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Development of a Total Telescoped Synthesis of a Renin Inhibitor Containing 3,4,5-Substituted Piperidine with Sterically Hindered Amide Bonds

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ABSTRACT: A telescoped synthesis for the manufacturing of a renin inhibitor containing 3,4,5-substituted piperidine with sterically hindered amide bonds via a five-step synthetic route is described. Highlights of this scalable synthesis include: (1) the byproduct-controlled amidation protocol using Ghosez's reagent in the presence of a mild acid scavenger for the formation of the first sterically hindered amide bond; (2) the chemoselective hydrolysis of a sterically hindered ester; (3) an efficient amidation reaction employing a soluble carbodiimide leading to the second sterically hindered amide bond; (4) filtration of the fumarate salt of the final drug substance, being the only necessary isolation step throughout the total synthesis. Without the necessity of isolating any intermediates, this telescoped process conserved equipment usage, consumed less solvents, and minimized process waste generation, energy consumption, personnel exposure, and environmental impact. It furnished kilogram quantities of high-quality active pharmaceutical ingredients.

INTRODUCTION

Recently, Novartis developed a 4-hydroxy-3,5-substituted piperidine (**1**, Figure 1) as a new class of highly efficacious

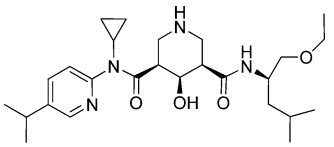

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Figure 1. A renin inhibitor.

oral direct renin inhibitor.[1] To probe its therapeutic potentials in humans, we needed to develop a facile and practical synthesis that allows the production of kilogram quantities of this active pharmaceutical ingredient (API) for the support of clinical trials. Since **1** consists of three fragments linked by two sterically hindered amide bonds, it was obvious that connecting them sequentially through an applicable amidation methodology was a logical approach (Scheme 1). This strategy was already employed by medicinal chemists, who developed a linear, four-step route for the synthesis of **1** (Scheme 2).[1] To employ this route for kilogram-scale manufacturing, we had to overcome several drawbacks.

The most challenging issue was to avoid several chromatographic purifications that were employed previously for each of the intermediates **4**, **5**, and **7**. Because the physical states of all intermediates (**4**, **5**, and **7**) are noncrystalline, the possibility of using crystallization−filtration as unit operations to obtain high-purity products was ruled out. Changing the sequence of the synthetic route involving the same building blocks was not considered, as this approach would still go through noncrystalline intermediate **7**. We therefore envisaged developing a telescoped synthesis from starting materials to the final drug substance. To achieve this goal, the impurity profiles must be controlled to acceptable levels after each single transformation. We report herein a five-step telescoped process that was scalable for the synthesis of the fumerate salt of **1** in kilogram quantities in high efficiency.

RESULTS AND DISCUSSION

Amidation of Sterically Hindered Amine and Carboxylic Acid. The telescoped synthesis for **1** started with the formation of **4** from sterically hindered amine **2** and carboxylic acid **3**. Amidation reactions involving sterically hindered amines or carboxylic acids, respectively, have been challenging tasks since racemization and/or side reactions are common competing pathways. These resulted in inefficient conversion, unreacted starting materials, or the formation of byproducts that often cannot be separated readily from the desired molecule. Several effective methodologies have been reported for the synthesis of sterically hindered amides with good efficiency.[2] However, after assessing the handling,[2a] cost,[2b,c] and commercial availability[2d,e] of coupling reagents utilized by these methods, we decided to try something different for the synthesis of **4**. Ghosez reported an efficient method for the synthesis of acyl chlorides under mild conditions employing 1-chloro-*N*,*N*-2-trimethyl-1-propenylamine **8** (Ghosez's reagent).[3] This reagent is inexpensive and commercially available and has been utilized for the synthesis of several sterically hindered amides in excellent yields.[4] To develop a telescoped process for the synthesis of **1**, it was critical to attain good quality of every single intermediate so that it can be used for the next step without further purification. Since Ghosez's reagent generates a water-soluble byproduct (*N*,*N*-dimethyli-

