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Construction of a (3*aR*,4*R*,9*bR*)-Hexahydropyrroloquinoline by Stereoselective Hydrogen-Mediated Domino Cyclization

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Supporting Information

ABSTRACT: A novel practical asymmetric route to a chiral hexahydropyrroloquinoline derivative **2**, a key fragment of TAK-480, is reported. The corresponding substrate, enamine **19**, was directly transformed to a diastereopure and enantiopure (3*aR*,4*R*,9*bR*)-hexahydropyrroloquinoline **16** through a rhodium-catalyzed hydrogen-mediated domino cyclization consisting of four steps; (1) asymmetric hydrogenation of enamine, (2) hydrogenation of iminium olefin in a lactam, (3) dehydration and catalytic sulfonation, and (4) *cis*-selective intramolecular cyclization. A tuned asymmetric catalyst [Rh(cod){(2*S*,4*S*)-PTBP-SKEWPHOS}]OTf that we previously developed was found to promote improved reaction activity and be the most suitable catalyst for a multikilogram manufacturing for preclinical research. The resulting stereoselective domino cyclization drastically reduced several synthetic steps, and the resulting waste compared to the discovery route that required chiral preparative high-performance liquid chromatography and silica gel column separation.

KEYWORDS: *asymmetric hydrogenation, domino reaction, hexahydropyrroloquinoline, Skewphos*

INTRODUCTION

In 2006, Takeda Pharmaceutical Company disclosed 4-(difluoromethoxy)-*N*-((1*R*,2*S*)-2-(((3*aR*,4*R*,9*bR*)-4-(methoxymethyl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-1-yl)carbonyl)cyclohexyl) benzamide (TAK-480, **1**) as an efficient antagonist for a tachykinin NK_2 receptor (Scheme 1).[1-(a)] TAK-480 shows potent binding affinity for human NK_2 receptors with a marked species and a 10 000-fold selectivity versus NK_1 and NK_3 receptors. The novel NK_2 receptor antagonist, TAK-480 improves visceral hypersensitivity and accelerates defecation without causing constipation in experimental animals. Furthermore, the potent functional blockade of NK_2 receptors in human colon has suggested the potential effectiveness of TAK-480 in irritable bowel syndrome (IBS) patients.[1]

Synthetically, TAK-480 possesses an extremely challenging molecular structure consisting of five stereocenters. A simple retrosynthetic analysis of **1** revealed that it can be disconnected into two main building blocks: (3*aS*,4*R*,9*bR*)-4-(methoxymethyl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (**2**) and (1*S*,2*R*)-2-(4-(difluoromethoxy)benzamido)-cyclohexane-1-carboxylic acid (**3**; Scheme 1). A synthesis of **3** was developed by our colleagues using an effective asymmetric hydrogenation. A novel ruthenium catalyst, [$Ru(OAc)_2${(*S*)-2,2′-bis(bis(3,5-di-tert-butyl-4-methoxyphenyl)phosphaneyl)-1,1′-binaphthalene}], was developed as a tuned catalyst to give the corresponding product (ethyl (1*S*,2*R*)-2-(4-(difluoromethoxy)benzamido)-cyclohexane-1-carboxylate) with high stereoselectivity (95.0% ee and 98.7% de) at a multikilogram scale. The product was converted to optically pure **3** through hydrolysis and recrystallization.[2]

Most of our efforts were thus focused toward the synthesis of **2**, a hexahydropyrroloquinoline ring bearing three chiral centers, and in this paper we describe details of a catalytic asymmetric approach to its preparation.

EARLY DEVELOPMENT

Compound **2·2HCl** had been originally prepared by medicinal chemists at gram scale and was obtained after two column separations: silica gel chromatography for separation of the two diastereomers (***rac-endo*-5** and ***rac-exo*-5**) and chiral preparative high-performance liquid chromatography (HPLC) separation of the two enantiomers (**7** and ***ent*-7**) of a single diastereomer (***rac-endo*-7**; Scheme 2, discovery route).[3] Besides the highly expensive and commercially unavailable starting material **4**, several issues were identified in this synthesis from a standpoint of practicality for a manufacturing process: (i) purification by silica gel and optical resolution by chiral preparative HPLC; (ii) *endo*/*exo* selectivity in the *aza*-Diels−Alder reaction; (iii) use of expensive reagents, for example, $Dy(OTf)_3$; (iv) no possibility for a purification step

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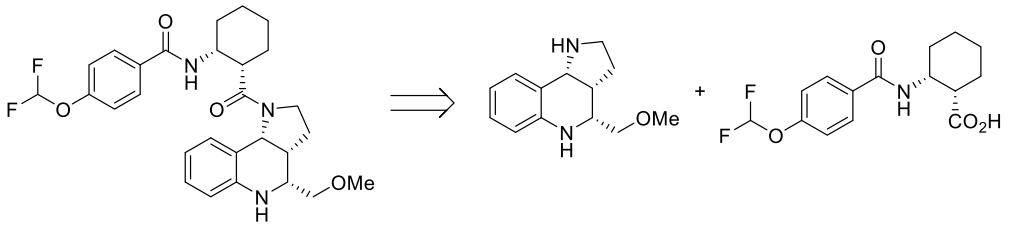
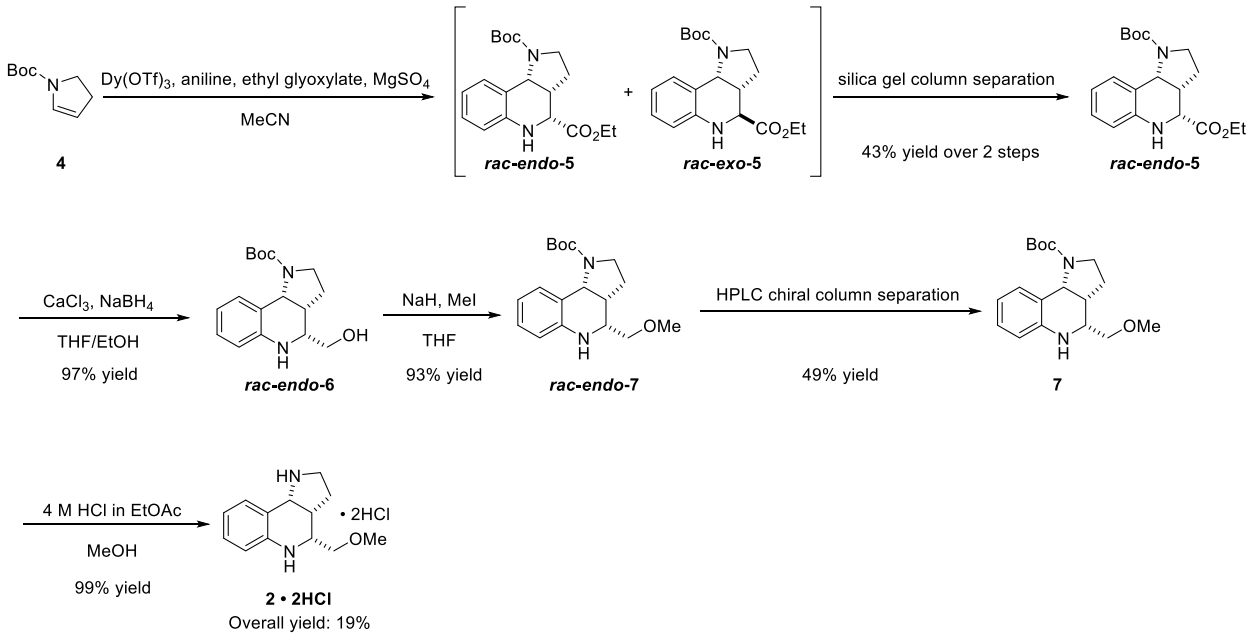
Scheme 1. Retrosynthetic Analysis of Clinical Candidate 1



Scheme 2. Discovery Route for Preparation of 2·2HCl



by crystallization, because all compounds from **4** to ***rac-endo*-6** were oils.

As a part of our drug development program, a practical asymmetric synthesis for multikilogram quantities of **2** for clinical candidate **1** was required, to be applied at large scale and with an increased overall yield. However, the diastereo- and enantioselective synthesis of hexahydropyrroloquinoline derivatives has not been well-studied. Many direct diastereoselective syntheses of racemic hexahydropyrroloquinolines have been reported for (+)-martineline and (−)-martinelic acid, isolated from the roots of Martinella iquitosensis by Witherup.[4] Martineline or (−)-martinelic acid has been shown to be a potent inhibitor for several G-protein coupled receptor systems including bradykinin (BK), histaminergic, α-adrenergic, and muscarinic receptors, in spite of having a different configuration to our target molecule.[5] As an asymmetric approach to prepare the hexahydropyrroloquinoline derivatives, a few different methodologies have been reported, using palladium-catalyzed intermolecular cyclization,[6] conjugate addition with a chiral building block,[7] asymmetric Povarov reaction catalyzed by chiral urea catalysts[8] or chiral phosphoric acid catalysts,[9] and asymmetric tandem Michael-aldol reaction.[10] Among them, the asymmetric Povarov reaction by Jacobsen and co-workers in 2010 provided 1-benzyl-4-ethyl (3*aR*,4*R*,9*bR*)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo[3,2-*c*]-quinoline-1,4-dicarboxylate as an endo product (>20:1 *dr*) with high enantioselectivity (97% ee).[8] Although this synthetic method was considered to be a useful direct route to the core tetrahydroquinoline structure, it was deemed unsuitable for large-scale supply because of complex industrial issues, such as those encountered for a reaction needing the use of activated molecular sieves at cryogenic temperature and a chiral catalyst preparation using an expensive chiral source, as well as the obtained diastereoselectivity being only moderate.

