.86 (s, 1 H); 4.37 (s, 2 H); 3.39 (s, 3 H); 2.95−2.89 (m, 1 H); 2.53 (s, 3 H); 0.76−0.67 (m, 2 H); 0.68−0.60 (m, 2 H). **$^{13}$C NMR (126 MHz, Acetone-$d_6$)**: $\delta$ 166.1, 142.9, 134.8, 132.1, 130.7, 125.5, 125.1, 91.8, 84.3, 60.4, 57.7, 23.9, 21.5, 6.3. **IR (neat)**: 3268, 2821, 1635, 1525, 1313, 1098, 1028. **HRMS**: (ESI) *m*/*z* calcd for $C_{15}H_{16}BrNO_2$ (M + H) 322.0437, found 322.0433 **Melting point**: 109.5−111.4 °C.

**3-Bromo-*N*-cyclopropyl-5-(3-methoxypropyl)-4-methyl Benzamide (11).** A visually clean and dry 10- gal Hastelloy autoclave, pretested for leaks, was charged with the 3-bromo-*N*-cyclopropyl-5-(3-methoxyprop-1-yn-1-yl)-4-methylbenzamide (1.60 kg, 1.0 equiv) and toluene (15 L, 10 mL/g). To the mixture was added the $PtO_2$ (64 g, 0.04 equiv) as a toluene (0.5 L) suspension, followed by the addition of the triethylamine (140 mL, 0.20 equiv). Toluene (30 L) was added to dilute the mixture. The vessel was purged three times with nitrogen, then three times with hydrogen. The final pressure of hydrogen was 25 psig. The mixture was initially agitated at 350 rpm at 20 °C. During the first 30 min, a 15 °C exotherm was observed (20 to 35 °C). After this initial exotherm, the agitation was increased to 650 rpm, and the mixture was stirred for another 4 h. The solution was transferred to 5-gal plastic containers. The reaction was performed three times on similar scale, then combined in a 140-L extractor. The assay yield on the combined organic layers was 4.40 kg, 91% as a dark-brown oil. To the crude toluene solution of 3-bromo-*N*-cyclopropyl-5-(3-methoxypropyl)-4-methyl benzamide (4.20 kg, 1 equiv) was added Darco KB-G (2.00 kg, 50 wt %), and the mixture was stirred at 20 °C for a period of 1.5 h. The mixture was filtered on Solka Floc (∼2 kg), rinsed 1 x toluene (3 mL/g, 12 L), 1 × toluene/MTBE 1:1 (3 mL/g, 12 L), 1 × toluene/MTBE 1:1 (2 mL/g, 8 L). Assay yield: 3.87 kg = 92%. The filtrate was concentrated to dryness (residual toluene: 1.2 equiv). The liquid residue was dissolved in MTBE (8 mL/g, 31 L). The temperature of the mixture was adjusted to 27 °C, then the solution was seeded with crystallized amide (0.4%, 15.7 g). The mixture was aged at 27 °C for 30 min, during which period the amide crystallized out of solution. Heptane (8 mL/g, 31 L) was then added over 1.5 h to further crystallize the amide. The mixture was aged 1 h, then filtered. The cake was rinsed with MTBE/heptane 1:10 (3 mL/g, 12 L), then 1 × 2 mL/g heptane (1 × 8 L). The material was dried on the frit for 40 h under a nitrogen atmosphere. Yield: 3.23 kg = 77% as a beige solid (97.3 A% by HPLC). **$^1$H NMR (500 MHz, acetone-$d_6$)**: $\delta$ 7.87 (m, 2 H); 7.65 (s, 1 H); 3.35 (t, $J$ = 6.12 Hz, 2 H); 3.27 (s, 3 H); 2.93−2.86 (m, 1 H); 2.75 (t, $J$ = 7.91 Hz, 2 H); 2.39 (s, 3 H); 1.80−1.72 (m, 2 H); 0.75−0.67 (m, 2 H); 0.61−0.56 (m, 2 H). **$^{13}$C NMR (126 MHz, acetone-$d_6$)**: $\delta$ 167.0, 143.6, 139.4, 134.7, 129.7, 128.0, 126.2, 72.2, 58.5, 31.7, 31.0, 23.8, 19.2, 6.4. **IR (neat)**: 3281, 2924, 2856, 1636, 1520, 1458, 1308, 1110, 1021. **HRMS**: (ESI) *m*/*z* calcd for $C_{15}H_{20}BrNO_2$ (M + H) 326.0750, found 326.0745. **Melting point**: 84.6−85.4 °C.