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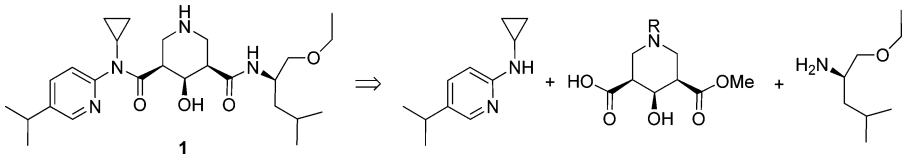
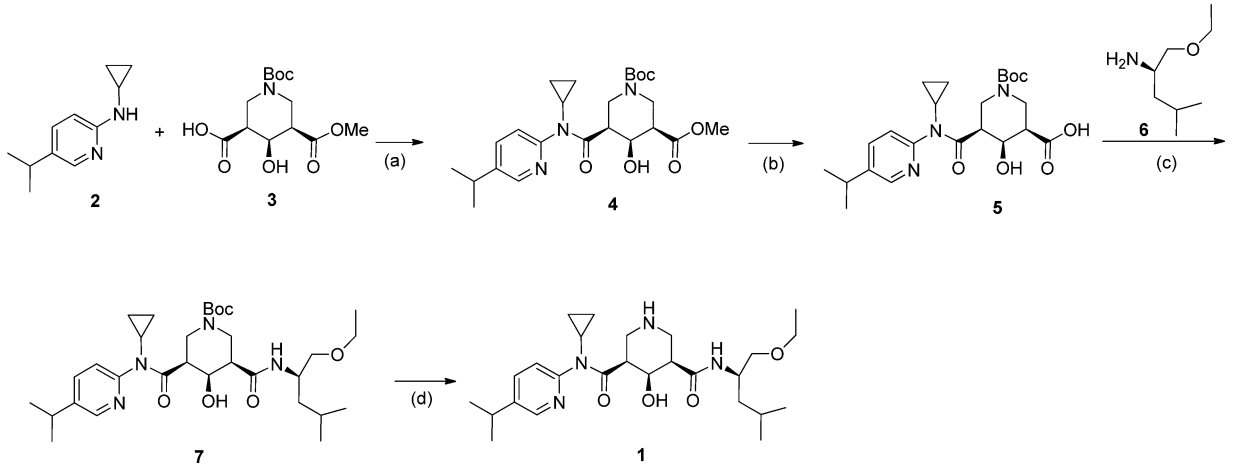
Scheme 1. Retrosynthetic analysis of 1



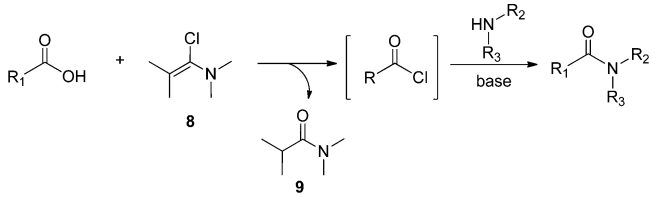
Scheme 2. Initial research synthesis[a] of 1



[a]Reagents and conditions: (a) Ghosez reagent, CH_2Cl_2, 0−25 °C, chromatography; (b) 2.5 equiv of LiOH, THF, 0 °C, chromatography; (c) EDC−HCl, HOAt, Et_3N, CH_2Cl_2, 25 °C, chromatography; (d) 4 *N* HCl, dioxane, 25 °C.

sobutyramide **9**, Scheme 3) that can easily be separated from the product by a simple aqueous work-up procedure, we probed whether **8** was an ideal coupling reagent for the formation of **4** without generating unacceptable impurity profiles.

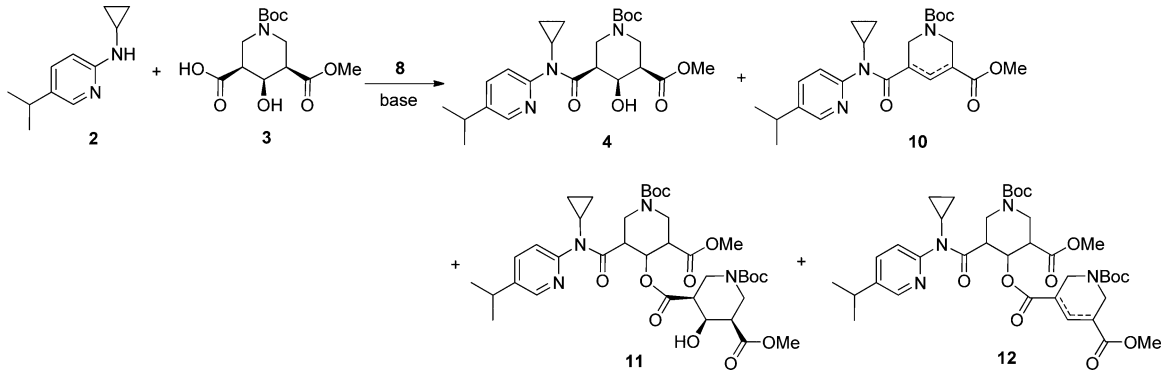
Scheme 3. Ghosez's reagent 8 for amide synthesis



