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Synthesis of Akt Inhibitor Ipatasertib. Part 2. Total Synthesis and First Kilogram Scale-up

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Supporting Information

ABSTRACT: Herein, the first-generation process to manufacture Akt inhibitor Ipatasertib through a late-stage convergent coupling of two challenging chiral components on multikilogram scale is described. The first of the two key components is a *trans*-substituted cyclopentylpyrimidine compound that contains both a methyl stereocenter, which is ultimately derived from the enzymatic resolution of a simple triester starting material, and an adjacent hydroxyl group, which is installed through an asymmetric reduction of the corresponding cyclopentylpyrimidine ketone substrate. A carbonylative esterification and subsequent Dieckmann cyclization sequence was developed to forge the cyclopentane ring in the target. The second key chiral component, a β^2-amino acid, is produced using an asymmetric aminomethylation (Mannich) reaction. The two chiral intermediates are then coupled in a three-stage endgame process to complete the assembly of Ipatasertib, which is isolated as a stable mono-HCl salt.

INTRODUCTION

Retrosynthetically, Ipatasertib is comprised of two chiral components, the cyclopentylpyrimidine core *trans*-**1** and β^2-amino acid (*S*)-**2** (Figure 1).[1] There are several key challenges

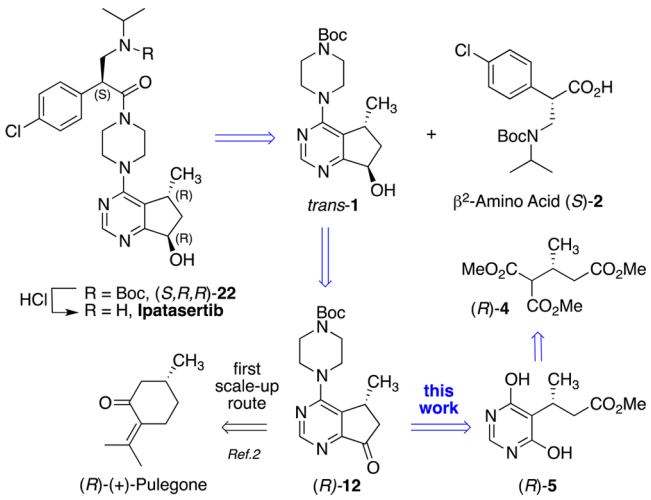

Figure 1. Retrosynthetic analysis for the synthesis of Ipatasertib.

to the synthesis and scale-up of Ipatasertib: (1) the source and control of the chiral purity of the starting materials are critical; (2) impurities formed during the coupling of the two chiral starting materials must be controlled, and (3) poor thermal stability of the free-base form of Ipatasertib leads to a β-elimination degradation product, which necessitates development of a stable mono-HCl salt form.

In Part 1 of this series,[2] the route scouting and early process development efforts focused on the identification of a new racemic route for the synthesis of a challenging cyclopentylpyrimidine compound (*R*)-**12** used in the preparation of *trans*-**1**. In the new strategy, dihydroxypyrimidine *rac*-**5**[3] was identified as a key intermediate that originated from a simple triester starting material bearing the requisite methyl stereocenter (*rac*-**4**). This intermediate set the stage for a downstream Dieckmann cyclization and decarboxylation of the resulting β-keto ester to afford ketone *rac*-**12** in seven steps from *rac*-**5**.[4]

The focus of the work reported herein entails the development of an asymmetric route to DHP (*R*)-**5** from the enzymatic resolution of precursor triester *rac*-**4**. The conversion of intermediate (*R*)-**5** into ketone (*R*)-**12** on multikilogram scale was subsequently achieved in high enantiopurity. From the chiral ketone (*R*)-**12**, alcohol *trans*-**1** was obtained via an asymmetric Noyori transfer hydrogenation using a chiral ruthenium catalyst.[5]

For preparation of the second chiral component, the β^2-amino acid (*S*)-**2**, an asymmetric aminomethylation (Mannich) reaction using Evans's chiral auxiliary was initially employed to access the desired target.[6] In the discovery synthesis, the method was successful in terms of providing enantiomerically enriched compound (*S*)-**2**. However, this chemistry was not immediately amenable to scale-up due to the use of cryogenic temperatures and silica gel chromatography for purification, where the product was isolated as a *syrup*. Herein we describe an improved process using the Evans's chiral auxiliary approach

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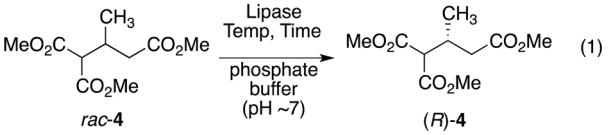
that enabled the production of kilogram-scale quantities of crystalline and enantiomerically pure β^2-amino acid (*S*)-**2**.

The convergent endgame synthesis of Ipatasertib commenced with the initial deprotection of the *tert*-butyloxycarbonyl (Boc)-protected *trans*-**1** core followed by amide bond formation with β^2-amino acid (*S*)-**2** to produce the *N*-Boc-protected API ((*S,R,R*)-**22**). Although the use of the guanidinium coupling reagent HBTU[7] was shown to be effective in providing the amide product without detectable epimerization, the byproducts generated were challenging to remove and required the development of alternative isolation conditions. The final deprotection step to remove the *N*-Boc group with HCl initially afforded Ipatasertib di-HCl, which was the final form employed in early biological investigations. However, hygroscopicity issues associated with Ipatasertib di-HCl and the unstable nature of the free-base form of the API led to the development of a stable mono-HCl salt form of Ipatasertib that will be described herein.

RESULTS AND DISCUSSION

1. Preparation of 2,6-Dihydroxypyrimidine (*R*)-5. Our first objective was to secure an efficient and scalable route to the substituted dihydroxypyrimidine (*R*)-**5** that was previously prepared only in racemic form through the condensation of triester *rac*-**4**[8] with formamidine acetate in 87% yield on 500 g scale.[2] Our efforts focused on developing a scalable route to enantiomerically pure triester (*R*)-**4** (eq 1). Two approaches

Table 1



(1)

were initially investigated to produce kilogram quantities of 2,6-dihydroxypyrimidine (*R*)-**5**. The first approach originated from the commercially available (*R*)-monomethyl 3-methylglutarate (MGM) substrate that involved a challenging cryogenic acylation reaction to access triester (*R*)-**4**,[9] whereas the second approach involved a more practical enzymatic resolution of triester *rac*-**4** and is the approach described below.[10]

Exploration to access triester (*R*)-**4** commenced with the screening of various hydrolytic lipases with the goal of identifying one that would lead to both high enantioselectivity and high conversion.[11] From the list of representative examples shown in Table 1, the commercially available lipase from *Candida rugosa* (entry 6) and lipase AYS "Amano" (entries 7 and 8) were shown to give (*R*)-**4** in 92−99% ee after extended reaction time (5−12 d). The enantioselectivity increased over time with both of these enzymes and is best illustrated by entry 6. Increasing the enzyme loading from 20 to 30 wt% in the case of the lipase AYS "Amano" reduced the resolution time from 7 days to 5 days (entry 8) without compromise to the enantioselectivity.[12] The isolated yields for both wild-type lipases were modest (50%), but reproducible.

In a separate study, a mutant form of *Chromobacterium* lipase (entry 9) was identified to be highly effective in the resolution of *rac*-**4**. Specifically, treatment of *rac*-**4** with 11 wt% of enzyme at 0 °C gave triester (*R*)-**4** in >99% ee and 79% yield after only 1 day, and this method was subsequently chosen for our first production batch of DHP (*R*)-**5**. On scale-up of this process, a mixture of triester (*R*)-**4** (27.6 kg) and SC-YM-1 enzyme (2.8 kg, 10 wt%) in phosphate buffer (pH 7.5) was agitated at 0 °C until the reaction was deemed complete (chiral purity >98% ee) after ∼19 h (Scheme 1). The triester product was extracted from the basic aqueous reaction mixture with MTBE and concentrated under reduced pressure to give (*R*)-**4** (12.9 kg, 99.8% ee) in 94% yield. Following the protocol established in the preceding Part I of this series, the crude triester (*R*)-**4** (12.9 kg) was used directly in the next step and reacted with formamidine acetate and NaOMe/MeOH to forge the DHP ring system. The product was precipitated from HCl in MeOH to give DHP (*R*)-**5** (8.7 kg, >99.9% ee, and >99 A%[13]) in 74% yield.[14]

2. Preparation of Ketone (*R*)-12 from DHP (*R*)-5. The seven-step synthesis of key intermediate ketone (*R*)-**12** from DHP (*R*)-**5** is illustrated in Scheme 2, where several

Table 1. Lipase Screen for Resolution of Triester *rac*-4[a]

entry	lipase	wt equiv	temp (°C)	time (h)	ee of 4[b] (%)	yield
1	*Candida antarctica* (Novozym 435)	0.1 w/w	10−15	36	0	nd
2	porcine pancreas	0.1 w/w	30−35	18	0	nd
3	lipase PS "Amano" SD	1.5 w/w	40−45	36	8	nd
4	protease *Bacillus licheniformis* (alcalase-2.4L, Novozyme Co.)	0.3 w/w	26−30	36	−82	nd
5	pig liver esterase (ICR-123, BioCatalytics/Codexis)	0.02 w/w	10−15	24	20	nd
6	*Candida rugosa*	0.1 w/w	40−45	i. 40 ii. 110 iii. 284	i. 52 ii. 76 iii. 92	12.5 g (50% from 50 g of *rac*-**4**); 98.9 A% GC purity[c]
7	lipase AYS "Amano"	0.2 w/w	30−35	170	98	2.5 g (50% from 10 g of *rac*-**4**); 99.3 A% GC purity[c]
8	lipase AYS "Amano"	0.3 w/w	30−35	127	99	2.5 g (50% from 10 g of *rac*-**4**); 99.2 A% GC purity[c]
9	*Chromobacterium* strain SC-YM-1	0.11 w/w	0	23	>99	4.49 g (79%)

[a]The reactions were performed by adding lipase to a mixture of *rac*-**4** in phosphate buffer (10 vol) and maintaining the pH 7.0−7.2 during the reaction at the specified temperature (see eq 1). At the end of the reaction, the pH was adjusted to pH 3−4 with aqueous 2 N HCl, extracted with MTBE, filtered, concentrated, and analyzed for A% purity by GC and chiral purity by HPLC. [b]Enantiomeric excess (ee) was measured by HPLC: Chiralpak IC column (4.6 × 150 mm, 5 μm); mobile phase = *n*-Hexane/EtOH (9:1); flow rate =1.0 mL/min; column temp = 23 °C; inj vol = 10 μL; detector wavelength = 210 nm; approx RRT of (*S*)-**4** = 1.07. [c]GC conditions: DB-5 column (30 m × 0.25 mm, 0.25 μm); flow rate = 3.0 mL/min; inj vol = 0.5 μL; inj temp = 250 °C; detector temperature = 280 °C; split ratio = 1:50; oven program = 60 °C (5 min); ramp to 250 °C (40 min) and hold at 250 °C (7 min). nd = not determined.