***N*-[3-Bromo-5-(3-methoxypropyl)-4-methylbenzyl]cyclopropanamine Mesylate (3-MsOH).** 3-Bromo-*N*-cyclopropyl-5-(3-methoxypropyl)-4-methyl benzamide (3.23 kg, 1.0 equiv) is dissolved in THF (26 L, 8 mL/g). Sodium borohydride (1.69 kg, 4.5 equiv) was added to the solution in three portions (200 g, 500 g, 990 g). $BF_3$·THF (5.5 L, 5.0 equiv) was added to the mixture over a period of 2 h to control the exotherm and keep the internal temperature below 30 °C (temperature range from 19.8 to 28.7 °C). After complete addition of the $BF_3$.THF, the mixture was warmed to 35 °C over 1.5 h and aged for a period of 18 h. The mixture was slowly poured on 3 N HCl (10 mL/g, 33 L) over a period of 2 h, while under a nitrogen atmosphere. The mixture was warmed to 50 °C and aged for a period of 2 h. The mixture was cooled to 25 °C and diluted with MTBE/heptane 1:1 (10 mL/g, 33 L). The layers were separated, and the organic layer was back extracted 1 × 2 mL/g 2 N HCl (2 × 7 L). Combined aqueous layers were basified to pH 14 using 10 N NaOH (12 L), then extracted with MTBE (2 × 7 mL/g, 2 × 23 L). Combined organic layers were washed with half-brine (5 mL/g, 16 L), brine (5 mL/g, 16 L). The organic layer was dried with $Na_2SO_4$ for 15 h, filtered via in-line filter, and concentrated under reduced pressure. MTBE (31 L, 10 mL/g) and i-PrOAc (19 L, 6 mL/g) are added to the crude *N*-[3-bromo-5-(3-methoxypropyl)-4-methylbenzyl]cyclopropanamine. MsOH (879 g, 0.91 equiv) was added as a THF (1 mL/g, 3.2 L) solution over a period of 90 min. After the addition of ∼5% of the MsOH, the solution was seeded (2% seeds, 62 g). The mixture was aged 2.5 h (final temperature = 24.8 °C), then filtered and rinsed 1 × 5 mL/g MTBE/i-PrOAc 5/1 (15 L), 1 × 5 mL/g MTBE (15 L). The salt was dried on frit under a $N_2$ atmosphere for 40 h. Yield: 3.67 kg, 89% as a snow-white powder (97.8 A% by HPLC). Charcterized as free base: **$^1$H NMR (500 MHz, $CHCl_3$-$d$)**: $\delta$ 7.34 (s, 1 H); 7.01 (s, 1 H); 3.71 (s, 2 H); 3.36 (t, $J$ = 6.2 Hz, 2 H); 3.32 (s, 3 H); 2.69 (t, $J$ = 7.8 Hz, 2 H); 2.34 (s, 3 H); 2.13−2.07 (m, 1 H); 1.97 (s, 1 H); 1.83−1.75 (m, 2 H); 0.43−0.37 (m, 2 H); 0.37−0.33 (m, 2 H). **$^{13}$C NMR (126 MHz, acetone-$d_6$)**: $\delta$ 142.0, 139.3, 134.0, 130.0, 128.2, 126.0, 71.8, 58.5, 52.7, 31.1, 30.2, 29.9, 18.6, 6.4. **IR (neat)**: 3085, 2921, 2868, 2824, 1554, 1431, 1333, 1200, 1113, 1010. **HRMS**: (ESI) *m*/*z* calcd for $C_{15}H_{22}BrNO$ (M + H) 312.0957, found 312.0955.

**2-Chloro-4-methoxypyridine (13).** 2,4-Dichloropyridine (2.09 kg) was dissolved in 14 L of toluene at room temperature. CuI (53.7 g), DMEDA (150 mL) and NaOMe (1.14 kg) were added in order under $N_2$. The mixture was stirred at 105−110 °C for 21 h. HPLC showed <0.4% of starting material, and the ratio of **13**:**13a** was 12.4 (270 nm). The mixture was filtered through 6 kg of silica with DCM (∼30 L). The desired product **13** elutes first. Fractions were concentrated to a minimum volume at 40 °C, 74 mmHg, followed by atmospheric distillation through

a glass helix-packed column to remove toluene and provide the title compound in 74% yield of 98 A% used as-is in the next step.

