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Selection of an Enantioselective Process for the Preparation of a CGRP Receptor Inhibitor

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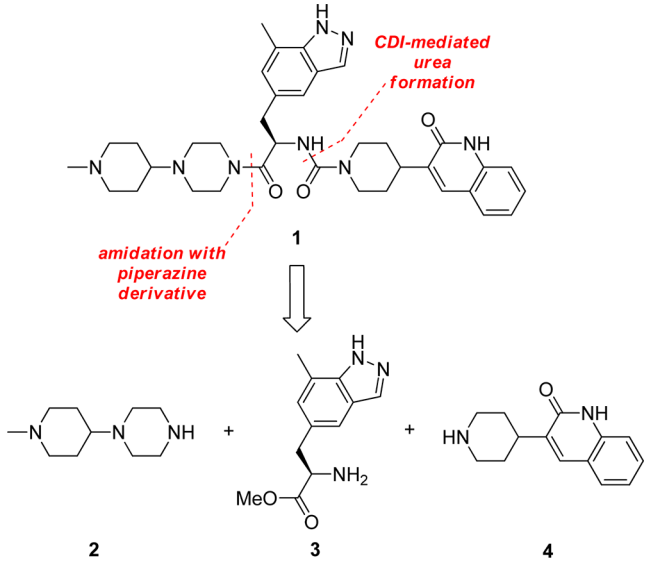
ABSTRACT: (*R*)-*N*-(3-(7-Methyl-1*H*-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (**1**) is a potent calcitonin gene-related peptide (CGRP) receptor antagonist. We have developed a convergent, stereoselective, and economical synthesis of the hydrochloride salt of **1** and demonstrated the synthesis on a multikilogram scale. Two different routes to the chiral indazolyl amino ester subunit were developed utilizing either a Rh-catalyzed asymmetric hydrogenation or a biocatalytic process to install the single chiral center. The advantages and disadvantages of each of these process routes are discussed, as are challenges addressed in the assembly of the final drug substance.

1. INTRODUCTION

Long-term treatment of migraine headaches is a significant unmet medical need. The discovery that the neuropeptide calcitonin gene-related peptide (CGRP) is involved in the pathophysiology of migraine[1] prompted intense research efforts to identify selective CGRP receptor antagonists. The medicinal chemistry efforts at Bristol-Myers Squibb[2] resulted in the identification of **1** as a potent and effective competitive CGRP antagonist for clinical evaluation. To support these clinical trials, an efficient large-scale synthesis of **1** was developed as described in this paper.

As shown in the retrosynthetic analysis in Scheme 1, the structure of **1** lends itself to straightforward assembly from three fragments. Of these, piperazine **2** is commercially available. An efficient synthesis of the known[3] 1-(1-methylpiperidin-4-yl)piperazine **4** was developed but will not be discussed here. Instead our focus will be on the development of an enantioselective route to the α-aminoester **3** and its elaboration to **1**.

Scheme 1. Retrosynthetic analysis for 1



Many synthetic approaches to chiral α-amino acids and esters have been reported.[4] Among these, *catalytic* protocols using enantioselective transition metal catalysis or enzymatic synthesis are especially process friendly. During our development efforts we explored both of these types of catalytic routes for the preparation of **3** and were then faced with the need to choose between the two approaches. Since α-amino esters are frequently encountered as pharmaceutical building blocks, we anticipate that our experience may be useful to others.

2. RESULTS AND DISCUSSION

2.1. Synthesis of 3 Using Asymmetric Hydrogenation.

For the synthesis of amino ester **3**, our Discovery Chemistry colleagues employed the reaction sequence shown in Scheme 2.[5] Initially the indolazine ring was introduced earlier in the sequence, but its presence was found to interfere with the asymmetric hydrogenation. Consequently, installation of the indolazine was deferred until after the hydrogenation step. The general strategy of Scheme 2 was adopted for our initial approach to **3**. However, several significant issues in the Discovery Chemistry route needed to be addressed prior to scale-up.

Preparation of Enamide ***8***. It was first necessary to establish a reliable synthesis of amidoacrylate **7**. We noted that unless **7** was purified chromatographically, impurities in the crude material interfered with its crystallization. Moreover, it became evident that isolated **7** was prone to polymerization. Therefore, we developed a through-process which provides a solution of **7**

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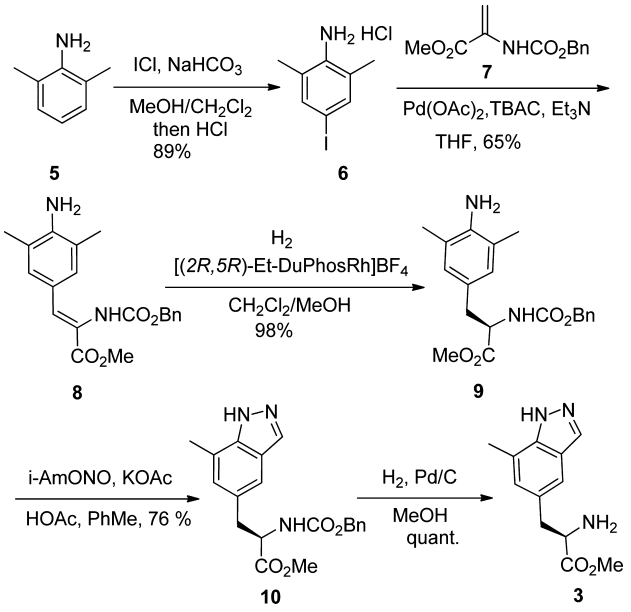
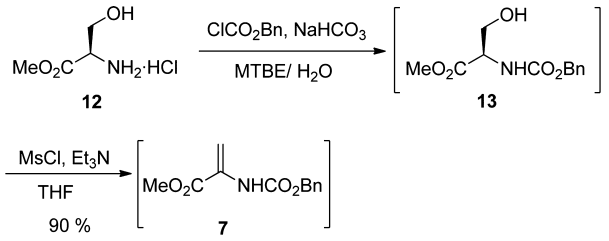
Scheme 2. The Discovery Chemistry synthesis of 3



(Scheme 3) that is taken into the subsequent Heck reaction without isolation.

Scheme 3. Process for the preparation of amidoacrylate 7

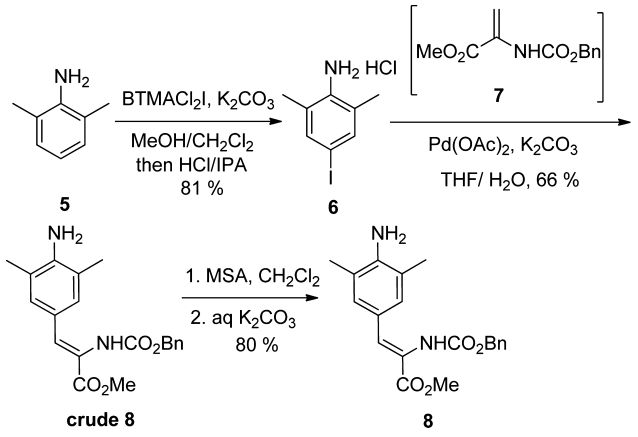


Commercially available serine methyl ester hydrochloride **12** was first Cbz protected under Schotten Baumann conditions[6] to produce **13**. After aqueous washes, the MTBE solvent was exchanged via vacuum distillation to THF, and the alcohol was then activated with methanesulfonyl chloride (MsCl) and underwent elimination in the presence of triethylamine at 0 °C. Concentration of the organic phase after aqueous workup provided a THF solution of **7**.