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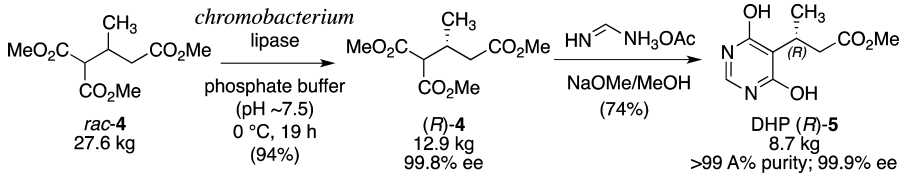
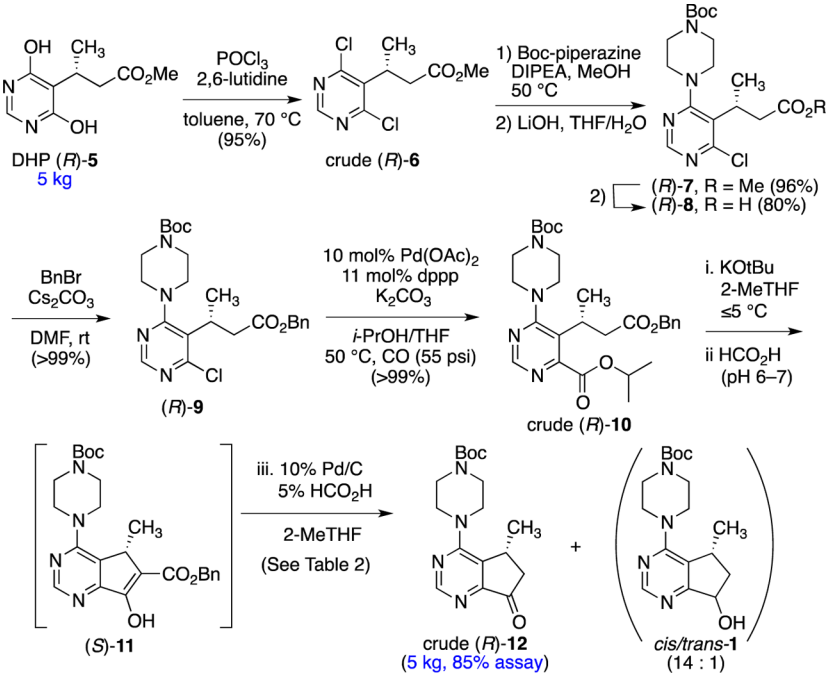
Scheme 1. Enzymatic Resolution Approach to DHP (*R*)-5



Scheme 2. First Kilogram Scale-up of Ketone (*R*)-12 from DHP (*R*)-5



modifications were made to the initial process to render the sequence amenable to scale-up.[15] Starting with 5.0 kg of DHP (*R*)-**5**, the dichlorination reaction using $POCl_3$ and 2,6-lutidine was performed in toluene instead of acetonitrile. The higher boiling point of toluene improved process safety on increased scale since the $POCl_3$ addition was exothermic, and the reagent had to be added as rapidly as possible to maintain good stirring. A second advantage of using toluene was that it allowed for a more efficient extractive aqueous work-up.[16] Using this procedure, the solid dichloropyrimidine (DCP) product (*R*)-**6** (5.63 kg) was produced in excellent yield and purity (95% yield, >98 A%). The subsequent S_NAr reaction of (*R*)-**6** with Boc-piperazine was performed in MeOH at 50 °C in the presence of diisopropylethylamine (DIPEA) as base, and the crude product (*R*)-**7** was isolated in 96% yield with 97 A% purity. Higher reaction temperatures (>50 °C) would increase the rate of the S_NAr reaction but would also favor the formation of a byproduct, arising from the double addition of *N*-Boc piperazine to (*R*)-**6**, which was only observed in trace amounts with the current conditions. The next step, involving methyl ester hydrolysis with LiOH in THF/H_2O, was uneventful when performed at ambient temperature (23 °C); however, at higher reaction temperatures (up to 55 °C), increased hydrolysis of the chloropyrimidine was observed, resulting in production of the corresponding hydroxypyrimidine carboxylic acid derivative. On scale-up, hydrolysis of methyl ester (*R*)-**7** (8.63 kg) was complete after stirring at room temperature for ~15 h, and the product carboxylic acid (*R*)-**8** (6.88 kg, 80% yield) was obtained in two crops after trituration of the isolated solids in MTBE. Re-esterification to the benzyl ester (*R*)-**9** was required for efficient decarboxylation in the downstream chemistry, as described in Part 1 of this series.[17] The use of benzyl bromide and Cs_2CO_3 in DMF gave quantitative conversion to benzyl ester (*R*)-**9**, which was isolated as a viscous oil with >98 A% purity.[18]

3. Carbonylation of Chloropyrimidine (*R*)-9. In order to generate the Dieckmann diester substrate (*R*)-**10**, the carbonylative esterification of the chloropyrimidine group of (*R*)-**9** was performed using $Pd(OAc)_2$/dppp and K_2CO_3 in 3:1 *i*-PrOH/THF at ~55 °C with 55 psi carbon monoxide.[19] Early findings revealed that thorough degassing to remove oxygen and efficient stirring were the two key factors that affected the yield of this reaction.[20] In a representative experiment (1.2 kg (*R*)-**9**, ~50 psi CO, 50 °C), the in-process control (IPC) by HPLC after 14 h indicated ~75% conversion to diester (*R*)-**10** with significant (~40 psi) gas uptake. Following a single re-pressurization of the reactor with CO (50 psi), the reaction eventually proceeded to completion. The reaction was filtered over a pad of silica gel to remove the Pd catalyst, oxidized ligand, and inorganic salts, affording the crude diester (*R*)-**10** (~1.3 kg, 95 A%). Several batches of benzyl ester (*R*)-**9** were processed under identical reaction conditions to produce a total of 9.3 kg of crude diester (*R*)-**10** with 98 A% purity in near-quantitative conversion.

4. Telescoped Dieckmann Cyclization and Decarboxylation Reactions. The key step in the synthesis of ketone (*R*)-**12** is the Dieckmann cyclization of diester (*R*)-**10**, followed by decarboxylation (eq 2). Although this two-step process was

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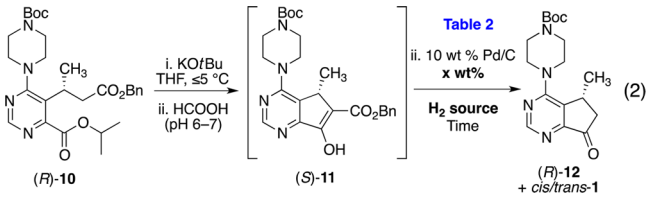

first demonstrated in the preparation of *rac*-**12** and proceeded in 91% yield with >99 A% purity, the original procedure was found to be problematic upon scale-up. The Dieckmann cyclization reaction, promoted by potassium *tert*-butoxide base, proceeded uneventfully to afford the β-keto ester intermediate (*S*)-**11**; however, decarboxylation of the benzyl ester group was much more challenging.[21] The main competing side reaction was over-reduction of the ketone group in compound **12** to the corresponding hydroxyl derivative **1**, where the undesired *cis*-diastereomer was favored as the major byproduct (up to ~17:1 *cis/trans*).[22] This undesired pathway proved to be difficult to control as the scale of the reaction was increased. The over-reduction product was less pronounced when Pd/alumina was used as catalyst, and this reaction typically gave ≤5 A% compound **1** (Table 2, entry 1). Unfortunately, the reduced reactivity of this catalyst often led to incomplete decarboxylation and low yields of ketone (*R*)-**12**. Conversely, the more active Pd/C catalyst successfully facilitated complete decarboxylation but resulted in more over-reduction product that favored *cis*-**1** (Table 2, entry 2).[23] Various sources of hydrogen were examined with the Pd/C catalyst system, including ammonium formate, methyl cyclohexadiene, and formic acid, the latter of which proved to be superior with respect to product yield (Table 2, entries 2–4). For the development and scale-up of this part of the telescoped reaction, the Pd/C catalyst was used, as it was deemed more important to achieve complete decarboxylation than to suppress over-reduction. This preference was a result of the difficulties experienced in the purification of *trans*-**1** with unreacted starting material present. However, under stress conditions, the hydrogenation could result in complete over-reduction to the alcohol product, as observed when using 50 wt% of 5% Pd/C catalyst over 30 h (Table 2, entry 6). Thus, it was important to carefully monitor the decarboxylation and stop the hydrogenation reaction as soon as intermediate (*S*)-**11** was consumed.

In addition to the catalyst, the solvent also played an important role in minimizing the formation of compound **1**. On the laboratory scale, use of THF in the Dieckmann cyclization and subsequent use of MeOH for the decarboxylation (formic acid, 10 wt% Pd/C) resulted in complete consumption of intermediate (*S*)-**11** after ~4 h, where 18% of the over-reduced product **1** was observed (Table 2, entry 7). When 2-MeTHF was employed for both the Dieckmann cyclization and the decarboxylation under otherwise similar reaction conditions, the decarboxylation reaction was complete in ~3 h, and the crude product ketone (*R*)-**12** was isolated in 73% yield containing only 3% of over-reduced compound **1** (Table 2, entry 8). Unfortunately, further scale-up (8 kg) of the two-step reaction sequence in 2-MeTHF as solvent still resulted in 15% compound **1** (Table 2, entry 9) in the crude ketone product (*R*)-**12** after isolation. The higher level of over-reduced product formed on larger scale was attributed to the difficulty experienced in terminating the hydrogenation after the decarboxylation was deemed complete.[24] Although we planned to address the over-reduction issue before any future scale-up of ketone (*R*)-**12** using this route, the presence of the alcohol mixture of **1** did not interfere with the next step (Noyori asymmetric ketone reduction), and the crude ketone could be used without further purification. Overall, starting with 5 kg of DHP (*R*)-**5**, a total of 5 kg crude ketone (*R*)-**12** (85 A%, containing 14:1 *cis/trans*-**1**) was produced in 54% isolated yield.

5. Noyori Asymmetric Transfer Hydrogenation of Ketone (*R*)-12. Reduction of the ketone group in (*R*)-**12** in the presence of a *non-chiral* catalyst is intrinsically *cis*-selective. For example, as illustrated in Table 2 (entry 6), transfer hydrogenation of (*R*)-**12** with Pd/C gave 88% de in favor of *cis*-**1**.[25] As was first exemplified in the medicinal chemistry route, to access the desired *trans* diastereomer, use of a chiral catalyst is necessary (Scheme 3).[26] In that report, transfer hydrogenation of ketone (*R*)-**12** with Noyori's [(*R*,*R*)-TsDPEN–Ru(*p*-cymene)Cl][27] catalyst gave *trans*-**1** in up to 91% de. These results were obtained using 0.01 equiv of catalyst loading with 1.2 equiv of HCOOH and 1.0 equiv of of Et_3N as the source of hydrogen in DCM.[28] Since our ketone substrate (*R*)-**12** obtained from the Dieckmann cyclization–decarboxylation chemistry already contained over-reduced alcohol **1**, we decided to retain the Noyori catalyst system in order to satisfy the tight timelines associated with this program.[29] Purification

Table 2. Conditions for Decarboxylation of β-Keto Ester (*S*)-11 to Crude Ketone (*R*)-12 (See Eq 2)

entry	scale (*R*)-**10** (g)	catalyst	source of H_2	time (h)	(yield); HPLC purity[a] of (*R*)-**12**	*cis/trans*-**1** (A%) in crude (*R*)-**12**[a]
1	20	2 wt% Pd/alumina	40 psi H_2	72	5 g (40%); 91.6 A%	4
2	17	10% Pd/C (10 wt%)	5% ammonium formate in *i*-PrOH (5 vol)	6	3.0 g (28%); 51.1 A%	11
3	17	10% Pd/C (10 wt%)	10 equiv of methylcyclohexadiene in *i*-PrOH (5 vol)	5	3.4 g (32%); 99.8 A%	nd
4	17	10% Pd/C (10 wt%)	5% HCOOH in *i*-PrOH (5 vol)	4	4.4 g (41%); 99.8 A%	nd
5	25	5% Pd/C (20 wt%)	5% HCOOH in MeOH (5 vol)	2	7.7 g (49%); 99.5 A%	nd
6	50	5% Pd/C (50 wt%)	5% HCOOH in MeOH (5 vol)	30	none isolated	20 g of **1** (63%); 94:6 *cis/trans*
7	470	10% Pd/C (10 wt%)	5% HCOOH in MeOH (5 vol)	4	360 g crude; 54.6 A%	18% (17:1 *cis/trans*)
8	110[b]	10% Pd/C (15 wt%)	5% HCOOH in 2-MeTHF (5 vol)	3	50 g crude (70%); 97.6 A%	3% (2:1 *cis/trans*)
9	8125[b]	10% Pd/C (15 wt%)	5% HCOOH in 2-MeTHF (5 vol)	4	5040 g crude (84%); 85.3 A%	15% (14:1 *cis/trans*)

[a]Measured by HPLC: ACE-3-C18, 4.6 × 150 mm, 3 μm; mobile phase A = 20 mM ammonium formate, pH 3.7; mobile phase B = MeOH; Gradient = 30–80% B (0–15 min), 80–90% B (15–16 min), 90–30% B (16–16.1 min), 30% B (16.1–20 min); flow rate = 0.8 mL/min; column temp = 30 °C; inj vol = 10 μL; detector wavelength = 280 nm; approximate RRT of *cis*-**1** = 0.94 and RRT of *trans*-**1** = 0.97. nd = not determined. [b]In these experiments, 2-MeTHF was used in place of THF for the Dieckmann cyclization.