**1-*tert*-Butyl 3-ethyl 2′-methoxy-5,6-dihydro-4,4′-bipyridine-1,3(2*H*)-dicarboxylate (15).** The vinyl triflate (prepared according to literature precedent)[19b] in 55 L of dioxane was treated with 7.36 kg of bis-pinacol diboron, 600 g of $Cl_2Pd$-(dppf), 8.13 kg of KOAc. The mixture was degassed with $N_2$ and heated to 90 °C. After aging for 8 h, the reaction was at 92.5% conversion. The reaction was allowed to cool slowly to room temperature overnight. The following morning the reaction had reached complete conversion. Isopropyl acetate (45 L) and water (80 L) were added and stirred for 10 min, and the layers were separated. The organic layer was washed with 40 L of water and then concentrated using a batch concentrator and flushed with 4 L of heptane to give an oil which was further diluted with 10 L of heptane. The oil was purified by silica gel eluting with heptane then a gradient of increasing amounts of ethyl acetate (up to 20%). The product-rich fractions were combined and stripped to an oil using the batch concentrator to give 7.9 kg (75%). A separate 22-L round-bottom flask (RBF) was charged with 7.75 L of 2-MeTHF which was degassed with multiple vacuum/nitrogen purges. To this solution was added X-Phos and palladium acetate which were stirred at room temperature for 5 min (a burgundy-colored solution formed). The solution was aged for one hour. This solution was then transferred to a 75-L RBF charged with 2.37 kg of the chloromethoxypyridine, the vinyl boronate, 10.36 L 2 M $K_3PO_4$ solution, and 15 L of 2-MeTHF. The solution was degassed with multiple vacuum/nitrogen purges. This solution was then heated to 58 °C at which point an exotherm further heated the mixture to 69 °C over the next 20 min. The reaction mixture then maintained a temperature of 67 °C for 1 h. The reaction was assayed and was complete by HPLC. The reaction mixture was then cooled to 25 °C, 600 g of EcoSorb C-941 was added, and the mixture was aged for 30 min. The mixture was then filtered through Solka Floc. The flask was rinsed with 2 L of 2-MeTHF. The cake was then washed with an additional 5 L of 2-MeTHF. The combined filtrate and wash were transferred into a 100-L extractor, and the aqueous layer was drawn off. The organic layer was washed with 14 L of dilute brine. The organic layer was then collected and transferred to a 50-L RBF. The solvent was then evaporated off and flushed with 16 L of heptane to remove residual 2-MeTHF. The mixture was stored on ice overnight and then chilled to −7 °C to give a thick slurry. The solids were filtered and rinsed with 2 × 2 L of cold heptane. The cake was then washed with 3 × 4 L of cold heptane and sucked dry to give 4.34 kg of a tan-gray solid. **$^1$H NMR (400 MHz, acetone-$d_6$)**: $\delta$ 8.09 (d, $J$ = 5.24 Hz, 1 H); 6.74 (d, $J$ = 5.23 Hz, 1 H); 6.55 (s, 1 H); 4.20 (s, 2 H); 3.93 (q, $J$ = 7.11 Hz, 2 H); 3.87 (s, 3 H); 3.60 (s, 2 H); 2.49−2.45 (m, 2 H); 1.46 (s, 9 H); 0.97−0.89 (m, 3 H). **$^{13}$C NMR (101 MHz, acetone-$d_6$)**: $\delta$ 166.4, 165.0, 154.8, 153.9, 147.4, 144.5, 126.8, 116.5, 109.3, 80.1, 72.7, 60.9, 53.5, 49.3, 28.5, 27.2, 13.8. **IR($\nu_{max}$ /cm$^{-1}$)**: 2981, 1696, 1387, 1235, 760; **HRMS** calculated for $C_{19}H_{26}N_2O_5$ ($M^+$): 362.1842; Found: 362.1823. **Melting point**: (EtOAc/Hex) 85.5−86.6 °C.

**Ethyl 2′-Methoxy-1-(trifluoroacetyl)-1,2,5,6-tetrahydro-4,4′-bipyridine-3-carboxylate (16).** 1-*tert*-Butyl 3-ethyl 2′-methoxy-5,6-dihydro-4,4′-bipyridine-1,3(2*H*)-dicarboxylate was dissolved (4.34 kg, 11.98 mol) in ethanol (28.2 L). To this mixture was added methanesulfonic acid (1.944 L, 29.9 mol). The mixture was heated to 55 °C, then slowly up to 65 °C. After heating for 1.5 h, 99.65% conversion was obtained, and the reaction was cooled. The solvent was then switched for IPAc (12 L), and 16 L of 10% sodium carbonate was added along with 900 g of solid sodium carbonate (pH ≈ 11). The layers were separated, and the aqueous layer was washed with 15 L of IPAc twice. The combined organic layers were washed with 10 L of water. This organic layer was concentrated to minimum volume, and then flushed with 5 L of 2-MeTHF. The volume was ajusted to 28 L of 2-MeTHF ($K_f$ = 200). Triethylamine (12.7 L ) was added to the mixture followed by TFAA (1.9 L) via addition funnel. The addition causes a temperature rise to 52 °C. The reaction was complete 5 min after the addition. The solution was cooled to 30 °C, 30 L of water was added. The layers were separated, and the organic layer was washed with 10 L of water and 12 L of 5 N HCl, and then the organic layer was washed with 15 L of water. The pH of the aqueous layer was then adjusted to 8 using 5 N NaOH, and then this aqueous layer was extracted with 2-MeTHF. The combined organic layers were dried over sodium sulfate. The suspension was then filtered and concentrated to ∼8 L ($K_f$ = 500). This solution was assayed to contain 3.6−3.7 kg (84−86% yield). **$^1$H NMR (600 MHz, DMSO-$d_6$, 363 K)**: $\delta$ 8.10 (d, $J$ = 5.20 Hz, 1 H); 6.77 (d, $J$ = 5.17 Hz, 1 H); 6.60 (s, 1 H); 4.40 (s, 2 H); 3.97−3.91 (m, 2 H); 3.86 (s, 3 H); 3.78 (s, 2 H); 2.57 (s, 2 H); 0.92 (s, 3 H). **$^{13}$C NMR**: Peaks were not assigned because of rotamers at room temperature. Spectra shown in Supporting Information. **IR($\nu_{max}$ /cm$^{-1}$)**: 2984, 1692, 1389, 1131, 1042. **HRMS** calculated for $C_{16}H_{17}F_3N_2O_4$ ($M^+$): 358.1140; Found: 358.1130.

**Ethyl (3*S*, 4*S*)-4-(1-Methyl-2-oxo-1,2-dihydropyridin-4-yl)-1-(trifluoroacetyl)piperidine-3-Carboxylate (18).** In a nitrogen-filled glovebox, ($O_2$ < 10 ppm) (*R*)-S-SL-J212-1 (46.9 g) was combined with (COD)Ru(Me-allyl)$_2$ (23.0 g) in a 1.0-L screw-cap bottle. $CH_2Cl_2$ (500 mL, $N_2$ degassed, anhydrous) was added. and the bottle was sealed with a cap. A red-brown catalyst solution was observed. The catalyst solution was transferred to a 2.0-L stainless steel vessel (see below) followed by a $CH_2Cl_2$ rinse (1.2 L). Additional $CH_2Cl_2$ (1.7 L) was added to a 2.0-L stainless steel vessel. The two stainless steel vessels were removed from the glovebox and connected via a t-joint. The t-joint was purged with a nitrogen stream prior to connection to the autoclave.