The results of our initial attempts to synthesize **4** from **2** and **3** in acetonitrile and by employing **8** as the coupling reagent in the presence of *N*,*N*-diisopropylethylamine (Hünig's base) as the acid scavenger were unsatisfactory. We observed the formation of three impurities, as suggested by LC-MS analyses: **10** (7%), **11**, and **12** (**11** plus **12**, 23%) (Scheme 4). As a result, the assay of **4** was determined to be only 70%, which was not acceptable. We subsequently performed a series of experiments intended to identify a protocol that could minimize impurity contents.

As revealed by a ^{1}H NMR study, mixing acid **3** with **8** in CD_3CN in the absence of a base led to a rapid and clean formation of acyl chloride **3c** (Scheme 5). No impurity was detected until amine **2** and Hünig's base were subsequently added. Based on these observations, we postulated that impurities **10**, **11**, and **12** presumably were generated through the elimination and Michael addition pathways from an in situ intermediate **4b** (Scheme 6). The elimination reaction may be promoted by the Ghosez's reagent **8**[5] and enhanced by an acid scavenger such as Hünig's base.

Scheme 4. Synthesis of sterically hindered amide 4



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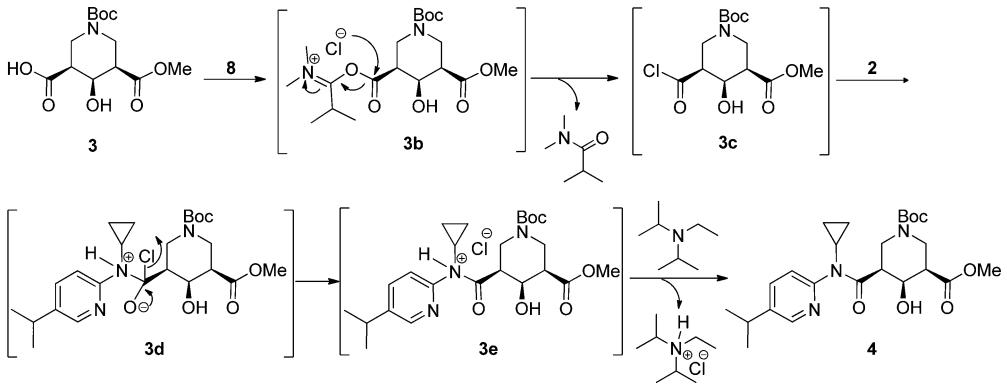
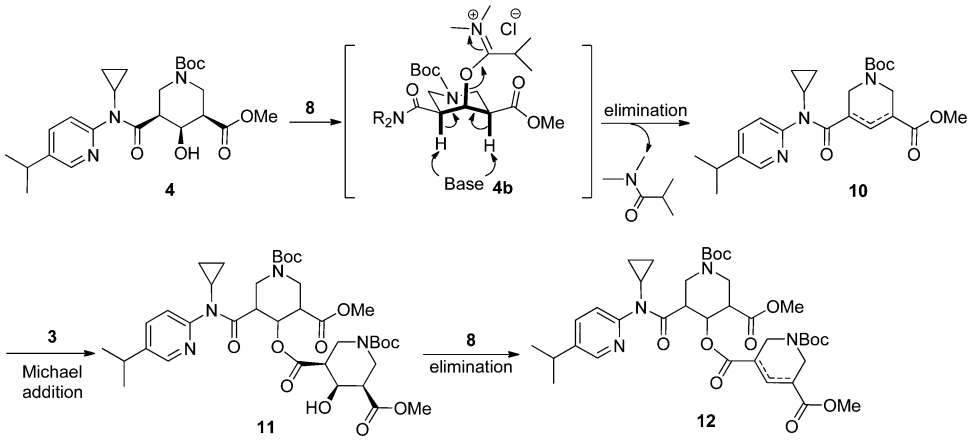
Scheme 5. Plausible mechanism for the amidation reaction employing Ghosez's reagent