We next focused on the preparation of iodoaniline **6** (Scheme 4). The iodination reagent used by the Discovery Chemistry group, iodine monochloride, generated a highly colored HCl salt of iodoaniline **6**, and the color persisted into the product of the Heck reaction. This issue was circumvented by replacing ICl with commercially available benzyltrimethylammonium dichloroiodate[7] ($BTMACl_2I$) which afforded **6** as an off-white hydrochloride salt. For the kilogram-scale preparation, a solution of **5** in methanol was added to a slurry of $BTMACl_2I$ and potassium carbonate in dichloromethane to provide addition control of the reaction exotherm. After filtration, an aqueous wash, and azeotropic drying, addition of a solution of HCl in 2-propanol allowed isolation of **6** as its HCl salt.

The hydrochloride salt of **6** smoothly underwent palladium(II) acetate-catalyzed Heck coupling with the aminoacrylate **7** in aqueous THF to provide crude enamide **8** (Scheme 4). The product could be purified by crystallization as a MSA salt and

Scheme 4. Process for the preparation of purified 8



was then free-based prior to use by treatment with aqueous potassium carbonate. At an 18 kg scale, enamide **8** was obtained in 52% overall yield and 95.2 wt %/wt purity.

Asymmetric Hydrogenation of Enamide 8. As noted previously (Scheme 2) an Et-DuPHOS-Rh catalyzed[8] hydrogenation had been used by the Discovery Chemistry group to produce amino ester **9** in excellent yield and selectivity. However, several issues weighed against further scale-up using this catalyst. The hydrogenation was slow and limited catalyst life necessitated a high catalyst loading (molar substrate-to-catalyst ratio) of 200. In addition, the reaction rate varied significantly for different batches of enamide **8**.

One contributor to the slow reaction rate when using the DuPHOS catalyst may be competitive binding of the aniline nitrogen atom. In support of this hypothesis, addition of a strong acid such as methanesulfonic acid (MSA) to protonate the amino group led to a faster reaction. This is illustrated using chromatographically purified enamide **8** in Figure 1 (compare reaction profiles 2 and 3).

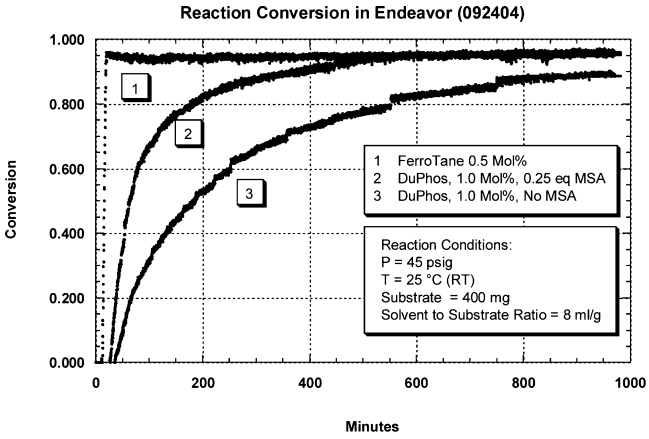


Figure 1. Reactivity of Et-FerroTANE-Rh catalyst vs Et-DuPHOS-Rh catalyst.

Also shown in Figure 1 (reaction profile 1), an even greater improvement in reaction rate was achieved by replacing the Et-DuPHOS ligand in the catalyst with the Et-FerroTANE ligand.[9] The structures of the two ligands are shown in Scheme 5. Using the Et-FerroTANE catalyst, the reaction time for hydrogenation of chromatographically purified **8** decreased to 1 h.

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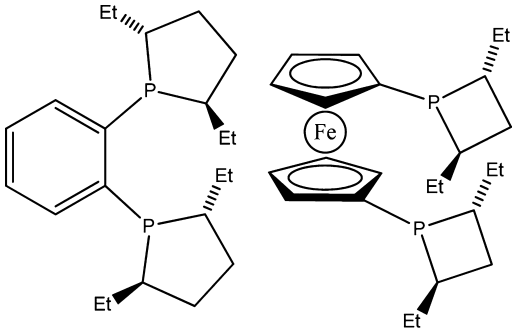
Scheme 5. Comparison of ligand structures



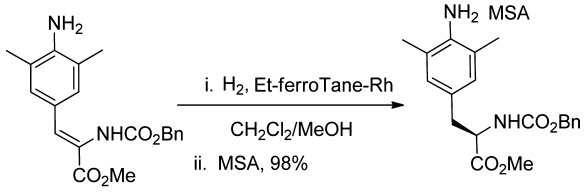
(+)-(R,R)-Et-DuPHOS (+)-(R,R)-Et-FerroTANE

This higher activity was obtained despite a lower catalyst loading of the FerroTANE vs the DuPHOS catalyst.

Even with this alternative catalyst, variability in reaction rate and catalyst life between different batches of enamide **8** remained an issue. We suspected that this was due to impurities deactivating the catalyst. In particular, it is known that residual chloride ion can have this effect.[10] Therefore, an additional purification step was introduced: Hot filtration of a solution of **8** in ethyl acetate followed by crystallization afforded purified enamide **8** in 86% yield.

Using this purified material the asymmetric hydrogenation of **8** using Et-FerrroTANE-Rh at a 0.25% catalyst loading performed consistently (Scheme 6). At the conclusion of the

Scheme 6. Process for the preparation of the MSA salt of 9



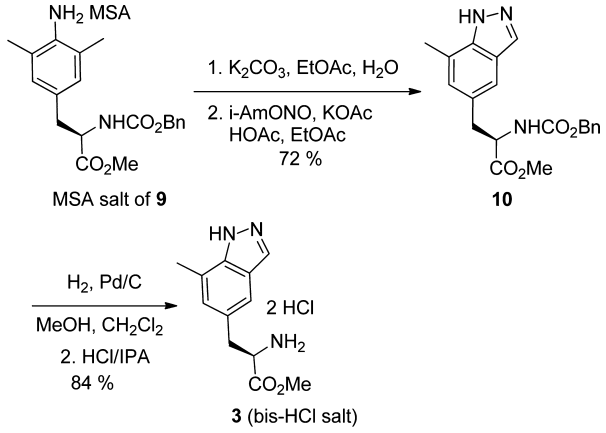
8 MSA salt of **9**

reaction the solution was subjected to polish filtration and solvent exchanged into ethyl acetate prior to precipitation of **9** as its MSA salt. A total of 14 kg of the MSA salt of **9** was produced in 96% overall yield and ~99% ee.

Preparation of Amino Ester 3. The indazole ring closure was based on the nitrosation route previously shown in Scheme 2. However, we noticed that initial batches of indazole **10** prepared in the laboratory had a dark brown coloration that would carry into the subsequent intermediate, amino ester **3**. The extent of this color formation correlated with the presence of trace levels of rhodium and palladium in the starting material **9** indicating the need to remove these contaminants prior to the nitrosation step. This was accomplished by filtering the ethyl acetate solution obtained upon free-basing through a Cuno carbon zeta pad. After azeotropic drying, this solution was used directly in the nitrosation.

Addition of isoamyl nitrite to the resulting solution after acidification with acetic acid smoothly transformed the aniline **9** to indazole **10** (Scheme 7). After neutralization of the acetic acid with aqueous potassium carbonate solution, **10** was isolated by solvent exchange into toluene and addition of heptane.