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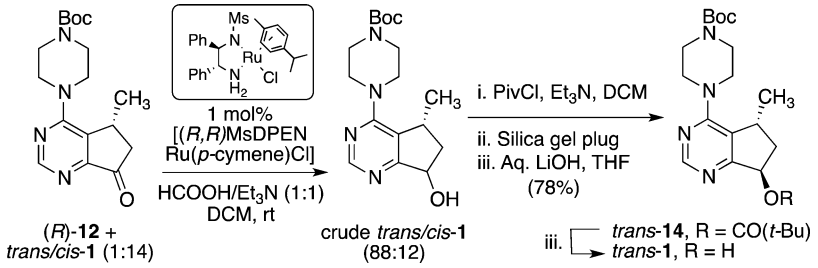
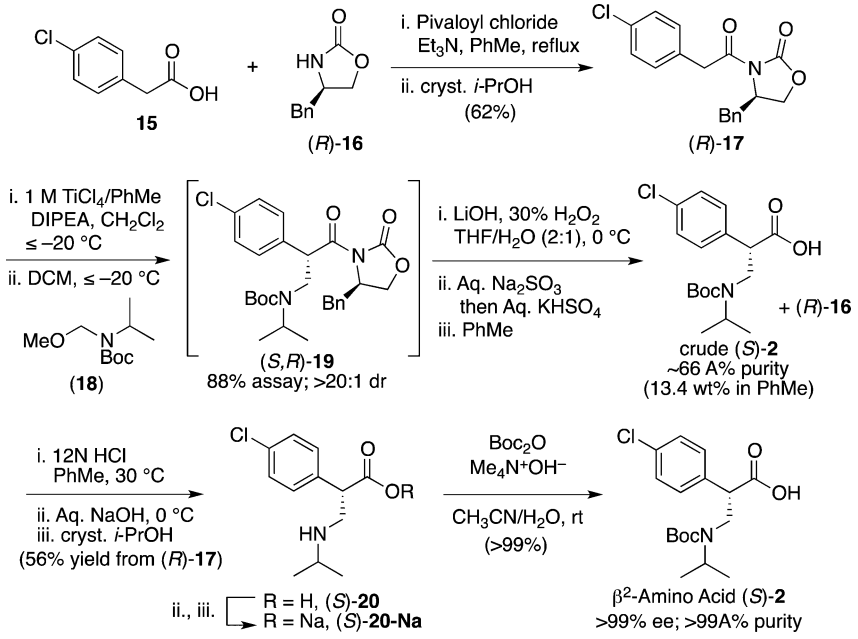
Scheme 3. Asymmetric Ketone Reduction, Derivatization, and Hydrolysis to *trans*-1



Scheme 4. Scale-up of the Chiral Auxiliary Route to β^2-Amino Acid (*S*)-2



of *trans*-**1** following the asymmetric transfer hydrogenation was implemented in order to reduce the levels of *cis*-**1** diastereomer to meet the desired specification (≤2 A%) for this intermediate.

In the production effort, the transfer hydrogenation of crude ketone (*R*)-**12** containing 15% of **1** (5.04 kg, 85 A%) was divided into three batches of ∼1.7 kg each. A DCM solution of the crude ketone mixture was charged with 1 mol% [(*R*,*R*)-MsDPEN−Ru(*p*-cymene)Cl] catalyst [S/C = 263:1] and HCO_2H/Et_3N (1.2:1.0)[30] and resulted in complete carbonyl reduction after 20 h at room temperature. For each batch, crude **1** (1.7 kg) was isolated by concentration under reduced pressure to an oil−solid matrix as a mixture of *trans*/*cis* diastereomers (76% de) by HPLC (Scheme 3).

The purification of the crude *trans*-**1** mixture ultimately required separation of the two diastereomers; however, crystallization was not efficient when *trans*-**1** was <95% de.[31] As a result, the hydroxyl group of **1** was acylated in order to provide a less polar compound that could be separated efficiently using silica gel chromatography. Additional research revealed that the pivalate ester derivative afforded the best separation of the corresponding diastereomers in comparison to the *p*-nitrobenzoate and acetate derivatives.[32] Therefore, the crude alcohol mixture was initially derivatized with pivaloyl chloride, after which the diastereomers were separated by silica gel chromatography to provide a total of 5.37 kg of ester *trans*-**14** with 98 A% purity.[33] Hydrolysis of the ester in *trans*-**14** gave a total of 3.8 kg *trans*-**1** (98.9% de, >99.9% ee, 98.2 A%).[34] In summary, *trans*-**1** was obtained in 48% overall yield from 5.0 kg DHP (*R*)-**5** in nine chemical steps, providing the first of two starting materials for the convergent synthesis of Ipatasertib.

6. Preparation of β^2-Amino Acid (*S*)-2. The scale-up process to access β^2-amino acid (*S*)-**2** using Evans's chiral auxiliary is illustrated in Scheme 4.[35] For preparation of acyl oxazolidinone derivative (*R*)-**17**,[36] the carboxylic acid **15** was activated via the mixed anhydride method with pivaloyl chloride. High conversion of product was achieved by the portionwise addition of the acid chloride reagent to a mixture of the carboxylic acid, chiral auxiliary, and Et_3N followed by heating to reflux. In the pilot plant, the coupling of 4-chlorophenylacetic acid **15** (17.4 kg) and (*R*)-4-benzyloxazolidin-2-one **16** proceeded to ∼92% conversion, and product (*R*)-**17** (17.4 kg) was isolated in 62% yield with 92.5 A% purity by HPLC. The subsequent asymmetric aminoalkylation reaction was performed using a protocol similar to that reported by Evans and co-workers, excepting modifications to the reaction temperature and concentration.[37] Specifically, good conversion and diastereoselectivity were achieved at a higher reaction temperature (−20 vs −78 °C) and increased concentration (21 vs 30 vol), effectively improving the convenience of the process. In the process, a DCM solution of acyl auxiliary (*R*)-**17** (17.4 kg) was initially treated with 1 M $TiCl_4$ in toluene at −20 °C, resulting in the bright red-orange titanium complex typically reported. Addition of DIPEA then led to the characteristic dark purple titanium enolate species,

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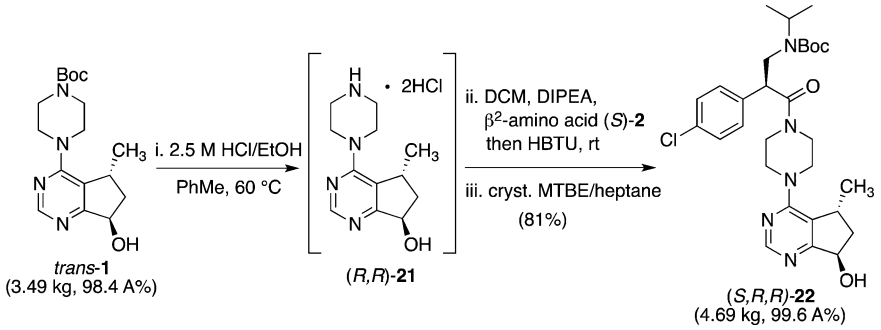
Scheme 5. Telescoped One-Pot Synthesis of Boc-API (*S,R,R*)-22



which was subsequently treated with *N*-Boc aminal **18**. Importantly, the slow addition of **18** and maintaining the internal temperature ≤ -20 °C were essential for good diastereoselectivity, and in-process HPLC analysis indicated complete consumption of (*R*)-**17** after 4 h.[38] Following aqueous work-up and solvent exchange into THF, the alkylation product (*S,R*)-**19** was produced in >20:1 dr. Hydrolysis of the auxiliary group was achieved by addition of lithium hydrogen peroxide, and the reaction was complete after ~3 h. After acidic aqueous work-up followed by extraction of the product into toluene, a solution of crude-**2** with ~66 A% purity was obtained.[39]

Attempts to purify crude (*S*)-**2** through the extractive removal of the oxazolidinone auxiliary and other reaction byproducts from the basic aqueous media resulted in significant product loss. Alternatively, a purification strategy relying on the Boc-deprotection of the amino group in crude (*S*)-**2** to form a highly aqueous-soluble amino acid sodium salt and subsequent extraction of the organic impurities was successful. A solution of crude (*S*)-**2** was treated with 12 N HCl to give the corresponding deprotected product (*S*)-**20**. After toluene extraction, the acidic aqueous layer was adjusted to pH 9 with aqueous NaOH resulting in the precipitation of product. The filtered solids were dried to give (*S*)-**20-Na** (7.65 kg, 60% yield, 99.5 A%, 97.8% ee). Since the product contained 1.1% of (*R*)-**2**, a recrystallization was required in order to avoid formation of diastereomers in the downstream chemistry during the coupling with *trans*-**1**. Recrystallization of (*S*)-**20-Na** from 2-propanol provided the product (*S*)-**20-Na** (6.85 kg, 99.7% ee, and 99.9 A%) in 56% overall yield from (*R*)-**17**.[40] A final Boc-reprotection of (*S*)-**20-Na** followed by precipitation from MTBE/heptane with continuous sparging of nitrogen resulted in 99% isolated yield of β^2-amino acid (*S*)-**2**.[41] The overall process produced a total of 8.9 kg of (*S*)-**2** in >99.9% ee and >99.9 A% purity as a free-flowing solid that would be used in the kilogram-scale synthesis of Ipatasertib.

7. First-Generation Process Route to Ipatasertib Mono-HCl. With *trans*-**1** and β^2-amino acid (*S*)-**2** in hand, it remained to first couple these key chiral components to produce the penultimate Boc-API (*S,R,R*)-**22**, and then to convert this compound into Ipatasertib mono-HCl. In the first step of the process, removal of the *N*-Boc protecting group in *trans*-**1** could be accomplished using either aqueous HCl, or HCl in EtOH along with toluene as co-solvent at elevated temperatures. Both reaction conditions required ≥3 equiv of the HCl in order to obtain complete deprotection to the piperazine (*R,R*)-**21**. In our early process chemistry batches, the piperazine (*R,R*)-**21** di-HCl salt was generated using 12 N HCl and was isolated as a solid by co-evaporation with toluene and concentration to dryness via rotary evaporation.[42] Unfortunately, the solid product was extremely hygroscopic and difficult to handle outside of an inert environment, and as a result we focused our development efforts on a telescoped process to the Boc-API (*S,R,R*)-**22** where piperazine (*R,R*)-**21** was not isolated. By using HCl in EtOH in the deprotection step, the concentrated mixture at the end of the reaction was found to be acceptable to carry forward into the coupling reaction. The same coupling protocol that we initially developed for the two-step reaction sequence involving HBTU, DIPEA, and DCM was shown to be equally effective in the one-pot process. Using the HBTU reagent resulted in complete conversion in the coupling reaction with no detectable epimerization of the β-amino acid moiety, thus other coupling reagents were not thoroughly investigated at this stage of the project.

On scale-up of the one-pot process to Boc-API (*S,R,R*)-**22**, deprotection of *trans*-**1** (3.49 kg) using 3 equiv of 2.5 M HCl in EtOH and toluene as co-solvent resulted in complete consumption of starting material after ~1 h at 60 °C (Scheme 5). Distillation and a co-evaporation with toluene afforded a suspension of (*R,R*)-**21** di-HCl that was then diluted with DCM and charged with excess DIPEA to give dissolution of the salt mixture. Next, addition of a DCM solution of β-amino acid (*S*)-**2** (1 equiv) followed by the HBTU reagent at room temperature resulted in complete consumption of starting material (*S*)-**2** after ~3 h.