In 2008, Tatsuta and co-workers at Waseda University and Kondo et al. at Takeda Pharmaceutical Company developed an efficient asymmetric synthesis of **2** using asymmetric hydrogenation of the enamine **12** and forward *cis*-stereoselective intramolecular cyclization (Scheme 3, first-generation asymmetric route of **2**).[11]

The first-generation asymmetric route toward **2** started from a commercially available and inexpensive material, pyrrolidine-2-one **8**, which was turned into the *p*-methoxybenzyl protected pyrrolidine-2-one **9** and alkylated with methyl 2-methoxyacetate to furnish ketone **10** in good yield. The ketone was then condensed with aniline to afford the *Z* form enamine **11** as a crystalline powder. The asymmetric catalyst combination of [Rh(cod)$_2$]OTf and (*S*)-(*R*)-SL-J210-2 obtained from Solvias was used for hydrogenation of the enamine **11** with *syn*-selectivity (*syn*/*anti* = 94/6) and high enantioselectivity (91% ee), affording the hydrogenation product ***syn*-12** within 24 h under a hydrogen pressure of 1 MPa at S/C = 25. The

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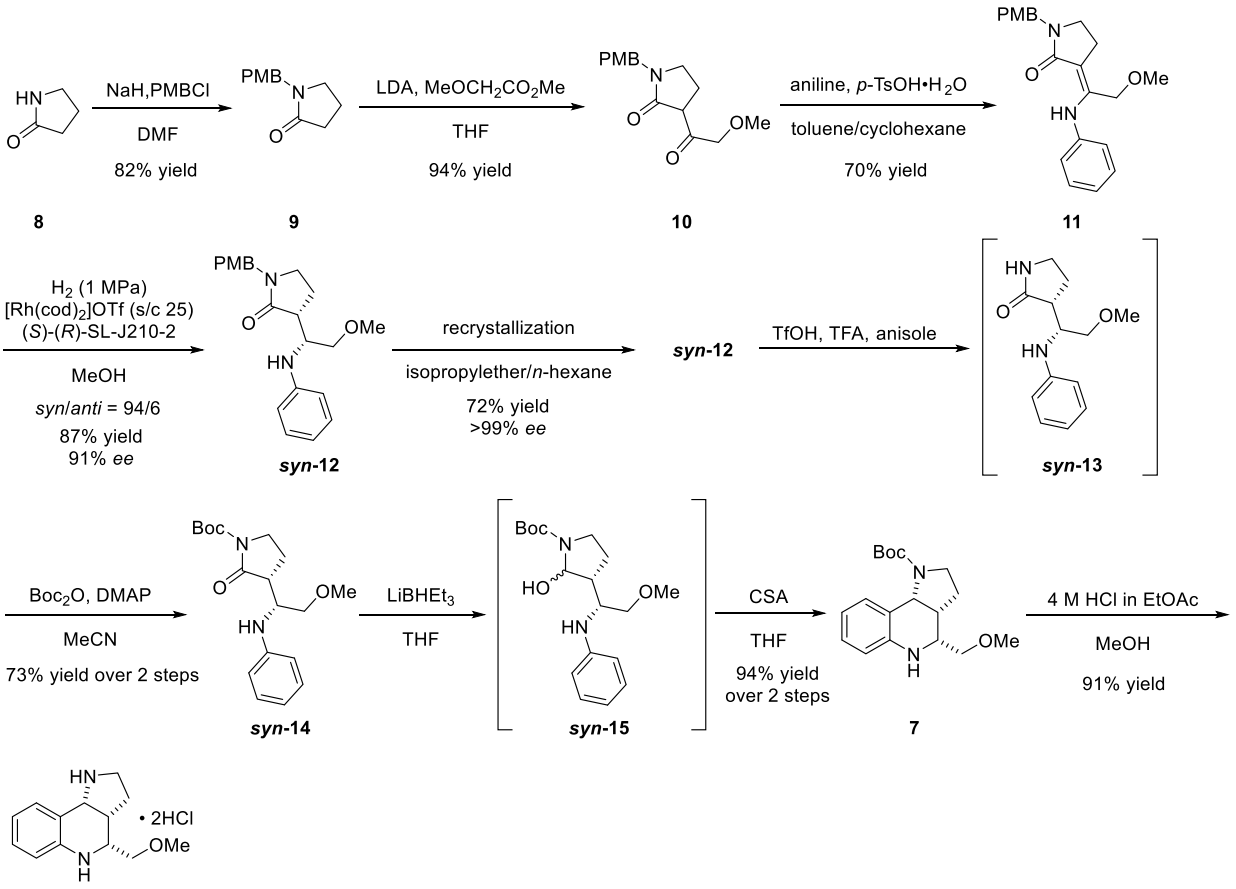
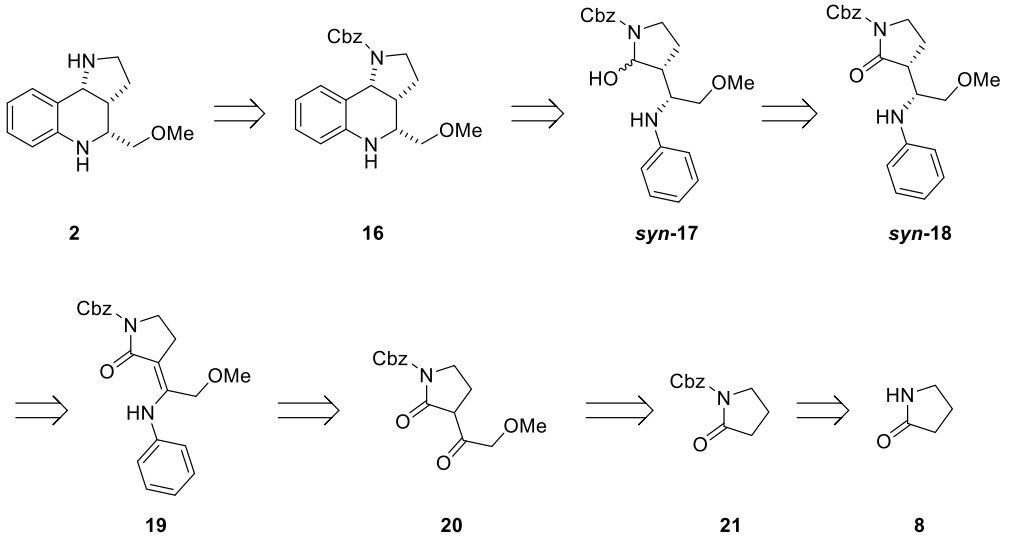
Scheme 3. First-Generation Asymmetric Route to 2



Scheme 4. Retrosynthesis of 2 for a Second-Generation Asymmetric Route



diastereopure and enantiopure ***syn*-12** was obtained in 72% yield with greater than 99% ee on recrystallization from a mixture of isopropyl ether and hexane. After the protecting group was changed from *p*-methoxybenzyl (PMB) to *tert*-butyloxycarbonyl (Boc), the carbonyl on the pyrrolidine ring was efficiently reduced at −78 °C with lithium triethyl borohydride. The crude mixture was directly used in a *cis*-selective intramolecular cyclization in the presence of camphorsulfonic acid, followed by deprotection under acidic conditions to obtain **2·2HCl**. To improve the first-generation asymmetric route, to give a practical manufacturing method, we initiated an investigation according to the retrosynthetic analysis shown in Scheme 4. The original aim was to replace the protecting group PMB with carboxybenzyl (Cbz), since the PMB-protected asymmetric hydrogenation product (***syn*-12**) could not be used in the subsequent carbonyl reduction step, and Cbz protection is easy to track by HPLC. However, as an unanticipated bonus it was surprisingly discovered that a novel

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Scheme 5. Operation Friendly Quenching Method for Acylation of 21

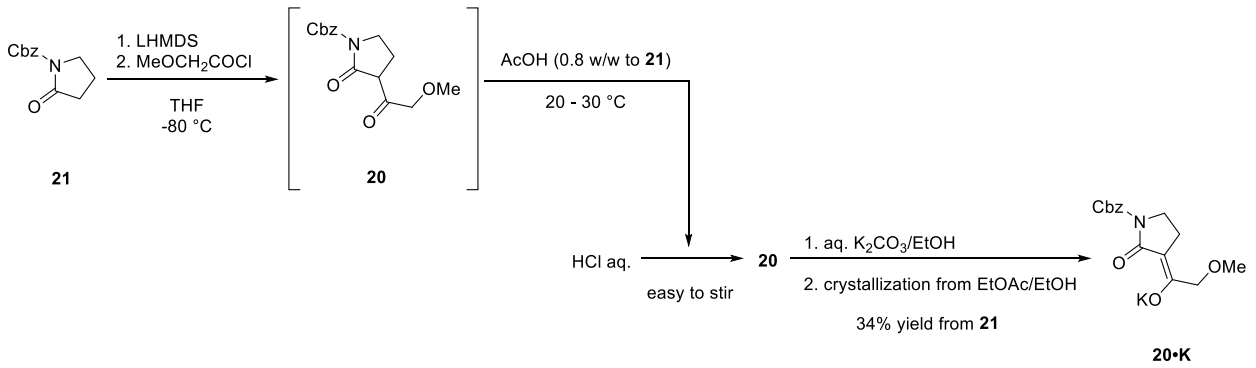
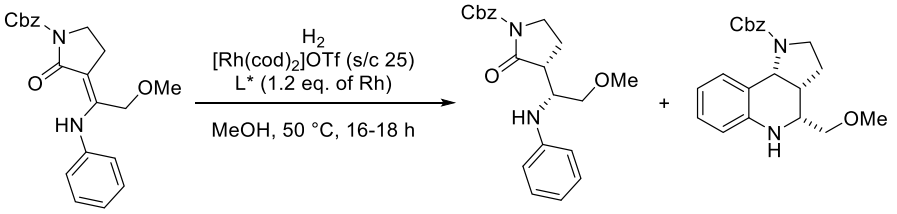
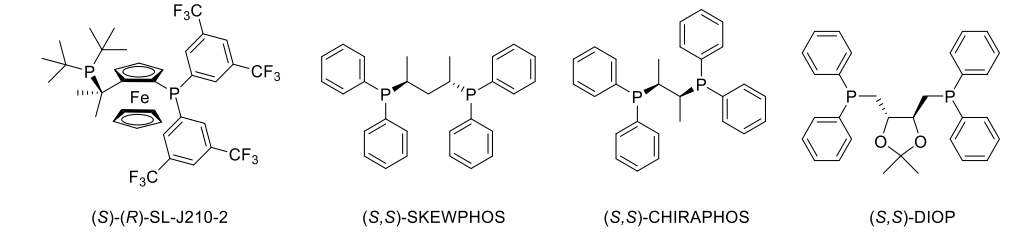