Scheme 7. Preparation of the aminoester 3 as its bis-HCl salt



MSA salt of **9** **10**

3 (bis-HCl salt)

The final step of the sequence is deprotection of the Cbz group by palladium on carbon hydrogenolysis. This appears conceptually simple but was complicated by the tendency of the ester to undergo hydrolysis under these conditions, presumably as a result of water in the carbon or methanol. The extent of the hydrolysis was greater when filtration of the mixture through a Celite bed for removal of the palladium catalyst was prolonged. The problem was alleviated by diluting the mixture so that the hydrolysis product, amino acid **14**, precipitated and was simultaneously removed during filtration. In this way the amount of **14** in the isolated hydrogenation product was diminished to <0.2%.[11]

Another significant issue with the scale-up of the hydrogenolysis step was inconsistency of the yield which varied from 53 to 89%. The problem was traced to carbon dioxide, a byproduct generated during the reaction. The carbon dioxide formed an amine carbonate salt precipitate with the amino ester **3** which was inadvertently removed during the filtration of the heterogeneous catalyst. (The precipitate was not fully characterized, and alternative formulation as a carbamic acid is possible.) Purging the reaction mixture at the end of the hydrogenation with nitrogen removed the carbon dioxide, and the carbonate salt disproportionated to regenerate amino ester **3**. This nitrogen purging solved the inconsistent yield issue and was incorporated into the process.

The freebase amino ester **3** was found to be an unstable, low-melting solid; we therefore chose to isolate it as the bis-hydrochloride salt, which had superior solid handling properties. To accomplish this, the filtered solution of **3** in methanol and ethyl acetate from the hydrogenolysis step was treated with a solution of HCl in 2-propanol to afford **3** bis-HCl, which was collected by filtration and vacuum dried. Two 1.8 kg batches of **3** bis-HCl were prepared following this protocol (83–86% yield, 98 wt % purity, >99.9% ee.

2.2. Biocatalytic Route to Amino Ester 3. Our enzymatic approach to **3** is summarized in Scheme 8. Since the indazole functionality is expected to be compatible with the biocatalytic transformation, the heterocycle can be introduced at the beginning of the synthesis. The stereogenic center is established by direct conversion of the indazolyl keto acid **15** to the indazolyl amino acid **14** promoted by a D-transaminase.

Preparation of Keto Acid Substrate 15. As shown in Scheme 9, commercially available aniline **16** was treated with *tert*-butyl nitrite to generate the indazole ring.

For the subsequent halogen–metal exchange, in order to avoid formation of the desbromo compound **21**, it was

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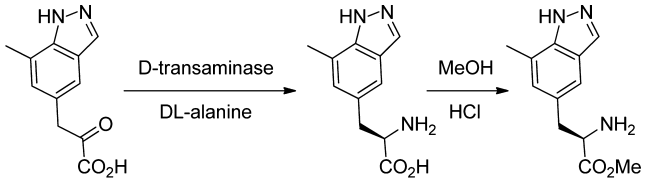
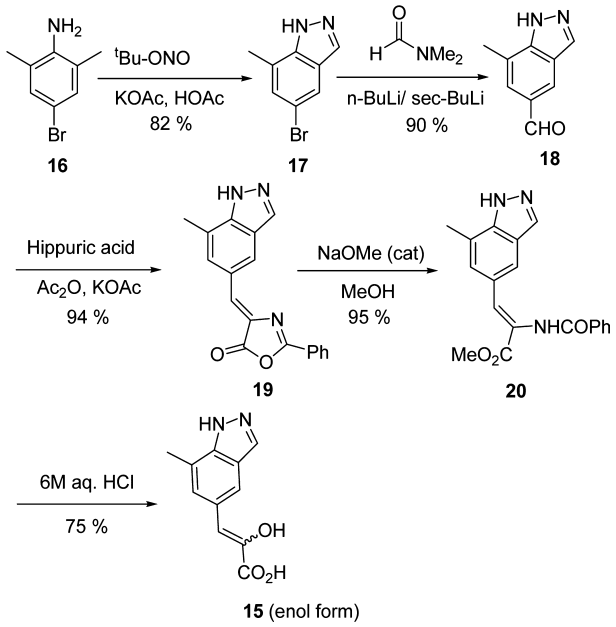
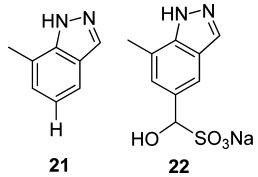
Scheme 8. Chemoenzymatic synthesis of aminoester 3



Scheme 9. Preparation of enzyme substrate 15



advantageous to first deprotonate the acidic NH proton of indazole **17** with 1 equiv of *n*-butyllithium prior to treatment with *sec*-butyllithium. After reaction of the resulting aryllithium with DMF, aldehyde **18** was readily separated from any unreacted bromoindazole **17** or indazole **21** by formation of the bisulfite adduct **22** and was extracted into the aqueous phase. Aldehyde **18** was then regenerated by treatment with aqueous sulfuric acid and was crystallized from a mixture of ethyl acetate and heptane.



The aldehyde **18** was next subjected to the Erlenmeyer synthesis[12] with hippuric acid in the presence of acetic anhydride and potassium acetate to afford 2-phenylazlactone **19**. When the reaction was complete, excess acetic anhydride was decomposed by charging water to the mixture. The 2-phenylazlactone **19**, which crystallized out of the reaction mixture, was found to be contaminated with the *N*-acetylated azlactone. To address this impurity we simply aged the crystallization slurry for at least 2 h to hydrolyze any *N*-acetylated azlactone prior to product filtration.

Ring-opening of 2-phenylazlactone **19** was effected in methanol with a catalytic amount of sodium methoxide. Unreacted sodium methoxide was neutralized with acetic acid prior to addition of water to crystallize *N*-benzoyl enamide **20**. The final hydrolysis to afford the enzyme substrate **15** proceeded readily upon treatment with 6 M hydrochloric acid at 95 °C. However, we initially found that removal of the benzoic acid side product was challenging.

To purge benzoic acid from keto acid **15** we took advantage of the relative solubility difference between the acids. Keto acid **15** has limited solubility in hot water or hot dilute acid compared with benzoic acid; thus, filtering the reaction mixture at >95 °C allowed the selective isolation of **15**. Under these conditions, **15** crystallized as its enol tautomer and contained <3% of residual benzoic acid. At this level residual benzoic acid did not interfere with the subsequent biocatalytic step.

Enzymatic Synthesis of Amino Acid 14. Initial efforts to convert keto acid **15** to amino acid **14** were carried out using a commercial D-transaminase from Biocatalytics, Inc. (now Codexis) and DL-alanine as the nitrogen source. Using this enzyme, the reaction tended to stall at ∼90% conversion apparently due to inhibition by the side product pyruvic acid. We initiated a research effort to identify an improved enzyme. While these efforts were underway we elected to scale up the process using the commercial enzyme.

Using this enzyme, the indazolyl acid **15** underwent transamination with DL-alanine serving as an amino donor at pH 7.5. At the end of the conversion, the reaction mixture was acidified with aqueous sulfuric acid to dissolve the reaction products while simultaneously precipitating the denatured enzyme. Following filtration of the acidic reaction mixture through Amberlite XAD16 resin, the filtrate was heated to ∼100 °C and was neutralized with sodium hydroxide to effect the crystallization of indazolyl amino acid **14** as a monohydrate. The enzymatic process was demonstrated on a 600-g scale in two batches to produce indazolyl amino acid **14** in 79% yield and >99% ee. Process details for this step were published previously.[13]

We subsequently discovered a D-transaminase from a soil organism identified as *Bacillus thuringiensis* which exhibited significantly diminished product inhibition. The purified enzyme was cloned and expressed in *E. coli* as described elsewhere.[13] In laboratory scale experiments, this enzyme was shown to offer additional advantages. In particular, the reaction time of 72 h for the commercial enzyme was decreased to 21 h using the BMS cloned enzyme. Moreover, the volume efficiency was improved from 33 L/kg to 17 L/kg.

Preparation of 3 via Fischer Esterification. Since we again wished to isolate the bis-hydrochloride of ester **3**, hydrogen chloride was employed as the esterification catalyst. Anhydrous HCl was conveniently generated by addition of acetyl chloride to methanol. Two issues needed to be addressed in this otherwise straightforward transformation.