Scheme 6. Postulated mechanism for the formation of impurities 10, 11, and 12



We postulated that a milder base whose pK_a (of the respective conjugated acid) is marginally greater than that of the conjugated acid **3e** formed in situ (Scheme 5) would be still strong enough to function as an acid scavenger but, on the other hand, weak enough to avoid the undesired elimination reactions leading to impurities **10**, **11**, and **12**. Since the calculated pK_a value of **2a** was reported to be 6.89 (Figure 2)[6]

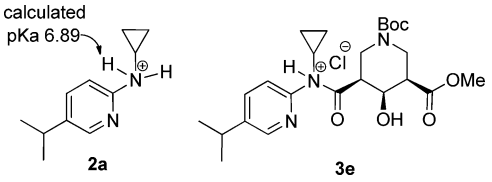


Figure 2. Structures of **2a** and **3e**.

and its structure is analogous to that of **3e**, we investigated the impacts of a couple of bases whose pK_a values are slightly greater than 6.89 and basicity lower in magnitudes than Hünig's base (pK_a 10.98). We were pleased to see a significant decline in the total level of impurities (**10**, **11**, and **12**) from 30% to 13% when *N*-methylmorpholine (pK_a 7.58) was utilized (Table 1, entry 2). Employing 2-*N*,*N*-dimethylaminopyridine (pK_a 7.04), we were able to obtain an excellent yield (98.4%) of **4** containing trace amounts (1.6% total) of impurities (Table 1, entry 3). It is noteworthy that the quality of **4**, after aqueous work-up, met our quality specifications and could be used in the next reaction step without any further purification. This protocol was reproducible on plant-scale.

Chemoselective Hydrolysis. Our initial effort to synthesize **5** by hydrolyzing the ester functionality of **4** with the following protocol, 1.0−1.1 equiv of LiOH/THF−H_2O 1:1/THF/0 °C, was problematic. Under these conditions, hydrolysis of both the ester and the amide group took place, which resulted in the formation of the undesired diacid **5b** (20%). Being unsatisfied with this uncontrolled hydrolysis reaction, we committed to identifying alternative conditions that suppress hydrolysis of the amide bond of **4**. The latter is presumably caused by the presence of the large excess of lithium hydroxide, which could trigger further hydrolysis driven by the release of a conjugated species **5d** from the tetrahedron

Table 1. Impact of basicity of the acid scavenger on the formation of impurities[a]

entry	base	pK_a[5]	% **2**[b]	% **10**[b]	% **11** plus **12**[b]	% **4**[b]
1	Hünig's base	10.98	0	7	23	70
2	*N*-methylmorpholine	7.58	10	7	6	87
3	2-*N*,*N*-dimethylaminopyridine	7.04	0	0.4	1.2	98.4

[a]Reaction was performed in acetonitrile. [b]Determined by HPLC analysis.

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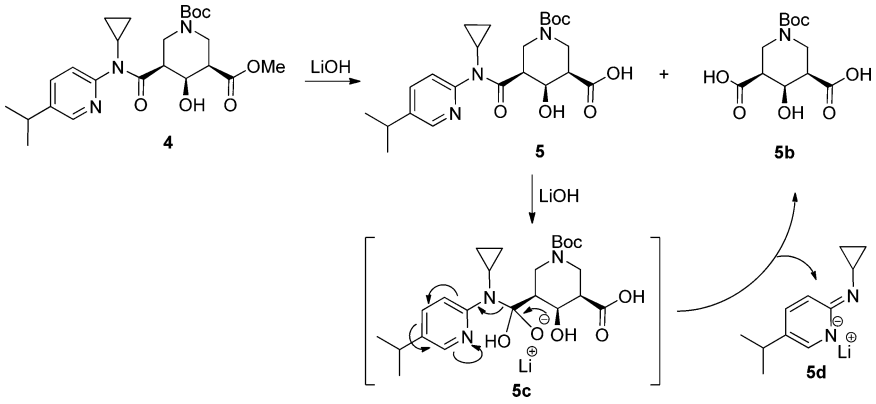
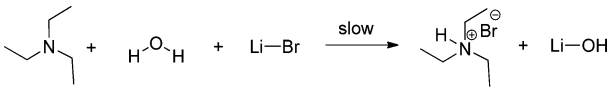
Scheme 7. Postulated mechanism for the formation of diacid 5b



intermediate **5c** (Scheme 7). We speculated that appropriate control of lithium hydroxide concentration to minimum at any given time would allow a chemoselective hydrolysis of the ester bond.