Table 1. Asymmetric Hydrogenation of 19[a]

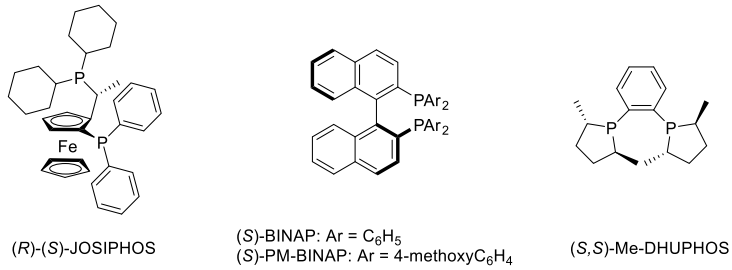


entry	L*	H_2 pressure (MPa)	16 % ee[c]	HPLC area%[b] 19	*syn*-18	*ent-syn*-18	16+*ent*-16
1	(*S*)-(*R*) SL-J210-2	1	n/a	70	4	2	0
2	(*S*,*S*)-SKEWPHOS	1	n/a	46	16	5	7
3	(*S*,*S*)-CHIRAPHOS	1	n/a	84	1	0	0
4	(*S*,*S*)-DIOP	1	n/a	84	2	1	0
5	(*R*)-(*S*)-JOSIPHOS	1	n/a	52	2	12	8
6	(*R*)-(*S*)-JOSIPHOS	5	n/a	43	2	6	25
7	(*S*,*S*)-SKEWPHOS	5	60	4	11	4	49
8	(*S*)-BINAP	5	n/a	88	1	1	0
9	(*S*)-PM-BINAP	5	n/a	85	2	1	0
10	(*S*,*S*)-Me-DUPHOS	5	71	28	24	8	16

[a]Reactions were conducted for 16−18 h at 50 °C using **19** in MeOH containing a Ru complex. [b]Assayed by chiral HPLC analysis condition B: CHIRALPAK AS-RH column (5 μm, 150 × 4.6 mm), MeCN/aq K_2HPO_4 (0.02 M) 4/6, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 220 nm (UV), t_R: 12.5 min (***syn*-18**), t_R: 15.3 min (***ent-syn*-18**), t_R: 22.3 min (**16**+***ent*-16**), t_R: 27.0 min (**19**). [c]Assayed by chiral HPLC analysis condition A: CHIRALPAK AD-H column (5 μm, 150 × 4.6 mm), hexane/2-propylalcohol 9/1, flow rate: 0.5 mL/min, oven temperature: 25 °C, detection: 220 nm (UV), t_R: 29.9 min (***ent*-16**), t_R: 33.3 min (**16**). n/a indicates not applicable.



L* =



stereoselective hydrogen-mediated domino cyclization was able to directly convert the enamine (**19**) to the hexahydropyrroloquinoline (**16**). After the catalysts were tuned, additives were screened, and reaction conditions were optimized, a second-

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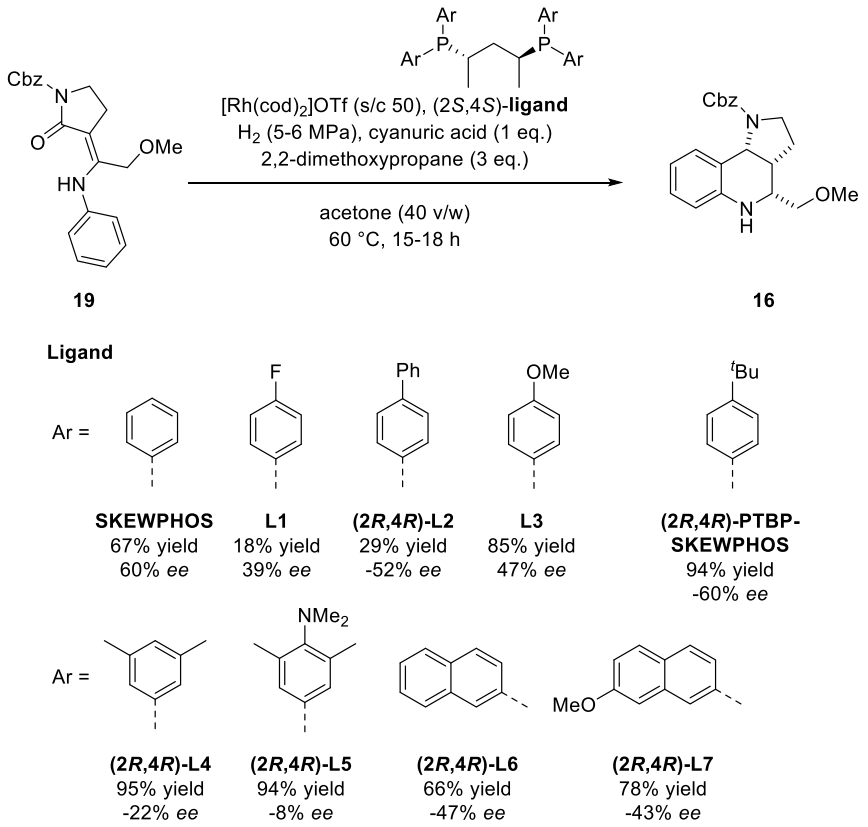

Figure 1. SKEWPHOS analogues used for ligand screening.

generation asymmetric route was established through asymmetric process development for scale-up synthesis. Herein, we disclose a highly efficient and robust synthetic method for a diastereo- and enantiopure hexahydropyrroloquinoline with a novel stereoselective hydrogen-mediated domino cyclization and the scale-up result of the reaction in a multikilogram manufacturing for preclinical research.

RESULTS AND DISCUSSION

Benzyl 3-(2-methoxyacetyl)-2-oxopyrrolidine-1-carboxylate 20 Synthesis. Cbz-protected pyrrolidin-2-one **21** was prepared by protection with Cbz-Cl after deprotonation of pyrrolidin-2-one **8**. Deprotonation of **8** was performed using sodium hydroxide in toluene at 110 °C while removing water generated from the reaction through an azeotropic distillation and then adding Cbz-Cl to the reaction mixture of deprotonated pyrrolidine-2-one at 0−10 °C. On a 75 kg scale of **8**, the crude product **21**, obtained in 94% yield, was used directly in the next step as an easy-to-handle tetrahydrofuran (THF) solution (209 kg with 87 wt % concentration) without further purification.

The *β*-acylation of Boc-protected pyrrolidin-2-one with chlorocarbonic acid methyl ester using lithium hexamethyldisilazide (LHMDS) as a base had been reported to proceed with 85% yield.[12] We confirmed that *β*-acylation of **21** with methoxyacetyl chloride under the literature condition proceeded with 68% yield. The acylation product **20** was obtained as a potassium salt powder, **20·K**, from potassium carbonate in EtOAc, because **20** was an oil and unstable in air. Unfortunately, although **20·K** was obtained in 56% yield from **21** without any operation issues at a lab scale, the isolated yield of **20·K** was not reproducible at a larger scale. On an 88 kg scale of **21**, a moderate decrease in the yield (37%) was observed, which was thought to be due to the large white aggregated substances that formed in the reaction mixture and inhibited mixing in the reactor during the reaction quenching step with a HCl aqueous solution. To avoid the mixing issue in scale-up manufacturing, the quenching method was examined further, and it was found that no aggregated substance was observed when AcOH (0.8 wt % to **21**) was added into the reaction mixture, although the isolated yield of **20·K** decreased from 56% to 34% because of workup issues (Scheme 5).

Benzyl (*Z*)-3-(2-methoxy-1-(phenylamino)-ethylidene)-2-oxopyrrolidine-1-carboxylate 19 Synthesis. Compound **20** free base was prepared by acidification of **20·K** and 1 M aqueous (aq) HCl in toluene. Then the free base of **20** in toluene was condensed with aniline in the presence of *p*-toluensulfonic acid in cyclohexane while removing water generated during reaction through an azeotropic distillation, to give enamine **19** as a substrate for asymmetric hydrogenation. The product **19** was purified by activated carbon treatment to remove the substances of inhibition for crystallization and crystallized from a mixture of ethyl acetate/heptane. Starting from 183 kg of **20·K**, 150 kg of **19** was produced with a yield of 74% in the manufacturing for preclinical research.

