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A Practical Synthesis of Renin Inhibitor MK-1597 (ACT-178882) via Catalytic Enantioselective Hydrogenation and Epimerization of Piperidine Intermediate

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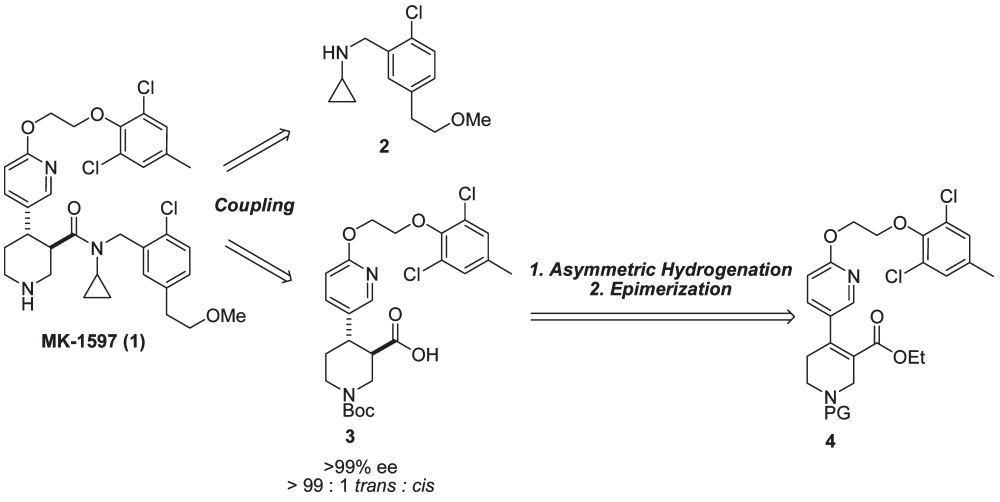

A practical enantioselective synthesis of renin inhibitor **MK-1597** (ACT-178882), a potential new treatment for hypertension, is described. The synthetic route provided **MK-1597** in nine steps and 29% overall yield from commercially available *p*-cresol (**7**). The key features of this sequence include a catalytic asymmetric hydrogenation of a tetrasubstituted ene−ester, a highly efficient epimerization/saponification sequence of **4** which sets both stereocenters of the molecule, and a short synthesis of amine fragment **2**.

Introduction

The renin−angiotensin aldosterone system (RAAS),[1] is known to play a key role in the regulation of blood pressure through several seminal studies culminating with the discovery of the angiotensin converting enzyme (ACE) inhibitors[2] and angiotensin II receptor blockers (ARBs).[3] Several antagonists of the RAAS pathway have emerged as effective treatments for hypertension.[4] A collaboration between Actelion[5] and our discovery efforts at Merck[1e] identified **MK-1597**[6] as a potent, selective inhibitor of the renin receptor and a promising lead in

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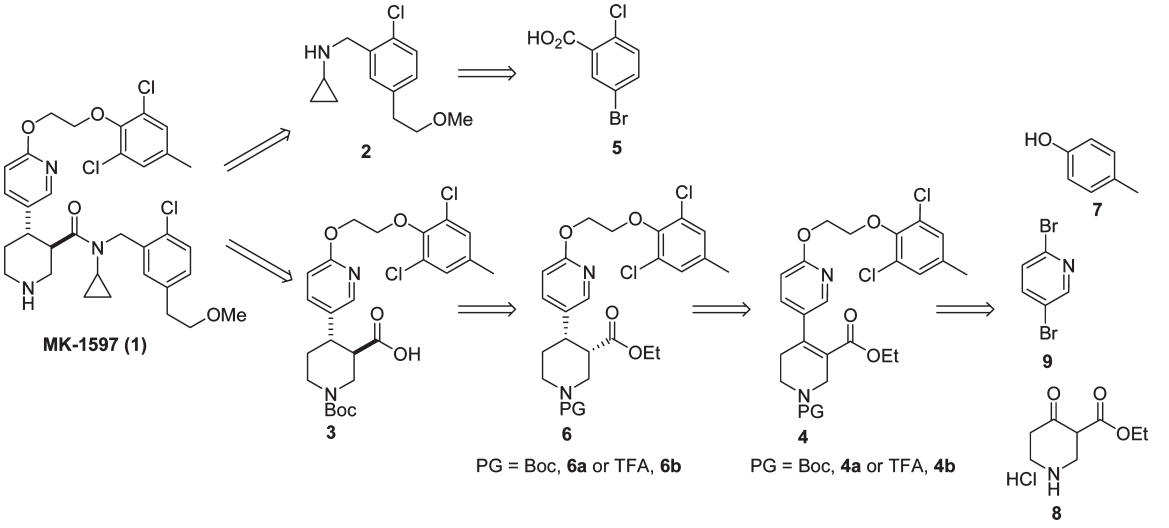
SCHEME 1. Retrosynthetic Approach to Renin Inhibitor MK-1597 (1)



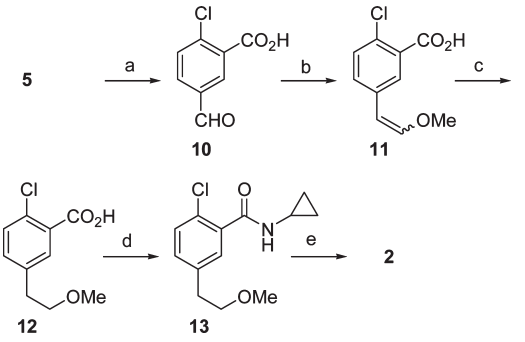
the treatment of hypertension. In order to support the development of this compound, we sought to develop a scalable synthesis of **MK-1597**. We describe herein a practical, chromatography-free, enantioselective synthesis of **MK-1597** that has been performed on multikilogram scale.

Our retrosynthetic analysis of **MK-1597** is shown in Scheme 1. We envisioned that **MK-1597** could be assembled by a coupling between piperidine carboxylic acid **3** and cyclopropylamine fragment **2**. The two stereocenters of carboxylic acid **3** could be installed via a catalytic asymmetric hydrogenation of a tetrasubstituted ene−ester **4** followed by an epimerization/saponification sequence. Ene−ester **4** in turn can be prepared from commercially available ethyl 4-oxopiperidine-3-carboxylate (**8**), 2,5-dibromopyridine (**9**) and *p*-cresol (**7**).

Results/Discussion

Preparation of Amine Side Chain 2. Amine **2** was prepared in five steps from cheap and readily available 5-bromo-2-chlorobenzoic acid (**5**) (Scheme 2). The synthesis started with a Bouveault reaction.[7] Thus, bromide **5** was converted to aldehyde **10** in 65% yield via Knochel's magnesium−halogen exchange protocol[8] followed by a DMF quench. Aldehyde **10** was subsequently reacted with NaH and $MeOCH_2PPh_3$ to furnish a 1:1 mixture of *E*- and *Z*-vinyl methyl ethers **11**.[9] The mixture of olefins was submitted to hydrogenation conditions using Pearlman's catalyst, providing carboxylic acid **12** in 96% yield and 94 A%.[10,11] CDI-mediated coupling of carboxylic acid **12** with cyclopropylamine in CH_3CN afforded amide **13** in 86% yield. In order to meet the purity criteria for amine **2** (> 95 A%), a recrystallization of amide **13** using hot iPAc/hexanes was performed resulting in an 83% recovery and a purity upgrade from 95 A% to 98 A%. Finally, a large-scale $BH_3 \cdot THF$ reduction[12] at 36 °C afforded 4.54 kg of crude amine **2** in 99% assay yield and 96 A%.

SCHEME 2. Synthesis of Amine Side Chain 2[a]



[a]Conditions: (a) 1. *i*PrMgCl, THF, −30 °C, 80%; 2. DMF, 0 °C; 3. HCl, 80%. (b) NaH, $MeOCH_2PPh_3$, THF, 50 °C, 86%. (c) H_2 (45 psi), $Pd(OH)_2/C$, EtOAc, 96%. (d) 1. CDI, CH_3CN; 2. cyclopropylamine, 30 °C, 86%. (e) $NaBH_4$, $BF_3 \cdot THF$, 36 °C, 99%.

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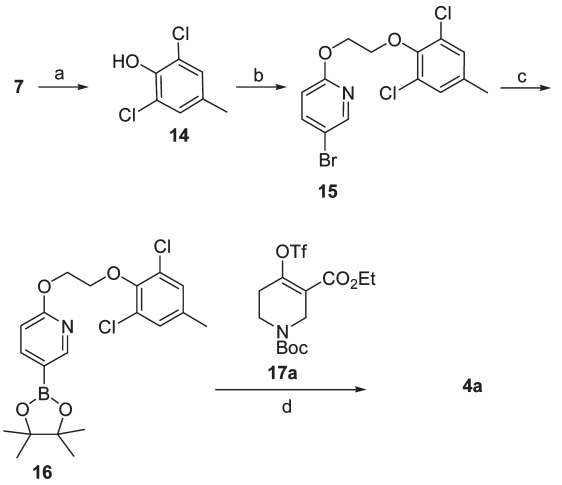
(10) A% = HPLC area percent monitored at 220 nm.

(11) Other Pt- and Rh-based metals were also tested; however, much lower reactivities and/or purity profiles were observed.