The aqueous work-up and purification of the (*S,R,R*)-**22** intermediate was critical in controlling the final purity of Ipatasertib, which was not crystalline in either the free-base or various salt forms. Unexpectedly, the most difficult impurities to remove were found to originate from the HBTU coupling reagent itself that produced stoichiometric amounts of tetramethylurea (TMU) and hexafluorophosphate anion (PF_6^-).[43] Washing the organic reaction mixture sequentially with saturated aqueous $NaHCO_3$ and saturated aqueous NH_4Cl effectively removed the HOBt from the organic phase; however, these washes were ineffective in removing the TMU and the PF_6 anion.[44] We found that replacing DCM with isopropyl acetate (IPAc) and washing with copious amounts of water allowed for complete removal of TMU from the crude Boc-API (*S,R,R*)-**22**. The PF_6 anion in turn required the use of a basic aqueous solution, and dilute aqueous NH_4OH was found to be the most efficient for coordinating and extracting the anion.[45] Having successfully removed the HBTU and PF_6-related impurities, the crystallization of crude Boc-API (*S,R,R*)-**22** could be performed; however, due to the high solubility of (*S,R,R*)-**22** in IPAc, an efficient crystallization from this solvent could not be developed. Alternatively, a seeded crystallization

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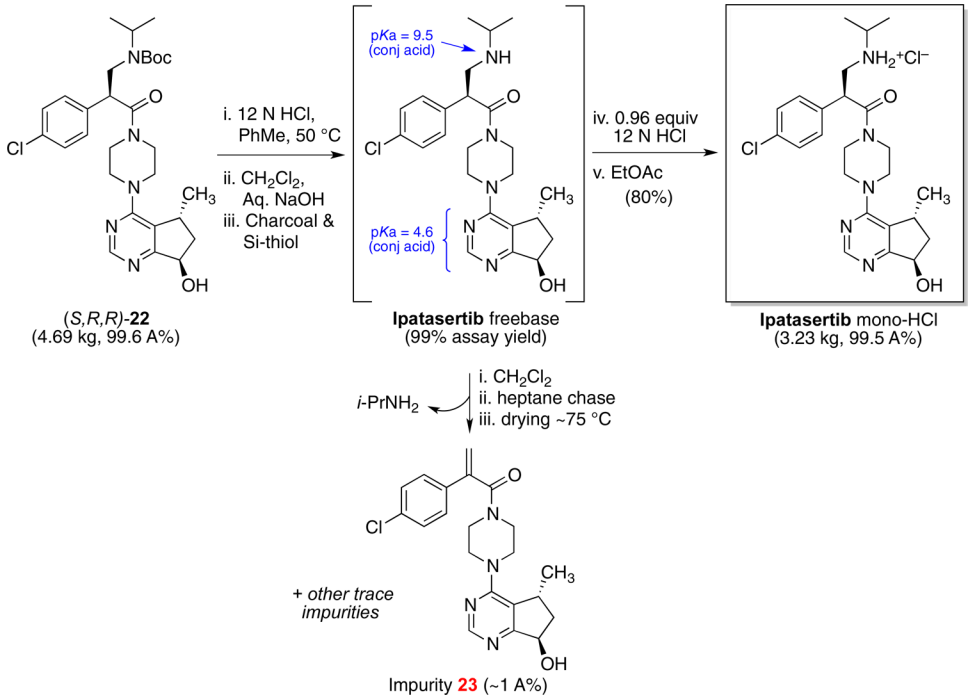
Scheme 6. Preparation of Ipatasertib Mono-HCl Salt from Boc-API (*S,R,R*)-22



from MTBE/heptane gave the best results where 5.06 kg of the amide product was produced in 81% yield with 99.6 A% purity.

What remained at this stage was cleavage of the *N*-Boc group in (*S,R,R*)-**22** and subsequent formation of Ipatasertib mono-HCl. In our early-stage development work, we found that the Boc-group deprotection also required ≥3 equiv of HCl (similar to the deprotection of *trans*-**1**) and resulted in Ipatasertib di-HCl upon isolation. This behavior is attributed to the two basic sites in the molecule as illustrated by the two pK_a values shown in Scheme 6. Since this di-HCl salt was hygroscopic, non-crystalline, and difficult to isolate, it was not suitable for formulation development. In contrast, we also attempted to isolate the less-hygroscopic free-base form of the API by way of concentration of the DCM solution under reduced pressure followed by drying at elevated temperatures (≤75 °C) to remove residual solvents. In this approach, we unexpectedly observed the formation of a major impurity that was identified as β-elimination product **23**.[46] Noteworthy, both the Boc-API (*S,R,R*)-**22** and Ipatasertib di-HCl compounds did not produce the β-elimination impurity **23** when dried at ∼100 °C for >24 h, which strongly suggested that the isopropyl amino group must be protected or protonated in order to prevent thermal degradation.[47]

Our salt selection strategy initially aimed to take advantage of the higher pK_a of the basic isopropylamino group (pK_a of conjugate acid ∼9.5) that was absent in impurity **23**.[48] This would provide a method to remove the elimination impurity **23** in the event that quantities were formed during the free-base step. In a laboratory demonstration, the free-base API (containing ∼1 A% of **23**) dissolved in DCM, was treated with ≤0.95 equiv of 12 N HCl resulting in a homogeneous biphasic solution. Azeotropic distillation with DCM followed by co-evaporation with EtOAc resulted in white slurry that was easily filtered and was characterized as Ipatasertib mono-HCl. This protocol resulted in complete purging of impurity **23** and provided a thermally stable mono-HCl salt form that could be safely dried at temperatures ≤80 °C over several days without risk of degradation.

On scale-up of the salt formation, the deprotection of Boc-API (*S,R,R*)-**22** (4.69 kg) in toluene with 12 N HCl was complete after ∼1 h. The reaction mixture was diluted with water, and the toluene layer containing any unreacted starting material and other organic impurities was removed. The aqueous layer was then basified to pH ≥ 12 with aqueous NaOH in order to extract the Ipatasertib free-base with DCM. After treatment of the DCM solution with charcoal and SiliaMetS thiol to remove colored impurities and trace heavy metals, filtration over Celite resulted in a 99% assay yield of Ipatasertib free-base. Next, the DCM solution was charged with 0.96 equiv of 12 N HCl, after which azeotropic distillation followed by solvent exchange to EtOAc produced a suspension of Ipatasertib mono-HCl. Filtration and drying of the solids in a filter dryer at ≤70 °C for ∼48 h resulted in Ipatasertib mono-HCl (3.23 kg, 99.5 A%) in 80% yield. The relative and absolute stereochemistry of Ipatasertib mono-HCl were successfully confirmed by single-crystal X-ray analysis (Figure 2).

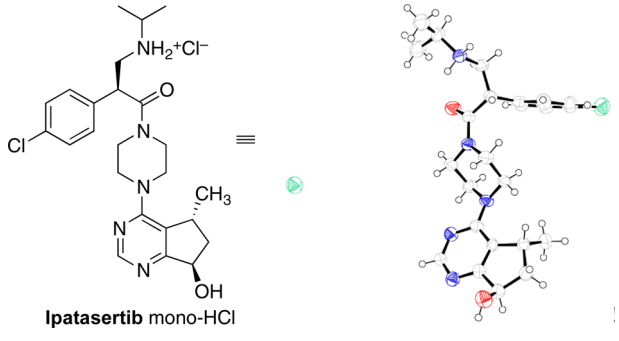


Figure 2. X-ray single-crystal structure of Ipatasertib mono-HCl.

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CONCLUSION

Herein we described the first successful multikilogram-scale convergent synthesis of the Akt inhibitor Ipatasertib mono-HCl. Preparation of a challenging cyclopentyl pyrimidine core *trans*-**1** was accomplished in 10 chemical steps from chiral DHP (*R*)-**5**. A Dieckmann cyclization−decarboxylation sequence was developed to forge the cyclopentyl ketone ring system of (*R*)-**12**, which was followed by an asymmetric transfer hydrogenation with Noyori's Ru-diamine catalyst to produce 3.8 kg of *trans*-**1** with 98.9% de in 48% overall yield. Synthesis of the β^2-amino acid (*S*)-**2** utilized the asymmetric Mannich reaction, where Evans's chiral oxazolidinone auxiliary was employed to set the relevant stereochemistry with >20:1 diastereoselectivity. This subsequently provided our first scale-up batch of β^2-amino acid (*S*)-**2** (8.9 kg) with >99% ee. Following the coupling of the two key components, we identified a crucial process to convert the Boc-API (*S,R,R*)-**22** intermediate into the thermally stable mono-HCl salt form. The new process led to the first successful production of cGMP Ipatasertib mono-HCl (3.23 kg) in high purity, providing drug substance to support the Phase 1 clinical demand.

EXPERIMENTAL SECTION

NMR measurements were carried out on a Bruker Avance 3, 500 MHz spectrometer equipped with a 5 mm, BBO, Z-gradient probe with TMS internal standard. Data for ^{1}H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; h, heptet; dd, doublet of doublet; m, multiplet), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (ppm). Trace metal analysis was performed by Intertek Pharmaceutical services using inductively coupled plasma atomic emission spectroscopy (ICP-AES). Melting points were measured by differential scanning calorimetry (DSC). All reactions were performed under an inert atmosphere. Unless otherwise noted, all chemicals were commercially available and used as received. SiliaMetS thiol (40−63 um, 60 Å) was purchased from Silicycle, and activated carbon was Darco G60, 100 mesh. Palladium acetate, 99.95%, was purchased from Kadai Technology Limited; *N*-Boc-piperazine was prepared at SAI Advantium; 1,3-bis-(diphenylphosphino)propane (dppp), 98%, was purchased from Strem; 4-chlorophenylacetic acid was purchased from Aldrich; and (*R*)-4-benzyl-2-oxazolidinone auxiliary, 99.0% [102029-44-7], was purchased from Jiangxi Kingnord Industrial Ltd. The chiral catalysts [(*R,R*)-MsDPEN−RuCl(*p*-cymene)], and [(*R,R*)-TsDPEN−Ru(*p*-cymene)Cl] were purchased from Johnson Matthey (Catalysis and Chiral Technologies). *O*-Benzotriazole-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU) was purchased from Oakwood Products, Inc. Analytical methods are found in the Supporting Information S1.

(*R*)-Trimethyl 2-Methylpropane-1,1,3-tricarboxylate, 4. An aqueous solution of Na_2HPO_4 (4.5 kg in 184 kg H_2O) with pH adjusted to 7.5 was charged with triester *rac*-**4** (27.6 kg, 119 mol) and *Cromobacterium* strain SC-YM-1 (2.8 kg, 10 wt%) at 0 °C. The reaction mixture was agitated at this temperature and the pH maintained between 7.0−7.6 until the reaction was deemed complete (~19 h) by HPLC (chiral purity: (*R*)-**4** >98% ee). The reaction mixture was charged with MTBE (55 kg) and Radiolite filter aid (0.8 kg), agitated, and then filtered. The organic layer of the filtrate was removed, and the aqueous layer was extracted with MTBE (14 kg) and then filtered. The aqueous was extracted once more with MTBE (14 kg), and then the organics were combined, washed with 5% aqueous $NaHCO_3$ (14 kg), and concentrated under reduced pressure to give triester (*R*)-**4** (12.9 kg, 94% yield, 99.8% ee) as a yellow oil. The crude triester product was used directly in the next step.

(*R*)-Methyl 3-(4,6-Dihydroxypyrimidin-5-yl)butanoate (DHP), 5. A reactor was charged with MeOH (51.6 kg) and formamidine acetate (6.1 kg, 58.7 mol, 1.05 equiv) and cooled to 0 °C with agitation. A 28% NaOMe/MeOH solution (32.2 kg, 167 mol, 3.9 equiv) was added over 1.5 h and then agitated for an additional 1 h. A solution of triester (*R*)-**4** (12.9 kg, 55.6 mol, 1.0 equiv) in MeOH (12.9 kg) was charged and the reaction mixture warmed to 25 °C. After 10 h, the reaction mixture was cooled to 0 °C, neutralized with aqueous HCl, and then concentrated under reduced pressure. The residue was diluted with MeOH, washed with MTBE, and acidified with aqueous HCl. The mixture was warmed to 60 °C, agitated for 1 h, cooled to 0 °C, and then filtered, and the solids were washed with H_2O to give DHP (*R*)-**5** (8.7 kg, 74% yield, 99.6 A%, 99.8% ee (220 nm) and 99.9% ee (254 nm)) as an off-white solid. HRMS calcd for $C_9H_{12}N_2O_4$ $[M+H]^+$ 213.087; found 213.0869. See Supporting Information S2 for the HPLC chromatograms of DHP (*R*)-**5** in Figure S2−2.6.

(*R*)-Methyl 3-(4,6-Dichloropyrimidin-5-yl)butanoate (DCP), 6.[3] A 50 gallon reactor was charged with DHP (*R*)-**5** (5.0 kg, 23.6 mol [99.8% ee, 99.6 A%; KF = 0.2% H_2O]), toluene (20 L), and 2,6-lutidine (2.7 L, 23.6 mol, 1 equiv) with agitation at room temperature. The mixture (white slurry) was warmed to 50 °C, and phosphorous oxychloride ($POCl_3$) (4.85 L, 53.02 mol) was added slowly over 1 h. The first quarter of $POCl_3$ added resulted in a gum-like residue and was exothermic (50 to 85 °C) for the first half of the addition. Upon compete addition of $POCl_3$, a clear brown solution was formed, and good agitation was possible. The reaction temperature was maintained at 70 °C for 24 h. IPC of the reaction mixture by TLC analysis (1:1 EtOAc/heptane) [R_f (*R*)-**6**) = 0.6, R_f (*R*)-**5**) = 0.1] indicated complete consumption of starting material. The reaction mixture was cooled to 0 °C and slowly charged with 20% aqueous NaOH (5.5 kg/28 L H_2O) [***Caution: Exothermic!***] until a final pH ~5.5 was achieved. The internal temperature during the addition was maintained at ≤30 °C. EtOAc (13 L, 2.5 vol) was charged to the mixture, which was then stirred for 30 min and filtered over Celite, and then the filter was rinsed with EtOAc (2 × 5 L). The organic layer was removed, and the aqueous layer was extracted with EtOAc (3 × 12 L). The combined organics were washed with saturated aqueous NH_4Cl (3 × 12 L) and brine (12 L), dried ($MgSO_4$), filtered through a glass fiber filter, and then concentrated under reduced pressure to give crude DCP (*R*)-**6** (5.63 kg, ~95 wt%, 98.7 A%) as a brown oil. HRMS calcd for $C_9H_{10}Cl_2N_2O_2$ $[M+H]^+$ 249.0192; found: 249.0190. Crystals formed upon standing overnight, and the crude product (contains residual 2,6-lutidine) was used directly in the next step. Note: approximately 0.4 A% of the monochlorination adduct was observed in the isolated product as determined by LCMS (M +H = 231 amu). See Supporting Information S2 for the ^{1}H NMR spectrum of DCP (*R*)-**6** (Figure S2−3.1) and HPLC chromatogram in Figure S2−3.2.