Benzyl (3*aR*,4*R*,9*bR*)-4-(Methoxymethyl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-1-carboxylate 16 Synthesis by Novel Stereoselective Hydrogen-Mediated Domino Cyclization. We first designed a small focused screen to assess the feasibility of asymmetric hydrogenation of enamine **19** to hydrogenation product ***syn*-18**. The screen started with a relatively small set of commercially available chiral bisphosphines (Table 1). [Rh-

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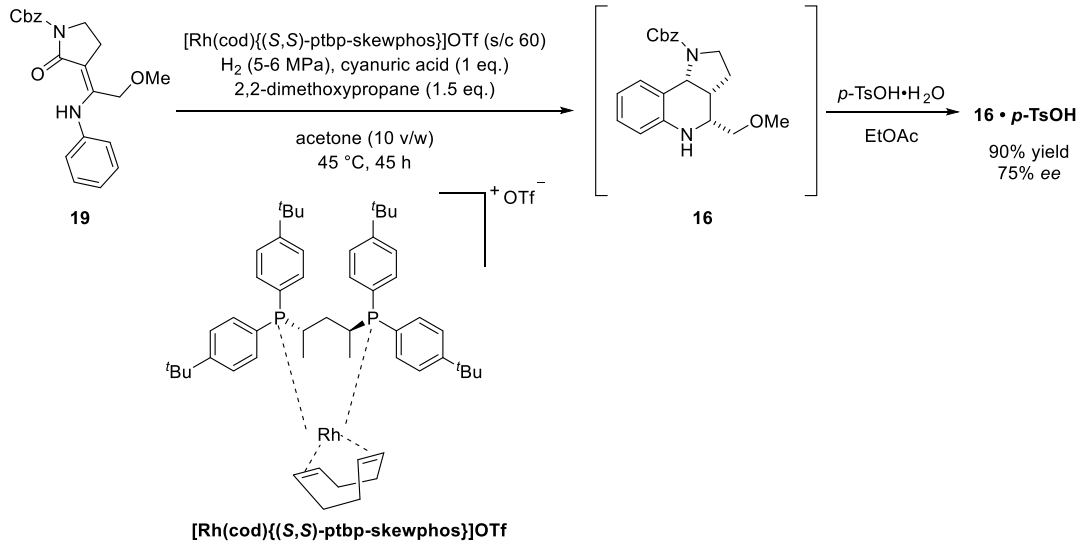
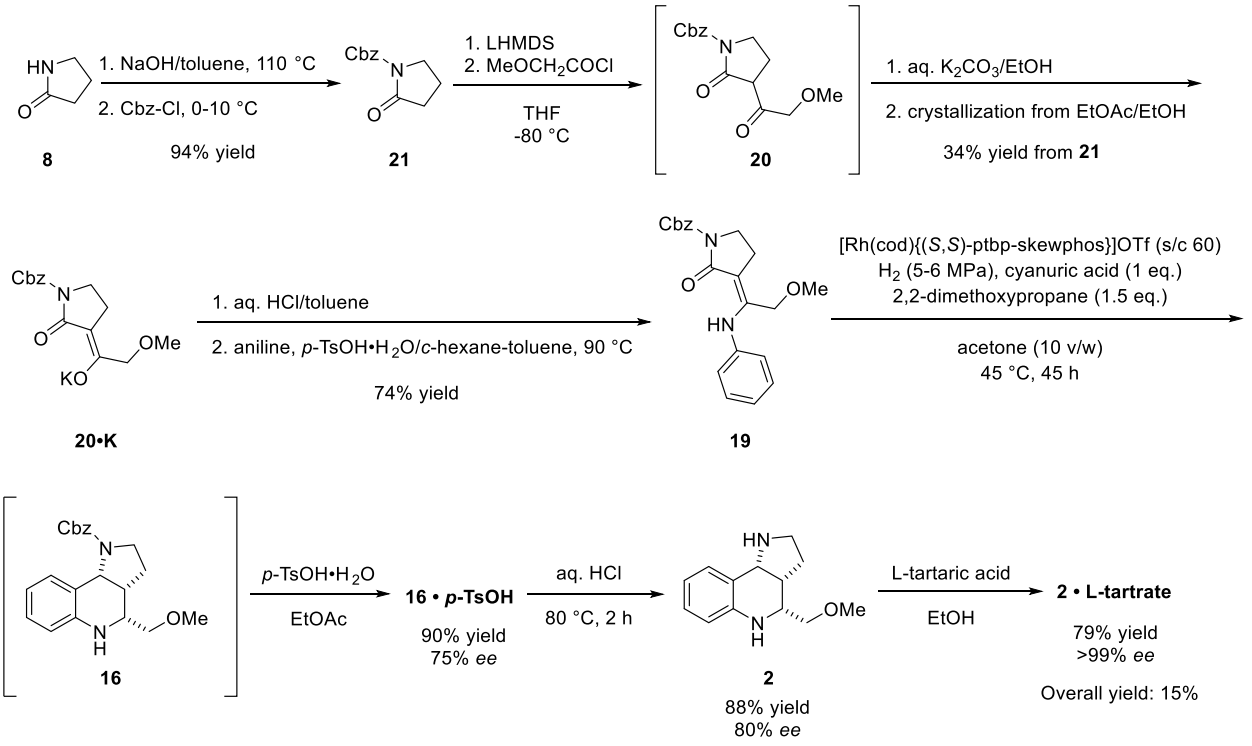
Scheme 6. Finalized Process for Stereoselective Hydrogen-Mediated Domino Cyclization



Scheme 7. Second-Generation Asymmetric Route to Hexahydropyrroloquinoline 2



$(cod)_2]$OTf was used as a metal precursor because of its demonstrated performance in the first-generation asymmetric route. The experiments were performed in MeOH under 1 and 5 MPa of hydrogen pressure at 50 °C.

The first-generation asymmetric route condition, using a $[Rh(cod)_2]$OTf and (*S*)-(*R*)-SL-J210-2 combination, gave low conversion (Table 1, entry 1), and other ligands such as CHIRAPHOS, DIOP, and BINAP gave similar results (entries 3, 4, 8, and 9). However, it was found that the hexahydropyrroloquinoline **16** could be slightly detected in the reaction mixture on HPLC analysis when SKEWPHOS and JOSIPHOS were used as the bisphosphine ligand under 1 MPa of hydrogen pressure (entries 2 and 5). Moreover, on increasing the hydrogen pressure to 5 MPa, the amount of **16** increased when using both of those ligands and when using Me-Duphos (entries 6, 7, and 10). The reaction proceeded with perfect diastereoselectivity and moderate enantioselectivity (60% ee) when using SKEWPHOS.

The result of exploring additives showed that the addition of cyanuric acid promoted the reaction, and 2,2-dimethoxypropane was found to have a role to trap the water that is generated as a byproduct in the reaction. After modifying SKEWPHOS ligands, we adopted (2*S*,4*S*)-PTBP-SKEWPHOS as the bisphosphine ligand because of the high conversion obtained without decrease of enantioselectivity compared to simple SKEWPHOS (Figure 1).

After optimization, the process for stereoselective hydrogen-mediated domino cyclization of **19** was finalized as shown in

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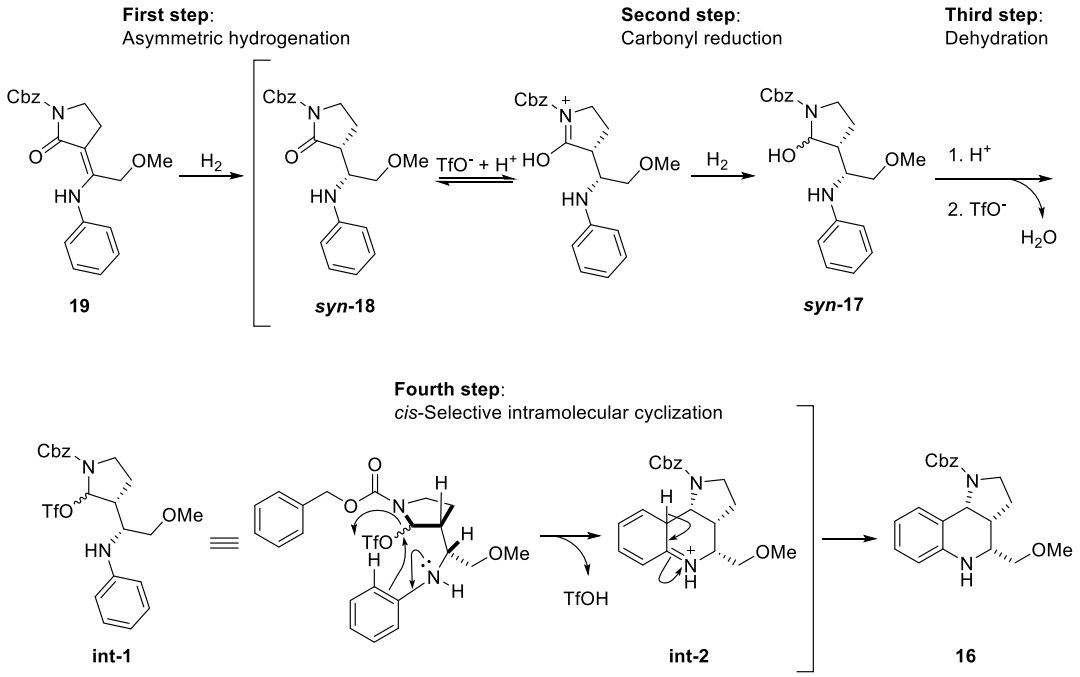
Scheme 8. Plausible Mechanism for Novel Stereoselective Hydrogen-Mediated Domino Cyclization



Scheme 6. The enamine **19** was dissolved in 10 vol of acetone and subjected to 1.66 mol % (substrate/catalyst ratio (s/c) 60) catalyst loading under 5−6 MPa hydrogen at 45 °C. Acetone was selected as the reaction solvent after the screening of various solvents (Supporting Information, page S21).

The asymmetric catalytic reaction was scaled up without any issues. Novel stereoselective hydrogen-mediated domino cyclization of **19** (37.5 kg), under the conditions shown in Scheme 6, gave **16** in good conversion (**19**/**16** HPLC area ratio = 2/98). Subsequent crystallization as a *p*-toluenesulfonic acid salt allowed the isolation of 48.3 kg of **16·*p*-TsOH** in 75% ee. Thus, a practical synthetic method was developed, including the manufacture of a novel chiral catalyst, [Rh(cod)-{(2*S*,4*S*)-PTBP-SKEWPHOS}]OTf, at large scale for manufacturing **16**.[13]

(3*aS*,4R,9*bR*)-4-(Methoxymethyl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 2 Synthesis. Deprotection was accomplished by treatment of **16·*p*-TsOH** with hydrochloric acid in water at 80 °C for 2 h. To remove the impurities, the reaction mixture was washed with toluene, and **2** was isolated by neutralization with aqueous sodium hydroxide solution. On a 127 kg scale of **16·*p*-TsOH**, the manufacturing operation was implemented to give 46 kg of **2** without any scale-up issues. The enantiomeric excess of **2** was slightly upgraded from 75% to 80% ee. To improve the enantiomeric excess of **2**, the diastereomeric salt formation in EtOH was conducted with L-tartaric acid, which is inexpensive and commercially available. As a result, 62 kg of **2·L-tartrate** was obtained with greater than 99% ee from 46 kg of **2** (80% ee; Scheme 7). In addition, direct use of **2·L-tartrate** for the final amide bond formation with **3** successfully produced **1**, TAK-480 (API), and the isolated API satisfied the quality for preclinical research.