First, attempts to directly esterify amino acid **14** as its monohydrate stalled at ∼95% conversion. Apparently the system reaches an equilibrium conversion of **14** and **3** as a result of the extra equivalent of water present in the monohydrate. Consistent with this explanation, when the monohydrate was replaced with the anhydrous bis-hydrochloride of amino acid **14**, the esterification proceeded to >99% completion.

The remaining issue was formation of an impurity derived from *N*-methylation of the indazole ring. Impurity **23** was not purged when the **3** bis-HCl salt was isolated from solvent methanol. When present, **23** gave rise to additional down-

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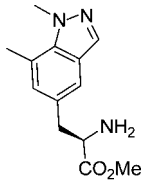
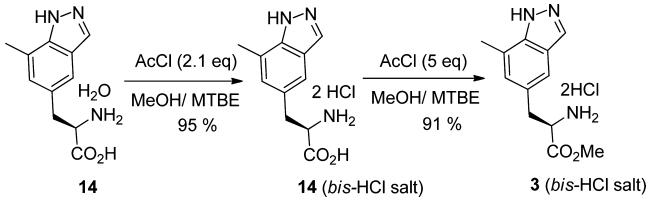
stream impurities which were difficult to remove and could potentially contaminate the API.



23

To address this issue, screening studies were undertaken to identify reaction conditions (equivalents of acetyl chloride, concentration, and temperature) where formation of **23** was minimized. The optimized conditions resulted in a reaction profile with <0.5% of **23**. It was further discovered that 1:1 MeOH/MTBE is an effective crystallization solvent which provides the bis-HCl salt of **3** with <0.2% of **23**. These elements were combined as shown in Scheme 10. This process was used to produce 2.2 kg of **3** (bis-HCl salt) in 98.6% purity with only 0.11% of **23** in the product.

Scheme 10. Conversion of 14 to the bis-HCl salt of 3 by Fischer esterification



2.3. Comparing the Two Routes. By this point it was evident that either of the two routes could provide kilogram quantities of amino ester **3**. To choose one route for further scale-up, we compared the two approaches across a number of criteria and process parameters.

Regarding Table 1, we should note that the reaction time and volume efficiency data for the BMS cloned enzyme have been used. These results were obtained in laboratory scale (6 g) conditions. However, our experience has been that such laboratory results are highly predictive for subsequent scale-up. To be conservative, we have retained the yield data for the large-scale run but expect that this would also be improved using our cloned enzyme. It can be seen from Table 1 that each technology exhibited particular advantages in this application.

Table 1. Comparison of asymmetric hydrogenation and biocatalytic routes

factor/catalyst	Et-FerroTANE-Rh	D-transaminase
yield of enantioselective step (%)	96	79
linear steps to **3** (bis-HCl salt)	6[a]	8[b]
overall yield to **3** (bis-HCl salt) (%)	25[a]	34[b]
enantiomeric excess (%)	>99.8	>99.7
product purity (%)	99.6	97
reaction time (h)	1	21
volumetric efficiency (L/kg)	8	17
catalyst availability	limited	readily available
required substrate purity	high	less critical
potential inhibitors	chloride, carbonate, etc.	pyruvate (side product)
oxygen sensitivity	highly oxygen sensitive	not oxygen sensitive

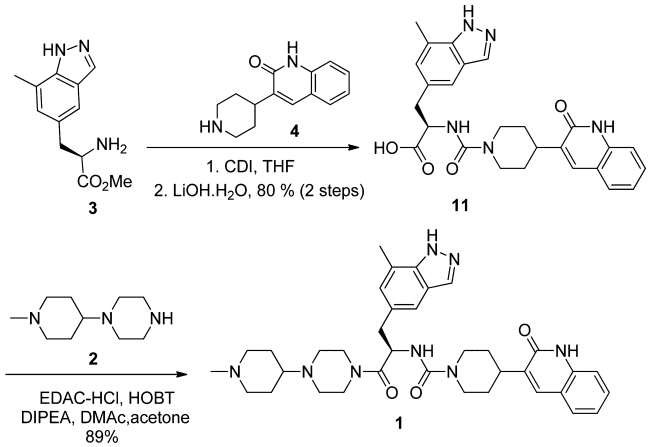
[a]Based on aniline **5** as starting material. [b]Based on bromide **16** as starting material.

The rhodium-catalyzed asymmetric hydrogenation provided a fast, clean reaction with excellent volumetric efficiency. The overall synthetic sequence required fewer process steps than for the enzymatic process. However, these advantages came at a cost. The Et-FerroTANE-Rh catalyst is proprietary and thus of limited availability.[14] In addition, substrate purity was critical to achieve a high turnover number (TON), necessitating a labor-intensive multistage purification procedure. In addition to these considerations, there was concern regarding the removal of Pd and Rh impurities from the intermediates and API. As a result, the enzymatic route was selected for future scale-up of **3**.

We also made an effort to compare the "greenness" of these two approaches but this was not as straightforward as might be imagined. The hydrogenation of **8** is an extremely clean reaction which produces no side-products whatsoever. However, the asymmetric hydrogenation here employs a soluble catalyst containing the scarce and precious metal rhodium. In contrast, the enzymatic reaction generates alanine-derived side-products which require disposal. The asymmetric hydrogenation involves the use of organic solvents (methanol and ethyl acetate) while the enzymatic process is carried out in water. However, this apparent advantage is counterbalanced by solvent disposal for the extra steps[15] required for substrate preparation in the enzymatic route.

2.4. The Synthetic Endgame. Assembly of API **1** from amino ester **3** involved two coupling steps as shown in Scheme 11. In particular, the initial CDI coupling proved sensitive to the reaction conditions. This reflects the fact that **3** is an ambident nucleophile: both the NH_2 group of the amino ester moiety and the NH of the indazole ring are reactive so that chemoselectivity is an important consideration.

Scheme 11. Endgame strategy for manufacture of API 1



*Preparation of Penultimate **11** by CDI Coupling.* As noted in Scheme 11, the CDI coupling and subsequent ester hydrolysis were telescoped for process efficiency. An investigation into this synthetic sequence showed that a variety of impurities were present in the isolated **11** depending on the reaction conditions and isolation protocol.

When the coupling was run at ambient temperature, up to 2% of **26** was formed (Scheme 12) and did not purge during

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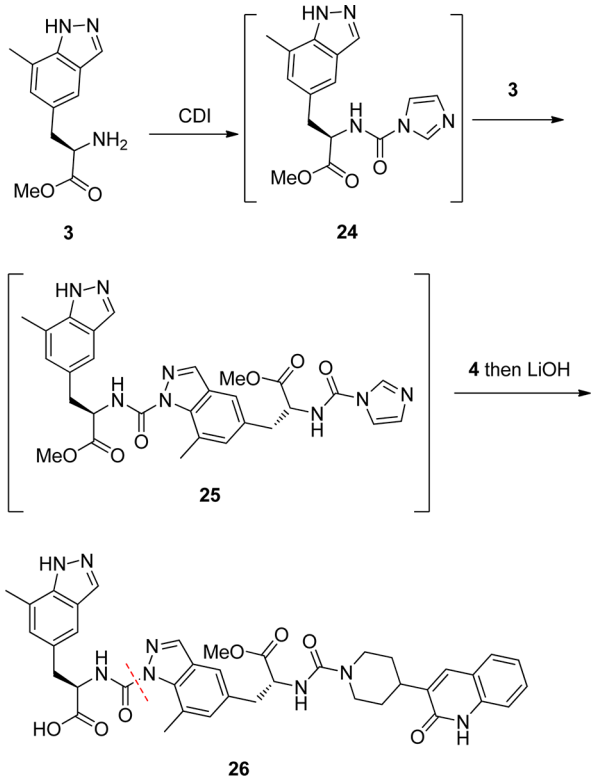
Scheme 12. Formation of process impurity 26