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

SCHEME 3. Synthesis of Hydrogenation Precursor 4a[a]

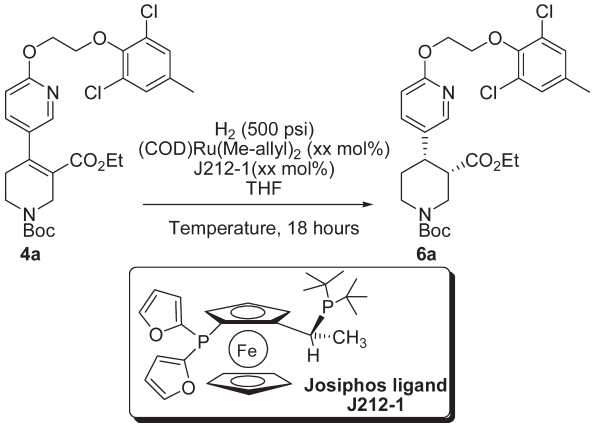


[a]Conditions: (a) NaOCl, CH_3CN, 89%. (b) 1. Ethylene carbonate, 1-methylimidazole, DMAc 110 °C; 2. KOH, dibromopyridine, 77%. (c) Bis-(pinacolato)diboron, $PdCl_2$(dppf), KOAc, DMAc, 80 °C, 71%. (d) Pd-$(PPh_3)_4$, Na_2CO_3, water, DME, 50 °C, 99%.

Preparation of Hydrogenation Precursor 4a. Ene−ester **4a** was prepared in 49% yield and four steps starting from *p*-cresol (**7**) (Scheme 3). Dichlorination of *p*-cresol (**7**) using commercial bleach cleanly provided **14** in 89% yield. Alkylation of phenol **14** with ethylene carbonate followed by S_NAr reaction on dibromopyridine **9** provided pyridine bromide **15**. Aryl boronate **16** was prepared using bis(pinacolato)-diboron and a palladium catalyst ($PdCl_2$(dppf)) in 71% yield.[13] Finally, Suzuki coupling between the aryl boronate **16** and the Boc-protected piperidine triflate **17a**[14] provided 99% yield of the tetrasubstituted ene−ester **4a**.

Asymmetric Hydrogenation. During the course of development we screened the tetrasubstituted ene−ester **4a** under microscale hydrogenation conditions[15] using H_2 (500 psi), a metal precursor and ligand (1: 1.05 ratio) in a solvent at 50 °C for 18 h, as a first pass approach.[16] Ru-, Ir-, and Rh-based metal precursors were tested using over 384 combinations of metal precursors, ligands, and solvents. While a few Rh catalysts did give some level of enantioselectivity, it is notable that Rh catalysts derived from representative ubiquitous ligand families such as BINAP and DuPhos gave no conversion.[17] In general, the reactivity was very poor, and only a small selection of conditions gave reasonable conversions. During our screen, we were pleased to find that Ru metal precursor (COD)Ru(Me-allyl)$_2$ and Josiphos ligand SL-J212-1 gave >90% ee albeit in low yield 30% (Table 1, entry 1). Further optimization revealed that a lower catalyst loading with a concurrent lower reaction temperature resulted in an increase in enantioselectivity from 91% ee to 99% ee while maintaining the yield to ~30% (entry 1 vs 2). At this stage we believed that the pyridine moiety was likely a catalyst inhibitor and that the addition of a Brønsted acid might help. However, the potential lability of the Boc group gave us concern with that approach. Nevertheless, $HBF_4 \cdot OEt_2$ was found to provide a considerable boost in reactivity from 36 to 96% conversion (entries 3−6 vs 2) while maintaining the enantioselectivities at 98−99%ee. The use of 0.9 equiv of $HBF_4 \cdot OEt_2$ resulted in a reasonably robust procedure and after Darco treatment[18] on scale provided 2.3 kg of **6a** in 84% isolated yield and 99% ee (entry 7).

TABLE 1. Selected Microscale Asymmetric Hydrogenation Screening Results[a]



entry	mol % of metal precursor	temperature (°C)	$HBF_4 \cdot OEt_2$ (equiv)	conv.[b] (%)	% ee
1	15	50	0	30	91
2	2.7	r.t.	0	29	99
3	2.7	r.t.	0.09	37	98
4	2.7	r.t.	0.37	65	98
5	2.7	r.t.	0.64	87	98
6	2.7	r.t.	0.9	96	99
7[c]	2.7	r.t.	0.9	84[d]	99

[a]Reaction conditions: (COD)Ru(Me-allyl)$_2$: SL-J212-1(1: 1.05), 500 psi H_2, 18 h. [b]Conversion is defined as the HPLC area % product/(starting material + product) observed at 210 nm. [c]1.89 kg scale. [d]Isolated yield.

Epimerization/Saponification Sequence. A study of the epimerization of the ester carbon center of piperidine **6a** is reported in Table 2. We were surprised and pleased to find that depending on the source of NaOEt tested (solid NaOEt in EtOH, a commercially available solution of 21 wt % NaOEt/EtOH in EtOH or 2 N NaOH in EtOH) different results were obtained (entries 1−3). The best *trans*/*cis* ratio (14:1) of the ester substrate **18** was obtained with the commercially available solution of 21 wt % NaOEt/EtOH (entry 2).[19] A direct epimerization/saponification using 5 equiv of 2 N NaOH in

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(14) Petersen, M. D.; Boye, S. V.; Nielsen, E. H.; Willumsen, J.; Sinning, S.; Wiborg, O.; Bols, M. *Bioorg. Med. Chem.* **2007**, *15*, 4159.

(15) For a description of the microscale screening conditions utilized in this study see: Shultz, C. S.; Krska, S. *Acc. Chem. Res.* **2007**, *40*, 1320.

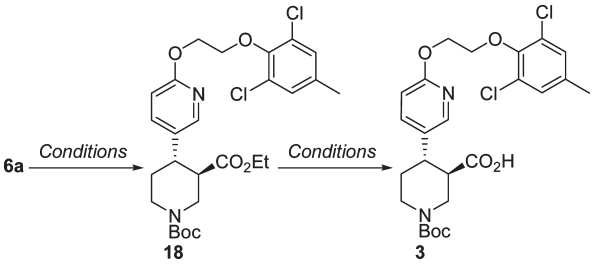
(16) Previous approaches to this class of intermediates include: (1) racemic hydrogenation followed by HPLC chiral separation: (a) Patane, M. A.; DiPardo, R. M.; Price, R. P.; Chang, R. S. L.; Ransom, R. W.; O'Malley, S. S.; Di Salvo, J.; Bock, M. G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2495. (b) Bachmann, S.; Scalone, M. Schnider, P. Process for the preparation of enantiomerically enriched cyclic β-aryl or heteroaryl carboxylic acids. U.S. Pat. Appl. 2007/0232653 A1, 2007; (2) resolution of the racemic carboxylic acid: ref 16a; (3) asymmetric hydrogenation on the carboxylic acid: ref 16b.

(17) Other ligands tested: (*S*)-xyl-BINAP, (*R*,*R*)-Me-DuPhos, (*R*,*R*,*S*,*S*)-Tangphos, W006-1, Catasium I, J004-1 and J212-1 (structures are available in the Supporting Information)

(18) The Darco treatment is necessary to reduce the metal content in the product. Before treatment the levels are >20000 ppm.

(19) Isolation of the product and resubjecting the esters to the same epimerization conditions did not change the *trans*/*cis* ratio observed.

TABLE 2. Epimerization/Saponification Sequence[a]



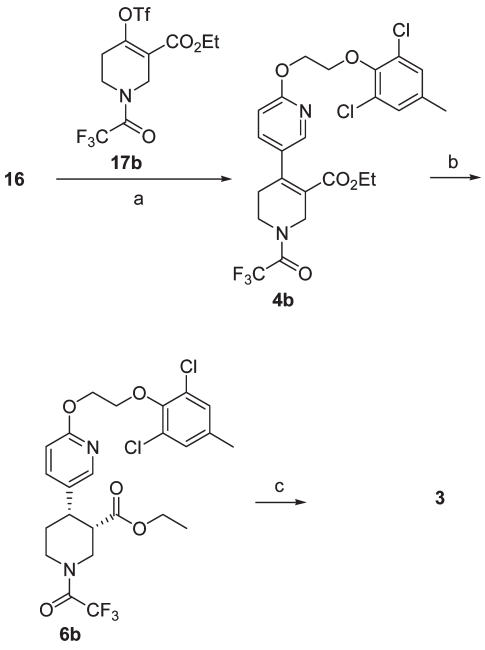
entry	conditions	**18** *trans*/*cis* ratio	**3** *trans*/*cis* ratio	yield (%)[b]
1	solid NaOEt, EtOH	only *cis*		n.d.
2	21 wt % NaOEt/EtOH, EtOH 70 °C	14:1		n.d.
3	1 equiv 2 N NaOH, EtOH, 70 °C	1:1		n.d.
4	5 equiv 2 N NaOH, EtOH, 70 °C	n.a.	10:1	n.d.
5	5 equiv 2 N NaOH, dioxane, 70 °C	n.a.	n.a.	no rx
6[c]	1) 5 equiv 21 wt % NaOEt/EtOH, EtOH, 70 °C 2) 5 equiv 2 N NaOH	14:1	99:1	83
7[d]	1) 5 equiv 21 wt % NaOEt/EtOH, EtOH 2) 5 equiv 2 N NaOH	14:1	> 120:1	84

[a]Unless otherwise stated, the reactions were run on 100-mg scale in 0.5 mL of solvent. [b]Isolated yield of **3**. [c]40-g scale. [d]4.8-kg scale.

EtOH and dioxane was also tested (entries 4−5).[20] A 10:1 ratio of *trans*-/*cis*-carboxylic acid substrate **3** was obtained (entry 4). Although promising, we knew that we would be unable to meet final purity criteria for **MK-1597** (> 97 A%) with this ratio. A purity upgrade after this stage would be difficult without a flash chromatography since we were unable to reject the diastereomer with subsequent crystallizations. Gratifyingly, a sequential epimerization with a solution of 21 wt % NaOEt/EtOH followed by an in situ saponification with 5 equiv of 2 N NaOH resulted in a 99:1 ratio of *trans*/*cis* of carboxylic acid **3** (entries 6). Presumably, under these conditions, the *trans*-ester **17** converts to the *trans*-carboxylic acid **3** faster than the *cis*-somer, and in parallel, the *cis* ester **6** would still equilibrate to the thermodynamically stable *trans*-isomer, providing a final *trans*/*cis* ratio of 99:1 for the carboxylic acid **3**. We were able to reproduce these results on 4.8 kg scale of **6a** providing 3.8 kg of carboxylic acid **3** in 84% yield, *trans*/*cis* ratio > 120:1 and 98.9 A%.