Karlsson et al. reported a protocol for ester hydrolysis employing relatively mild conditions: 1 equiv of ester substrate/3 equiv of Et_3N/10 equiv of LiBr/CH_3CN containing 2 vol % of water/25 °C.[7] This methodology was not only applicable to a variety of esters with excellent yields but also can chemoselectively hydrolyze esters in the presence of an amide functionality. We hypothesized that Karlsson's protocol probably generates low concentrations of lithium hydroxide in situ at any given time (Scheme 8), which attacks preferentially the carbonyl group of esters relative to that of an amide attributing to a lower activation required for the former reaction.

Scheme 8

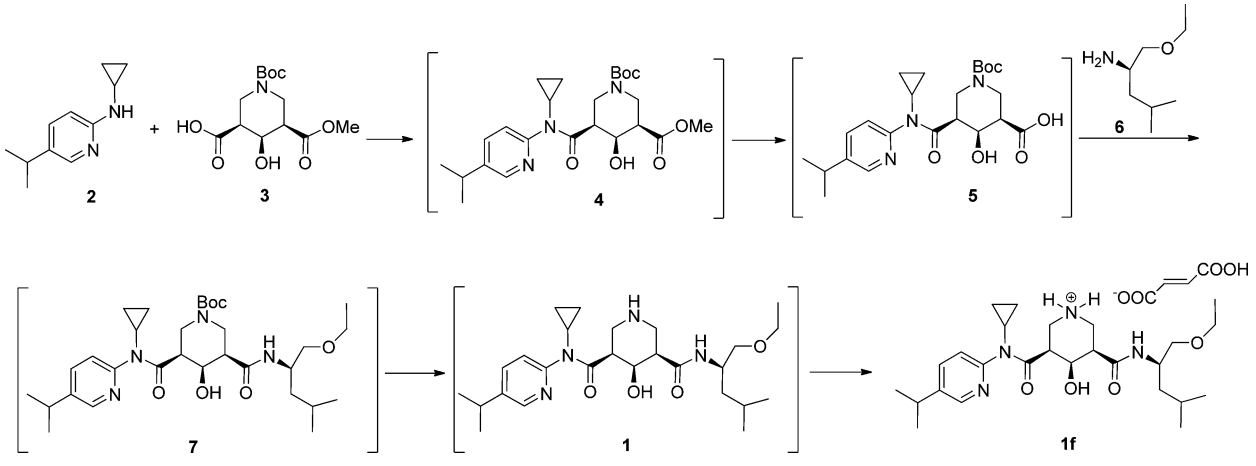


After a moderate optimization of Karlsson's protocol, we were able to selectively hydrolyze the ester group in 99% yield (determined by HPLC) by employing the following conditions: 1 equiv of **4**/5 equiv of Et_3N/10 equiv of LiBr/5 equiv of H_2O/CH_3CN/25 °C/6 h. Hydrolysis of the amide bond of **4** was fully avoided, as no diacid **5b** had been detected during the course of saponification reaction. This can be achieved only if the end-point of saponification was carefully monitored by HPLC to avoid further amide hydrolysis. The clean and efficient conversion of **4** to **5** contributed to a successful operation in the plant affording **5** with 99% purity without the requirement of further purification.