Ethyl 2′-methoxy-1-(trifluoroacetyl)-1,2,5,6-tetrahydro-4,4′-bipyridine-3-carboxylate (5.95 kg, 28.8 wt % in 2-MeTHF) was drawn into the autoclave under partial vacuum followed by 2-MeTHF rinse (4.0 L). $HBF_4 \cdot OEt_2$ (781 mL) was drawn into the autoclave under partial vacuum followed by 2-MeTHF rinse (1.0 L). An exotherm was observed upon addition of $HBF_4 \cdot OEt_2$ to 33 °C. An additional volume of 2-MeTHF (2.7 L) was added to the autoclave. The autoclave solution was cooled to 25 °C before catalyst addition. The autoclave was sealed and purged with $N_2$ (3 × 40 psig). The catalyst assembly described above was connected to the autoclave via flex tubing and under partial vaccum. The catalyst solution was drawn into the autoclave followed by the $CH_2Cl_2$ (1.8 L) rinse. The reactor was sealed and the headspace exchanged with $H_2$ (3 × 350 psig). The $H_2$ pressure was set at 300 psig, agitation was begun, and the reaction was heated to 50 °C. Once the reaction had reached a temperature of 45 °C, the $H_2$ pressure was adjusted to reach 350 psig. The reaction was sampled after 5 h. The product conversion was observed to be 99.4%. The product ee was observed to be above 98.5%. The batch (17 L) was removed through the eductor tube prior to cooling and drummed. $CH_2Cl_2$ (16.0 L) was added to the autoclave, and agitation was performed for 30 min. The

solution was then filtered on Solka Floc, and the organics were then washed with brine.

The crude 2-methoxypyridyl ester was transferred to a 50-L RBF flask, and solvent was switched to DMF (3.4 L/kg, 10.7 L). The flask was charged with trimethylsulfoxonium iodide (3.85 kg) and magnesium hydroxide (1.02 kg). The mixture was heated to 98 °C and aged for a period of 2 h. HPLC showed >98% conversion to the desired *N*-methylpyrrolidone. The mixture was transferred via vacuum into a 50-L extractor charged with biphasic solution of 4 N HCl (9 L) and dichloromethane (8 L) over 20 min with cooling to keep the internal temperature below 30 °C; the flask was rinsed with 2 L dichloromethane and 3 L 2 N HCl and this solution was charged to the extractor as well. The organic layer was removed and the remaining aqueous layer back-extracted with dichloromethane (6 L). The organic layers were then subjected to successive washes: water (6 L × 2), 10% LiCl—water (6 L × 2) then 1% LiCl—water (6 L × 1). The organics were then diluted with MTBE (40 L) then washed with 10% LiCl—water (20 L × 3). Organics were collected, then all three 10% LiCl—water washes were back-extracted with 9:1 i-PrOAc/DCM (20 L × 2). All organic fractions were transferred via in-line filter (10 $\mu$m) into a 50-L RBF connected to batch concentrator to remove solvents in vacuo. After concentration to a thick, yellow slurry, the material was flushed with MTBE (20 L) and concentrated to ~8 L volume. i-PrOAc (1 L) was added, rinsing the flask edges, and additional MTBE was added until the volume was ~12 L. The slurry was stirred at room temperature for 24 h. The slurry was filtered into a Teflon filter-pot, washing the flask with 10% i-PrOAc/MTBE (2 L). The filter cake was then washed with 10% i-PrOAc/MTBE (2 L × 2) and dried under vacuum under an $N_2$-tent. After 3 h, the yellow solid was transferred into three Pyrex trays and stored in the vacuum oven. After 5 days, 2.50 kg (79% yield) of mustard-yellow solid was collected. ICP-Metals analysis indicated Ru 95 ppm, Fe 65 ppm, and Pd 22 ppm. Product was 92.7 A% by HPLC analysis. **$^1$H NMR (600 MHz, DMSO-$d_6$, 323 K) Major rotamer**: $\delta$ 7.57 (dd, $J$ = 7.00, 4.61 Hz, 1 H); 6.15—6.11 (m, 2 H); 4.54 (d, $J$ = 13.57 Hz, 1 H); 3.98 (d, $J$ = 14.07 Hz, 1 H); 3.92—3.80 (m, 2 H); 3.39 (d, $J$ = 13.33 Hz, 1 H); 3.34 (s, 3 H); 3.25 (dd, $J$ = 13.59, 3.55 Hz, 1 H); 3.14 (s, 1 H); 3.07—3.02 (m, 1 H); 2.30—2.15 (m, 1 H); 1.78 (t, $J$ = 13.70 Hz, 1 H); 0.98 (td, $J$ = 7.09, 3.95 Hz, 3 H). **$^{13}$C NMR**: Peaks were not assigned because of rotamers at room temperature. Spectra shown in Supporting Information. **IR($\nu_{max}$ /cm$^{-1}$)**: 1681, 1657, 1594, 1139, 867. **[$\alpha$]$_D$**: −18.8° ($c$ = 3.0, $CH_2Cl_2$). **HRMS** calculated for $C_{16}H_{19}F_3N_2O_4$ ($M^+$): 360.1297; Found: 360.1306; **Melting point**: (i-PrOAc/MTBE): 140.1—141.3 °C.