Alternative Synthesis of Carboxylic Acid 3. Although the asymmetric hydrogenation with a Boc protecting group was viable on ~2.5 kg scale, for even larger-scale campaigns a more robust procedure was necessary to address the lability of the Boc-substrates **4a** and **6a** under acidic conditions. We subsequently tested the TFA ene−ester **4b** because of its ability to tolerate the acidic hydrogenation reaction conditions (Scheme 4). We were pleased to find that the (COD)Ru(Me-allyl)$_2$ catalyst provided 92% yield and 99% ee of **6b** under the same conditions. We have run preliminary experiments in order to determine the mechanism by which the reduction occurs. Substrate **4b** was subjected to D_2 under the same reaction conditions. Analysis of the reaction at partial conversion (~35%) revealed that the major product had incorporated three deuterium atoms in the molecule. The unreacted olefin **4b**, however, showed no evidence of deuterium incorporation. These results suggest that a rearrangement step may be involved in the process and is enantioselective.[21]

SCHEME 4. Alternative Synthesis of Carboxylic acid 3[a]



[a]Conditions: (a) 1. Pd(dppf)Cl$_2$, KHCO$_3$, water, 2-MeTHF, 60 °C; 2. 4 N HCl, dioxane; 3. aqueous NaHCO$_3$, 80%. (b) SL-J212-1, Ru(cod)-(methallyl)$_2$, HBF$_4$·OEt$_2$, 2-MeTHF, 1000 psi H$_2$, 23 °C, 92%, 99%ee. (c) 1. 21 wt % NaOEt/EtOH; 2. water; 3. Boc$_2$O; 4. 2 N NaOH, 70 °C, 88%.

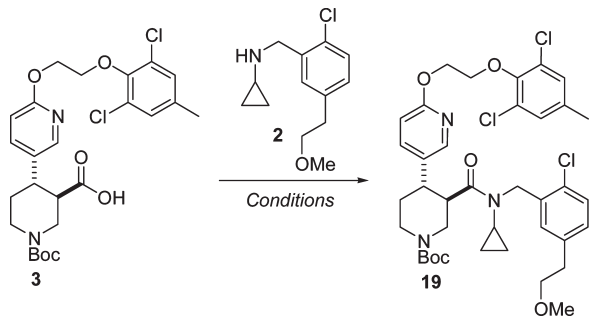
Similar conditions were used to convert the TFA protected piperidine **6b** to carboxylic acid **3**. Thus a one-pot in situ TFA deprotection, Boc protection, epimerization and hydrolysis sequence allowed the preparation of 3.9 kg of **3** in 88% yield and > 100:1 *trans*/*cis* ratio.

Amidation. A series of coupling conditions for carboxylic acid **3** with amine fragment **2** have been explored (Table 3). Although, HATU coupling was the highest yielding and cleanest reaction to provide **19** (96% yield and 97.7 A%), the cost of this reagent is prohibitive on scale. After a screen

(20) The rate of dissolution or solubility of different NaOEt sources in ethanol may explain the different results observed.

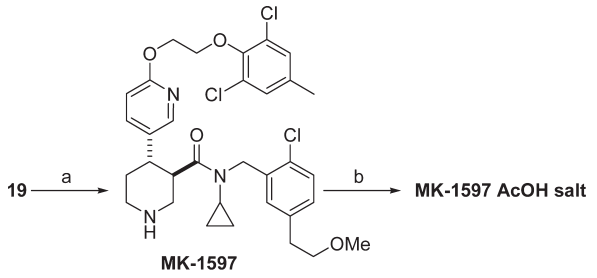
(21) A full mechanism analysis is underway and will be reported in due course.

TABLE 3. Amidation



entry	coupling reagent	yield (%)	purity (A%)
1	oxalyl chloride	50	nd
2	CDI	0	nd
3	EDC-HCl, HOBt	85	65
4	HATU	96	97.7
5	MsCl, 1-methylimidazole	21	nd
6	TsCl, 4-methylmorpholine	70	nd
7	TsCl, 1-methylimidazole	94	86

SCHEME 5. End Game



Conditions: (a) 1. H_3PO_4, 70 °C, 95%. 2. D-tartaric acid, 90 °C, 90%. 3. NaOH, MTBE, 99%. (b) AcOH, MTBE, Heptane, 83%.

of coupling agents, we opted for a cheaper mixed anhydride approach using TsCl/1-methylimidazole activation/amidation. This reagent gave a similar yield (94%) to HATU, albeit in a lower purity profile (86 A%). The low purity profile can be further upgraded during the subsequent salt formations.

End Game. Completion of the synthesis for **MK-1597** is outlined in Scheme 5. H_3PO_4[22] was used to cleave the Boc protecting group and provided 3.91 kg of **MK-1597** in 93% yield and 91.8 A%. Rejection of impurities was possible during the work up through a pH swing with aqueous MsOH. Thus, the organic layer was treated with aqueous MsOH, which formed a water-soluble salt with **MK-1597**. This layer was washed with MTBE to remove impurities and then basified with NaOH and re-extracted to recover **MK-1597**. This process allowed us a slight increase in purity profile from 86 A% for the amidation to 91.8 A% for the Boc deprotection and a reduction of the metal content of the final compound **MK-1597** (Ru = from 17 to 11 ppm and Pd = from 56 to 2 ppm). At this stage the purity of **MK-1597** was further upgraded to 98.6 A% with a bis-D-tartrate salt formation/salt break. Finally, **MK-1597 · AcOH** was identified as a crystalline and bioavailable form for development. Therefore, **MK-1597** was dissolved in MTBE and a solution of AcOH in heptane was added. The slurry was filtered and dried. **MK-1597 · AcOH** was isolated as a white crystalline salt (Ru = 5 ppm, Pd = < 1 ppm, 2.94 kg, 83% yield, 98.6 A%).

(22) Alternatively 10 equiv of TFA can be used with carefull monitoring of the KF.

Conclusion

In conclusion, a practical large-scale chromatography free synthesis of renin inhibitor **MK-1597**, a potential new treatment for hypertension, was developed. The synthetic route provided **MK-1597**, as its acetate salt, in 9 steps (isolated intermediates) and 29% overall yield from commercially available *p*-cresol (**7**). The key features of this sequence include a catalytic asymmetric hydrogenation of a tetrasubstituted ene−ester and a highly efficient epimerization/saponification sequence of **4** which sets both stereocenters of the molecule, and a short synthesis of amine fragment **2**. This approach was used to successfully produce 2.94 kg of **MK-1597** acetate salt.

Experimental Section

2-Chloro-5-formylbenzoic Acid (10). A 100-L reactor equipped with an overhead stirrer, a nitrogen inlet, and a temperature probe was charged with THF (15 L, predegassed by bubbling nitrogen for 30 min) followed by 5-bromo-2-chlorobenzoic acid (**5**) (5027.3 g, 21.35 mol). The solution was degassed by bubbling nitrogen for 15 min then cooled to −30 °C. *i*PrMgCl (2.0 M/THF, 27.8 L, 55.5 mol) was slowly added via an addition funnel. The rate of addition was controlled such that for the first equivalent of *i*PrMgCl (10.7 L), the temperature stayed below 0 °C and for the second equivalent it stayed below −20 °C. The slurry was aged O/N from −20 °C to rt (> 99% conversion). The reaction mixture was cooled to 0 °C, and a solution of DMF (4.15 L, 53.4 mol) in THF (16 L) was slowly added with vigorous stirring. The rate of addition was controlled in order to keep the temperature below 25 °C. The thick slurry was aged at 10−15 °C for 1 h at which point 4 N HCl (23.5 L, 93.9 mol) was added slowly. The reaction mixture was stirred at rt for 30 min until all solids dissolved. The batch was transferred to a 150-L extractor, and the two layers were cut. The organic layer was successively washed with 10 wt %/wt aqueous LiCl, (15 L), 1 M Na_2CO_3 (32 L) and 1 M Na_2CO_3 (21 L). The combined Na_2CO_3 layers were washed with MTBE (25 L), cooled to 0 °C, and acidified with 6 N HCl (15.9 L). The resulting slurry was filtered through a filter pot. The solid obtained was washed with water (32 L) and heptane (40 L) and dried under vacuum with a flow of nitrogen until KF analysis showed < 5500 ppm of water. Aldehyde **10** was thus obtained as a white solid (3410 g, 92 wt %, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.51 (d, 1H, J = 1.9 Hz), 8.01 (dd, 1H, J = 8.2, 1.9 Hz), 7.69 (d, 1H, J = 8.2 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 190.8, 165.3, 139.1, 135.5, 132.7, 132.6, 132.3, 131.7; IR 2922, 1701, 1665, 1286, 1244, 1199, 1049, 911, 832, 783 cm^{-1}; HRMS (ESI) (m/z): [M + H]$^+$ calcd for $C_8H_6ClO_3$, 185.0000; found 184.9997.