Formation of the Second Sterically Hindered Amide Bond. To install the second amide bond, starting from carboxylic acid **5** and amine **6**, the medicinal chemists utilized an amidation protocol: *N*-(3-(dimethylamino)propyl)-*N*′-ethyl-carbodiimide hydrochloride (EDC)[8] as the coupling reagent and 1-hydroxy-7-azabenzotriazole (HOAt) as the promoter. One advantage of this methodology is the formation of an acyl urea byproduct that is water-soluble and can be easily separated from the product by aqueous work-up. Therefore, we decided to keep EDC but to replace the hazardous HOAt (explosion potential) by a safer promoter 1-hydroxybenzotriazole (HOBt), which had been used successfully for an amide synthesis in our pilot plant.[9] Employing EDC−HOBt for the amidation reaction involving **5** and **6**, we were able to synthesize sterically hindered amide **7** in 99% yield (determined by HPLC) with >98% purity in our plant. Amide **7** was produced as a solution in isopropyl acetate and used for the final step without further purification.

End-Game Synthesis and Fumarate Salt Formation. To synthesize the desired drug substance, the solution of penultimate compound **7** in isopropyl acetate was treated with 6 *N* aqueous solution of hydrochloric acid. This biphasic system

Scheme 9. Total telescoped synthesis of 1



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required no phase-transfer catalyst and efficiently removed the Boc protecting group from **7** to furnish **1** in 99% yield (determined by HPLC) with >98% purity as a solution in ethyl acetate, after work-up and solvent exchange. Since the fumarate salt **1f** (Scheme 9) is the required active pharmaceutical ingredient, the final synthesis required the conversion of free base **1** to this organic salt. Accordingly, the solution of **1** in ethyl acetate was reacted with a solution of fumaric acid in ethanol. This binary-solvent system was selected since it can produce a fumarate salt in the desired polymorph. The pharmaceutical salt **1f** was isolated by filtration, the only isolation throughout the entire total synthesis. The telescoped synthesis afforded 33.5 kg of API with 99% purity in 54% overall yield from 31.5 kg of **3** in our plant.

■ CONCLUSIONS

A telescoped process was developed for the manufacturing of **1f** via a five-step synthetic route without isolating any intermediates (Scheme 9). Guided by plausible reaction mechanisms we proposed, optimization of each individual reaction step was accomplished by minimizing impurity profiles. The goal of developing a total telescoped and scalable synthesis was achieved. Highlights of this scalable synthesis include: (1) the byproduct-controlled amidation protocol using Ghosez's reagent in the presence of a mild acid scavenger for the formation of the first sterically hindered amide bond; (2) the chemoselective hydrolysis of a sterically hindered ester; (3) an efficient amidation reaction employing a soluble carbodiimide leading to the second sterically hindered amide bond; (4) filtration of the fumarate salt of the final drug substance, being the only necessary isolation step throughout the total synthesis. Without the necessity of isolating any intermediates, this telescoped process conserved equipment usage, consumed less solvents, and minimized process waste generation, energy consumption, personnel exposure, and environmental impact. Additionally, telescoping of the steps achieved "unit operation economy" as it avoided necessary operations required for reactor cleanings compared to if intermediates had been isolated, which traditionally utilizes solvents, water, detergents, and energy (for refluxing, distilling, etc.). We propose to include these cleaning solvents and materials into the process mass intensity calculation[10] to reflect the reality.[11] In conclusion, this telescoped synthesis furnished kilogram quantities of high-quality active pharmaceutical ingredient.

■ EXPERIMENTAL SECTION

General. Starting materials **2**[1] and **3**[12] were purchased form CiVentiChem and Archimica Chemicals, respectively. Compound **6**[1] was purchased from Richmond Chemical Corporation. Reverse-phase HPLC analyses were performed on an Agilent HPLC system with a DAD detector (area normalization).