(*R*)-*tert*-Butyl 4-(6-Chloro-5-(4-methoxy-4-oxobutan-2-yl)pyrimidin-4-yl)piperazine-1-carboxylate, 7. A 50 gallon reactor was charged with Boc-piperazine (4.63 kg,

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24.84 mol, 1.1 equiv) and MeOH (20 L. 3.6 vol) with agitation at room temperature until the solids dissolved. A solution of DCP (*R*)-**6** (5.63 kg, 22.58 mol, 1.0 equiv) in MeOH (15 L, 2.7 vol) and then DIPEA (4.34 L, 24.84 mol, 1.1 equiv) were charged to reaction mixture and warmed to 50 °C. Analysis by TLC (1:1 EtOAc/heptane) [R_f (*R*)-**7** = 0.4, R_f (*R*)-**6** = 0.6] indicated complete consumption of starting material after 4 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to a light brown residue. The residue was dissolved in EtOAc (50 L), washed with saturated NH_4Cl (2 × 20 L) and brine (20 L), dried (Mg_2SO_4), filtered, and concentrated to give crude (*R*)-**7** (8.68 kg, 96% yield, 97.4 A%) as a brown viscous oil. HRMS calcd for $C_{18}H_{27}ClN_4O_4$ $[M+H]^+$ 399.1793; found 399.1784. The crude product was used directly in the next step.

(*R*)-3-(4-(4-(*tert*-Butoxycarbonyl)piperazin-1-yl)-6-chloropyrimidin-5-yl)butanoic Acid, 8. A 50 gallon reactor was charged with a solution of (*R*)-**7** (8.63 kg, 21.62 mol) in THF (36.5 L) with agitation at room temperature. A solution of $LiOH·H_2O$ (2.72 kg, 64.87 mol, 3 equiv) dissolved in H_2O (19 L) was charged and the mixture agitated at room temperature overnight. Analysis by TLC (1:1 EtOAc/heptane) [R_f (*R*)-**8** = 0.1, R_f (*R*)-**7** = 0.4] indicated complete consumption of starting material after 15 h. The reaction mixture was cooled to 0 °C and then slowly charged with 6 N HCl (11.5 L, 1.3 vol) over 1 h to achieve pH 2−3 while maintaining the internal temperature ≤20 °C. The mixture was charged with EtOAc (35 L) and stirred vigorously for 30 min, and then the layers were separated. The aqueous layer was extracted with EtOAc (3 × 35 L), and the organics were combined, washed with saturated NH_4Cl (2 × 45 L) and brine (40 L), dried over Mg_2SO_4, filtered, and then concentrated to a light pink solid. The solids were slurried in MTBE (15 L), agitated for 3−4 h at room temperature, and filtered, and the wet cake was washed with MTBE (2 × 5 L). The solids were dried under vacuum at 30 °C to give carboxylic acid (*R*)-**8** (1st crop: 6.0 kg, 72.1% yield, 98.6 A%).

A second crop of product was obtained by concentration of the filtrates under reduced pressure to a yellow residue followed by addition of a solution of 10:1 MTBE/DCM (2.2 L) with agitation at room temperature overnight. The precipitated solids were filtered and washed with MTBE (2 × 0.5 L), the filtrate was concentrated again, and the process was repeated using 10:1 MTBE/DCM (1.1 L) and MTBE wash (3 × 0.4 L). The solids were combined and dried under vacuum at 30 °C to give a second crop of carboxylic acid (*R*)-**8** (2nd crop: 0.88 kg, 10.5% yield, 96.6 A%); HRMS calcd for $C_{17}H_{25}ClN_2O_2$ $[M+H]^+$ 385.1637; found: 385.1631. See Supporting Information S2 for the ^1H NMR spectrum ($CDCl_3$) of carboxylic acid (*R*)-**8** (1st crop) in Figure S2−3.5 and the HPLC chromatogram (270 nm) of the second crop in Figure S2−3.6.

(*R*)-*tert*-Butyl 4-(5-(4-(Benzyloxy)-4-oxobutan-2-yl)-6-chloropyrimidin-4-yl)piperazine-1-carboxylate, 9. A 22 L, three-neck round-bottom flask equipped with a mechanical stirrer was charged with carboxylic acid (*R*)-**8** (2.75 kg, 7.15 mol, 1.0 equiv), DMF (13.0 L), and benzyl bromide (1.28 kg, 7.50 mol, 1.05 equiv) with agitation at room temperature.[49] The solution was charged with Cs_2CO_3 (2.45 kg, 7.50 mol, 1.05 equiv) in three portions at a rate to maintain the internal temperature <40 °C (exotherm observed from 20 to 35 °C). Analysis by TLC (1:1 EtOAc/heptane) [R_f (*R*)-**9** = 0.4, R_f (*R*)-**8** = 0.2] indicated complete consumption of starting material after 15 h. The mixture was filtered over a pad of Celite 545 (1 kg) and washed with EtOAc (3 × 2 L). The filtrate was diluted with EtOAc (12 L) and washed with saturated aqueous NH_4Cl (8 L), and the aqueous part was then extracted with EtOAc (3 × 6 L). The combined organics were washed with saturated aqueous NH_4Cl (2 × 8 L) and brine (10 L), dried over Mg_2SO_4, filtered, and concentrated under reduced pressure to give benzyl ester (*R*)-**9** (3.42 kg, 98.6 A%, >theoretical yield) as a viscous brown oil. Four batches of compound (*R*)-**8** (7.27 kg total) were processed to give a total of 9.06 kg benzyl ester (*R*)-**9**. See Supporting Information S2 for a representative ^1H NMR spectrum ($CDCl_3$) of benzyl ester (*R*)-**9** in Figure S2−3.7, and HPLC chromatogram (270 nm) in Figure S2−3.8.

(*R*)-Isopropyl 5-(4-(Benzyloxy)-4-oxobutan-2-yl)-6-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)pyrimidine-4-carboxylate, 10. [***Caution:*** *Carbon monoxide gas (CO) is poisonous! A CO detector must be used and the reaction performed in a well ventilated hood. All equipment and connections were leak-tested with nitrogen gas and soap solution before use.*] A 5-gallon autoclave was charged with crude benzyl ester (*R*)-**9** (1.71 kg, 3.60 mol), THF (4.0 L), and 2-propanol (6.0 L) with agitation at room temperature. The solution was sparged with nitrogen, and the vessel was pressurized (25 psi) five times with heating to 35−40 °C. The mixture was then charged with a slurry of $Pd(OAc)_2$ (0.081 kg, 0.36 mol, 0.10 equiv) and dppp (0.163 kg, 0.40 mol, 0.11 equiv) in 2-propanol (2.0 L) and warmed to 40−45 °C with good agitation. The autoclave was pressurized and evacuated with 2 × 25 psi N_2, stirred for 20 min 40−45 °C to dissolve the rust-red solids, and then charged with a slurry of K_2CO_3, 325 mesh (0.299 kg, 2.16 mol, 0.6 equiv) in 2-propanol (2.0 L). The autoclave was pressurized, evacuated with 5 × 25 psi N_2 and carbon monoxide (CO) gas 5 × 40 psi, and then pressurized to 55 psi. The reaction mixture was agitated at 50 °C and maintained at 55 psi CO for ≥50 h. The reaction was analyzed by TLC and HPLC and sampled by slow evacuation of CO gas and sparging with N_2 5 × 25 psi. Analysis by TLC (1:1 EtOAc/heptane) [R_f (*R*)-**10** = 0.5, R_f (*R*)-**9** = 0.4] and HPLC [R_f (*R*)-**10**) = 12.10 min, R_f (*R*)-**9** = 12.67 min] indicated complete consumption of starting material after 50 h. The reaction mixture was cooled to room temperature, charged with silica gel (0.4 kg) and Celite 545 (0.4 kg), and then agitated for 2 h. The mixture was filtered over silica gel (1.0 kg) and washed with EtOAc (4−5 L) until product was no longer observed in the filtrate. The filtrates were concentrated under reduced pressure (bath temp ∼45 °C) to give diester (*R*)-**10** (1.9 kg, >100% yield; contains residual solvents and dppp ligand) as a viscous dark brown oil. A total of six batches of benzyl ester (*R*)-**9** were processed to produce 10 kg crude diester (*R*)-**10** (see Supporting Information for the lot summary information).

For the purification of diester (*R*)-**10**, six batches of diester (*R*)-**10** were combined, dissolved in a total of 18 L MTBE, and then slurried with silica gel (3 kg) with agitation for 1 h. This slurry was charged in a 2-L sintered funnel and rinsed with EtOAc. The mixture was filtered through a pad of silica gel and washed with MTBE (∼10 L). The filtrate was concentrated under reduced pressure to give pure diester (*R*)-**10** (9.3 kg, 92.8%, 97.7 A%) as viscous dark yellow oil. Note: Plug filtration over a pad of silica gel removes dppp[O] that can otherwise interfere with the ruthenium catalyzed asymmetric ketone reduction. See Supporting Information S2 for the ^1H NMR spectrum ($CDCl_3$) of diester (*R*)-**10** in Figure S2−3.9, and HPLC chromatogram (270 nm) in Figure S2−3.10.

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(*R*)-*tert*-Butyl 4-(5-Methyl-7-oxo-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazine-1-carboxylate, 12. A reactor was charged with diester (*R*)-**10** (8.13 kg, 15.4 mol), 2-MeTHF (82 L, 10 vol), sparged with nitrogen (20 min), and cooled to 0 °C with agitation. Under an inert atmosphere, potassium *tert*-butoxide (1.91 kg, 17.0 mol, 1.1 equiv) was charged slowly (exothermic) in two portions to the solution of the diester while maintaining the internal temperature ≤5 °C. IPC by TLC analysis (1:1 EtOAc/heptane) [R_f (*S*)-**11** = 0.1, R_f (*R*)-**10** = 0.5] indicated complete consumption of starting material after 30 min. The reaction mixture was cooled to −5 to 0 °C, and formic acid, 98% (1.1 kg, 23.1 mol, 1.5 equiv), was charged at a rate to maintain internal temperature <5 °C and obtain a final pH 6−7, resulting in a yellow slurry. A separate vessel was charged with 10 wt% Pd/C [50% wet] (1.2 kg, 15 wt%) and 5% formic acid (2.1 L) in 2-MeTHF (20 L), which was then transferred to the reaction mixture of intermediate (*S*)-**11** at a rate to maintain the internal temperature <10 °C. The vessel was rinsed with 2-MeTHF (20 L), and then the reaction mixture was slowly warmed to ∼20 °C over 1 h. The reaction was monitored by TLC analysis (9:1 EtOAc/MeOH) [R_f (*R*)-**10** = 0.4, R_f (*S*)-**11** = 0.1, R_f (*R*)-**12** = 0.3], which indicated complete consumption of starting material (**11**) and formation of the over-reduced alcohol **1**. The reaction mixture was slowly quenched with saturated aqueous $NaHCO_3$ (60 L) at a rate to maintain minimum foaming. The reaction mixture was filtered over Celite 545 (4 kg) and rinsed with 2-MeTHF (50 L). The filtrate was extracted with EtOAc (50 L), and the organics were washed with saturated aqueous $NaHCO_3$ (2 × 60 L). The combined aqueous part (∼120 L) was extracted with EtOAc (100 L), and the organics were combined and then washed with brine (100 L). The agitated organics were charged with charcoal (3 kg, 35 wt%) and Mg_2SO_4 (7.5 kg, 90 wt%). The mixture was filtered and the solution concentrated under reduced pressure at <45 °C to a minimum stir volume. The mixture was charged with CH_2Cl_2[50] (25 L), filtered, and concentrated to give crude-(*R*)-**12** (5.04 kg, 85 A% containing approximately 14:1 *trans*/*cis*-**1** by HPLC) as a light brown semi-solid. See Supporting Information S2 for the ^{1}H NMR spectrum ($CDCl_3$) of crude ketone (*R*)-**12** in Figure S2−3.11, HPLC chromatogram (280 nm) in Figure S2−3.12, and for the ^{1}H and ^{13}C NMR spectra ($CDCl_3$) of *β*-keto ester intermediate (*S*)-**11** in Figure S2−3.22A and Figure S2−3.22B, respectively.