2-Chloro-5-(2-methoxyvinyl)benzoic Acid, 1:1 *E*:*Z* Isomers (11). A 100-L reactor equipped with an overhead stirrer, a refluxed condenser, a nitrogen inlet, and a temperature probe was charged with THF (20 L). NaH (60%, 745 g, 17.88 mol) was added, and the suspension was cooled to 0 °C. A solution of aldehyde **10** (3137 g, 16.25 mol) in THF (7 L) was added to the suspension over the course of 1 h in order to control the gas evolution and the exotherm ($T \leq$ 20 °C). (Methoxymethyl)-triphenylphosphonium chloride (7.45 kg, 21.1 mol) was added at rt to the reaction mixture (phosphonium *NOT* soluble in THF). It was then heated to 40−45 °C, and NaH 60% in oil (945 g, 23.63 mol) was added portion wise (~10 portions) to control the exotherm and the gas evolution. The slurry was aged at 50 °C for 1 h

and turned dark orange (which is an indication that the reaction is complete). The slurry was then cooled to rt and aged overnight. NaOH (1 N, 16.5 L), MTBE (16.5 L), and half brine (16.5 L) were added to the slurry, and the layers were cut. The organic layer was washed with 1 M NaOH (16.5 L). The combined aqueous layer was washed twice with IPAc (2 × 15 L), then cooled to 0 °C at which point 6 N HCl (36 L) was slowly added until pH = 1. The slurry was aged at 10 °C for 15 min then filtered through a filter pot, and the solid was washed with water (60 L). The pale-yellow solid thus obtained was dried under vacuum with a flow of nitrogen for 48−72 h, yielding 3099 g (86% yield) of a 1:1 mixture of *E*/*Z* isomers (**11**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, 1H, J = 2.2 Hz), 7.86 (d, 1H, J = 2.2 Hz), 7.70 (dd, 1H, J = 8.4, 2.2 Hz), 7.38 (d, 1H, J = 8.4 Hz), 7.37 (d, 1H, J = 8.3 Hz), 7.32 (dd, 1H, J = 8.4, 2.2 Hz), 7.10 (d, 1H, J = 13.0 Hz), 6.23 (d, 1H, J = 7.0 Hz), 5.78 (d, 1H, J = 13.0 Hz), 5.21 (d, 1H, J = 7.0 Hz), 3.82 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 166.4, 166.3, 150.8, 150.1, 136.2, 135.5, 131.9, 131.0, 130.9, 130.7, 130.6, 129.3, 128.6, 127.7, 103.2, 103.1, 60.6, 56.3; IR 2936, 2824, 2536, 1702, 1647, 1285, 1238, 1193, 1092, 1042, 918, 828 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M + H]^+$ calcd for $C_{10}H_{10}ClO_3$, 213.0313; found 213.0315.

2-Chloro-5-(2-methoxyethyl)benzoic Acid (12). A 5-gal carboy container was charged with alkenes **11** (3080 g, 14.49 mol), and it was dissolved with EtOAc (10 L). The resulting solution was sucked into a 10-gal reactor, and the carboy was then rinsed with fresh EtOAc (2 L). The rinsate was then added to the vessel as well. This was repeated a second time. Twenty weight percent $Pd(OH)_2$/C (308 g, 10 wt %) was added to a flask containing EtOAc (2 L), and this solution was next sucked into the reactor. Fresh EtOAc (10.7 L) was added to the vessel. The batch was precooled to 15 °C, and the agitation rate was set to 800 rpm at the start of reaction. The reaction mixture was agitated under a hydrogen pressure of 45 psi. After 18 h, the resulting batch was dropped, and the reactor was rinsed with fresh EtOAc (15 L). The batch was filtered on a pad of solka floc using an 18-in. filter pot, and EtOAc (15 L) was used to rinse the pad. The desired compound was kept as an EtOAc solution, and it was assayed: 2980 g (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, 1H, J = 1.9 Hz), 7.41 (d, 1H, J = 8.2 Hz), 7.35 (dd, 1H, J = 8.2, 2.1 Hz), 3.63 (t, 2H, J = 6.6 Hz), 3.36 (s, 3H), 2.91 (t, 2H, J = 6.6 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 166.7, 138.9, 133.3, 131.8, 130.6, 130.5, 130.4, 72.5, 57.7, 34.9; IR 2926, 2868, 2826, 2638, 2579, 1693, 1297, 1261, 1200, 1104, 1042, 657 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M + H]^+$ calcd for $C_{10}H_{12}ClO_3$, 215.0469; found 215.0468.

2-Chloro-*N*-cyclopropyl-5-(2-methoxyethyl)benzamide (13). The carboxylic acid (**12**) solution in EtOAc (5780 g, 26.93 mol) (from the hydrogenation vessel) was inline filtered with an activated carbon cartridge and concentrated with the batch-concentrator to a final volume of 48 L. The batch was cooled to 10 °C, and CDI (5240 g, 32.31 mol) was added in 10 portions over 30 min. The reaction mixture was aged at rt for 1.5 h. Cyclopropylamine (2.83 L, 40.40 mol) was added via the dropping funnel fitted with a piece of Nalgene tubing immersed in the reaction mixture. The rate of addition was controlled such that the temperature did not exceed 33.5 °C. The addition took 30 min. The batch was aged at 30 °C for 1.5 h then cooled to rt. The batch was transferred to a 150-L extractor and cooled to 15 °C. HCl (3 N, 36 L, 107.7 mol) was added with stirring. The temperature was maintained between 20 and 25 °C. Fresh EtOAc (23.5 L) was added. The two layers were cut, and the organic layer was successively washed with 1 M Na_2CO_3 (36 L) followed by half-saturated brine (36 L). HPLC assay of the EtOAc layer showed 5880 g (86% yield). The crude batch was inline filtered in a visually clean 100-L reactor and was subsequently batch-concentrated and solvent-switched to IPAc. At this point, there was 2.5% left of EtOAc compare to iPAc. Fresh IPAc (8 L) was added to the batch to make a solution of final volume = 23.2 L. The batch was heated to 70 °C until a clear solution was obtained, then it was cooled to 65 °C at which point hexanes (12 L) was slowly added over 1 h between 62.5 and 65 °C. The batch was further cooled to 60 °C and seeded with seeds (17.5 g). The batch was slowly cooled to 55 °C over 45 min then to rt and aged for 10 h at rt. The next morning, the mother liquors were analyzed by HPLC and showed 808 g of amide lost to the mother liquors (14%). The batch was filtered and rinsed with 10% iPAc/hexanes (24 L) followed by hexanes (20 L). The batch was dried on the filter pot under vacuum and a flow of nitrogen for 24 h and yielded 4820 g (71% yield, 100 wt %) of **13** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, 1H, J = 2.1 Hz), 7.29 (d, 1H, J = 8.2 Hz), 7.22 (dd, 1H, J = 8.2, 2.2 Hz), 6.29 (br, 1H), 3.59 (t, 2H, J = 6.7 Hz), 3.33 (s, 3H), 2.92 (m, 1H), 2.86 (t, 2H, J = 6.7 Hz), 0.88 (m, 2H), 0.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 138.2, 134.7, 131.5, 130.0, 129.7, 128.2, 72.6, 58.4, 35.1, 22.9, 6.5; IR 3258, 1642, 1531, 1317, 1121, 726 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{17}ClNO_2$, 254.0942; found 254.0944.

***N*-[2-Chloro-5-(2-methoxyethyl)benzyl]cyclopropanamine (2).** A 100-L reactor equipped with an overhead stirrer, a nitrogen inlet, a reflux condenser, and a temperature probe was charged with THF (24 L) followed by amide **13** (4799 g, 18.20 mol). Once all the amide was in solution, $NaBH_4$ (2862 g, 75.66 mol) was added in one portion at rt. $BF_3 \cdot THF$ (9.4 L, 85.12 mol) was slowly added over 1.5 h such that the internal temperature never exceeded 36 °C. The slurry was aged at 37 °C overnight (97% conversion). The reaction mixture was cooled to 10 °C and slowly transferred into a 150-L extractor containing cool (6 °C) 3 N HCl (28.4 L). The quench was performed over 4 h to control the gas evolution and the exotherm. Vigorous stirring was also maintained throughout the operation. The white precipitate was filtered on a filter pot and washed with MTBE (24 L). The filtrate was transferred to a clean 150-L extractor, and more MTBE (24 L) was added. The layers were cut, and the organic layer was washed 3 × 2 N HCl (3 × 20 L). The combined aqueous layer was washed with MTBE (20 L), cooled to 10 °C, and basified with 50 wt/wt aqueous NaOH (20 L) until pH > 10. The rate of addition of 50 wt/wt aqueous NaOH was such that internal temperature was maintained below 26 °C. The batch was extracted with 2 × MTBE (2 × 45 L), and the combined organic layer was washed with water (20 L), dried over Na_2SO4 (8 kg), filtered, and concentrated, yielding the desired amine **2**: 6448 g (70.4 wt %, 95.85 A%, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, 1H, J = 8.2 Hz), 7.21 (d, 1H, J = 2.0 Hz), 7.06 (dd, 1H, J_1 = 2.1 Hz, J_2 = 8.1 Hz), 3.90 (s, 2H), 3.57 (t, 2H, J = 6.9 Hz), 3.34 (s, 3H), 2.84 (t, 2H, J = 6.9 Hz), 2.11 (m, 1H), 1.93 (br, 2H), 0.47−0.40 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 137.4, 131.4, 130.8, 129.2, 128.6, 73.1, 58.5, 51.1, 35.4, 29.7, 6.4; IR 3314, 3083, 2925, 2866, 2826, 1648, 1470, 1374, 1107, 1039, 1014, 811, 752 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{19}ClNO$, 240.1150; found 240.1148.