■ REACTION MECHANISM

A plausible mechanism for the novel stereoselective hydrogen-mediated domino cyclization is depicted in Scheme 8. As a result of exploring the first-generation asymmetric route for **7**, we considered the four steps leading to the product **16**: (1) rhodium-catalyzed asymmetric hydrogenation of enamine **19** (**19** → ***syn*-18**), (2) rhodium-catalyzed hydrogenation of an iminium ion from lactam (***syn*-18** → ***syn*-17**), (3) dehydration and catalytic sulfonation (***syn*-17** → **int-1**), (4) *cis*-selective intramolecular cyclization (**int-1** → **int-2**). Our considerations on the domino cyclization are shown below.

(1) Rhodium-catalyzed asymmetric hydrogenation of enamine **19** (**19** → ***syn*-18**).

We confirmed that the enantioselectivity of **16** is decided in this step, and ***anti*-18** was not detected in the reaction mixture by HPLC analysis under the condition in Table 1, entry 7. On the one hand, this suggests that the asymmetric hydrogenation is perfectly *syn*-selective, and enamine **19** was the predicted *Z* form.[14] On the other hand, when $[Ru(Cp)(MeCN)_3]PF_6$, $[Cu(MeCN)_4]PF_6$, $[Pd_2Cl_2(allyl)_2]$, and $[Zn(OTf)_2]$ were used as the metal precursor, the reaction did not proceed. Moreover, $[Ir(cod)_2]BF_4$ and $[Rh(cod)Cl]_2$ (neutral complex) did not give **16** and gave only small amounts of ***syn*-18**.

(2) Reduction of a carbonyl group in lactam (***syn*-18** → ***syn*-17**).

We predicted that the hydrogenation of ***syn*-18** would not proceed in the absence of sulfonate anion, because the hydrogenation of **19** using the neutral rhodium complex ($[Rh(cod)Cl]_2$) stopped at ***syn*-18**. Additionally, it has been reported that *N*-methyl-2-pyrrolidine can be isolated as an *N*-methyl-2-pyrrolidonium tosylate salt.[15] Therefore, on the one hand, we thought that the iminium form of ***syn*-18** generated by trifluoromethanesulfonic acid (formed from the trifluoromethanesulfonate anion of $[Rh(cod)_2]OTf$ and a proton from heterolytic cleavage of H_2), could be easily hydrogenated by the rhodium-bisphosphine catalyst in the reaction mixture. On the other hand, the effect of protection

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group was contributed to facilitate this step, because PMB-protected **19** did not proceed in this step. We predicted the impact of electronic effect by protecting group.

(3) Dehydration and catalytic sulfonation (***syn*-17** → **int-1**). The fact that 10-camphorsulfonic acid ((±)-CSA) catalyzed a facile one-pot synthesis of 1,3,4-oxadiazoles has been reported,[16] and $Cu(OTf)_2$ instead of (±)-CSA also gave the same reaction. With reference to the mechanism for the synthesis of 1,3,4-oxadiazoles in the report, the domino cyclization can be described as follows: ***syn*-17** is protonated in the presence of trifluoromethanesulfonic acid, generated from the trifluoromethanesulfonate anion of $[Rh(cod)_2]OTf$ and a proton from heterolytic cleavage of H_2. In turn, the protonated ***syn*-17** eliminates a water molecule and forms a sulfonate complex **int-1**.

(4) *cis*-Selective intramolecular cyclization (**int-1** → **int-2**). The aniline moiety of **int-1** only promotes the elimination of trifluoromethanesulfonic acid when it approaches from the α face of the pyrrolidine ring (*cis*-selective intramolecular cyclization). No suitable intramolecular overlap for bond formation is attained by approaching from the β face of the pyrrolidine ring.

CONCLUSION

In this study, a novel stereoselective hydrogen-mediated domino cyclization of carbamate-protected enamines facilitated by a cationic rhodium catalyst has been discovered. The reaction allows a novel short-cut method for the synthesis of **16**, which helps to drastically reduce the number of synthetic steps and waste associated with the process in comparison to the first-generation asymmetric route to **2**. This second-generation asymmetric route to construct the hexahydropyrroloquinoline derivative **2** has been successfully applied for multikilogram scale production. Further optimization of this process should focus on reduction of the catalyst loading and yield improvement for the β-acylation step of Cbz-protected pyrrolidine-2-one **21**.

EXPERIMENTAL SECTION

General Remarks. All reagents and solvents were purchased commercially and used without further purification. HPLC analysis was performed on HITACHI 7400 instruments or SHIMADZU LC-10ADvp instruments. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$, CD_3OD, or D_2O solutions at 500 and 126 MHz, respectively, using a Bruker Avance-III spectrometer for analysis of **21**, **20·K**, **19**, ***syn*-18**, **16·*p*-TsOH**, **2**, and **2·L-tartrate**. IR spectrum was measured using a SHIMADZU IR Prestige-21. High-resolution mass spectrometry (HRMS) spectra were measured using a SHIMADZU LCMS-IT-TOF, and melting points were measured using a SIBATA B-545 apparatus. Specific rotations were measured using a JASCO P-1030.

Lab-Scale Synthesis of Benzyl 2-oxopyrrolidine-1-carboxylate (21). To a four-necked round-bottom flask with an attached Dean−Stark trap were charged pyrrolidin-2-one (24.20 g, 0.284 mol, 1.0 equiv), powder sodium hydroxide (11.40 g, 0.285 mol, 1.00 equiv), and toluene (480 mL, 20 vol). The suspension was heated to reflux (110 °C) and stirred for 18 h while removing the water (removed water: ca. 4.8 mL). The reaction mixture was cooled to −5 °C, and benzyl chloroformate (48.60 g, 0.285 mol, 1.00 equiv) was added dropwise in 15 min and stirred for 1 h with the internal temperature maintained below 10 °C. The reaction mixture was quenched by addition of 121 mL of water in 5 min at 5−10 °C. The phases were separated, and the organic layer was washed with 121 mL of a 5% aqueous potassium hydrogen sulfate solution, then with water (2 × 121 mL). The phases were separated, and the organic layer was dried over magnesium sulfate. The resulting mixtures were filtered to remove insolubles, and the cake was washed with an appropriate amount of toluene. The filtrate was evaporated to dryness under reduced pressure and diluted with an appropriate amount of tetrahydrofuran. The diluted solution was evaporated to yield **21** as a colorless oil (60.00 g, 96% yield, 83.9 area% HPLC purity). ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.36 (m, 2H), 7.20−7.30 (m, 3H), 5.17 (s, 2H), 3.70 (t, J = 7.25 Hz, 2H), 2.41 (t, J = 8.04 Hz, 2H), 1.90 (quin, J = 7.65 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 151.4, 135.4, 128.6, 128.4, 128.2, 67.8, 46.4, 32.7, 17.5. HPLC: YMC-Pack ODS-A A-302 column (5 μm, 150 × 4.6 mm), MeCN/aq KH_2PO_4 (0.05 M) 2/3, flow rate: 1.0 mL/min, oven temperature: 30 °C, detection: 220 nm (UV), t_R: 5.2 min (**21**).

Lab-Scale Synthesis of Potassium 1-(1-((benzyloxy)-carbonyl)-2-oxopyrrolidin-3-ylidene)-2-methoxyethan-1-olate (20·K). All reactions were performed under a positive pressure of nitrogen. To a four-necked round-bottom flask were charged bis(trimethylsilyl)amine (32.39 g, 0.200 mol, 2.19 equiv) and tetrahydrofuran (80 mL, 4 vol). The solution was cooled to −80 °C, and *n*-butyllithium (125 mL of a 1.6 M solution in hexane, 0.200 mol, 2.19 equiv) was added dropwise in 20 min with the internal temperature maintained below −60 °C. The solution was stirred at −80 °C for 1 h. To this solution was added a solution of **21** (20.00 g, 0.091 mol, 1.0 equiv) in tetrahydrofuran (20 mL), with the internal temperature maintained below −60 °C. The solution was stirred at −80 °C for 1 h, and then a solution of 2-methoxy acetyl chloride (14.84 g, 0.137 mol, 1.51 equiv) in tetrahydrofuran (20 mL) was added, with the internal temperature maintained below −60 °C. This solution was stirred at −80 °C for 2 h, and the reaction was quenched by addition of a 6 M aqueous hydrogen chloride solution (50 mL) with the internal temperature maintained below −20 °C. Water (25 mL) and toluene (100 mL) were added, and the mixture was warmed to room temperature. The phases were separated, and the organic layer was washed with water (2 × 75 mL) and evaporated to dryness under reduced pressure. The oil was then diluted with ethyl alcohol (140 mL, 5 vol), and a 40% aqueous potassium carbonate solution (94.50 g, 30 equiv) was added. The suspension was stirred at room temperature overnight. Water (94.5 mL) was added to the suspension to dissolve the slurry, and ethyl acetate (168 mL) was added. The phases were separated, and the organic layer was evaporated to 32.71 g of concentrates under reduced pressure. The concentrates were then diluted with ethyl alcohol (28 mL, 1.4 vol) and ethyl acetate (280 mL, 14 vol). The suspension was stirred at room temperature for 2 h. The solid was collected by filtration, and the cake was washed with ethyl acetate and dried under vacuum at 60 °C to yield **20·K** as a pale yellow solid (13.46 g, 45% yield, 87.7 area% HPLC purity). ^1H NMR (500 MHz, CD_3OD) δ 7.24−7.41 (m, 5H), 5.18 (s, 2H), 4.52−4.59 (m, 2H), 3.66 (t, J = 8.04 Hz, 2H), 3.35 (s, 3H), 2.60 (t, J = 8.04 Hz, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 182.3, 169.9, 152.9, 136.6, 128.1, 127.8, 127.5,

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94.3, 73.1, 66.3, 57.3, 43.0, 21.2. HRMS (*m*/*z*, electrospray ionization (ESI)$^+$) for $C_{15}H_{17}NO_5$ as a free base $(M+H)^+$ calcd 292.1179, measured 292.1186. HPLC: YMC-Pack ODS-A A-302 column (5 μm, 150 × 4.6 mm), MeCN/aq KH_2PO_4 (0.05 M) 2/3, flow rate: 1.0 mL/min, oven temperature: 30 °C, detection: 220 nm (UV), t_R: 5.9 min (**20**).