Preparation of *tert*-Butyl 4-((5*R*,7*R*)-7-Hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)-piperazine-1-carboxylate, Crude-1. A 50 L reactor was charged with crude (*R*)-**12** (1.43 kg, 4.31 mol by assay, 1.68 kg crude weight) and DCM (25 L), and then the agitated solution was sparged with nitrogen ∼30 min. Triethylamine (0.60 L, 4.33 mol, 1.0 equiv) was added in one portion, followed by slow addition of formic acid (0.91 L, 5.05 mol, 1.2 equiv) over 15 min. [***Caution:*** *Addition of formic acid is exothermic and fumes!*] The reaction mixture was sparged with nitrogen, charged with [(*R*,*R*)-MsDPEN−RuCl(*p*-cymene)] catalyst **13** (19.2 g, 0.04 mol, 0.01 equiv; [S/C = 263:1]), and then agitated at room temperature overnight. The reaction was monitored by HPLC [R_t (*trans*-**1**) = 13.72 min, R_t (*cis*-**1**) = 14.06 min, R_t ((*R*)-**12**) = 14.58 min] and found to be complete after consumption of starting material (20 h). The reaction mixture was concentrated under reduced pressure at ≤45 °C to give crude-**1** (1.7 kg) as a dark brown oil−solid. Two additional batches of crude ketone (*R*)-**12** (1.43 kg) were processed under identical conditions to give a total of ∼5.1 kg of crude-**1** containing an 88:12 *trans*/*cis* mixture of diastereomers.[51]

Derivatization of Crude-1 and Purification of Pivalate Ester *trans*-14. A 50 L reactor containing a solution of crude-**1** (2.5 kg, 7.5 mol) in CH_2Cl_2 (25 L) was charged with pivaloyl chloride (0.99 kg, 8.22 mol, 1.1 equiv) followed by DIPEA (1.16 kg, 8.97 mol, 1.2 equiv) at room temperature. [***Caution:*** *Exothermic!*] The reaction was monitored by TLC analysis (9:1 EtOAc/MeOH) R_f (*trans*-**14**) = 0.8, R_f (*trans*-**1**) = 0.2, indicated complete consumption of starting material (*trans*-**1**) after 2 h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (12 L), and the layers were separated. The aqueous was extracted with CH_2Cl_2 (2 × 2 L), and then the combined organics were washed with saturated aqueous NH_4Cl (12 L), dried (Mg_2SO_4), filtered, and concentrated under reduced pressure to give crude-**14** (∼3.1 kg) as a dark brown oil-solid. An additional reaction of equivalent size was performed to give a combined total of ∼6.2 kg of crude-**14** with 75:25 *trans*/*cis* by HPLC. Purification by silica gel plug filtration was performed by dissolving 2.5 kg of crude-**14** in 85:15 heptane/EtOAc (5 L) and eluting with the same ratio of solvent over a bed of silica gel (35 kg, ∼14 g/g **14**). The *trans*-**14** isomer eluted first; the separation was monitored by TLC (1:1 EtOAc/MeOH) [R_f *trans*-**14** = 0.5, R_f *cis*-**14** = 0.4]. The heptane/EtOAc solution (∼800 L) of product was concentrated under reduced pressure to give *trans*-**14** (1.24 kg, 98.1 A%) as a viscous dark yellow oil. Two additional batches of crude-**14** (2.4 and 2.3 kg) were purified in a similar process to give a total of 3.74 kg *trans*-**14** (>98 A%, see Supporting Information S2, Figures S2−3.15−17). An additional second crop of 1.63 kg of *trans*-**14** with ∼95 A% purity was also obtained.

Ester Hydrolysis to Hydroxyl *trans*-1. A 50 L reactor containing a solution of *trans*-**14** (3.74 kg, 8.94 mol) in THF (22.5 L) was charged with an aqueous solution of LiOH−H_2O (1.13 kg, 26.81 mol, 3.0 equiv in 11.3 L of H_2O) with agitation at room temperature. The hydrolysis was monitored by HPLC [R_t *trans*-**1** = 5.48 min, R_t *trans*-**14** = 9.43 min] and deemed complete after 20 h. The reaction mixture was charged with brine (20 L) and EtOAc (20 L) and stirred for 20 min before separation of the organic layer. The aqueous layer was extracted with EtOAc (2 × 10 L), and then the combined organics were treated with charcoal (0.37 kg) and agitated for 30 min at room temperature. The mixture was treated with $MgSO_4$ (0.37 kg), filtered, and concentrated under reduced pressure to give *trans*-**1** (2.70 kg, 90.4% yield with 98.6 A% and 99.4:0.6 *trans*/*cis* by chiral HPLC). A second batch performed under identical reaction conditions gave *trans*-**1** (1.12 kg, 94.1% yield with 96.1 A% and 99.2/0.8 *trans*/*cis* by chiral HPLC). The two lots of pure *trans*-**1** were combined to give 3.80 kg (98.2 A%, 98.8% de and >99.9% ee by chiral HPLC): ^{1}H NMR (600 MHz, DMSO-d_6) 8.46 (s, 1H), 5.39 (s, 1H), 4.85 (t, *J* = 6.7 Hz, 1H), 3.67 (m, *J* = 3.4 Hz, 2H), 3.55 (m, *J* = 3.5 Hz, 2H), 3.52 (m, *J* = 3.2 Hz, 2H), 3.46 (m, *J* = 5.5 Hz, 2H), 3.39 (m, *J* = 5.6 Hz, 2H), 1.96 (m, *J* = 4.6 Hz, 2H), 1.42 (s, 9H), 1.09 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) 172.0, 159.6, 156.4, 153.8, 120.8, 79.0, 72.0, 45.0 (2C), 43.6−42.5 (2C), 40.9, 34.4, 28.8 (3C), 19.8. HRMS calcd for $C_{17}H_{24}N_4O_3$ $[M+H]^+$ 335.2078; found 335.2078. Trace metal analysis by ICP-AES showed Pd and Ru <2 ppm. See Supporting Information S2 for the NMR spectra of *trans*-**1**: (^{1}H) in Figure S2−3.18A and (^{13}C) in Figure S2−3.18B, and the HPLC chromatograms in Figure S2−3.19 (254 nm, chiral) and Figure S2−3.20 (280 nm). See Supporting

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Information S1 and S2 for the characterization and NMR spectral data of *cis*-**1** (^{1}H) in Figure S2−3.21 and (^{13}C) in Figure S2−3.21B.

(*R*)-4-Benzyl-3-(2-(4-chlorophenyl)acetyl)oxazolidin-2-one, 17.[52] An 800 L reactor was charged with 4-chlorophenylacetic acid **15** (17.4 kg, 102.0 mol, 1.2 equiv), (*R*)-benzyl-2-oxazolidinone **16**[53] (15.0 kg, 84.7 mol, 1.0 equiv), and toluene (181 kg, 14 vol), and the stirred suspension was cooled to 15 °C. Triethylamine (34 kg, 336 mol, 4 equiv) was charged to the mixture, and the solids were allowed to dissolve. Pivaloyl chloride (13.0 kg, 108 mol, 1.28 equiv) was added slowly at a rate to maintain the temperature below 30 °C. The reaction mixture was heated to reflux and stirred overnight. Analysis by HPLC showed (*R*)-**16** (3.3 min) = 8.5%, (*R*)-**17** (6.9 min) = 91.5 A%. The mixture was cooled to ∼20 °C, water (120 kg) was charged to the reactor, and the mixture was stirred for 10 min. After 10 min, the layers were separated and the organics washed with 4% aqueous $NaHCO_3$ (120 kg) and 10% aqueous NH_4Cl (45 kg), dried over Na_2SO_4 (5 kg), and filtered into a clean 200 L reactor. The organics were concentrated via distillation to a minimum working volume, and then 2-propanol (82 kg) was charged to the reactor, followed by another distillation to a minimum working volume (maintained internal temperature ≤45 °C). Additional 2-propanol (35 kg) was added, distillation to a minimum working volume resulted in a suspension that was filtered, and the filter cake was rinsed with 2-propanol (2 × 2 kg).[54] The wet cake was dried under vacuum maintaining internal temperature ≤50 °C until a constant weight was achieved, resulting in (*R*)-**17** (17.40 kg, 92.5 A% [Method 2.11]) in 62% yield as an off-white solid. The product was of sufficient purity to carry forward to the next step. The structural data of (*R*)-**17** is consistent with that reported in the literature.[1a]

Preparation of *tert*-Butyl (*S*)-3-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-2-(4-chlorophenyl)-3-oxopropyl-(isopropyl)carbamate, 19.[55] A dry 800 L reactor was charged with (*R*)-**17** (17.4 kg, 52.7 mol, 1.0 equiv) and CH_2Cl_2 (332 kg, 19 vol) with agitation at room temperature. The contents were cooled to ≤ −20 °C, and a solution of 1 M $TiCl_4$ in toluene (54.0 kg, 54.0 mol, 1.05 equiv) was charged slowly charged slowly in order to maintain an internal temperature ≤ 10 °C. Note: This step is exothermic, and the solution will turn orange to orange-red during the charge. The mixture was agitated at ≤ −20 °C for ∼2 h, and then DIPEA (7.5 kg, 57.7 mol, 1.1 equiv) is slowly charged over ∼2 h period. The temperature during this charge is maintained ≤ −10 °C, and the solution should turn dark purple. The contents were agitated at ≤ −20 °C for ∼1.5 h, and then a solution of Boc-aminal **18**[56] in CH_2Cl_2 (13.9 kg, 1.3 equiv of **18** (for preparation, see Supporting Information S1), 50.6 kg total weight including DCM) was added at such a at such a rate in order to maintain an internal temperature ≤ 10 °C (addition time ∼1 h). The reaction mixture was stirred at ≤ −20 °C for 4 h and then assayed by HPLC for conversion of (*R*)-**17** to product (*S*, *R*)-**19** (reaction complete when (*R*)-**17** ≤10 A% by HPLC). A 10 mL sample was removed and quenched into 15 wt% NH_4Cl (5 mL), and the bottom DCM layer analyzed. Upon completion, the reaction mixture was warmed to 0 °C, and then 25% aqueous NH_4Cl (36 kg) was charged maintaining internal reaction temperature <10 °C (emulsion observed). After agitation for 90 min, water (36 kg) was charged to solubilize the solids, and then the layers were allowed to separate. The aqueous layer is removed, and the organics are washed with 25 wt% aqueous NH_4Cl (36 kg) and 15% aqueous NaCl (36 kg), dried over Na_2SO_4 (10 kg), and filtered into a clean 800 L reactor. The organics are distilled to a minimum working volume while maintaining the internal temperature ≤35 °C. Tetrahydrofuran (166 kg) is charged and distillation continued until half the volume of THF added is distilled. The THF solution was cooled to 20 °C and assayed to give 25 wt% of (*S*,*R*)-**19** in THF, indicating 28.8 kg and 109% (solution) yield. A 100 mL sample was removed, concentrated to dryness, and analyzed by HPLC to gave 88.4 A% purity for (*S*,*R*)-**19**, containing 1.2% of the *R*,*R*-diastereomer [Method 2.11]. The structure was consistent with the reported literature.[5] The crude product was used directly in the next step.