2,6-Dichloro-4-methylphenol (14).[23] A 400 L reactor equipped with an overhead stirrer, a nitrogen inlet and an addition funnel was charged with *p*-cresol (**7**) (8000 g, 74 mol) and acetonitrile (40 L). The solution was cooled to 0 °C and 10% aqueous sodium hypochlorite solution (127 kg, 169 mol) was added over 2 h keeping the temperature < 5 °C. On complete addition the batch was allowed to warm to 18 °C and stirred overnight when HPLC showed complete reaction. The batch was cooled to 10 °C and MTBE (66 L) was charged followed by solid sodium bisulfite (3850 g, 37 mol) in portions ensuring the temperature does not exceed 18 °C. The batch was aged for 1 h when starch iodide paper indicated no oxidant present. Concentrated hydrochloric acid (12.4 kg, 126 mol) was then added

(23) Gauvreau, D.; Huffman, M. A.; Hughes, G.; Itoh, T.; Yin, J.; Lau, S.; O'Shea, P. Process for the preparation of diazabicyclo[3.3.1]nonane derivatives. WO 2008/088690 A2, 2008.

while keeping the temperature < 10 °C (pH of aqueous phase = 5−5.5). The batch was warmed to 15 °C, and the aqueous phase was separated. The MTBE solution of 2,6-dichloro-4-methylphenol **14** was assayed at 11.6 kg (89% yield) and carried forward into the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1H,), 5.75 (s, 1H), 2.27 (s, 3H).

5-Bromo-2-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]pyridine (15). A 100-L reactor equipped with an overhead stirrer, a nitrogen inlet, a reflux condenser, and an addition funnel was charged with ethylene carbonate (2200 g, 29.75 mol) and DMAc (16.7 L). The solution was heated to reflux. A solution of the 2,6-dichloro-4-methylphenol **14** (5000 g, 28.24 mol) and imidazole (190 g, 2.8 mol) in DMAc (7 L) was added over 15 min. The solution was heated at reflux for 2 h and then cooled to 25−30 °C. Potassium hydroxide (2220 g, 39.6 mol) was added and the mixture stirred for 30 min at rt. 2,5-Dibromopyridine (**9**) (6700 g, 28.28 mol) was added and the mixture was heated to 80−90 °C and aged overnight. The mixture was then allowed to cool slightly and water (72 L) was added. The mixture was cooled to 20−25 °C and then filtered. The cake was copiously washed with water (172 L) and ethanol (72 L). The cake was dried under a nitrogen stream to afford 8637 g (77%) of **15** as a pale-beige solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.68 (d, 1H, J = 8.5 Hz), 7.11 (s, 2H), 6.75 (d, 1H, J = 9 Hz), 4.68 (apparent s (br), 2H), 4.37 (apparent s (br), 2H); 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 148.9, 147.3, 141.1, 135.5, 129.4, 128.8, 113.1, 111.9, 71.5, 65.2, 20.5; IR 2972, 2929, 2869, 1586, 1476, 1450, 1351, 1280, 1264, 1042, 932, 843, 824, 798, 676 cm^{-1}; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{14}H_{12}BrCl_2NO_2$, 397.9321; found 397.9319.

2-[2-(2,6-Dichloro-4-methyl-phenoxy)ethoxy]-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine (16). A 400-L reactor equipped with an overhead stirrer, a nitrogen inlet, and an addition funnel was charged with aryl bromide **15** (12.37 kg, 32.8 mol), pinacol diboron (10.0 kg, 39.4 mol), potassium acetate (9.66 kg, 98.4 mol), and DMAc (92.7 kg). The solution was degassed three times with nitrogen/vacuum purges. The mixture was then inerted with subsurface nitrogen sparging for 15 min. $PdCl_2$(dppf)−CH_2Cl_2 (804 g, 0.984 mol) was added, and subsurface nitrogen sparging continued for an additional 15 min. The batch was heated to 80−85 °C and aged for 20 h when HPLC showed complete reaction. The reaction mixture was then allowed to cool to 20−25 °C, and water (99 kg) and isopropyl acetate (87 kg) were added. The mixture was stirred for 30 min and allowed to settle overnight. The aqueous layer was cut, and then the organic layer was washed with water (50 kg). The organic layer was then concentrated under reduced pressure at < 40 °C to a volume of 25−30 L. The concentrated iPAc solution was diluted with *n*-heptane (20.5 kg), and the solution was passed through a pad of silica gel (10 kg). The silica pad was washed through with 1:1 iPAc/*n*-heptane (120 L). The filtrate and washes were concentrated under reduced pressure at < 40 °C to ∼25−30 L. Isopropanol (50 kg) was added and the solution concentrated again by distillation at < 40 °C to a volume of ∼30 L. Isopropanol (50 kg) was added, and the resulting slurry stirred at 20 °C over the weekend. The solid was collected by filtration, and the cake washed with isopropanol (20 kg) and dried in vacuo at 40 °C to afford 9.943 kg (71% yield, 96.5 A%) of pinacoloborate ester **16** as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.95 (d, 1H, J = 8.5 Hz), 7.11 (s, 2H), 6.79 (d, 1H, J = 8 Hz), 4.75 (apparent s (br), 2H), 4.38 (apparent s (br), 2H); 2.29 (s, 3H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 153.9, 149.0, 144.6, 135.3, 129.3, 128.8, 110.7, 83.8, 71.7, 64.8, 25.0, 24.8, 20.5; IR 2972, 2929, 2869, 1600, 1474, 1449, 1401, 1366, 1345, 1319, 1286, 1264, 1146, 1129, 1098, 1048, 1065 cm^{-1}; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{20}H_{24}BCl_2NO_4$, 446.1071; found 446.1085.

6-[2-(2,6-Dichloro-4-methyl-phenoxy)ethoxy]-5′,6′-dihydro-2′*H*-[3,4′]bipyridinyl-1′,3′-dicarboxylic Acid 1′-*tert*-Butyl Ester 3′-Ethyl Ester (4a). A 75-L reactor equipped with an overhead stirrer, a nitrogen inlet, a reflux condenser, and an addition funnel was charged with pinacol borate **16** (3096 g, 7.30 mol), triflate **17** (2945 g, 7.3 mol), DME (11.7 L) and 2 M Na_2CO_3 (11.7 L). The solution was heated to 50 °C and was aged under N_2 for 5 min. Solid $Pd(PPh_3)_4$ (84 g, 0.073 mol) was charged, and the reaction mixture was warmed to reflux temperature (83 °C). After 1 h a cloudy mixture formed, and HPLC showed no triflate. The resultant was batch-concentrated to remove DME. MTBE (7.3 L) and water (7.3 L) were added, and the mixture was transferred to a 100-L extractor with heptane (14.6 L) and water (7.3 L). The reaction flask was rinsed with MTBE (7.3 L), and the solution was combined with that in the extractor. The aqueous layer was cut, and the organic layer was washed twice with water (2 × 14.6 L). The organic solution was filtered through a pad of silica gel (2.0 kg), and the pad was rinsed with 1:1 MTBE/heptane (7.3 L). The concentration of the filtrate under reduced pressure afforded compound **4a** as a light-brown oil (4000 g, 99%). ^{1}H NMR (500 MHz, acetone-d_6) δ 7.96 (d, 1H, J = 6 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.25 (d, 2H, J = 9 Hz), 6.79 (t, 1H, J = 8.5 Hz), 4.71 (s (br), 2H), 4.40 (s (br), 2H), 4.23 (s (br), 2H), 3.96 (s (br), 2H), 3.62 (s (br), 2H), 2.54 (s (br), 2H), 2.32 (s (br), 3H), 1.48 (s, 9H), 0.96 (s (br), 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 164.1, 162.8, 154.0, 149.1, 144.9, 142.7, 140.5, 137.9, 137.6, 136.0, 131.0, 129.5, 128.5, 125.9, 110.1, 109.5, 82.6, 80.2, 79.2, 71.9, 64.8, 64.6, 60.0, 59.3, 44.0, 40.4, 39.2, 32.4, 27.7, 27.3, 19.5, 13.6, 13.3; IR 2977, 2932, 1693, 1601, 1475, 1366, 1287, 1257, 1161, 1041, 893, 849, 797, 765 cm^{-1}; HRMS (ESI) (m/z): [M + Na]$^+$ calcd for $C_{27}H_{32}Cl_2N_2O_6Na$, 575.1507; found 575.1516.

(3′*S*,4′*S*)-6-[2-(2,6-Dichloro-4-methyl-phenoxy)ethoxy]-3′,4′,5′,6′-tetrahydro-2′*H*-[3,4′]bipyridinyl-1′,3′-dicarboxylic Acid 1′-*tert*-Butyl Ester 3′-Ethyl Ester (6a). Catalyst Preparation. In a nitrogen-filled glovebox, (O_2 < 10 ppm) SL-J212-1 (93.3 g, 0.179 mol) was combined with (COD)Ru(Me-allyl)$_2$ (54.3 g, 0.170 mol) in a 2-L round-bottom flask followed by anhydrous, degassed CH_2Cl_2 (1.0 L). A red-brown catalyst solution was observed with some solids persisting. The round-bottom flask was removed from the glovebox and connected to a N_2 manifold. The catalyst solution was cooled to 0−5 °C, and HBF_4*OEt_2 (43.9 mL, 0.323 mol) was added dropwise via syringe through the rubber stopper over 20−30 min. After acid addition the catalyst solution was warmed to room temperature and then returned to the nitrogen-filled glovebox. The catalyst solution was transferred to a 2.0-L stainless steel vessel followed by a CH_2Cl_2 rinse (250 mL). Additional CH_2Cl_2 (250 mL) was added to a 0.5-L stainless steel vessel, and the two vessels were connected via a ball-valve.