**(3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)piperidine-3-carboxylic Acid (2).** (3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)piperidine-3-carboxylic acid (2.46 kg) was dissolved in ethanol (4.1 L/kg, 10 L). Solid sodium ethoxide (0.56 kg) was added to the flask, (the temperature climbed from 18 to 28 °C) and the yellow solution was stirred for 1 h. Water (150 mL) was added to the reaction mixture, over 5 min. (the temperature climbed from 24 to 29 °C) and the solution was stirred for 1 h. Boc-anhydride (1.90 L) was added to the reaction mixture, over 15 min. (the temperature climbed from 22 to 29 °C) and the solution was stirred for 1 h. HPLC showed complete conversion to the Boc-piperidine, with a ratio of ~trans:cis =23:1. Sodium hydroxide (17.1 L, 2M) was added to the flask, and the solution heated to 70 °C via external steam bath for 1 h. HPLC showed complete hydrolysis to the acid, with a ratio of ~*trans*:*cis* = 150:1. The mixture was cooled to 30 °C, and the solution was concentrated to ~20 L volume, such that most of the ethanol was removed. The material was transferred to a 50 L extractor, and washed with MTBE (6 L). The aqueous layer (pH ≈ 14) was recharged to the extractor, then acidified to pH ≈ 1 by addition of concentrated HCl (2.7 L) and 6 N HCl (2 L) to afford a slurry. This slurry was extracted with 2-methyltetrahydrofuran (2-MeTHF, 15 kg). The aqueous layer was then back-extracted with 2-MeTHF (5 kg). The combined organic fractions were then washed with half-brine (10 L). The organics were then concentrated in vacuo to afford a slushy pale-yellow solid, ~4.3 kg. The solid was transferred to a 50-L RBF equipped with mechanical stirrer, nitrogen inlet, and temperature probe and suspended in MTBE (12 L). The slurry was stirred at room temperature for 18 h. The slurry was filtered, washing the flask with 2 L of the residual mother liquors. The filter cake was then washed with MTBE (1 L) and dried under vacuum under an $N_2$-tent. After 4 h, the white solid was transferred into five Pyrex trays and stored in the vacuum oven at room temperature. After 3 days, 2.10 kg (91% yield) of white solid was collected. ICP-Metals analysis indicated Ru, Fe, and Pd were all <10 ppm. **$^1$H NMR (400 MHz, DMSO-$d_6$)**: $\delta$ 12.42 (s, 1 H); 7.57 (d, $J$ = 6.83 Hz, 1 H); 6.20—6.14 (m, 2 H); 4.20 (s, 1 H); 4.00 (s, 1 H); 3.34 (s, 3 H); 2.81—2.43 (m, 4 H); 1.66 (d, $J$ = 12.98 Hz, 1 H); 1.40 (m, 10 H). **$^{13}$C NMR (101 MHz, DMSO-$d_6$)**: $\delta$ 173.0, 161.9, 156.0, 153.6, 139.2, 116.3, 105.1, 79.1, 46.2, 43.7, 36.3, 30.9, 28.0. (overlapping peaks, no other peaks detected even after prolonged scans.) **IR($\nu_{max}$ /cm$^{-1}$)**: 2919, 1682, 1533, 1426, 1167, 785; **[$\alpha$]$_D$**: +19.9° ($c$ = 3.0, $CH_2Cl_2$). **HRMS** calculated for $C_{17}H_{24}N_2O_5$ ($M^+$): 336.1685; Found: 336.1680; **Melting point** (water): 208.0—209.1 °C.

***tert*-Butyl (3*R*,4*S*)-3-{[[3-Bromo-5-(3-methoxypropyl)-4-methylbenzyl](cyclopropyl)amino]carbonyl}-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)piperidine-1-carboxylate (19).** (3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)piperidine-3-carboxylic acid (1.99 kg, 5.92 mol) was suspended in 2-MeTHF (24 L). TsCl (1.466 kg, 7.69 mol) was then added followed by MeCN (4 L). The temperature was cooled to −20 °C (IPA/dry ice). To this stirring suspension was added NMI (2.122 L, 26.6 mol) via addition funnel over 25 min (initial temp −19.9 °C, final temperature = −3.7 °C, max $T$ = −2.9 °C). Another 5 L of MeCN was added to dissolve the solids forming which caused a colour change to yellow and dissolved the suspension. The reaction was stirred at −8 °C for 55 min. (max $T$ = −5 °C, min $T$ = −9 °C). An aliquot was removed and quenched with α-methylbenzylamine. HPLC analysis revealed near complete (>95%) consumption of the starting acid. The amine-MsOH salt (2.66 kg, 6.51 mol) was dissolved in DCM (7.96 L) and added to the reaction which caused the reaction to become immediately clear. The solution was added over 25 min, and the temperature was at 3 °C by the end of the addition. The reaction was left stirring overnight at room temperature. In the morning an aliquot was analyzed by HPLC showing near complete conversion. Acetic anhydride (0.084 L, 0.887 mol) was added to the mixture and stirred at room temperature for another 30 min. The reaction was then concentrated by removing 20 L of solvent. The resulting suspension was transferred to the 100-L extractor. Six liters of water and 2 L of i-PrOAc were added to rinse the reactor. Four liters of water, 10 L of brine, and 18 L of i-PrOAc were then added, and the layers were cut. The aqueous layer was then back