Crude (*S*)-3-(*tert*-Butoxycarbonyl(isopropyl)amino)-2-(4-chlorophenyl)propanoic Acid, Crude-(*S*)-2. An 800 L reactor was charged with $LiOH·H_2O$ (5.6 kg, 133.5 mol, 2.5 equiv) and water (185 kg, 7 vol) with agitation at room temperature until the solids dissolved. Tetrahydrofuran (221 kg) was then charged into the reactor followed by the slow addition of 30% H_2O_2 (13.5 kg, 105.4, 2.0 equiv) such that the internal temperature does not exceed 30 °C. The contents were cooled to ∼0 °C, and then the THF solution of crude (*S*,*R*)-**19** (26.4 kg, 52.7 mol, 1.0 equiv, 115.1 kg total weight) was charged slowly so that the internal temperature is maintained between 0 and −10 °C. The mixture was then agitated at ∼0 °C for 3 h and assayed by HPLC for conversion of crude (*S*,*R*)-**19** to crude-**2** (reaction deemed complete when crude (*S*,*R*)-**19** ≤2 A% HPLC). HPLC sample preparation: A 10 mL sample was removed and quenched into 12.5 wt% aqueous Na_2SO_3 (5 mL) and EtOAc (5 mL). Upon completion, the reactor is slowly charged with 12.5 wt% aqueous Na_2SO_3 (55 kg) maintaining internal reaction temperature <10 °C. After stirring 90 min, the pH of the reaction mixture was recorded (pH 14 by litmus). A solution of 27 wt% aqueous $KHSO_4$ (70 kg) was slowly charged was charged slowly to the reactor while maintaining internal temperature <15 °C until the pH was between 2 and 3. Toluene (114 kg) was charged to the reactor, the mixture was stirred at ∼20 °C for 15 min, and then the layers were allowed to separate (1 h). The layers were separated, and the aqueous layer was extracted with toluene (2 × 79 kg). The combined organics were dried (Na_2SO_4), filtered into a clean reactor, and distilled to a minimum working volume (internal temperature maintained ≤45 °C). Toluene (342 kg) was charged to the reactor and then distilled to a minimum working volume (internal temperature maintained ≤45 °C). The process was repeated with additional charge of toluene (87.2 kg). A 100 mL sample was removed and concentrated to dryness to afford 23.3 g. The bulk toluene solution was assayed to be 13.4 wt% crude (*S*)-**2** and ∼66 A% purity [Method 2.11]. Note: Residual chiral auxiliary (*R*)-**16** is still present but is removed in the next step.

(*S*)-2-(4-Chlorophenyl)-3-(isopropylamino)propanoic Acid Sodium Salt, (*S*)-20-Na. A toluene solution of crude (*S*)-**2** (18.0 kg, 52.7 mol, 1.0 equiv, 173.1 kg total from the previous step) was charged into a 800 L reactor with agitation at room temperature. Concentrated HCl (16.0 kg, 158 mol, 3 equiv) was slowly pumped into the reactor with good agitation, and the pump was rinsed with H_2O (2 kg). The reaction mixture was warmed to 30 °C, and after 6 h IPC by HPLC indicated the Boc group deprotection was complete (crude (*S*)-**2** ≤1.0 A% HPLC). Note: For sampling, a 10 mL aliquot was removed from the reactor containing two layers, and both layers were analyzed by HPLC for starting material. The

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agitation was stopped, and the layers were separated. The aqueous layer (pH 0 by litmus) containing the product was extracted with toluene (3 × 80 kg), and then the aqueous layer was charged back into the reactor, and EtOAc (132 kg) was charged. The biphasic mixture was agitated at ∼0 °C for 20 min, and then aqueous 25 wt% NaOH (23.2 kg) was slowly charged to the reactor until pH 9 (litmus) was obtained. The internal temperature was maintained ≤10 °C during the hydroxide addition and resulted in precipitation of product **20-Na**. The mixture was stirred at ∼5 °C for 1 h and then filtered into a Nutsche filter, and the wet cake was washed with EtOAc (2 × 8 L). The solids were dried in a vacuum (45 °C, 13 h) to give sodium carboxylate **20-Na** (7.65 kg, 99.5 A%) in 60% yield. The chiral purity measured 98.9:1.1 *S*/R = 97.8% ee by HPLC [Method 2.10].

For crystallization, 2-propanol (180 kg, 24 vol) was charged to the reactor containing crude **20-Na** (7.65 kg), and the mixture was heated to reflux (IT = 79 °C) for 1 h. The solution was allowed to cool to 20 °C over ∼3 h and maintained agitation for an additional 4 h. The solids were filtered, and the filter cake was washed with 2-propanol (40 kg) and then dried in a vacuum oven at 45 °C (internal) to constant weight (∼10 h), giving sodium carboxylate (*S*)-**20-Na** (6.85 kg), in 90% yield from crude **20-Na**, with 99.7% ee and 99.9 A% [Methods 2.10 and 2.11] as white solid. The product was used directly in the next step.

(*S*)-3-(*tert*-Butoxycarbonyl(isopropyl)amino)-2-(4-chlorophenyl)propanoic Acid, β^2-Amino Acid (*S*)-2. A HDPE container was charged with tetramethylammonium hydroxide ($Me_4N^+OH^-$) (9.7 kg, 53.5 mol, 2.1 equiv) and H_2O (20 kg) and agitated at room temperature until a solution was obtained. A separate HDPE container was charged with di-*tert*-butyl dicarbonate (Boc_2O) (9.8 kg, 44.9 mol, 1.7 equiv) and acetonitrile (11 kg, 1.6 vol), and the mixture was agitated until a solution was observed. The tetramethylammonium hydroxide solution was slowly charged into a solution of sodium carboxylate (*S*)-**20-Na** (6.85 kg, 25.8 mol, 1.0 equiv) and acetonitrile (150 L, 22 vol), maintaining the internal temperature ≤20 °C during the addition. The reaction mixture was cooled to ∼15 °C, and then the di-*tert*-butyl dicarbonate solution was charged over ∼1 h, maintaining the internal temperature ≤20 °C. The reaction mixture was warmed to ∼25 °C for 4 h and then sampled. In-process analysis indicated the Boc protection was complete (∼1.4 A% HPLC (*S*)-**20-Na** remaining). The contents were distilled (IT ≤35 °C) until a minimum working volume was achieved. The reactor was charged with 2% NaOH (68 kg) and MTBE (40 kg), and the mixture was agitated for 15 min. The layers were separated, and the basic aqueous (pH 11) was extracted again with MTBE (60 kg). The aqueous was acidified slowly with 27 wt% aqueous $KHSO_4$ (47 kg) until pH 3 was obtained. [***Caution:*** *This step is exothermic and IT should be maintained* <25 °C.] The agitation was stopped, and the layers were allowed to separate over 1 h, and the upper layer was removed. MTBE (35 kg) was charged to the reactor containing the aqueous layer and agitated for 15 min. The MTBE layer was removed, dried (Na_2SO_4), filtered, and concentrated via rotary evaporation (bath temp. = 40 °C) until ∼90% of the solvent was removed. Heptane (5 L) was charged and the solution distilled via rotary evaporation (bath temp. = 40 °C) until ∼85% of the solvent was removed. The solution was then sparged with nitrogen at 38 °C for >20 min resulting in crystallization of the product. The suspension was further concentrated to dryness and then the solids oven-dried (≤50 °C) to constant weight to give β^2-amino acid (*S*)-**2** (8.85 kg, >99% ee and >99 A% [Methods 2.10 and 2.11]) in 99% yield. See Supporting Information S2 for the NMR spectra of β^2-amino acid (*S*)-**2**: (^{1}H) Figure S2−5.1 and (^{13}C) Figure S2−5.2.

***tert*-Butyl (*S*)-2-(4-Chlorophenyl)-3-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]-pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl(isopropyl)-carbamate, 22.** A 100 L reactor was charged with *trans*-**1** (3.49 kg, 10.4 mol, 1.0 equiv), toluene (16 L, 5 vol), and 2.5 M HCl in EtOH (12.5 L, 31.2 mol, 3.0 equiv) with agitation. The reaction mixture was warmed to 60 °C, and after 1 h, HPLC analysis showed no starting material remained. The reaction mixture was co-evaporated with toluene (9.5 L) and distilled to ∼22 L. The biphasic mixture of crude-**21** was cooled to room temperature, charged with CH_2Cl_2 (16 L) and then DIPEA (9.0 L, 5.0 equiv), and agitated for ∼30 min. A solution of β^2-amino acid (*S*)-**2** (3.57 kg, 10.5 mol, 1.0 equiv) and CH_2Cl_2 (14 L) was charged to the batch containing (*R*,*R*)-**21**, and the reactor was rinsed with CH_2Cl_2 (3.5 L). The reaction mixture was charged with HBTU (4.49 kg, 11.85 mol, 1.13 equiv) in two portions at room temperature and monitored by HPLC. Analysis of the reaction mixture after 3 h showed amino acid (*S*)-**2** = 0.53 A% by HPLC and met specification ((*S*)-**2** ≤ 1%). The reaction mixture was charged with 7.4 wt% aqueous $NaHCO_3$ (20 L) with good agitation, the aqueous layer was removed, and then solvent exchanged from CH_2Cl_2 to IPAc (20 L). The IPAc solution was washed with aqueous 0.6 N NH_4OH (2 × 21 L), 25 wt% aqueous NH_4Cl (20 L), and then H_2O (2 × 20 L). A final wash of the organics with H_2O (20 L) in combination with 25 wt% aqueous NH_4Cl (3 L) provided a clear phase separation. Analysis of the organic layer by GC for tetramethylurea (TMU) content indicated below specification of ≤0.15 wt%. The batch was charged with a slurry of charcoal (0.7 kg, 20 wt%) in IPAc (6.5 L) and SiliaMetS thiol (1 kg, 20 wt%) and then warmed to 47 °C for 18 h. The mixture was cooled to ambient temperature and filtered over Celite (3 kg). The filtered solids were rinsed with IPAc (19 L), and the filtrate was concentrated then solvent exchanged from IPAc into MTBE (∼25 L). The MTBE mixture was heated to an internal temperature of 50 °C for complete dissolution of solids and then slowly cooled to 40 °C over 2.3 h. A slurry of seed material Boc-API (*S*,*R*,*R*)-**22** (12 g, 0.5 wt%) in heptane (1 L) was added and the mixture cooled to 36 °C over 30 min. Additional heptane (5.9 L, 1.7 vol) was slowly charged, and the slurry was cooled to 25 °C and then aged overnight. The crystallized product was filtered and rinsed with heptane (6 L), and then the filter cake was dried at ≤55 °C under reduced pressure to give Boc-API (*S*,*R*,*R*)-**22** (4.69 kg, 81% yield, 99.6 A % [Method 2.2]; ruthenium content by IPC-AES = 11 ppm]) as a white solid. Analysis by CAD-HPLC showed PF_6 anion = 0.35% [Method 2.3]. The filtrate from the crystallization contained an additional ∼820 g (*S*,*R*,*R*)-**22** by weight assay. HRMS calcd for $C_{29}H_{40}ClN_5O_4$ $[M+H]^+$ 558.2841; found: 558.2838. Spectral data are consistent with those previously reported.[1a]

(*S*)-2-(4-Chlorophenyl)-1-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)-piperazin-1-yl)-3-(isopropylamino)propan-1-one, Ipatasertib Mono-HCl. A 100 L reactor containing an agitated solution of Boc-API (*S*,*R*,*R*)-**22** (4.57 kg, 8.19 mol) and toluene (20 L) was slowly charged with 12 N HCl (2.1 L, 24.6 mol, 3 equiv) at room temperature. The mixture was heated to 50 °C