Hydrogenation. Ene−ester **4a** (30.3 wt %) in THF (6.23 kg, 3.42 mol) was drawn into an autoclave under partial vacuum followed by THF rinse (3.5 L). Batch temperature was brought to 0−5 °C. HBF_4*OEt_2 (422 mL, 3.08 mol) was added in five portions while monitoring batch temperature (maintained < 15 °C). The autoclave was sealed and purged with N_2 (3 × 40 psig). The catalyst assembly was connected to the autoclave via flex tubing, and under partial vacuum the catalyst solution was drawn into the autoclave followed by the CH_2Cl_2 (250 mL) rinse. The reactor was sealed and the headspace exchanged with H_2 (3 × 800 psig). Agitation was begun, and the reaction temperature was maintained at 15 °C for 20 h. The reaction was sampled after 20 h, and there was 0.2 A% ene−ester **4a** remaining. The product ee was observed to be 99%, and there was 3.5 A% de-Boc (SM + product) observed. The reaction was vented, and the product solution (12.2 kg) was drummed into a chilled receiving flask (0−5 °C). The autoclave was rinsed with IPAc (5.0 L). A 100-L cylindrical reaction vessel was charged with the cooled hydrogenation stream (∼12.5 L total volume, 1.89 kg chiral ester **6a**), the iPAc flush (5.0 L), additional iPAc (21.0 L), and cooled to 5 °C. The batch was washed with 7.5 wt % aqueous $NaHCO_3$ (11.4 L) and saturated aqueous NaCl (11.4 L), keeping the temperature between 4 and 8 °C. The layers are dark on

dark, but one can see the interface with a flashlight, and there is gray solid at the interface.

Darco Treatment: (Two Hydrogenation Batches Combined). The solution containing the chiral ester **6a** was added to a 100-L RB flask and treated with Darco KB-G (1.9 kg), aged for 2 h, filtered through solka floc, and the cake was washed with iPAc (5.0 L). The batch was then concentrated to 3.68 kg of a 62.7 wt % oil (2.3 kg assay, 84% yield, 99% ee). $[\alpha]_D = -47.3$ (*c* 1.2, EtOH); (at rt mixture of rotamers) ^{1}H NMR (500 MHz, acetone-d_6) δ 8.08 (s, 1H), 7.65 (d, 1 H, J = 8.4 Hz), 7.25 (s, 2H), 6.73 (d, 1H, J = 8.6 Hz), 4.67 (s, 2H), 4.43 (s (br), 1H), 4.38 (apparent s (br), 2H), 4.26 (s (br), 1H), 3.96 (m, 1H), 3.89 (s (br), 1H), 3.28 (s (br), 1H), 3.22 (s (br), 1H), 3.15 (s (br), 1H), 3.01 (s (br), 1H), 2.91 (s, 1H), 2.84 (s, 3H), 2.64 (s, 1H), 2.32 (s, 3H), 1.67 (d, 1H, J = 12.7 Hz), 1.45 (s, 10H), 1.09 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 171.4, 162.6, 149.1, 145.8, 138.4, 137.1, 131.5, 129.5, 128.5, 110.2, 78.6, 71.9, 64.6, 59.6, 45.3, 27.8, 19.6, 13.6; IR 2975, 2930, 1703, 1690, 1605, 1474, 1426, 1365, 1256, 1156, 1118, 1028, 1003, 798 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M + Na]^+$ calcd for $C_{27}H_{34}Cl_2N_2O_6$, 575.1686; found 575.1697.

Procedure 1 (from 6a): (3′*R*,4′*S*)-6-[2-(2,6-Dichloro-4-methyl-phenoxy)ethoxy]-3′,4′,5′,6′-tetrahydro-2′*H*-[3,4′]bipyridinyl-1′,3′-dicarboxylic Acid 1′-*tert*-Butyl Ester (3). A 100-L vessel equipped with an overhead stirrer, a vacuum inlet, and a temperature probe was charged with the ester **6a** solution in iPAc (8.63 mol). The solution was concentrated under vacuum (10−30 mmHg, 30 °C) and solvent switched to ethanol (^{1}H NMR indicated 18% residual iPAc). The flask was then equipped with a nitrogen inlet and a reflux condenser and charged with EtOH (25 L) and NaOEt/EtOH 21 wt % (14 L, 43.2 mol) and heated at 70 °C for 1 h. At this time an HPLC assay showed a ~14:1 *trans*/*cis* ratio of the ester and some hydrolysis to the carboxylic acid. NaOH (2 N, 22 L, 44 mol) was then added, and the batch was heated to 70 °C for an additional hour. At this time an HPLC assay showed no more ester. Most of the ethanol was evaporated from the batch before being transferred into a 150-L extractor. MTBE (40 L) was added into the extractor, and the solution was cooled to 0 °C. HCl (4 N 20 L) was then added at such a rate to maintain the internal temperature below 20 °C. The pH was adjusted to ~5 by adding extra 2 N HCl (0.3 L) and 10% KH_2PO_4 (12 L). The two layers were cut, and the organic layer was washed with more 10% KH_2PO_4 (40 L) followed by half-saturated brine (20 L), dried over Na_2SO_4 (3 kg) and inline-filtered (Carbon-cap 75 HD, Whatman Inc.) into a 100-L vessel and concentrated under vacuum (10−30 mmHg, 30 °C) to a final volume of ~20 L. The resulting solution was stirred for 1 h at room temperature, and hexanes (10 L) was added. The batch was seeded (34.53 g), and more hexanes (20 L) was added. The slurry was aged at room temperature overnight and for 2 h at 0 °C. Supernatant assay showed 9.75 g/L. The slurry was filtered through a filter pot, and the solid obtained was washed twice with 1:1 cold hexanes:MTBE (0 °C, 2 × 10 L). The solid was dried overnight under vacuum and nitrogen sweep to give acid **3** as a brown powder: 3810.4 g (84% yield, 98.9 A%, 99 wt %, *trans*/*cis* ratio > 120:1). $[\alpha]_D = +5.71$ (*c* 0.80, EtOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.8 (d, 1H, J = 2.5 Hz), 7.66 (dd, 1H, J = 8.5, 2.5 Hz), 7.25 (s, 2H), 6.74 (d, 1H, J = 8.5 Hz), 4.66 (t, 2H, J = 5 Hz), 4.41 (s (br), 1H), 4.38 (t, 2H, J = 5 Hz), 4.22 (s (br), 1H), 2.97 (td, 2H, J = 12, 3.5 Hz), 2.87 (s (br), 1H), 2.72 (td, 2H, J = 12, 4 Hz), 2.31 (s, 3H), 1.79 (m, 1H), 1.68 (qd, 1H, J = 12.5, 4.5 Hz), 1.49 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 172.6, 162.5, 153.9, 149.1, 145.8, 137.9, 136.0, 131.9, 129.5, 128.5, 110.6, 79.1, 71.9, 64.5, 41.9, 27.7, 19.4; IR 1713, 1472, 1444, 1286, 1262, 1233, 1191, 1126, 1050, 935, 925, 849, 825 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M + H]^+$ calcd for $C_{25}H_{30}Cl_2N_2O_6$, 525.1559; found 525.1557.

1-(2,2,2-Trifluoro-acetyl)-4-trifluoromethanesulfonyloxy-1,2,5,6-tetrahydro-pyridine-3-carboxylic Acid Ethyl Ester (17b). TFA Protection. The suspension of ethyl 4-oxopiperidine-3-carboxylate (5980 g, 28.8 mol) in MeTHF (48 L) was cooled to 3 °C under nitrogen. Triethylamine (10.1 L, 72 mol) was charged, followed by the addition of trifluoroacetic anhydride (4.2 L, 30.2 mol) over 60 min at 4−5 °C. The resulting slurry was aged at < 5 °C for another 10 min, and a sample was taken to confirm < 0.8% starting material by HPLC. HCl (2 N, 6 L) was poured, and the mixture was transferred to a 100-L extractor. The reaction flask was rinsed with 2 N HCl (30 L), and the solution was also transferred to the extractor. The aqueous layer was cut, and the organic layer was washed with water (36 L) and 10% $KHCO_3$ (36 L). After the washes, 38.7 kg of organic solution was obtained. By NMR it was pure enough for the next reaction. The bulky organic solution was batch concentrated to get the TFA-protected piperidinone as a yellow oil, and it was used for the next reaction without further purification.

Triflation. The TFA-protected piperidinone was dissolved in DCM (40 L), and triethylamine (6.0 L, 43 mol) was charged. The mixture was cooled to −28 °C under nitrogen, triflic anhydride (5.27 L, 31.4 mol) was added over 60 min at ←10 °C. Resulting solution was aged at ←10 °C for another 10 min, and a sample was taken to confirm < 0.6% TFA-protected piperidinone by HPLC. Water (11 L) was poured into the flask, and the mixture was transferred to a 100-L extractor containing water (11 L). The aqueous layer was cut, and the organic layer was washed with 2 N HCl (22 L), water (22 L), 10% $KHCO_3$ (22 L), and water (22 L). The organic solution was concentrated by batch concentration to about 30 L, and heptane (30 L) was charged. The mixture was further concentrated to about 40 L (slurry was generated, and the heavy slurry was filtered at 37 °C. The cake was rinsed with heptane (11 L). After drying under a nitrogen stream, 10.353 kg (91%, > 99 A%) of product **17b** was obtained as light brown color solid. ^{1}H NMR (600 MHz, DMSO-d_6, 90 °C): δ 4.48 (s, 1 H); 4.28 (q, J = 7.10 Hz, 1 H); 3.85 (t, J = 5.86 Hz, 1 H); 3.02 (s, 1 H); 2.72 (s, 2 H); 1.29 (t, J = 7.09 Hz, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.95, 161.88, 155.16, 155.09, 154.9, 154.8, 154.6, 151.2, 150.1, 122.0, 119.8, 119.6, 119.5, 117.6, 116.9, 115.3, 115.3, 114.4, 62.2, 62.1, 43.6, 42.4, 41.9, 29.1, 27.8, 13.9, 13.9; IR 1697, 1461, 1418, 1245, 1207, 1135, 1045, 902, 831, 758, 621 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M + H]^+$ calcd for $C_{11}H_{11}F_6NO_6S$, 400.0289; found 400.0292.