Lab-Scale Synthesis of Benzyl 3-(2-methoxy-1-(phenylamino)ethylidene)-2-oxopyrrolidine-1-carboxylate (19). To a separatory funnel were charged **20·K** (100.00 g, 0.304 mol, 1.0 equiv), 1 M aqueous hydrogen chloride solution (500 mL, 0.500 mol, 1.50 equiv), and toluene (1 L, 10 vol). After they were mixed, the phases were separated, and the organic layer was washed with water (5 L). To a four-necked round-bottom flask with an attached Dean−Stark trap were charged this organic layer, aniline (25.45 g, 0.273 mol, 0.90 equiv), and *p*-toluenesulfonic acid monohydrate (0.58 g, 0.003 mol, 0.01 equiv). The suspension was heated to reflux (93 °C) and stirred for 2 h while removing the water. Then the reaction mixture was cooled to room temperature, before 500 mL of a 5 w/v% aqueous acetic acid solution was added. The phases were separated, and the organic layer was washed with 500 mL of a 5w/v% aqueous potassium bicarbonate solution, followed by water (2 × 500 mL). The organic layer was evaporated to 87.34 g of concentrates under reduced pressure. The concentrates were dissolved in methyl alcohol (10 L), and activated carbon (Shirasagi-A, 10.00 g) was added. The suspension was stirred at room temperature for 30 min and filtered. The filter cake was rinsed with methyl alcohol (100 mL), and the filtrates were evaporated to dryness under reduced pressure. The crude oil was dissolved with 500 mL of ethyl acetate and evaporated to dryness under reduced pressure. The crude oil was dissolved in 50 mL of ethyl acetate and cooled to −10 °C. A seed crystal of **19** was added, and heptane (400 mL) was added dropwise over 1 h at 0 °C. The resulting suspension was then warmed to room temperature and aged for 1 h. The solid was collected by filtration, and the cake was washed with 150 mL of a 10/1 v/v heptane−ethyl acetate solution and dried at 50 °C under vacuum to yield **19** as a pale yellow solid (67.31 g, 60% yield, 95.1 area% HPLC purity). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.57 (s, 1H), 7.46 (d, J = 7.88 Hz, 2H), 7.35−7.40 (m, 2H), 7.32 (d, J = 7.88 Hz, 3H), 7.10−7.15 (m, 3H), 5.32 (s, 2H), 4.04 (s, 2H), 3.83 (t, J = 7.72 Hz, 2H), 3.36 (s, 3H), 2.80 (t, J = 7.88 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 152.3, 150.6, 139.3, 135.9, 129.2, 128.6, 128.2, 128.1, 124.4, 122.8, 98.7, 68.0, 67.6, 58.5, 43.6, 21.0. Anal. Calcd for $C_{21}H_{12}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.63; H, 6.02; N, 7.72%. HPLC: YMC-Pack ODS-A A-302 column (5 μm, 150 × 4.6 mm), MeCN/aq KH_2PO_4 (0.05 M, adjusted to pH 7 by 10% aq KOH) 55/45, flow rate: 1.0 mL/min, oven temperature: 30 °C, detection: 220 nm (UV), t_R: 11.2 min (**19**).

Authentic Sample Synthesis of Benzyl (R)-3-((R)-2-methoxy-1-(phenylamino)ethyl)-2-oxopyrrolidine-1-carboxylate (syn-18). To a 120 mL stainless steel autoclave equipped with a Teflon-coated stirring bar was added **19** (2.00 g, 5.46 mmol, 1.0 equiv). The atmosphere was evacuated and filled with argon gas seven times. To a 50 mL Schlenk tube were added $[Rh(cod)Cl]_2$ (134.6 mg, 0.273 mmol, 0.05 equiv) and (2*S*,4*S*)-SKEWPHOS (264.6 mg, 0.601 mmol, 0.11 equiv). The atmosphere was evacuated and filled with argon gas seven times, and this was followed by the addition of dehydrated acetone (10 mL). The mixture was stirred at room temperature for 1 h and then added to **19** in a 120 mL stainless steel autoclave. The used Schlenk tube was washed with dehydrated acetone (10 mL) three times, and the combined washings were added to the autoclave. Hydrogen was initially introduced into the autoclave at a pressure of 0.1 MPa, before being reduced to atmospheric pressure by carefully releasing the stop valve. After this procedure was repeated 10 times, the hydrogen pressure was introduced at 6 MPa, and the solution was stirred at 50 °C for 10 h. The solution was cooled to room temperature, and hydrogen gas was then carefully vented. After evaporation of the solvent, the residue (***syn*-18**/***anti*-18** = 4/1) was purified by silica gel chromatography, eluted with 1:2 hexane−ethyl acetate to give the pure hydrogenation product ***syn*-18** (1.14 g, 57% yield, 99.0 area% HPLC purity, 24.4% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.75 (m, 2H), 7.31−7.40 (m, 3H), 7.17 (t, J = 7.72 Hz, 2H), 6.69−6.76 (m, 3H), 5.22−5.33 (m, 2H), 4.11−4.31 (m, 1H), 3.92−4.07 (m, 1H), 3.77−3.87 (m, 1H), 3.60−3.69 (m, 2H), 3.54 (dd, J = 9.46, 5.04 Hz, 1H), 3.34 (s, 3H), 2.94 (td, J = 9.54, 4.26 Hz, 1H), 2.13−2.22 (m, 1H), 2.03−2.13 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 151.5, 147.0, 135.4, 129.4, 128.6, 128.4, 128.2, 118.3, 114.3, 73.4, 68.0, 59.1, 53.3, 45.8, 44.8, 20.8. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.55; H, 6.48; N, 7.63%. Liquid chromatography−mass spectrometry (LC-MS) (ESI): t_R = 7.27 min (97.9 area%); *m*/*z* 368, t_R = 7.71 min (1.4 area%); *m*/*z* 368 as an ***anti*-18**. HPLC: YMC-Pack ODS-A A-302 column (5 μm, 150 × 4.6 mm), MeCN/aq KH_2PO_4 (0.05 M, adjusted to pH 7 by 10% aq KOH) 55/45, flow rate: 1.0 mL/min, oven temperature: 30 °C, detection: 220 nm (UV), t_R: 7.2 min (***rac-syn*-18**), t_R: 7.6 min (***rac-anti*-18**). Chiral HPLC: CHIRALPAK AS-RH column (5 μm, 150 × 4.6 mm), MeCN/aq K_2HPO_4 (0.05 M) 45/55, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 220 nm (UV), t_R: 7.6 min (***syn*-18**), t_R: 9.6 min (***ent-syn*-18**).

Lab-Scale Synthesis of Benzyl (3aR,4R,9bR)-4-(methoxymethyl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-c]-quinoline-1-carboxylate para-toluenesulfonate (16·p-TsOH). To a 120 mL stainless steel autoclave equipped with a Teflon-coated stirring bar were added **19** (4.00 g, 10.92 mmol, 1.0 equiv) and cyanuric acid (1.41 g, 10.92 mmol, 1.00 equiv). The atmosphere was evacuated and filled with argon gas seven times. To a 50 mL Schlenk tube were added $[Rh(cod)_2]OTf$ (102.3 mg, 0.218 mmol, 0.020 equiv = s/c 50) and (2*S*,4*S*)-PTBP-SKEWPHOS (174.2 mg, 0.262 mmol, 0.024 equiv). The atmosphere was evacuated and filled with argon gas seven times, and this was followed by the addition of dehydrated acetone (20 mL). The mixture was stirred at room temperature for 1 h and then added to the above mixture of **19** and cyanuric acid. The used Schlenk tube was washed with dehydrated acetone (60 mL) and 2,2-dimethoxypropane (3.90 mL, 32.75 mmol, 3.00 equiv), and the washings were added to the autoclave. Hydrogen was initially introduced into the autoclave at a pressure of 0.1 MPa, before being reduced to atmospheric pressure by carefully releasing the stop valve. After this procedure was repeated 10 times, the hydrogen pressure was introduced at 6 MPa, and the solution was stirred at 50 °C for 20 h. The solution was cooled to room temperature, and hydrogen gas was then carefully vented. After evaporation of the solvent, the residue (1% assay yield of **19**, 5% assay yield of ***syn*-18** (***anti*-18** was not detected), and 92% assay yield of **16** with 64% ee) was evaporated to dryness. The residue was diluted with ethyl acetate (40 mL) and evaporated to dryness. The residue was diluted with ethyl acetate (40 mL) and

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filtered, and the filter cake was rinsed with ethyl acetate (10 mL). The seed crystal of **16·*p*-TsOH** was inoculated to the filtrate, and *p*-toluenesulfonic acid (2.07 g, 10.88 mmol, 1.00 equiv) was added at room temperature. The resulting suspension was aged for 1 h. The solid was collected by filtration, and the cake was washed with ethyl acetate (15 mL) before being dried at 50 °C under vacuum to yield **16·*p*-TsOH** as a colorless solid (4.75 g, 83% yield, 95.7 area% HPLC purity, 63.1% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18−7.93 (m, 11H), 7.05 (d, J = 7.88 Hz, 2H), 5.13−5.38 (m, 3H), 3.89−4.10 (m, 2H), 3.71−3.88 (m, 1H), 3.19−3.40 (m, 4H), 2.71−2.89 (m, 1H), 2.30 (s, 3H), 1.82−2.09 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 155.0, 141.2, 140.5, 136.6, 131.4, 131.0, 130.0, 129.5, 129.4, 129.0, 128.9, 128.8, 128.7, 128.6, 128.3, 128.1, 127.8, 125.9, 123.7, 123.6, 70.2, 70.1, 67.5, 67.3, 59.3, 55.4, 55.2, 53.1, 52.8, 45.5, 36.9, 36.1, 22.9, 21.9, 21.3. Anal. Calcd for $C_{28}H_{32}N_2O_6S$: C, 64.10; H, 6.15; N, 5.34; S, 6.11. Found: C, 63.82; H, 6.29; N, 5.33; S, 6.12%. HPLC: YMC-Pack ODS-A A-302 column (5 μm, 150 × 4.6 mm), MeCN/aq KH_2PO_4 (0.05 M, adjusted to pH 7 by 10% aq KOH) 55/45, flow rate: 1.0 mL/min, oven temperature: 30 °C, detection: 220 nm (UV), t_R: 10.2 min (**16**). Chiral HPLC: CHIRALPAK AD-H column (5 μm, 150 × 4.6 mm), hexane/2-propylalcohol 9/1, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 220 nm (UV), t_R: 12.0 min (***ent*-16**), t_R: 13.2 min (**16**).