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and the reaction monitored by HPLC for consumption of (*S*,*R*,*R*)-**22** (not detected after 1 h). The reaction mixture was then diluted with H_2O (12 L) and agitated, and the layers allowed to separate. The lower aqueous layer containing Ipatasertib di-HCl was removed, and the organic layer was washed with H_2O (4 L). The aqueous extracts were combined and distilled under reduced pressure in order to remove residual toluene (∼2 L). The aqueous solution was cooled to 20 °C, and CH_2Cl_2 (14 L) was added. To the biphasic mixture was slowly added 5 N NaOH (6.3 L) until pH >12 with good agitation. The layers were allowed to separate, and the bottom organic layer was removed. The basic aqueous layer was extracted again with CH_2Cl_2 (16 L), and the combined organics were washed with saturated aqueous $NaHCO_3$ (15 kg) followed by brine (19 kg). The organics were dried over anhydrous Na_2SO_4 (2.79 kg) and then filtered. A slurry of charcoal (0.91 kg, 20 wt%) in CH_2Cl_2 (1 L) was added to the filtrate followed by SiliaMetS thiol (1 kg, 20 wt%) and the mixture maintained at 22 °C for ∼4 h. The mixture was filtered through a pad of Celite (3.4 kg) and rinsed with CH_2Cl_2 (12 L) until no product was observed eluting from the filter. HPLC weight assay of the filtrate indicated 3.74 kg (8.17 mol) of Ipatasertib free-base. The free-base solution at 19 °C was slowly charged with 12 N HCl (0.65 L, 0.96 equiv), and then the mixture was distilled under reduced pressure to a minimum working volume (∼10 L). Additional CH_2Cl_2 (10 L) was charged to the reactor, and the solution was distilled until water was no longer observed in the distillate. To the DCM solution was slowly charged EtOAc (33 L). The mixture was distilled to a minimum working volume (∼20 L), charged with EtOAc (20 L), and then distilled. EtOAc (15 L) was added to the mixture, agitated 4 h, and then filtered. The filter cake was rinsed with EtOAc (12 L), and the solids were dried at ≤70 °C with nitrogen purge for ∼48 h. The product was discharged from the filter dryer to give Ipatasertib mono-HCl (3.23 kg, 80% yield) as an off-white solid. Analytical results: 99.7 A% [0.26% *S*,*R*,*S*-diastereomer observed)]; impurity **23** (M399) was not detected (<0.02 A%) [Method 2.2]; ruthenium content by IPC-AES = 5 ppm; analysis for PF_6 anion by CAD-HPLC resulted in not detected [Method 2.3]; residual solvent = 0.4% EtOAc; ion chromatography (IC) = 8.5% chloride (1.14 salt equivalent); DSC = 141 °C; FTIR (neat) 3269 (br OH), 2961−2865 (N−H stretch), 1637 (C═O stretch); ^{1}H NMR (600 MHz, DMSO-d_6) 9.39 (s, 1H), 8.64 (s, 1H), 8.49 (s, 1H), 7.49 (q, *J* = 2.9 Hz, 2H), 7.41 (q, *J* = 2.9 Hz, 2H), 5.58 (s, 1H), 4.91 (t, *J* = 6.9 Hz, 1H), 4.78 (dd, *J* = 8.9, 4.5 Hz, 1H), 3.81 (m, *J* = 3.3 Hz, 1H), 3.68 (m, *J* = 3.3 Hz, 1H), 3.67 (m, *J* = 3.1 Hz, 1H), 3.65 (m, *J* = 3.2 Hz, 1H), 3.63 (m, *J* = 3.6 Hz, 1H), 3.59 (m, *J* = 4.3 Hz, 1H), 3.51 (m, *J* = 3.5 Hz, 1H), 3.46 (m, *J* = 3.5 Hz, 1H), 3.36 (m, *J* = 3.2 Hz, 1H), 3.30 (m, *J* = 5.7 Hz, 1H), 3.21 (m, *J* = 3.4 Hz, 1H), 2.98 (m, *J* = 5.8 Hz, 1H), 1.97 (m, *J* = 4.8 Hz, 2H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.25 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) 170.2, 168.2, 159.4, 155.2, 135.3, 132.5, 129.7 (2C), 129.1 (2C), 120.8, 71.7, 50.4, 47.0, 44.8, 44.5, 44.1, 41.4, 40.8, 34.5, 19.8, 18.4, 18.1; HRMS calcd for $C_{24}H_{32}ClN_5O_2$ 457.2245; found $[M+H]^+$ 458.2306.

■ ASSOCIATED CONTENT

Supporting Information

Supporting Information S1 describes the analytical methods used during the preparation of cyclopentylpyrimidine *trans*-**1**, β^2-amino acid (*S*)-**2**, and Ipatasertib; Supporting Information S1 also provides an alternative procedure for the preparation of 2,6-dihydroxypyrimidine (*R*)-**5** from (*R*)-MGM. Spectral and chromatographic data for the key compounds are found in S2. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

API: Active Pharmaceutical Ingredient
cGMP: Current Good Manufacturing Practice
Boc: *tert*-butoxycarbonyl
DCM: dichloromethane
Dppp: 1,3-bis(diphenylphosphino)propane
TsDPEN: (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenyl-1,2-ethanediamine
MsDPEN: (1*R*,2*R*)-*N*-(methanesulfonyl)-1,2-diphenyl-1,2-ethanediamine

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(9) The experimental details to prepare triester (*R*)-**4** from (*R*)-monomethyl methylglutarate (MGM) can be found in the Supporting Information S1.

(10) Although DHP *rac*-**5** was also a viable substrate for enzymatic resolution, a preliminary screen of various commercial lipases was not promising, and this approach was not pursued. Similarly, the classical resolution of the carboxylic acid derivative of DHP *rac*-**5** with (*R*)- or (*S*)-α-methylbenzylamine resulted in only poor selectivity (highest chiral ratio observed was ∼60:40).

(11) In a similar approach, the enzymatic resolution of dimethyl 3-methylpentanedioate, the precursor to triester *rac*-**4**, to produce (*R*)-3-methylglutaric acid monomethyl ester (MGM) was reported by Alvarez and co-workers in ref 8.

(12) Increasing the enzyme loading of lipase AYS "Amano" further to 50 wt% had a deleterious effect and resulted in enantiomeric ratio of 4.1:95.9 after 250 h (10 d).

(13) A% indicates area% purity by HPLC unless otherwise noted throughout the manuscript.

(14) See Supporting Information S1 for the preparation of DHP (*R*)-**5** using triester (*R*)-**4** from this route.

(15) See ref 2 for the initial *proof-of-principle* synthesis of ketone *rac*-**12**.

(16) Similar good results for the conversion of DHP **5** to DCP **6** were obtained using Et_3N instead of 2,6-lutidine, and although 1,2-dichloroethane could also be substituted for toluene, the reaction times were extended from ∼24 to 48 h for complete conversion.

(17) Other common ester derivatives of (*R*)-**9** prepared did not lead to efficient decarboxylation following the Dieckmann cyclization reaction; see ref 2.

(18) A major side product from the combination of benzyl chloride and K_2CO_3 for re-esterification was the lactone product, which was not observed using the current conditions. See Supporting Information S1, section 4.4, for the proposed structure.

(19) The origin of this work is described in Part 1 of this series (ref 2).

(20) (a) Higher reaction temperatures led to S_NAr of the chloropyrimidine with the 2-propanol to give the aryl isopropyl ether. In addition, poor stirring of the heterogeneous reaction mixture resulted in a significant amount of the same byproduct. Formation of the isopropyl ester byproduct from transesterification was not an issue using the optimized reaction conditions. (b) For a good discussion of the influence of the reaction variables such as CO pressure and effect of base on the carbonylation reaction, see: Barnard, C. F. *Org. Process Res. Dev.* **2008**, *12*, 566−574.

(21) β-Keto ester intermediate (*S*)-**11** has been isolated by acidification with glacial AcOH (or aqueous HCl) to pH 5−6, followed by aqueous work-up and extraction with EtOAc. The concentrated organics resulted in a solid product that was slurried in MTBE/petroleum ether (1:2) to afford white solids after filtration. From one experiment, 119 g of diester (*R*)-**10** gave 84 g of β-keto ester (*S*)-**11** in 80% isolated yield. This isolation procedure was not favored due to the loss of yield on work-up, and it was speculated that the product was sensitive to oxidation at the enolic position with exposure to air.

(22) We also observed epimerization of the methyl stereocenter during this two-step process and speculate that it can occur through formation of a dianion intermediate during the Dieckmann cyclization step with KOtBu. The authors thank Dr. Lee Latimer for a related reference describing the dianion formation of 1-indanone: Trost, B. M.; Latimer, L. H. *J. Org. Chem.* **1977**, *42*, 3212−3214. Further mechanistic studies for the epimerization β-keto ester **11** are warranted.

(23) We considered the strategy of converting ketone (*R*)-**12** selectively to *cis*-**1** and then inverting the hydroxyl group via a Mitsunobu reaction to obtain *trans*-**1**; however, this was not practical since it required two extra steps and purification would still be needed to separate the diastereomers.

(24) (a) Use of a stronger base such as aqueous NaOH could result in decomposition of ketone (*R*)-**12** via cross-aldol-type condensation. (b) Not quenching the formic acid at the end of this reaction also resulted in cleavage of the Boc group.

(25) The highest *cis* diastereoselectivity observed with heterogeneous hydrogenation was from using 5% Pd/C Type A405038 catalyst (Johnson Matthey, 5 bar H_2, 40 °C in EtOAc), which gave >99% conversion to *cis*-**1** with 96% de after 16 h.

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(27) (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522. (c) Magano, J.; Dunetz, J. R. *Org. Process Res. Dev.* **2012**, *16*, 1156−1184.

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(29) The [(*R,R*)MsDPEN−Ru(*p*-cymene)Cl] catalyst was used in our first kilogram scale-up campaign for the reduction of ketone (*R*)-**12** since it was readily available and gave good activity and selectivity (∼90% de) compared to the [(*R,R*)TsDPEN−Ru(*p*-cymene)Cl] catalyst (≤92% de) in a screening study starting with pure ketone (*R*)-**12**.

(30) Using a 1:1 mixture of $HCCOH/Et_3N$ versus a 5:2 mixture (as originally reported by Noyori in ref 27b) generally gave ∼10% higher de of *trans*-**1** product with the [(*R,R*)TsDPEN−Ru(*p*-cymene)Cl] catalyst.

(31) Crystallization of *trans*-**1** was not optimized at this stage of the project but was achieved from several single solvents, such as EtOAc, IPAc, or MTBE. Alternatively, the *cis/trans*-**1** diastereomers could be separated without derivatization using preparative HPLC (column, CHIRALPAK IC, 20 μm, 11 × 25 cm; mobile phase, MeOH/0.05% DMEA; flow rate, 570 mL/min; column temp, 25 °C; UV detection, 320 nm). We acknowledge Chiral Technologies Inc. for identifying these separation conditions.

(32) The *p*-nitrobenzoate ester of **1** was used for separation of diastereomers by silica gel chromatography in the medicinal chemistry synthesis (see ref 1a).

(33) Attempted crystallization of the pivalate ester *trans*-**14**, as well as the acetate and *p*-nitrobenzoate derivatives, was not successful from CPME, DCM/petroleum ether, EtOAc/hexanes, *i*-PrOH, or acetone solvents.

(34) Trace metal analysis of *trans*-**1** using ICP-AES indicated that both ruthenium and palladium were efficiently removed in the purification process and both were ≤2 ppm.

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(40) Recrystallization of carboxylic acid (*S*)-**20** from acetonitrile was also successful in increasing the enantiopurity of the product from 97% ee to >99% ee; however, the product was more hygroscopic than the (*S*)-**20-Na** crystallized from 2-propanol and made the filtration more difficult.
(41) Although a coupling reaction between the unprotected carboxylic acid (*S*)-**20** and deprotected *trans*-**1** was possible, a Boc group was required for purification of the penultimate (*S,R,R*)-**22** via crystallization.
(42) Extraction of the piperazine (*R,R*)-**21** product from an acidic or basic aqueous phase was not possible due to the high aqueous solubility.
(43) (a) Hexafluorophosphate (PF_6) anion is not listed as a pharmaceutically acceptable salt: Haynes, D. A.; Jones, W.; Motherwell, W. D. S. *J. Pharm. Sci.* **2005**, *94*, 2111−2120. (b) See also: Wigman, L.; Remarchuk, T.; Gomez, S. R.; Kumar, A.; Dong, M. W.; Medley, C. D.; Chetwyn, N. P. Byproducts of Commonly Used Coupling Reagents: Origin, Toxicological Evaluation and Methods for Determination. *Am. Pharm. Rev.* **2014**, *17*, No. 1.
(44) The presence of TMU and PF_6 anion was detected using ^1H and ^{19}F NMR spectroscopy of a concentrated aliquot of the organic phase during the extraction. See Supporting Information S1 for the analytical details.
(45) Other aqueous solutions were also found effective in removing the PF_6 anion, including 10% aq LiOH and 10% aq Na_2CO_3.
(46) See Supporting Information S1 for the preparation of Ipatasertib free-base and the structural determination of β-elimination product **23** by NMR spectroscopy. A second minor impurity, **M416** (RRT = 0.80), with mass $[M+H]^+$ = 416 amu, was also formed in ∼0.2% by HPLC.
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(49) A major side product obtained using the combination of benzyl chloride and K_2CO_3 was the six-membered-ring lactone that was observed up to 10 A% (by LCMS). Lactone formation was not observed using the current conditions.
(50) The crude ketone **12** was co-evaporated with DCM to remove residual EtOAc and 2-MeTHF prior to the subsequent asymmetric transfer hydrogenation step since the presence of these solvents resulted in a lower %de of *trans*-**1**.
(51) In a later campaign, ketone (*R*)-**12** (11.3 kg) that was free of over-reduced product was reduced under similar reaction conditions except using 1 mol% of [(*R,R*)-TsDPEN−Ru(*p*-cymene)Cl] catalyst and gave a 96:4 *trans/cis*-**1** mixture in 93% assay yield. After aqueous work-up and solvent exchange into MeOH, scavenging with 50 wt% SiliaMetS thiol at 55 °C for 18 h resulted in 64 ppm Ru by ICP-AES.
(52) For a previous report of (*R*)-**17**, see: Prashad, M.; Kim, H.-Y.; Har, D.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **1998**, *39*, 9369−9372.
(53) The chiral auxiliary (*R*)-**16** had a specific rotation $[\alpha]^{18}_D$ +63.2° (*c* = 1) and melting point = 87.6−88.0 °C.
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