6-[2-(2,6-Dichloro-4-methyl-phenoxy)ethoxy]-1′-(2,2,2-trifluoro-acetyl)-1′,2′,5′,6′-tetrahydro-[3,4′]bipyridinyl-3′-carboxylic Acid Ethyl Ester (4b). A 100-L vessel equipped with an overhead stirrer, a nitrogen inlet, a reflux condenser, and an addition funnel was charged with borane **16** (9500 g, 22.4 mol), triflate **17b** (8500 g, 21.3 mol), Pd(dppf)Cl_2 (313 g, 0.383 mol), $KHCO_3$ (5300 g, 52.9 mol), 2-MeTHF (47.5 L), and water (14.3 L). The reaction mixture was degassed with N_2/vacuum purges and then heated to 60 °C and aged for 1 h. The reaction mixture was cooled to room temperature and transferred into the 180-L extractor containing 5% NaH_2PO_4 (48 L). The bottom aqueous layer was cut away, and hexanes (50 L) was added to the organic layer. The organic layer was then washed with brine (30 L). The remaining organic layer was then diluted with more hexanes (38 L). The organic layer was collected and passed through a 10 kg silica gel plug in an 18" filter pot. The cake was washed with 1:1 2-MeTHF: hexanes (12 L). The filtrate was concentrated to a volume of ca. 28 L and then diluted back to 48 L with 2-MeTHF. The solution was then treated with slow addition of 4 N HCl in dioxane (10 L) and allowed to stir overnight. The solids were then filtered, washed with 1:1 2-MeTHF/hexanes, and dried under a nitrogen sweep to give 11.2 kg (90% yield) of **4b** HCl salt.

Salt Break. The solid was then charged into a 100-L cylindrical vessel containing 2-MeTHF (55 L), water (28 L), and $NaHCO_3$ (3.0 kg). The mixture was stirred for 30 min and then allowed to settle. The aqueous layer was collected, and the organic layer was treated with H_2O (12 L) and NaCl (2.0 kg). After stirring for 15 min the layers were allowed to settle and

then separated. The organic layer was dried over Na_2SO_4 and then sucked into a batch concentrator through a 5 μm line filter and concentrated to ~10 L. The batch was then diluted back to ~35 L with 2-MeTHF. The batch was then drummed off into polyjugs to give 32.8 kg of a 28.4 wt % solution. (9.32 kg assay, 80% overall yield). ^{1}H NMR (500 MHz, $CDCl_3$) (at r.t. see mixture of rotamers): δ 8.02 (s, 1H), 7.63 (d, 1H, J = 8.5 Hz), 7.26 (s, 2H), 6.82 (d, 1H, J = 8.5 Hz), 4.72 (t, 2H, J = 4 Hz), 4.53 (s, 1H), 4.50 (s, 1H), 4.41 (t, 2H, J = 4 Hz), 4.10−3.97 (m, 2H), 3.92 (t, 2H, J = 5.5 Hz), 2.76 (s, 1H), 2.71 (s, 1H), 2.32 (s, 3H), 2.07 (s, 1H), 1.02−0.94 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 163.1, 154.7 (q, J = 35.4 Hz), 149.0, 144.9, 144.4, 143.2, 138.1, 136.0, 130.3, 129.5, 128.5, 124.2, 123.9, 116.7 (q, J = 277.5 Hz), 110.2, 71.8, 64.8, 60.4, 44.6, 43.3, 42.1, 39.9, 32.9, 31.6, 19.6, 13.3; IR 2982, 1692, 1600, 1474, 1376, 1287, 1258, 1199, 1175, 1133, 1046, 935, 792 cm^{-1}; HRMS (ESI) (m/z): $[M + Na]^+$ calcd for $C_{24}H_{23}Cl_2F_3N_2O_5Na$, 569.0828; found 569.0848.

Procedure 2 (from 6b): (3′*R*,4′*S*)-6-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]-3′,4′,5′,6′-tetrahydro-2′*H*-[3,4′]bipyridinyl-1′,3′-dicarboxylic Acid 1′-*tert*-Butyl Ester (3). Catalyst Preparation. In a nitrogen filled glovebox, (O_2 < 10 ppm) SL-J212-1 (230.4 g, 0.441 mol) was combined with (COD)Ru(Me-allyl)$_2$ (134.2 g, 0.42 mol) in a 1 gallon blow can followed by anhydrous, degassed CH_2Cl_2 (2.5 L).

Hydrogenation. Ene−ester (**4b**) 28.4 wt % in 2-MeTHF (32.4 kg, 16.8 mol) was drawn into an autoclave under partial vacuum followed by 2-MeTHF rinse bringing the batch volume to 300 L. $HBF_{4*}OEt_2$ (3.40 kg, 21.0 mol)) was added slowly while monitoring the batch temperature (maintained < 40 °C). The autoclave was sealed and purged with N_2 (3 × 40 psig). The catalyst solution was introduced into the autoclave. The reactor was sealed, and then the pressure was tested to 1000 psig N_2. The reactor was then vented and pressurized with H_2 to 1000 psig. Agitation was begun and the reaction temperature maintained at 23 °C for 43 h. The reaction was vented, and HPLC confirmed < 0.1 A% ene−ester **4b** with an ee of > 99%. Aqueous $NaHCO_3$ (100.0 kg, 7.5 wt %) was added slowly to the hydrogenation batch, while maintaining a batch temperature < 30 °C. The aqueous layer was confirmed to have pH ≈ 8. The aqueous layer was cut away, and the organic layer was washed with water (150 L). The organic layer (282.6 kg) was assayed, and the concentration of chiral ester was determined to be 3.0 wt % (8.48 kg, 15.44 mol). The batch was then distilled to a final weight of 71.0 kg. 2-MeTHF (12.0 kg) was used to rinse the distillation vessel. Into a visually clean and dry 160 L extractor, the ester **6b** solution was added and rinsed with small amount of fresh 2-MeTHF.

Darco Treatment. The solution was then treated with Darco KB-G (4.3 kg) for 2 h., filtered over silica gel (4.3 kg)on bed of solka floc and washed with 2-MeTHF (50 L). The solution was line filtered using a whatman polycap 75 HD to a visually clean and dry 100 L rbf equipped with a thermocouple, overhead mechanical stirrer and attached to a batch concentrator and the 2-MeTHF was removed in vacuo. The material was flushed with EtOH (25 L), concentrated and diluted to a final volume of 25 L. (Assayed at 8.48 kg, 15.44 mol, 92% yield).

TFA Deprotection, Boc Protection, Epimerization and Hydrolysis Sequence. A 75-L vessel equipped with an overhead stirrer, a nitrogen inlet, and a temperature probe was charged with *cis*-ester **6b** (4400 g, 8.01 mol) and EtOH (20 L). The solution was cooled to 5 °C, and NaOEt/EtOH (21 wt %, 3.59 L, 9.61 mol) was added over 15 min. The reaction mixture was allowed to warm to ~15 °C over 4 h. Water (173 mL, 9.61 mol) was added, and the reaction mixture was stirred for 10 h and then cooled to 5 °C. Boc_2O (2098 g, 9.61 mol) was added portionwise as a neat melt (GAS EVOLUTION!). The reaction mixture was aged for 30 min while allowing to warm to rt. NaOH (2 M, 20.0 L, 40.0 mol) was added over 15−20 min, and the reaction mixture was heated to 70 °C for 2 h. Once cooled to rt, the reaction mixture was transferred to an extractor filled with IPAc (20 L) and 2 N HCl (24.03 L, 48.1 mol). The layers were cut, and the aqueous layer (should be acidic, pH < 4) was extracted with IPAc (20 L). The combined organic layers were washed with half-saturated brine (2 × 10 L), batch concentrated, and flushed with fresh IPAc (20 L). Once the final volume was ~16 L, the solution was warmed to 70 °C while heptane (40 L) was added. The temperature was cooled to ~50 °C, additional heptane (40 L) was added, and the solution was cooled to rt overnight. The solid was filtered, washed with 5:1 heptane/IPAc (20 L) and flushed with N_2 for 20 h. Product can be dried under vacuum/N_2 flush at 70 °C to bring water level at or below 3000 ppm. 3.9 kg *trans*-acid **3** was isolated as a beige powder (88% yield, 95 wt %, 7.05 mol, *trans*/*cis* ratio > 100:1).