Lab-Scale Synthesis of (3aS,4R,9bR)-4-(Methoxymethyl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-c]quinoline (2). To a four-necked round-bottom flask were charged **16·*p*-TsOH** (47.37 g, 90.29 mmol, 1.0 equiv) and a 6 M aqueous hydrogen chloride solution (237 mL, 0.142 mol, 15.75 equiv). This suspension was heated to 80 °C and stirred for 2 h. The reaction mixture was cooled to 25 °C, and toluene (237 mL) was added. The phases were separated, and activated carbon (Shirasagi-A, 3.16 g) was added to the aqueous layer. The suspension was stirred at room temperature for 30 min and filtered, and then the filter cake was rinsed with water (119 mL). An 8 M aqueous sodium hydroxide solution (288 mL) was added dropwise to the filtrate with the internal temperature maintained below 30 °C. The resulting suspension was stirred at room temperature for 1 h. The solid was collected by filtration, and the cake was washed with water (95 mL) and dried at 60 °C under vacuum to yield **2** as a colorless solid (16.88 g, 86% yield, 94.7 area% HPLC purity, 70.2% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 7.57 Hz, 1H), 7.02 (t, J = 7.57 Hz, 1H), 6.75 (t, J = 7.41 Hz, 1H), 6.57 (d, J = 7.88 Hz, 1H), 4.42 (d, J = 7.88 Hz, 1H), 4.09 (s, 1H), 3.61−3.68 (m, 1H), 3.46−3.51 (m, 1H), 3.41 (s, 3H), 3.37−3.41 (m, 1H), 2.88−2.96 (m, 1H), 2.80−2.88 (m, 1H), 2.37−2.47 (m, 1H), 1.97 (br s, 1H), 1.75−1.84 (m, 1H), 1.64−1.73 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 129.0, 127.5, 125.4, 119.0, 114.9, 75.5, 59.0, 57.7, 52.5, 45.6, 41.0, 24.9. HPLC: YMC-Pack ODS-A A-302 column (5 μm, 150 × 4.6 mm), MeCN/aq KH_2PO_4 (0.05 M, adjusted to pH 7 by 10% aq KOH) 55/45, flow rate: 1.0 mL/min, oven temperature: 30 °C, detection: 220 nm (UV), t_R: 2.2 min (**2**). Chiral HPLC: CHIRALCEL OD-RH column (5 μm, 150 × 4.6 mm), MeCN/aq KPF_6 (0.10 M) 15/85, flow rate: 1.0 mL/min, oven temperature: 25 °C, detection: 254 nm (UV), t_R: 16.0 min (***ent*-2**), t_R: 17.7 min (**2**).

Lab-Scale Synthesis of (3aS,4R,9bR)-4-(Methoxymethyl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-c]quinoline L-tartrate (2·L-tartrate). To a four-necked round-bottom flask were charged L-tartaric acid (6.19 g, 41.24 mmol, 1.00 equiv) and ethyl alcohol (248 mL, 27.6 vol). The suspension was heated to 50 °C to dissolve all solids. The seed crystal of **2·L-tartrate** was inoculated, and **2** (9.00 g, 41.22 mmol, 1.0 equiv) was added at 50 °C. The resulting suspension was aged at 50 °C for 30 min and cooled to room temperature. The solid was aged for 1 h and collected by filtration, and then the cake was washed with ethyl alcohol (54 mL) and dried at 50 °C under vacuum to yield **2·L-tartrate** as a colorless solid (11.75 g, 77% yield, 99.1 area% HPLC purity, 97.9% ee). ^{1}H NMR (500 MHz, D_2O) δ 7.12−7.25 (m, 2H), 6.80−6.90 (m, 1H), 6.73−6.78 (m, 1H), 5.02 (d, J = 10.0 Hz, 1H), 4.42 (s, 2H), 3.42−3.59 (m, 3H), 3.34 (s, 3H), 3.12−3.28 (m, 2H), 2.73−2.88 (m, 1H), 1.85−2.11 (m, 2H). ^{13}C NMR (126 MHz, D_2O) δ 176.4, 145.8, 130.2, 129.6, 120.2, 116.8, 116.5, 73.5, 72.8, 58.5, 57.8, 51.2, 44.7, 38.7, 22.7.

Authentic Sample Synthesis of (3aS,4R,9bR)-4-(methoxymethyl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-c]-quinoline L-tartrate (2·L-tartrate). To a four-necked round-bottom flask were charged L-tartaric acid (3.00 g, 20.0 mmol, 1.00 equiv) and ethyl alcohol (15 mL, 3.4 vol). The suspension was heated to 70 °C to dissolve all solids, before **2** (4.37 g, 20.0 mmol, 1.0 equiv, >99.9% ee) and ethyl acetate (30 mL, 6.9 vol) were added at 70 °C. The resulting suspension was aged at 70 °C for 30 min and cooled to room temperature. The solid was aged overnight and collected by filtration, and then the cake was washed with a 1/2 v/v ethyl alcohol−ethyl acetate solution and dried at 50 °C under vacuum to yield **2·L-tartrate** as a colorless solid (7.19 g, 98% yield, 98.8 area% HPLC purity, >99.9% ee). mp 175 °C; [α]20D −16.3° (c = 1.0, H_2O); IR (KBr): 3385, 3319, 3275, 3051, 2870, 2843, 2737, 2515, 2453, 1701, 1611, 1553, 1491, 1408, 1373, 1308, 1263, 1136, and 877 cm^{-1}. ^{1}H NMR (500 MHz, D_2O) δ 7.07−7.21 (m, 2H), 6.81 (t, J = 7.57 Hz, 1H), 6.72 (d, J = 8.20 Hz, 1H), 4.98 (d, J = 9.14 Hz, 1H), 4.39 (s, 2H), 3.38−3.56 (m, 3H), 3.31 (s, 3H), 3.08−3.24 (m, 2H), 2.70−2.84 (m, 1H), 1.82−2.04 (m, 2H). ^{13}C NMR (126 MHz, D_2O) δ 176.4, 145.8, 130.1, 129.5, 120.2, 116.8, 116.5, 73.5, 72.8, 58.5, 57.7, 51.2, 44.7, 38.6, 22.7. Anal. Calcd for $C_{17}H_{24}N_2O_7$: C, 55.43; H, 6.57; N, 7.60. Found: C, 55.38; H, 6.69; N, 7.52%. HRMS (m/z, ESI$^+$) for $C_{12}H_{18}N_2O$ as a free base $(M+H)^+$ calcd 219.1492, measd 219.1463.

Manufacturing for Preclinical Research. Kilogram-Scale Synthesis of Benzyl 2-oxopyrrolidine-1-carboxylate (21). To a reactor were charged sodium hydroxide (35.6 kg, 0.890 kmol, 1.00 equiv), pyrrolidin-2-one (75.0 kg, 0.881 kmol, 1.0 equiv), and toluene (1297.5 kg). This suspension was heated to 110 °C for 12 h, while azeotropic dehydration by toluene distillation was performed. Fresh toluene (total 6487.5 kg) was used to replace the toluene removed by azeotropic dehydration. The reaction mixture was cooled to 0 °C, and to the suspension was added benzyl chloroformate (151.8 kg, 0.890 kmol, 1.00 equiv) over 2 h with the internal temperature maintained below 10 °C. The reaction mixture was stirred at 5 °C for 1 h, and the reaction was quenched by addition of water (375 L) over 15 min with the internal temperature maintained below 10 °C. The mixture was warmed to 23 °C. The phases were separated, and the organic layer was washed with 387.4 kg of a 5% aqueous potassium hydrogen sulfate solution, then with water (2 × 375 L). The phases were separated, and magnesium sulfite (30.0 kg) was added to the organic layer. The mixture was filtered, and the cake was washed with toluene (64.9 kg). The filtrate was concentrated under reduced

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pressure to the extent possible. Tetrahydrofuran (333.4 kg) was added, and the mixture was concentrated under reduced pressure to the extent possible. The concentrates were diluted with tetrahydrofuran (26.7 kg), and the resulting solution containing **21** (181.80 kg of **21** in 209.05 kg solution, 86.9 w/w% assay, 94.1% yield) was used directly in the next step. HPLC analysis of a sample evaporated to dryness matched the analysis of one from the lab-scale synthesis.