(3*R*,4*S*,5*S*)-1-*tert*-Butyl-3-methyl-*b*-cyclopropyl(5-isopropylpyridin-2-yl)carbamoyl-4-hydroxypiperidine-1,3-dicarboxylate (4, Laboratory Scale Process). To a solution of **3** (60.0 g, 198 mmol) in acetonitrile (800 mL) was added 1-chloro-*N*,*N*-2-trimethyl-1-propenylamine (32.6 g, 238 mmol) over 20 min at 0 °C. The suspension was stirred at 0 °C for 1 h to obtain a clear solution. The resulting solution was cooled to −10 °C and charged to a solution of **2** (42.0 g, 238 mmol), 2-(dimethylamino)pyridine (36.4 g, 298 mmol), and acetonitrile (600 mL) at −10 °C. The mixture was stirred for 30 min at −10 °C. A solution of citric acid (100 g) in water (400 mL) was added, and the mixture was warmed to 25 °C. Acetonitrile was distilled off at 25 °C under reduced pressure. To the residue, ethyl acetate (800 mL) and water (400 mL) were added. The organic layer was separated, washed with water (600 mL), 10% (w/w) aqueous $NaHCO_3$ solution (600 mL), 10% (w/w) aqueous NaCl solution (600 mL), and concentrated at 25 °C under reduced pressure until a final volume of ∼160 mL was reached. Acetonitrile was added to the residue until a final weight of 900 g (∼950 mL) was reached to obtain **4** (91.4 g, 198 mmol, 100% yield as is) as a solution, which was used for the next step without further purification. HPLC for **4** (t_R = 8.32 min, identical to authentic sample) 98.4% purity; **2** (t_R = 3.92 min): Agilent SB-C18 150 × 3 mm, flow rate = 1 mL/min, 40 °C, gradient elution from 10:90 A−B to 90:10 A−B over 15 min; A = acetonitrile; B = 0.1% TFA in water; UV λ = 254 nm.

(3*R*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-(cyclopropyl(5-isopropylpyridin-2-yl)carbamoyl)-4-hydroxypiperidine-3-carboxylic acid (5, Laboratory Scale Process). To the acetonitrile solution of **4** (900 g, containing 91.4 g of **4**, 198 mmol as is) were added water (20 mL, 1.1 mol), lithium bromide (172 g, 1.98 mol), and triethylamine (100 g, 990 mmol) at 20 °C. The mixture was stirred at 20 °C for 6 h. Water (800 mL) was added, and the mixture was concentrated at 20 °C under reduced pressure until all acetonitrile was collected. The remaining aqueous solution was washed with *tert*-butyl methyl ether (2 × 400 mL) and adjusted to pH 2 with 15% (w/w) aqueous $KHSO_4$ solution. Product was extracted with isopropyl acetate (2 × 600 mL). The combined organic layer was washed with water (600 mL), 10% (w/w) aqueous NaCl solution (600 mL), and concentrated at 25 °C under reduced pressure until a final volume of ∼950 mL (∼900 g) was reached to afford **5** (88.6 g, 198 mmol, 100% yield as is) as a solution in isopropyl acetate, which was used for the next step without further purification. HPLC for **5** (t_R = 7.15 min, identical to authentic sample) 99% purity; **4** (t_R = 8.32 min): Agilent SB-C18 150 × 3 mm, flow rate = 1 mL/min, 40 °C, gradient elution from 10:90 A−B to 90:10 A−B over 15 min; A = acetonitrile; B = 0.1% TFA in water; UV λ = 254 nm.

(3*S*,4*R*,5*R*)-*tert*-Butyl-3-(cyclopropyl-(5-isopropylpyridin-2-yl)carbamoyl)-5-((*R*)-1-ethoxy-4-methylpentan-2-ylcarbamoyl)-4-hydroxypiperidine-1-carboxylate (7, Laboratory Scale Process). To the isopropyl acetate solution of **5** (900 g, containing 88.6 g of **5**, 198 mmol as is) at 0 °C was added water (20 mL), HOBt (5.34 g, 39.6 mmol; **CAUTION**: dry HOBt can be explosive), **6** (43.2 g, 238 mmol), *N*-methylmorpholine (24 g, 238 mmol), and EDC (45.6 g, 238 mmol). The mixture was warmed to 25 °C and stirred for 6 h. Water (600 mL) was charged. The organic layer was separated and washed with 10% (w/w) aqueous $NaHCO_3$ solution (600 mL), 10% (w/w) aqueous citric acid solution (600 mL), and 10% (w/w) aqueous NaCl solution (600 mL). The organic solution was concentrated at 25 °C under reduced pressure until a final volume of ∼600 mL (∼600 g) was reached to furnish **7** (113.7 g, 198 mmol, 100% yield as is) as a solution in isopropyl acetate, which was used for the next step without further purification. HPLC for **7** (t_R = 10.0 min, identical to authentic sample), 99.4% purity; **5** (t_R = 7.15 min): Agilent SB-C18 150 × 3 mm, flow rate = 1 mL/min, 40 °C, gradient elution from 10:90 A−B to 90:10 A−B over 15 min; A = acetonitrile; B = 0.1% TFA in water; UV λ = 254 nm.