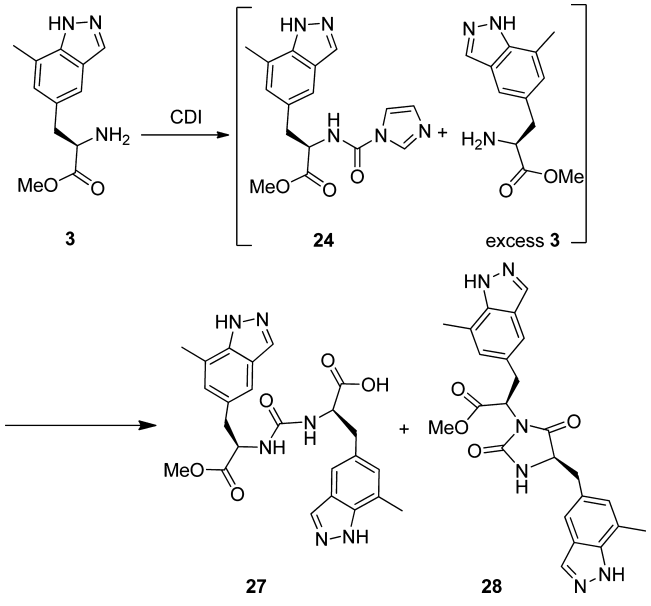


isolation of **11**. Laboratory studies revealed that the indazolyl urea linkage is unstable at higher temperatures. Consequently, impurity **26** was controlled by simply running the coupling at 40 °C.

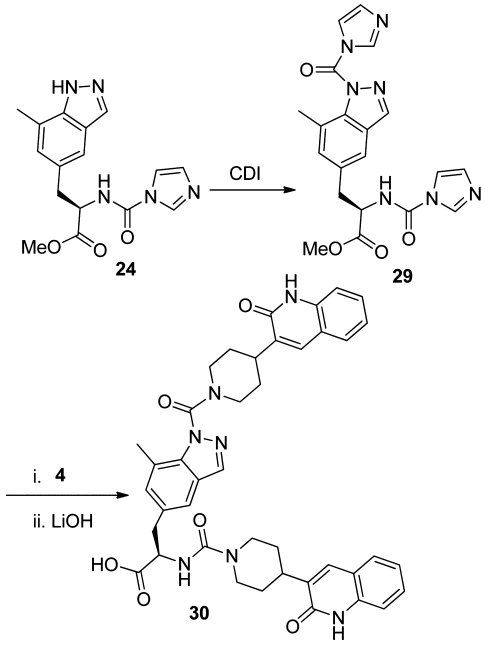
Stoichiometry was also critical. Undercharging of CDI led to some unreacted amino ester **3**, which then coupled with activated amino ester **24** to generate the undesired symmetric urea impurity **27** and the hydantoin **28** (Scheme 13).

Conversely, overcharging CDI afforded process impurity **30**, which resulted from activation of the indazolyl nitrogen atom followed by coupling with two molecules of piperidinyl quinolinone **4** (Scheme 14).

Scheme 13. Impurities generated from undercharging CDI



Scheme 14. Process impurity 30 formed by overcharging CDI



Process impurities **32** and **33** were formed when amino acid **14** was present in **3** (bis-HCl salt). These presumably arise by activation of the carboxylic acid moiety by CDI followed by undesired peptide coupling with either **4** or an additional molecule of **3** (Scheme 15). These impurities were controlled to <0.2% by setting the amino acid **14** specification for the starting material **13** to <0.5%. At this level any resulting downstream impurities were purged during isolation of the API.

Given the large impact of small deviations from precise stoichiometry, a tactical decision was made to use a slight excess (1.2 equiv) of CDI. This approach left **30** as the sole process impurity, which we were able to control by taking advantage of the selectivity observed when the various components of the reaction mixture react with water. After generation of the activated intermediate **24** water selectively reacts with the excess CDI as well as the doubly activated intermediate **29** which leads to **30**. In contrast, the activated intermediate **24** was stable for up to an hour in the presence of water (5 equiv) at −10 °C.[16] The modified process incorporating these conditions consistently afforded penultimate **11** containing <0.2% of impurity **30**.

The amorphous nature of compound **11** made it susceptible to entrapment of salts during isolation, thus forming gummy solids. This could be avoided by slow addition of the reaction mixture to an aqueous hydrochloric acid quench with efficient agitation. This reverse addition protocol generated well dispersed solids with acceptable filtration properties. After filtration, the cake was washed with copious amounts of water to remove salts and dimethylamine (formed from the cleavage of DMF by the lithium hydroxide).

A final issue was the decomposition of **11** during drying. The penultimate **11** degraded by urea bond cleavage to form 2−3% of amino acid **14** and piperidinyl quinolinone **4** during drying at 50 °C. Laboratory experimentation revealed that any potential

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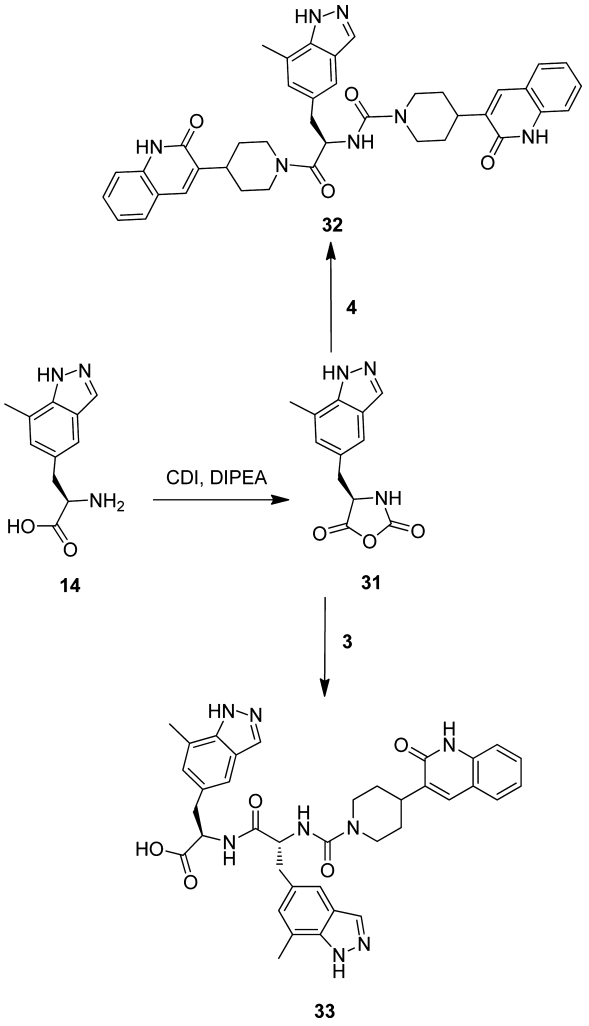
Scheme 15. Impurities generated from amino acid 14 in 3 (bis-HCl salt)

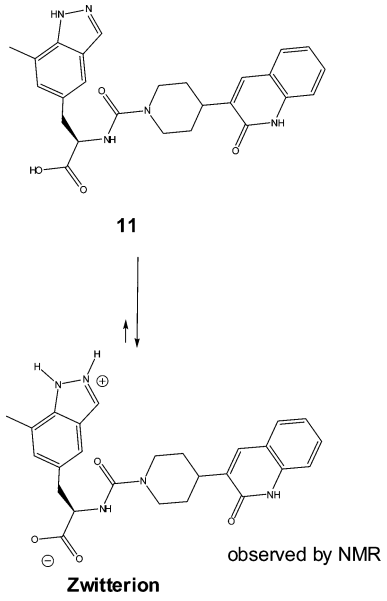


residual levels of HCl, LiOH, dimethylamine or LiCl were not the root cause of this degradation. This led us to speculate that the degradation may be facilitated by the carboxylic acid moiety of **11**. This possibility is supported by ^{1}H NMR studies, which showed that the indazole N−H resonance at 13.04 ppm in **11** was a rather broad peak of two protons between 12.4 and 13.4 ppm. This implies the potential existence of **11** as a zwitterion (Scheme 16), and the carboxylate anion may serve as the nucleophile to attack the urea carbonyl group to break the urea bond.