extracted with 15 L of i-PrOAc. The organic layers were then combined, cooled to 14 °C, and washed with 10 mL/g of 0.5 N HCl. This was followed by a 2/3 sat. $NaHCO_3$ (10 mL/g) and brine wash (10 mL/g). The crude organic solution was carried through to the next step. **$^1$H NMR (400 MHz, $CHCl_3$-*d*)**: $\delta$ 7.07 (d, $J$ = 6.82 Hz, 1 H); 7.01 (s, 1 H); 6.81 (s, 1 H); 6.32 (s, 1 H); 5.99 (d, $J$ = 6.64 Hz, 1 H); 4.45−4.81 (m, 1 H); 4.43−3.70 (m, 3 H); 3.40 (s, 3 H); 3.36−3.28 (m, 6 H); 2.98 (t, $J$ = 11.68 Hz, 1 H); 2.80 (s, 2 H); 2.62 (t, $J$ = 7.74 Hz, 2 H); 2.39 (s, 1 H); 2.29 (s, 3 H); 1.77−1.68 (m, 3 H); 1.44 (s, 10 H); 0.84 (s, 3 H); 0.64 (s, 1 H). **$^{13}$C NMR (101 MHz, $CHCl_3$-*d*)**: $\delta$ 174.0, 162.9, 156.5, 154.2, 142.0, 137.8, 136.6, 134.3, 129.6, 128.3, 125.9, 116.8, 107.5, 80.0, 77.2, 71.7, 58.5, 48.9, 46.7, 45.5, 44.4, 43.4, 37.3, 31.1, 30.2, 29.7, 28.4, 18.7, 9.4. **IR($\nu_{max}$ /cm$^{-1}$)**: 2921, 1695, 1646, 1421, 1116, 877. **[α]$_D$**: +29.0° ($c$ = 3.0, $CH_2Cl_2$). **HRMS** calculated for $C_{32}H_{44}BrN_3O_5$ ($M^+$): 629.2464; Found: 629.2483; **Melting point** (2-MeTHF): 172.4−173.8 °C

**(3*R*,4*S*)-*N*-[3-Bromo-5-(3-methoxypropyl)-4-methylbenzyl]-*N*-cyclopropyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-piperidine-3-carboxamide (1).** The 2-MeTHF solution of *N*-Boc-**1** (3.568 kg, 5.66 mol) was placed via in-line filter into a 100-L RBF. The solvent was evaporated, which caused solids to crash out. After 30 L were evaporated and all of organics phases had been added, MeOH was added slowly while continuing evaporation which caused everything to dissolve. Once the solution was completely clear, addition of MeOH was ceased and evaporation was continued. After evaporation of another 25 L, DCM was added to the mixture while continuing evaporation. After 35 L of DCM had been added the evaporation was ceased. NMR analysis suggests that DCM/MeOH ratio is >15:1. The final volume was adjusted by adding 1 L of MeOH. HPLC analysis revealed the solution to be 25 wt%. To this solution was added slowly via addition funnel phosphoric acid (3.5 L, 51.8 mol) at 15 °C. This caused a controlled exotherm which rose to ∼26 °C. The reaction was heated to 28 °C which caused a slow, delayed exotherm to 34.3 °C over 40 min. After 1.25 h the reaction was complete by HPLC analysis. The reaction was cooled to 10 °C and diluted with water (12 L, 4 mL/g). The contents of the flask were transferred to the extractor which is precharged with MTBE (∼5.5 mL/g ∼20 L). The flask was rinsed with 4 L of MTBE and 4 L of water which were transferred to the extractor, and the layers were cut. The combined aqueous layers were washed with 20 L of MTBE/DCM (4:1). The acidic aqueous layer was then added to a cooled (10 °C) solution of KOH 8 N (12.9 L, 103 mol) and 20 L of 2-MeTHF. After the addition was complete (causes solution to become milky) pH of the aqueous (wet pH paper) was 13. Eight liters of 2-MeTHF and 28 L of i-PrOAc were then added, and the phases were cut. The aqueous was then reloaded and extracted with 30 L of 1:1 (2-MeTHF/i-PrOAc). The organics were then combined and washed with 20 L of 2/3 brine (3.4 kg of NaCl) and then stored over the weekend at room temperature protected from light (with foil). Assay of the organics revealed **1** (2.615 kg, 4.93 mol, 83% over two steps) with LCAP of ∼97%.