Kilogram-Scale Synthesis of Potassium 1-(1-((Benzyloxy)-carbonyl)-2-oxopyrrolidin-3-ylidene)-2-methoxyethan-1-olate (20·K). All reactions were performed under a positive pressure of nitrogen. To a reactor A were charged bis-(trimethylsilyl)amine (116.5 kg, 0.722 kmol, 1.81 equiv) and tetrahydrofuran (304.8 kg, 4 vol). The solution was cooled to −80 °C, and *n*-butyllithium (309.1 kg of a 1.6 M solution in hexane, 0.755 kmol, 1.88 equiv) was added dropwise over 6 h with the internal temperature maintained below −55 °C. The charging line was washed with tetrahydrofuran (7.9 kg), and the resulting solution was stirred with the internal temperature maintained below −55 °C for 1 h. To this solution was added a solution of **21** (87.9 kg, 0.401 kmol, 1.0 equiv) in tetrahydrofuran (70.3 kg) over 1.5 h, with the internal temperature maintained below −60 °C. The charging line was washed with tetrahydrofuran (7.8 kg), and the resulting solution was stirred with the internal temperature maintained below −60 °C for 1 h. To this solution was added a solution of 2-methoxy acetyl chloride (47.9 kg, 0.441 kmol, 1.10 equiv) in tetrahydrofuran (70.3 kg), with the internal temperature maintained below −60 °C over 3 h. The charging line was washed with tetrahydrofuran (7.8 kg), and the resulting solution was stirred for 1.5 h with the internal temperature maintained below −60 °C. Then the mixture was warmed to 5 °C, and the reaction was quenched by addition of acetic acid (69.2 kg) over 40 min with the internal temperature maintained below 15 °C, and toluene (380.2 kg) was added with the internal temperature maintained below 10 °C. To 4 M aqueous hydrogen chloride solution (374.7 kg) in a reactor B was added the reaction mixture from reactor A over 0.5 h, and the mixture was then stirred for 10 min. The phases were separated, and the organic layer was washed with an 8% sodium hydrogen carbonate solution (3 × 439.2 kg) and water (440.0 kg). The organic layer was concentrated under reduced pressure to the extent possible. The oil was then diluted with ethyl alcohol (461.0 kg, 6.6 vol), and a 40% aqueous potassium carbonate solution (415.3 kg, 3.00 equiv) was added. The resulting suspension was stirred at 25 °C for 10 h. Water (416.0 kg) was added to the suspension to dissolve the slurry, and then ethyl acetate (631.9 kg) was added. The phases were separated, and the organic layer was concentrated under reduced pressure to the extent possible. The concentrates were then diluted with ethyl alcohol (347.4 kg, 5 vol) and concentrated under reduced pressure to remove the organics (ca. 260 L). Ethyl alcohol (347.4 kg, 5 vol) was added, and the reaction mixture was concentrated under reduced pressure to remove the organics (ca. 435 L). Ethyl acetate (1506.9 kg, 21.6 vol) was added, and the suspension was stirred at 25 °C for 3 h. The solid was collected by filtration, and the cake was washed with 143 L of a 10/1 v/v ethyl acetate−ethyl alcohol solution and dried under vacuum at 60 °C to yield **20·K** as a pale yellow solid (44.6 kg, 34% yield). HPLC analysis of a sample matched that of a sample from a lab-scale synthesis.

Kilogram-Scale Synthesis of Benzyl 3-(2-methoxy-1-(phenylamino)ethylidene)-2-oxopyrrolidine-1-carboxylate (19). To a reactor were charged 1 M aqueous hydrogen chloride solution (978 kg, 0.978 kmol, 1.76 equiv), **20·K**(183.4 kg, 0.557 kmol, 1.0 equiv), and toluene (1586.4 kg, 10.0 vol). The reaction mixture was stirred for 10 min at 25 °C. The phases were separated, and the organic layer was washed with water (917.0 kg, 5 vol). Aniline (49.3 kg, 0.529 mol, 0.95 equiv), *p*-toluenesulfonic acid monohydrate (1.06 kg, 5.572 mol, 0.01 equiv), cyclohexane (1912.3 kg, 13.5 vol), and toluene (888.4 kg, 5.6 vol) were added to the organic layer. The reaction mixture was heated to 96 °C for 2 h to allow azeotropic dehydration of the organic solvent (2580 L of 6/4 v/v a cyclohexane−toluene mixture was used to replace the solvent removed by azeotropic dehydration). The reaction mixture was then cooled to 0 °C, and a 5% aqueous acetic acid solution (922.1 kg, 1.38 equiv) was added at 3 °C followed by stirring for 10 min. The phases were separated, and the organic layer was washed with a 5% aqueous sodium hydrogen carbonate solution (950.5 kg). The organic layer was washed with water (2 × 917.0 kg) and concentrated under reduced pressure to the extent possible. The concentrates were then diluted with methyl alcohol (1305.6 kg, 9 vol). Activated carbon (18.3 kg) was added to the methyl alcohol solution, and the suspension was stirred for 0.5 h at 23 °C. The mixture was filtered, and the cake was washed with methyl alcohol (145.1 kg). The filtrate was concentrated under reduced pressure to the extent possible. Ethyl acetate (827.3 kg) was added, and the mixture was concentrated under reduced pressure to the extent possible. The concentrates were diluted with ethyl acetate (82.7 kg) and cooled to 6 °C. A seed of **19** (69.0 g) was added, and heptane (504.7 kg, 4.0 vol) was added to promote the crystallization over 2 h with the internal temperature maintained below 15 °C. The suspension was warmed to 25 °C and aged for 9 h. The solid was collected by filtration, and the cake was washed with 555 L of a 4/1 v/v heptane−ethyl acetate solution and dried under vacuum at 40 °C to yield **19** as a pale yellow solid (150.1 kg, 74% yield). HPLC analysis of a sample matched that of one from the lab-scale synthesis.

Kilogram-Scale Synthesis of Benzyl (3aR,4R,9bR)-4-(methoxymethyl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-c]quinoline-1-carboxylate para-toluenesulfonate (16·p-TsOH). A 500 L pressure reactor was charged with **19** (37.5 kg, 0.102 kmol, 1.0 equiv), cyanuric acid (13.2 kg, 0.102 kmol, 1.00 equiv), and [Rh(cod){(2*S*,4*S*)-ptbp-skewphos}]OTf (1741.5 g, 1.70 mol, 0.0167 equiv, s/c 60). The reactor was evacuated to −0.09 MPa and then filled with nitrogen to 0.10 MPa. This operation was repeated five times. To the reactor were added 2,2-dimethoxypropane (16.0 kg, 0.154 kmol, 1.51 equiv) and anhydrous acetone (375 L, 10 vol) by nitrogen gas feed. The reactor was pressurized with nitrogen (0.60 MPa), vented three times, and then pressurized with hydrogen (0.60 MPa) and vented three times. The hydrogen pressure was set to 3.0 MPa, and heating was started. After a reaction temperature of 45 °C was reached, the pressure was adjusted to 5.5 MPa. The reaction mixture was stirred with the hydrogen pressure maintained within the range of 5.0−6.0 MPa at 40−50 °C (set point 45 °C) for 48 h. The reactor was cooled below 30 °C, and the hydrogen was carefully vented. The reactor was pressurized with nitrogen (0.60 MPa) and vented six times. The reaction mixture was concentrated under reduced pressure to the extent possible. Ethyl acetate (187.5 L, 5 vol) was added, and the mixture was concentrated under reduced pressure to the extent possible. The concentrates were

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diluted with ethyl acetate (375.0 L, 10 vol) and stirred at 25 °C for 1 h. The insolubles were removed by filtration and washed with ethyl acetate (93.8 L, 2.5 vol). *p*-Toluenesulfonic acid (19.5 kg, 0.103 kmol, 1.00 equiv) was added to the filtrate, and the mixture was stirred at 25 °C for 1 h. The solid was collected by filtration, and the cake was washed with ethyl acetate (350 L, 10 vol) before being dried at 50 °C under vacuum to yield **16·*p*-TsOH** as a colorless solid (48.3 kg, 90% yield, 75.0% ee). HPLC analysis of a sample matched that of one from the lab-scale synthesis.

Kilogram-Scale Synthesis of (3aS,4R,9bR)-4-(Methoxymethyl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-c]quinoline (2). To a reactor were charged **16·*p*-TsOH** (127.1 kg, 0.243 kmol, 1.0 equiv) and a 6 M aqueous hydrogen chloride solution (686.3 kg, 4.12 kmol, 16.95 equiv). The resulting suspension was heated to 80 °C, stirred for 2 h, and then cooled to 25 °C before adding toluene (635.5 L, 5 vol). After they were stirred for 15 min, the phases were separated, and activated carbon (Shirasagi-A, 8.6 kg) was added to the aqueous layer. The suspension was stirred at 25 °C for 30 min and filtered, and the filter cake was rinsed with water (127 L, 1 vol). An 8 M aqueous sodium hydroxide solution (762.6 L, 6 vol) was added dropwise to the filtrate with the internal temperature maintained below 30 °C. The resulting suspension was stirred at room temperature for 2 h. The solid was collected by filtration, and the cake was washed with water (254.2 L, 2 vol) before being dried at 50 °C under vacuum to yield **2** as a colorless solid (46.4 kg, 88% yield, 80.0% ee). HPLC analysis of a sample matched that of one from the lab-scale synthesis.

Kilogram-Scale Synthesis of (3aS,4R,9bR)-4-(Methoxymethyl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[3,2-c]quinoline L-tartrate (2·L-tartrate). To a four-necked round-bottom flask were charged L-tartaric acid (31.9 kg, 0.213 kmol, 1.00 equiv) and ethyl alcohol (1300 L, 28 vol). The suspension was heated to 50 °C to dissolve the solid, and then a seed crystal of **2·L-tartrate** (5 g) was inoculated, and **2** (46.4 kg, 0.213 kmol, 1.0 equiv) was added at 50 °C. The resulting suspension was aged at 50 °C for 30 min and cooled to 25 °C. The solid was aged for 2 h before being collected by filtration, and then the cake was washed with ethyl alcohol (278.4 L, 6 vol) and dried at 50 °C under vacuum to yield **2·L-tartrate** as a colorless solid (62.0 kg, 79% yield, >99.9% ee). HPLC analysis of a sample matched that of one from the lab-scale synthesis.

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via Internet at The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00365.

General analytical methods and copies of HPLC chromatogram, ^{1}H NMR and ^{13}C NMR for compounds **21**, **20·K**, **19**, ***syn*-18**, **16·*p*-TsOH**, **2**, and **2·L-tartrate** (PDF)

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Notes

The authors declare no competing financial interest.

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