Decreasing the oven temperature to 40 °C limited decomposition to <0.1% over 63 h of drying while Dynochem modeling revealed that the rate of drying was controlled by moisture transport from inside the wet cake. To minimize drying time we utilized an agitated filter-dryer in a two stage protocol. The wet cake was first deliquored for at least 12 h at ambient temperature with minimum agitation, thus avoiding the formation of gummy balls. This was followed by warming to 40 °C with intermittent agitation. The telescoped process was then utilized to produce 1.7 kg of penultimate **11** in 80% yield and a purity of 95.6% and 99.3% ee.

Final Coupling to Produce 1. Initial polymorph screening revealed that **1** can crystallize in several neat and solvated forms, none of which were appropriate for development.

Scheme 16. Zwitterionic form of 11

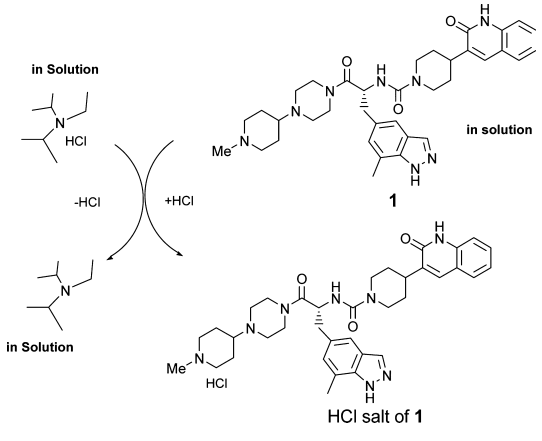


Fortunately, automated high-throughput screening studies identified the hydrochloride salt as an acceptable form.

Preparation of **1** requires amidation of the carboxylic acid **11** with piperazine **2** as previously shown in Scheme 11. Screening several commercial coupling reagents identified EDAC/HOBT as a promising system.

The principal challenge for this step was achieving a high volume efficiency. Here we benefitted from solvent screening studies, which revealed that **1** (HCl salt) has a very low solubility in a mixture of dimethyl acetamide (DMAc) and acetone. We envisioned the use of DMAc as reaction solvent so that subsequent addition of acetone and hydrochloric acid would allow the crystallization of the product when the amidation was complete. We were pleasantly surprised to observe that adding acetone to the reaction mixture and seeding with **1** (HCl salt) crystals caused the desired API crystals to form without the need for any extra hydrochloric acid. Evidently the free base of **1** generated from the reaction equilibrates with DIPEA-HCl to form the HCl salt of **1** and DIPEA free base (Scheme 17).[17] This direct precipitation of the HCl salt of **1** resulted in a satisfactory volume efficiency of ∼25 L/kg.

Scheme 17. In situ formation of 1 (HCl salt)



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Solvent screening also revealed that, in contrast to enantiomerically pure **1** (HCl salt), the racemic salt is virtually insoluble in ethanol. Thus filtration of an ethanol solution of the product reduced the levels of the undesired enantiomer of **1** below the limits of detection. Simple addition of heptane to recrystallize the product routinely provided **1** (HCl salt) of >99.9% ee.

This amidation/recrystallization sequence was scaled up to produce 1.8 kg of **1** (HCl salt) in 89% yield with a purity of 99.9% and >99.9% ee. The overall route was deemed suitable for future pilot plant campaigns to produce the HCl salt of **1**.

3. CONCLUSION

We have described development of a robust and practical route to the CGRP antagonist **1** (HCl salt) based on a convergent synthesis, which utilizes readily available starting materials, makes use of differing physical properties to facilitate isolations, and is applicable to further scale up. As a part of this effort, two processes were developed to prepare multikilogram quantities of amino ester **3** using either asymmetric transition metal catalysis or biocatalysis, each route offering different advantages from a process chemistry perspective. The biocatalytic route was selected for further development based on three considerations: (1) Exhaustive purification of enamide substrate **8** was required to achieve a high turnover number (TON) in the asymmetric hydrogenation. In contrast, the biocatalytic route is more tolerant of impurities down to 95% starting material purity. (2) The transition metal-catalyzed route required use of a proprietary catalyst available from a single vendor. In contrast, D-transaminase enzymes are widely available for the biocatalytic route. Furthermore a highly active D-transaminase enzyme was developed and expressed in recombinant *E. coli* and was produced efficiently by fermentation at BMS. (3) The biocatalyic route eliminated concerns about the removal of Pd and Rh residues from the API.

Three aspects of the endgame are noteworthy. The first is the use of water to quench excess CDI while not decomposing the activated intermediate **24**. Our approach should have general utility for reactions involving CDI and ambident nucleophiles. The other two points underscore the importance of determining the physical properties of reaction intermediates when designing synthetic protocols. In order to maximize process throughput, the low solubility of the final product **1** (HCl salt) in a mixture of DMAc and acetone was exploited by adding acetone to the reaction mixture to crystallize the product directly. In addition, the low solubility of the HCl salt of *rac*-**1** in ethanol was utilized to further upgrade the enantiomeric purity. The optimized process operations were shown to be robust and allowed production of the active pharmaceutical ingredient **1** (HCl salt) in multikilogram quantities.

4. EXPERIMENTAL PROCEDURES

The experiments outlined below provide representative procedures for what was run on scale in the kilo/pilot-plant facilities. NMR chemical shifts (δ) are given in ppm and infrared data (ν_{max}) are given in cm^{-1}.

4-Iodo-2,6-dimethylaniline Hydrochloride (6). Benzyltrimethylammonium dicholoroiodate ($BTMACl_2I$, 68.3 kg, 196.1 mol), potassium carbonate (30.1 kg, 217.5 mol), and dichloromethane (604 L) were sequentially charged to a reactor, and the resulting slurry was cooled to 5 °C. A solution of 2,6-dimethylaniline **5** (23.5 kg, 194.2 mol) in methanol (177 L) was charged over 1 h at <15 °C. The charging line was rinsed with methanol (59 L) into the reactor. The reaction mixture was warmed to 20 °C over 30 min and was stirred for an additional 30 min to complete consumption of **5**. The reaction mixture was filtered through a 20 μm polypropylene cloth to remove the inorganic solids. The reactor and filter cake were rinsed with dichloromethane (71 L), and the combined filtrate was distilled under reduced pressure at 20 °C to a volume of ~235 L. Ethyl acetate (235 L) was charged, and the distillation was continued under reduced pressure to an end point of <5% v/v of methanol. Ethyl acetate (235 L) was charged to adjust the volume to ~470 L. A solution of sodium chloride (12 kg) in water (202 L) was charged to the solution, and the mixture was stirred for 20 min. After phase separation, the aqueous layer (bottom) was discarded. The organic solution was washed with a solution of sodium chloride (7 kg) in water (134 L), the phases were separated, and the solution was distilled under reduced pressure at 20 °C to a volume of ~235 L. Ethyl acetate (235 L) was charged, and the distillation was continued under reduced pressure at 20 °C to an end point of <2% v/v of water. Ethyl acetate (282 L) was charged to the solution to adjust the volume to ~518 L, and the solution was polish filtered through a 10 μm in-line filter. The filtrate was adjusted with ethyl acetate to a final volume of ~588 L. The solution was cooled to 15 °C, and a solution of HCl in IPA (5 M, 46.0 kg, 252 mol) was charged over 30 min, while maintaining the temperature at <25 °C. The resulting slurry was stirred at 20 °C for 2 h and filtered. The cake was washed with ethyl acetate (2 × 117 L) and dried by vacuum suction on the filter for 1 h. The product cake was further dried under vacuum (35 °C, 25 mmHg) to afford 4-iodo-2,6-dimethylaniline hydrochloride (**6**) (47.8 kg, 81% yield, 96.0 area %, 93.3 wt.%) as an off-white crystalline solid; mp 168.4 °C; ^{1}H NMR (500 MHz DMSO-d_6) δ 9.67 (br, 3 H), 7.74 (s, 2 H), 2.33 (s, 6 H); ^{13}C NMR (100 MHz DMSO-d_6) δ 136.7, 133.2, 130.4, 91.9, 17.3; IR (KBr pellet) ν_{max} 3435, 2924, 2704, 2650, 2509, 2472, 2218, 1981, 1732, 1615, 1586, 1567, 1518, 1474, 1463, 1454, 1402, 1386, 1290, 1264, 1176, 1105, 1093, 1037, 1027, 915, 877, 858, 838, 704; Anal. Calcd for $C_8H_{11}ClIN$: C, 33.89; H, 3.91; Cl, 12.50; I, 44.76; N, 4.94. Found: C, 34.19; H, 3.84; Cl, 12.93; I, 43.21; N, 4.84.