**(3*R*,4*S*)-*N*-[3-Bromo-5-(3-methoxypropyl)-4-methylbenzyl]-*N*-cyclopropyl-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-piperidine-3-carboxamide (1-HCl).** The solution of **1** (2.54 kg, 4.79 mol) was charged in 100-L flask, and the solvent was switched to IPA. The free base was flushed with 20 L of IPA, and the volume was adjusted to yield a 33 wt % solution in IPA (∼2 mL/g). Another 7.5 L of IPA was added, bringing the final concentration at ∼5 mL/g. The solution was cooled in an acetone/ice bath to −3.5 °C. Added to the mixture was 61.5 g of **1**-HCl seeds along with water (0.254 L). HCl in ether (3.1 L, 6.20 mol) was then added over 60 min (start $T$ = −3.5 °C, end = 11 °C). The solution was then warmed to room temperature and aged overnight. The next day, MTBE (25.9 L) was added over 30 min, and the solution was cooled to 5 °C. After aging for 1 h, the suspension was then filtered. The flask was rinsed with combined 4 L of MTBE and 4 L of mother liquors, then another 4 L of MTBE. The pad was rinsed with 8 L of 1:1 IPA/MTBE. The solid was then dried under a $N_2$ tent overnight. In the morning (drying for 20 h) a small sample was taken, and residual solvent analysis was performed which showed it to be dry. After drying for an additional 5 h, **1** HCl (2.57 kg, 4.53 mol, 95% recovery) was collected as a white solid (98.4 LCAP, > 99.9% ee, residual solvents: 0.07% $Et_2O$ and 0.42% IPA, Moisture 0.3%). **$^1$H NMR** (400 MHz, $H_2O$-$d_2$): $\delta$ 7.16 (d, $J$ = 6.85 Hz, 1 H); 6.74−6.56 (m, 1 H); 6.57 (s, 1 H); 6.20 (s, 1 H); 6.10 (d, $J$ = 6.94 Hz, 1 H); 4.51 (d, $J$ = 14.48 Hz, 1 H); 3.81 (t, $J$ = 11.54 Hz, 1 H); 3.50−3.30 (m, 3 H); 3.22−3.06 (m, 8 H); 3.06−2.78 (m, 3 H); 2.31 (d, $J$ = 9.94 Hz, 3 H); 1.95 (s, 3 H); 1.88 (d, $J$ = 14.15 Hz, 1 H); 1.77 (q, $J$ = 13.60 Hz, 1 H); 1.45 (t, $J$ = 7.48 Hz, 2 H); 0.94 (d, $J$ = 7.68 Hz, 1 H); 0.75−0.62 (m, 2 H); 0.50 (s, 1 H). **$^{13}$C NMR** (101 MHz, $H_2O$-$d_2$): $\delta$ 173.7, 164.0, 156.2, 142.3, 139.9, 136.0, 134.7, 129.6, 128.8, 125.6, 116.3, 108.6, 71.8, 58.1, 45.2, 43.4, 41.7, 38.2, 30.8, 30.6, 29.6, 28.3, 18.5, 10.6, 8.2. **IR($\nu_{max}$ /cm$^{-1}$)**: 1657, 1597, 1398. 1118, 962; **HRMS** calculated for free base $C_{27}H_{36}BrN_3O_3$ ($M^+$): 529.1940; Found: 529.1923. **Melting point** (IPA/MTBE): 222.1−222.9 °C.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Complete characterization data and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org/

## ■ AUTHOR INFORMATION

**Corresponding Author**
*Louis-Charles.Campeau@merck.com.

## ■ ACKNOWLEDGMENT

We thank Ravi Sharma and Wayne Mullet for analytical support. Austin Chen is thanked for helpful discussions. We thank Dan Sorensen for helpful assistance with NMR experiments.

## ■ REFERENCES

(1) Kearney, P. M.; Whelton, M.; Reynolds, K.; Muntner, P.; Whelton, P. K.; He, H. *Lancet* **2005**, *365*, 217.

(2) Ong, K. L.; Cheung, B. M. Y.; Man, Y. B.; Lau, C. P.; Lam, K. S. L. *Hypertension* **2007**, *49*, 69.

(3) (a) MacGregor, G. A.; Markandu, N. D.; Roulston, J. E.; Jones, J. C.; Morton, J. J. *Nature* **1981**, *291*, 329. (b) Weber, M. A. *Am. J. Hypertens.* **1999**, *12*, 189S. (c) Weir, M. R.; Dzau, V. J. *Am. J. Hypertens.* **1999**, *12*, 205S. (d) Brewster, U. C.; Perazella, M. A. *Am. J. Med.* **2004**, *116*, 263.

(4) (a) Zaman, M. A.; Oparil, S.; Calhoun, D. A. *Nat. Rev. Drug Discovery* **2002**, *1*, 621. (b) Kasani, A.; Subedi, R.; Stier, M.; Holsworth, D. D.; Maiti, S. N. *Heterocycles* **2007**, *73*, 47. (c) Fisher, N. D. L.; Hollenberg, N. K. *J. Am. Soc. Nephrol.* **2005**, *16*, 592. (d) Rahuel, J.; Rasetti, V.; Maibaum, J.; Rueger, H.; Goschke, R.; Cohen, N.-C.; Stutz, S.; Cumin, F.; Fuhrer, W.; Wood, J. M.; Gruetter, M. G. *Chem. Biol.* **2000**, *7*, 493. (e) Wood, J. M.; Stanton, J. L.; Hofbauer, K. G. *J. Enzyme*

*Inhib.* **1987**, *1*, 169. (f) Rahuel, J.; Priestle, J. P.; Gruetter, M. G. *J. Struct. Biol.* **1991**, *107*, 227. (e) Webb, R. L.; Schiering, N.; Sedrani, N.; Maibaum, J. *J. Med. Chem.* **2010**, *53*, 7490.

(5) Norris, K.; Vaughn, C. *Expert Rev. Cardiovasc. Ther.* **2003**, *1*, 51.