(3*S*,4*R*,5*R*)-*N*3-Cyclopropyl-*N*5-((*R*)-1-ethoxy-4-methylpentan-2-yl)-4-hydroxy-*N*3-(5-isopropylpyridin-2-yl)-

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piperidine-3,5-dicarboxamide (1, Laboratory Scale Process). To the isopropyl acetate solution of **7** (600 g, containing 113.7 g of **7**, 198 mmol as is) at 0 °C was added 6 *N* aqueous HCl solution (496 g). The mixture was stirred at 0 °C for 5 h. Isopropyl acetate (500 mL), 50% (w/w) aqueous NaOH solution (246 g), and NaCl (40 g) were added in sequence at 0 °C. The organic layer was separated and saved. The aqueous layer was extracted with isopropyl acetate (600 mL). The combined organic layer was washed with saturated NaCl solution (600 mL), filtered over a pad of Celite, and concentrated at 25 °C under reduced pressure until a final volume of ∼120 mL was reached. Ethyl acetate (600 mL) was added, filtered over a pad of Celite, and concentrated at 25 °C under reduced pressure until a final volume of ∼120 mL was reached. The remaining solution was diluted with ethyl acetate (200 mL) to obtain **1** (94 g, 198 mmol as is) as a solution (300 g) in ethyl acetate, which was used for the next step without further purification. HPLC for **1** (t_R = 6.2 min, identical to authentic sample), 98.5% purity; **7** (t_R = 10.0 min): Agilent SB-C18 150 × 3 mm, flow rate = 1 mL/min, 40 °C, gradient elution from 10:90 A−B to 90:10 A−B over 15 min; A = acetonitrile; B = 0.1% TFA in water; UV λ = 254 nm.

(3*S*,4*R*,5*R*)-*N*3-Cyclopropyl-*N*5-((*R*)-1-ethoxy-4-methylpentan-2-yl)-4-hydroxy-*N*3-(5-isopropylpyridin-2-yl)-piperidine-3,5-dicarboxamide, Monofumarate Salt (1f, Laboratory Scale Process). To a solution of fumaric acid (11.5 g, 99 mmol), ethanol (115 mL), and ethyl acetate (230 mL) at 40 °C was added the ethyl acetate solution of **1** (150 g, containing 47 g of **1**, 99 mmol). The solution was filtered over a pad of Celite and diluted with ethyl acetate (520 mL) at 40 °C. To the clear solution, seeds was added and stirred at 40 °C for 1 h. The mixture was cooled to 25 °C over 1 h. Ethyl acetate (200 mL) was added and stirred for 16 h. The precipitate was filtered, washed with a mixture of ethanol and ethyl acetate (1:9 v/v, 2 × 100 mL), and dried under reduced pressure at 40 °C for 16 h to afford **1f** (25.2 g, 42.7 mmol, 43% overall yield from **2**) as an off-white solid: mp 207−213 °C; ^{1}H NMR (500 MHz, DMSO-d_6); 8.35 (d, J = 1.3 Hz, 1H), 7.75 (dd, J = 7.8, 1.3 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 6.47 (s, 2H), 4.37 (br s, 1H), 3.92 (m, 1H), 3.42 (m, 2H), 3.30 (m, 1H), 3.20−3.10 (m, 2H), 3.10−2.95 (m, 5H), 1.57 (m, 1H), 1.30 (m, 2H), 1.24 (d, J = 8.3 Hz, 6H), 1.08 (t, J = 6.5 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H), 0.80 (m, 2 H), 0.55 (m, 1H), 0.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 172.6, 169.6, 167.8, 152.4, 146.8, 141.8, 135.8, 135.0, 121.7, 72.4, 65.5, 64.2, 46.2, 44.4, 42.7, 30.5, 29.9, 24.2, 23.4, 21.8, 15.0, 8.8; MS (ESI) m/z 475.1 (M + H$^+$); HPLC for **1** (t_R = 6.2 min), purity 99.0%: Agilent SB-C18 150 × 3 mm, flow rate = 1 mL/min, 40 °C, gradient elution from 10:90 A−B to 90:10 A−B over 15 min; A = acetonitrile; B = 0.1% TFA in water; UV λ = 254 nm.

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Notes

The authors declare no competing financial interest.

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