Methyl 2-(Benzyloxycarbonylamino)acrylate (7). Sodium bicarbonate (44.4 kg, 527.2 mol) and water (410 L) were charged to a reactor, and the mixture was agitated for 15 min. The resulting solution was treated with a solution of serine methyl ester hydrochloride, **12** (82.0 kg, 159.8 mol), in water (328 L) over 1 h at such a rate as to control off-gassing. The solution was stirred at 20 °C for 15 min, and benzyl chloroformate (27.3 kg, 159.8 mol) was charged over 30 min. The charging line was rinsed with MTBE (214 L) into the reactor. The biphasic solution was stirred at 20 °C over 5 h to complete consumption of benzyl chloroformate. MTBE (528 L) was charged to the reactor, and the mixture was stirred for an additional 15 min. After the phases were separated, the aqueous layer (bottom) was discarded. A solution of sodium chloride (16 kg) in water (164 L) was added, and the mixture was stirred for 15 min. After the phases were separated, the aqueous layer (bottom) was discarded, and the solution was concentrated under reduced pressure at <25 °C to a volume of 250 L. THF (643 L) was charged, and the distillation was continued under reduced pressure at 20 °C to an end point of

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<750 ppm of water. THF (370 L) was charged to adjust the volume to ~620 L. The solution of the alcohol **13** was cooled to 0 °C, and methanesulfonyl chloride (22.0 kg, 191.7 mol) was charged over 30 min. The mixture was stirred for 30 min, and the triethylamine (50.1 kg, 495 mol) was charged while maintaining the internal temperature <25 °C. The reaction mixture was warmed to 25 °C and was stirred for 2 h to complete consumption of the intermediate mesylate. A solution of ammonium chloride (41.0 kg) in water (300 L) was charged, and the mixture was stirred vigorously for 15 min. After the phases were separated, the aqueous layer (bottom) was discarded, and the solution was concentrated under reduced pressure at <25 °C to a volume of ~90 L. The concentration of the solution was adjusted with THF (26 L) to produce a THF solution of methyl 2-(benzyloxycarbonylamino)acrylate, **7** (137 kg of solution, 24.8 wt % of **7**, 90.4% solution yield).

An aliquot was concentrated in vacuo for characterization. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.41−7.35 (m, 5 H), 7.30 (bs, 1 H), 5.82 (d, J = 1.52 Hz, 1 H), 5.19 (s, 2 H), 3.85 (s, 3 H); ^{13}C NMR (400 MHz $CDCl_3$) δ 164.1, 153.1, 135.8, 130.9, 128.5, 128.2, 106.0, 67.0, 52.9.

Methyl 3-(4-Amino-3,5-dimethylphenyl)-2-(benzyloxycarbonylamino)acrylate (8). *Heck Reaction to Produce Crude **8**.* 4-Iodo-2,6-dimethylaniline (**6**) (32.9 kg, 108.3 mol), tetra-*n*-butyl ammonium chloride (TBAC, 15.0 kg, 54.1 mol), potassium carbonate (K_2CO_3, 52.4 kg, 378.9 mol), and water (100 L) were sequentially charged to the reactor. The solution of **7** in THF (128.5 kg, 31.83 kg of **7**, 135.3 mol) was charged, and the mixture was stirred for 20 min. The palladium(II) acetate (1.21 g, 5.4 mmol) was charged, and the reaction mixture was heated to 70 °C. The reaction mixture was stirred at 65−70 °C over 5 h until complete consumption of **6**. The reaction mixture was cooled to <40 °C and was mixed with water (33 L) and THF (165 L). The mixture was stirred for 15 min and filtered through a 2 in. Celite bed (2 kg) followed by polish filtration though a 10 μm Cuno cartridge in-line filter to remove the insoluble palladium residue. The reactor, Celite cake, and cartridge were rinsed with THF (37 L), and the combined filtrates were allowed to settle. After the phases were separated, the aqueous layer (bottom) was discarded, and the solution was washed with a solution of sodium chloride (3 kg) in water (33 L). The solution was distilled under reduced pressure at 35 °C to a volume of ~165 L. Methanol (334 L) was charged to the solution, and the distillation continued under reduced pressure at 35 °C to an end point of <2% v/v of THF. Methanol (215 L) was charged to adjust the volume to ~380 L. The resulting slurry was cooled to 25 °C, and water (165 L) was charged while maintaining the internal temperature between 20 and 25 °C. The slurry was stirred at 20 °C for 1 h and was filtered. The cake was washed with a solution of methanol (66 L) in water (66 L) and was dried by vacuum suction of the filter for 1 h. The product cake was further dried under vacuum (50 °C, 25 mmHg) to afford the crude **8** (25.2 kg, 65.7% yield, 94.1 area %) as a dark-yellow, crystalline solid.

*Procedure for Formation of MSA Salt of **8** and Free Basing.* Crude **8** (23 kg, 64.9 mol), dichloromethane (206 L) and isopropyl alcohol (19 L) were sequentially charged to a reactor, and the resulting solution was cooled to 5 °C. The solution was stirred for 15 min, and methanesulfonic acid (6.9 kg, 71 mol) was charged while maintaining the internal temperature <20 °C. The mixture was warmed to 20 °C, and the salt began to precipitate after approximately 30 min of stirring. The slurry was stirred for additional 3 h and was filtered. The cake was washed with dichloromethane (57 L) and dried by vacuum suction on the filter for ~3 h. The partially dried MSA salt was charged back into the reactor followed by methanol (201 L) and water (23 L). The mixture was stirred at 20 °C for 15 min, and a solution of potassium carbonate (11.2 kg, 81.1 mol) in water (135 L) was charged while maintaining the temperature at ~20 °C. The slurry was stirred at 20 °C for 1 h and filtered. The cake was washed with a solution of methanol (36 L) in water (33 L) and was dried by vacuum suction of the filter for 1 h. The product cake was further dried under vacuum (50 °C, 25 mmHg) to afford methyl 3-(4-amino-3,5-dimethylphenyl)-2-(benzyloxycarbonylamino)acrylate, **8**, (18.3 kg, 79.6% yield, 97.6 area %, 95.2 wt %) as a yellow, crystalline solid..