(3′*R*,4′*S*)-3′-{[2-Chloro-5-(2-methoxy-ethyl)-benzyl]cyclopropylcarbamoyl}-6-[2-(2,6-dichloro-4-methyl-phenoxy)ethoxy]-3′,4′,5′,6′-tetrahydro-2′*H*-[3,4′]bipyridinyl-1′-carboxylic Acid *tert*-Butyl Ester (19). A 100-L vessel equipped with an overhead stirrer, a vacuum inlet, a nitrogen inlet, and a temperature probe was charged with *trans*-acid **3** (3840 g, 6.94 mol), MeCN (8.00 L), 2-MeTHF (8.00 L), and tosyl chloride (1747 g, 9.16 mol). The slurry was cooled to −20 °C, and 1-methylimidazole (1.942 L, 24.36 mol) was added over 15 min, dissolving the slurry and warming the mixture to −10 °C. The reaction mixture was stirred for 3 h while internal temperature was kept between −10 and −5 °C. Amine **2** (2031 g, 8.47 mol) in MeCN (2 L) and 2-MeTHF (2 L) was then added over 5 min, and the reaction was allowed to warm to rt and stirred for 16 h under N_2. An extractor was charged with 2-MeTHF/MTBE (3:1) (20 L) and cooled to 15 °C, and the reaction mixture was transferred into it. Water (20 L) was added, and the layers were separated. The aqueous layer was extracted with 2-MeTHF/MTBE (3:1) (20 L). The combined organics were successively washed with 0.5 N NaOH (20 L), 0.5 N HCl (20 L), and water (20 L). The organic layer was then treated with 2.5 kg Darco KB-G for 1 h and filtered over solka floc, and the pad was washed with 2-MeTHF/MTBE (3:1) (20 L) to give 4.87 kg (94% yield, 86 A%) of coupled product **19**. $[\alpha]_D$ = −0.96 (*c* 1.87, EtOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.06 (s, 1H), 7.67 (d, 1H, J = 8.5 Hz), 7.25 (s, 2H), 7.22 (d, 1H, J = 8 Hz), 7.08 (d, 1H, J = 8 Hz), 6.73 (d, 1H, J = 8.5 Hz), 6.55 (s, 1H), 4.68 (t, 2H, J = 4 Hz), 4.57 (d (br), 1H, J = 15.5 Hz), 4.42 (d (br), 1H, J = 15.5 Hz), 4.39 (t, 2H, J = 4 Hz), 4.29 (s (br), 2H), 3.64 (t, 1H, J = 10 Hz), 3.48 (t, 2H, J = 6.5 Hz), 3.26 (s, 3H), 3.21−3.16 (m, 1H), 2.96 (s (br), 3H), 2.68 (apparent s (br), 2H), 2.62 (apparent s (br), 1H), 2.31 (s, 3H), 1.80 (s (br), 2H), 1.51 (s, 9H), 1.46 (s, 1H), 1.20 (d, 1H, J = 8 Hz), 0.96 (s, (br), 1H), 0.84 (s (br), 2H), 0.57 (s (br), 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.1, 162.4, 149.1, 146.1, 138.7, 138.2, 136.0, 135.3, 132.1, 129.5, 128.84, 128.81, 128.7, 128.5, 110.6, 79.0, 72.8, 71.8, 66.9, 64.6, 57.7, 47.5, 46.8, 41.8, 35.2, 32.0, 30.4, 29.9, 27.8, 21.2, 19.5, 13.6, 8.6; IR 2972, 2929, 2869, 1736, 1691, 1649, 1605, 1474, 1426, 1406, 1365, 1285, 1255, 1231, 1160, 1115, 1042, 984, 828, 798 cm^{-1}; HRMS (ESI) (m/z): $[M - H]^+$ calcd for $C_{38}H_{45}Cl_3N_3O_6$, 746.2530; found 746.2532.

(3′*R*,4′*S*)-6-[2-(2,6-Dichloro-4-methyl-phenoxy)ethoxy]-1′,2′,3′,4′,5′,6′-hexahydro-[3,4′]bipyridinyl-3′-carboxylic Acid [2-Chloro-5-(2-methoxy-ethyl)benzyl]cyclopropylamide (MK-1597). A 50-L vessel equipped with an overhead stirrer, a vacuum inlet, a nitrogen inlet, and a temperature probe was charged with compound **19** (4800 g, 6.42 mol) in solution in ~10 L of 2-MeTHF and fresh MTBE (10 L). Phosphoric acid (85 wt %, 5 L, 74 mol) was added over 10 min, and the reaction mixture was heated to 60 °C for 16 h. It was diluted with MTBE (10 L), cooled to 0 °C, and quenched with 5 N NaOH (~18 L) to reach pH > 12. The layers were cut, and the aqueous layer was back-extracted with MTBE (10 L). The combined organic layers were washed with water (5 L) and then extracted with 40% v/v aq MsOH (3 × 10 L). The combined aqueous MsOH layers were washed with MTBE (5 L). Fresh MTBE (20 L) was added, and the heterogeneous mixture was

cooled to 0 °C and basified with 10 N NaOH (~19 L) to pH > 12. The layers were cut, and the aqueous layer was back-extracted with MTBE (2 × 5 L). The combined organic layers were washed with half-saturated brine (2 × 10 L), dried over Na_2SO_4, and batch concentrated to give **MK-1597** (**1**) (3.95 kg, 95% yield, 91.8 A%).

Bis-D-Tartrate Salt Formation and Salt Break. MK-1597 (3900 g, 6.03 mol) was dissolved in THF (30 L), then D-tartaric acid (1809 g, 12.06 mol) was added, and the reaction mixture was stirred at rt for 20 h. MTBE (45 L) was added over 1 h, and the slurry was aged for 1 h. The solid was filtered through a filter pot, washed with 1.5:1 MTBE/THF (35 L), and dried under nitrogen sweep to give 5100 g of **MK-1597 bis-D-tartrate salt** (90%). Into a visually clean and dry 160-L extractor was introduced MTBE (16 L) and 1 M NaOH (20 L). **MK-1597 bis-D-tartrate salt** (4.5 kg, 4.66 mol) was added, and the slurry was vigorously stirred for 3 h to completely dissolve the salt. The layers were cut, and the organic layer was washed with half-saturated brine (2 × 10 L). The organic solution was assayed at 2.9 kg of **MK-1597** and dried over Na_2SO_4 and $MgSO_4$ to bring the water level down to 5000 ppm. A sample was analyzed: $[\alpha]_D = +14.4$ (*c* 1.06, EtOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.05 (d, 1H, J = 0.2 Hz), 7.67 (dd, 1H, J = 8.5, 2.5 Hz), 7.26 (s, 2H), 7.22 (d, 1H, J = 8 Hz), 7.07 (dd, 1H, J = 8.5, 2 Hz), 6.74 (d, 1H, J = 8.5 Hz), 6.53 (s, 1H), 4.68 (t, 2H, J = 4.5 Hz), 4.52 (d, 1H, J = 16 Hz), 4.46 (d, 1H, J = 16 Hz), 4.39 (t, 2H, J = 4.5 Hz), 3.65 (td, 1H, J = 11, 4 Hz), 3.47 (t, 2H, J = 6.5 Hz), 3.37 (dd, 1H, J = 12.5, 3.5 Hz), 3.16−3.07 (m, 2H), 2.76−2.63 (m, 5H), 2.32 (s, 3H), 2.07 (quint, 1H, J = 2 Hz), 1.84−1.73 (m, 3H), 0.89−0.79 (m, 2H), 0.72−0.67 (m, 1H), 0.48−0.43 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 175.3, 162.2, 149.0, 146.1, 138.7, 138.3, 136.0, 135.7, 133.2, 129.4, 128.7, 128.61, 128.56, 128.51, 110.4, 72.8, 71.8, 64.5, 57.6, 50.2, 48.3, 47.6, 46.8, 41.8, 35.2, 33.5, 30.3, 29.4, 27.0, 19.4, 9.06, 7.78; IR 3492, 3312, 2970, 2933, 1645, 1606, 1476, 1404, 1260, 1203, 1077, 1036, 797 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M + H]^+$ calcd for $C_{33}H_{38}Cl_3N_3O_4$, 646.2001; found 646.1996.

(3′*R*,4′*S*)-6-[2-(2,6-Dichloro-4-methyl-phenoxy)ethoxy]-1′,2′,3′,4′,5′,6′-hexahydro-[3,4′]bipyridinyl-3′-carboxylic Acid [2-Chloro-5-(2-methoxy-ethyl)benzyl]cyclopropylamide Acetate (MK-1597 AcOH Salt). A 100-L vessel equipped with an overhead stirrer, a vacuum inlet, a nitrogen inlet, an addition funnel, and a temperature probe was charged with a solution of **MK-1597** (3141 g, 4.85 mol) in MTBE, and fresh MTBE (20 L) was added (filtered through an inline filter, Polycap 36 HD, 1 μm, Whatman Inc.). A solution of AcOH (600 mL, 10.48 mol) in heptane (4 L) was filtered through an inline filter (Polycap 36 HD, 1 μm, Whatman Inc.) into the addition funnel. AcOH/heptane (500 mL) was added before seeding (22.28 g). The slurry was aged at room temperature for 30 min, and the rest of AcOH/heptane solution (4.1 L) was added over 35 min. The slurry was aged at room temperature for 3 h and at 0 °C for 30 min. The slurry was filtered through a filter pot, and the solid obtained was washed with cold (0 °C) 10% heptane in MTBE (3 × 3 L) and with cold (0 °C) 1:1 heptane/MTBE (10 L). The solid was dried under vacuum and nitrogen sweep and filtered over a sieve to give the **MK-1597 AcOH salt** as a white powder: 2941.6 g (83% AY, 98.6 A%). Ru content: 5 ppm, Pd content: < 1 ppm. $[\alpha]_D = +20.3$ (*c* 1.12, EtOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.06 (s, 1H), 7.69 (d, 1H, J = 8.5 Hz), 7.26 (s, 2H), 7.22 (d, 1H, J = 8 Hz), 7.07 (d, 1H, J = 8 Hz), 6.74 (d, 1H, J = 8 Hz), 6.53 (s, 1H), 4.68 (t, 2H, J = 4 Hz), 4.52 (d, 1H, J = 16 Hz), 4.46 (d, 1H, J = 16 Hz), 4.39 (t, 2H, J = 4 Hz), 3.81−3.77 (m, 1H), 3.47 (t, 2H, J = 6.5 Hz), 3.41 (d, 1H, J = 11.5 Hz), 3.25 (s, 3H), 3.21 (d, 1H, J = 15 Hz), 3.12 (t, 1H, J = 14 Hz), 2.79 (q, 2H, J = 17.5, 12.5 Hz), 2.75−2.59 (m, 3H), 2.32 (s, 3H), 1.95 (s, 3H), 1.95−1.90 (m, 1H), 1.81 (d, 1H, J = 13.5 Hz), 0.89−0.81 (m, 2H), 0.75−0.70 (m, 1H), 0.48−0.44 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 175.3, 162.3, 149.0, 146.1, 138.7, 138.3, 136.0, 135.6, 129.6, 129.4, 128.7, 128.64, 128.60, 128.50, 110.4, 72.8, 71.8, 64.5, 57.6, 47.6, 47.2, 41.6, 35.2, 30.4, 19.4, 8.97, 7.91; IR 1636, 1602, 1472, 1408, 1266, 1114, 1034, 1011, 839, 648 cm^{-1}; HRMS (ESI) (*m*/*z*): $[M + H]^+$ calcd for $C_{33}H_{38}Cl_3N_3O_4$, 646.2001; found 646.1996.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.