(6) (a) Chen, A.; Campeau, L.-C.; Cauchon, E.; Chefson, A.; Ducharme, Y.; Dubé, D.; Fournier, P.-A.; Gagné, S.; Grimm, E.; Han, Y.; Houle, R.; Huang, J.-Q.; Lacombe, P.; Laliberté, S.; Lévesque, J.-F.; Liu, S.; MacDonald, D.; Mackay, B.; McKay, D.; Regan, C.; Regan, H.; Stump, G.; Toulmond, S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3970. (b) Chen, A.; Bayly, C.; Bezençon, O.; Richard-Bildstein, S.; Dubé, D.; Dubé, L.; Gagné, S.; Gallant, M.; Gaudreault, M.; Grimm, E.; Houle, R.; Lacombe, L.; Laliberté, S.; Lévesque, J.-F.; Liu, S.; MacDonald, D.; Mackay, B.; Martin, D.; McKay, D.; Powell, D.; Remen, L.; Soisson, S.; Toulmond, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2204.

(7) Sonogashira coupling on the ester **6** afforded only ~5% of bis-coupled product.

(8) For effects of metal ion salts on hydrogenations, see:Yang, X.; Liu, H. *Appl. Catal.* **1997**, *164*, 197.

(9) In contrast esters **6** and **7** are oils.

(10) Elliott, E. L.; Ray, C. R.; Kraft, S.; Atkins, J. R.; Moore, J. S. *J. Org. Chem.* **2006**, *71*, 5282.

(11) The acid dissolved in MTBE (4 mL/g) could be extracted into 1 N NaOH (8 mL/g), and additional MTBE washes removed impurities. Reacidification of the aqueous layer using 6 N HCl followed by extraction with i-PrOAc resulted in high purity of the desired compound.

(12) Kleiner, H.-J.; Wissmann, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 133.

(13) ICP analysis showed residual Pd = 31 ppm and Cu = 2 ppm.

(14) Both $Cs_2CO_3$ and $Et_3N$ were screened.

(15) For the large-scale in situ preparation of $BH_3$—THF see: Kanth, J. V. B.; Brown, H. C. *Inorg. Chem.* **2000**, *39*, 1795 and references therein.

(16) Molinaro, C.; Roy, A.; Schultz, S.; Lau, S.; Trinh, T.; Angelaud, R.; O'Shea, P. D.; Cameron, M.; Corley, E.; Steinhuebel, D.; Weisel, M.; Krska, S. *J. Org. Chem.* **2011**, *76*, 1062.

(17) For a review on the use of asymmetric hydrogenation at Merck, see: Shultz, S. C.; Krska, S. K. *Acc. Chem. Res.* **2007**, *12*, 1320.

(18) (a) Ikehara, M.; Tanaka, S. *Tetrahedron Lett.* **1974**, *15*, 497. (b) Lanni, E. L.; Bosscher, M. A.; Ooms, B. D.; Shandro, C. A.; Ellsworth, B. A.; Anderson, C. E. *J. Org. Chem.* **2008**, *73*, 6425. (c) Bowman, W. R.; Bridge, C. F. *Synth. Commun.* **1999**, *29*, 4051. (d) Itami, K.; Yamazaki, D.; Yoshida, J.-I. *Org. Lett.* **2003**, *5*, 2161.

(19) (a) Elitzin, V. I.; Harvey, K. A.; Kim, H.; Salmons, M.; Sharp, M. J.; Tabet, E. A.; Toczko, M. A. *Org. Process Res. Dev.* **2010**, *14*, 912.

(20) Solvents affording the best ratios (>10:1) were dioxane (100% conversion), toluene (<50% conversion), and CPME (90% conversion). A reaction in dioxane on 100-g scale afforded a ratio, after fractional distillation, of ~100:1 in 70% isolated yield.

(21) Ruggeri, S. G.; Vanderplas, B. C.; Anderson, B. G.; Breitenbach, R.; Urban, F. J.; Stewart, A. M., III; Young, G. R. *Org. Process Res. Dev.* **2008**, *12*, 411.

(22) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484.

(23) More than one equivalent of $HBF_4$ is required for protonation of the pyridine which otherwise acts as a poison for the reaction. This resulted in partial deprotection of the piperidine, which is also a catalyst poison.

(24) For reviews on asymmetric hydrogenations, see: (a) Takaya, T.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993, p 1. (b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272. (c) Jakel, C.; Paciello, R. *Chem. Rev.* **2006**, *106*, 2912.

(25) <1 mol% catalyst loadings led to variable results: some reactions afforded 100% conversion while others afforded <5% conversion. We opted to use 1 mol% catalyst in order to guarantee a robust process.

(26) (a) Humphrey, G. R.; Miller, R. A.; Maligres, P. E.; Weissman, S. *PCT Int. Appl.* 68; WO/2009/088729 A1 20090716 , 2009; CAN 151:14835; AN 2009:859685 (b) Humphrey, G. R.; Pye, P. J.; Zhong, Y.-L.; Angelaud, R.; Askin, D.; Belyk, K. M.; Maligres, P. E.; Mancheno, D. E.; Miller, R. A.; Reamer, R. A.; Weissman, S. A. *Org. Process Res. Dev.* **2011**, *15*, 73.

(27) Reactions under anhydrous conditions were very slow and led to incomplete conversion of the pyridine to the pyridone.

(28) Wakasugi, K.; Iida, A.; Misaki, T.; Nishii, Y.; Tanabe, Y. *Adv. Synth. Catal.* **2003**, *345*, 1209.