Purification by Hot Filtration. Methyl 3-(4-amino-3,5-dimethylphenyl)-2-(benzyloxycarbonylamino)acrylate, **8** (17.1 kg, 48.3 mol), and ethyl acetate (282 L) were charged to a reactor. The mixture was heated to ~70 °C and stirred for 15 min to generate a solution. The hot solution was filtered through a preheated (65 °C) plate filter containing a 2 in. bed of Celite (2 kg). The reactor and plate filter were washed with preheated ethyl acetate (34 L), and the combined filtrate was concentrated under reduced pressure at 55 °C to a final volume of ~68 L. The slurry was warmed to 60 °C and stirred for 20 min. The slurry was cooled to 20 °C over 3 h and filtered. The product cake was washed with ethyl acetate (34 L) and dried by vacuum suction of the filter for 1 h. The product cake was further dried under vacuum (50 °C, 25 mmHg) to afford purified methyl 3-(4-amino-3,5-dimethylphenyl)-2-(benzyloxycarbonylamino)acrylate, **8** (14.7 kg, 86% yield, 98 area %, 97 wt %), as a bright-yellow crystalline solid; mp 143.6 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 8.80 (s, 1 H), 7.55−7.30 (m, 8 H), 5.14 (m, 2 H), 3.69 (s 3 H), 2.07 (s 6 H); ^{13}C NMR (400 MHz $CDCl_3$) δ 165.8, 154.5, 146.6, 137.0, 135.5, 130.7, 128.0, 127.4, 127.1, 120.1, 119.78, 119.3, 65.1, 51.5, 17.5; IR (KBr pellet) ν_{max} 3456, 3376, 3313, 3062, 3002, 2949, 2903, 2853, 1960, 1822, 1723, 1686, 1646, 1622, 1587, 1506, 1494, 1464, 1454, 1440, 1423, 1381, 1369, 1341, 1326, 1279, 1228, 1166, 1126, 1079, 1053, 1026, 999, 980, 964, 944, 906, 886, 876, 801, 775, 739, 697, 649; Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.51; H, 6.31; N, 7.97.

Methyl (*R*)-3-(4-Amino-3,5-dimethylphenyl)-2-(benzyloxycarbonylamino)-propanoate Methanesulfonate Salt [9 (MSA)]. The enamide **8** (1.7 kg, 4.7 mol), methanol (7 L) and dichloromethane (7 L) were sequentially charged to 20-L glass-lined reactor, and the mixture was stirred for 15 min. The mixture was purged three times at 30 psi with nitrogen, and the catalyst, (+)-1,1′-bis-(2*R*,4*R*)-2,4-diethylphosphotano)-ferrocene-(1,5-cyclooctadiene)rhodium(I)tetrafluoroborate (Et-ferrotane-Rh, 8.6 g, 11.7 mmol, 0.25 mol %), was charged. The charging flask was rinsed with dichloromethane (0.5 L) into the reactor. The slurry was again purged three times at 30 psi with nitrogen followed by hydrogen at 30 psi. The hydrogen pressure was set at 45 psi, and the reaction mixture was stirred at 25 °C for 1 h to complete consumption of **8**. The reaction mixture was filtered through a 10 μm polypropylene polish filter cloth. The reactor and polish filter cloth were rinsed with ethyl acetate (16 L), and this rinse was combined with the filtrate.

The hydrogenation reactor was cleaned with dilute aqueous nitric acid followed by a methanol rinse in between batches. Three additional batches of 1.65 kg input per batch were performed, and the filtrates of the four batches were combined.

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The solution was distilled under reduced pressure at 35 °C to a volume of ∼20 L. Ethyl acetate (67 L) was charged, and the distillation was continued under reduced pressure at 35 °C to an end point of <0.5% v/v of methanol. Ethyl acetate (42 L) was charged to adjust the volume to ∼59 L. A solution of methanesulfonic acid (0.49 kg, 5.1 mol) in ethyl acetate (29 L) was charged at ∼25 °C over 1 h. The resulting slurry was stirred at 20 °C for 2 h and was filtered. The cake was washed with ethyl acetate (9 L) and was dried by vacuum suction on the filter for 1 h. The product cake was further dried under vacuum (40 °C, 25 mmHg) to afford methyl (*R*)-3-(4-amino-3,5-dimethylphenyl)-2-(benzyloxycarbonylamino)propanoate methanesulfonate salt [**9** (MSA)] (8.1 kg, 96.1% yield, 99.6 area %, 99.3 wt %, 99.0% ee) as a white crystalline solid.

Another set of three batches of 1.65 kg input per batch were performed to produce an additional 6.1 kg of the MSA salt of **9** (96.5% yield, 99.5 area %, 98.9 wt %, 98.9% ee); mp 180.3 °C; $[\alpha]_D^{25}$ +17.03 (*c* 1.00, MeOH). ^{1}H NMR (400 MHz DMSO-d_6) δ 7.84 (d, *J* = 8.1 Hz, 1 H), 7.42−7.24 (m, 5 H), 7.02 (s, 2 H), 4.99 (dd, *J* = 5.0, 8.9 Hz, 2 H), 4.23 (ddd, *J* = 5.1, 8.2, 10.0 Hz, 1 H), 2.98−2.79 (m, 2 H), 2.34 (s, 3 H), 2.29 (3, 6 H); ^{13}C NMR (125 MHz DMSO-d_6) δ 172.2, 155.9, 136.8, 136.1, 130.4, 129.6, 128.3, 127.8, 127.6, 79.3, 78.9, 78.6, 65.4, 55.4, 51.9, 35.6, 17.6; IR (KBr pellet) ν_{max} 3355 (br), 2956, 2607, 1740, 1694, 1659, 1631, 1610, 1531, 1491, 1446, 1383, 1321, 1294, 1242, 1162, 1068, 1040, 1024, 868, 777, 699, 560; Anal. Calcd for $C_{21}H_{28}N_2O_7S$: C, 55.73; H, 6.23; N, 6.19; S, 7.08. Found: C, 55.91; H, 6.30; N, 6.08; S, 6.85.

Methyl (*R*)-2-(Benzyloxycarbonylamino)-3-(7-methyl-1*H*-indazol-5-yl)-propanoate (10). Methyl (*R*)-3-(4-amino-3,5-dimethylphenyl)-2-(benzyloxycarbonylamino)-propanoate methanesulfonate salt, **9** (MSA salt) (6.07 kg, 13.4 mol) and ethyl acetate (74 L) was charged to a reactor, and the mixture was stirred at 20 °C for 10 min. A solution of potassium carbonate (2.0 kg, 14.1 mol) in water (30 L) was charged while maintaining internal temperature at 20 °C. The charging line was rinsed with water (5 L) to the reactor, and the mixture was stirred for 30 min. The mixture was filtered through a 2 in. bed of Celite (1.2 kg) followed by polish filtration though a 10 μm Cuno cartridge in-line filter to remove any insoluble material. The reactor, Celite cake and cartridge were rinsed with ethyl acetate (13 L) to the reactor. After the phases were separated, the aqueous (bottom) was discarded. The solution was washed with a solution of sodium chloride (1.5 kg) in water (30 L). The ethyl acetate solution was filtered through a Cuno Zeta pad (R55SP) at a rate of 1.5 L/min to remove residual metals. The reactor and the Zeta pad were rinsed with ethyl acetate (13 L), and the rinse was combined with the filtrate. An aliquot of the combined filtrates was analyzed to ensure the residual palladium and rhodium levels were <10 ppm. The solution was distilled under reduced pressure at 35 °C to a volume of ∼55 L and a water content of <2.3%. Potassium acetate (1.64 kg, 16.76 mols) was added followed by acetic acid (1.21 kg, 20.12 mols, 1.5 equiv), and the mixture was stirred for 10 min. Isoamyl nitrite (96%, 1.8 kg, 14.8 mol) was charged over 30 min, and the charging lines were rinsed with ethyl acetate (26 L) to the reactor. The reaction was heated to 65 °C and was stirred for ∼5 h to ensure complete consumption of **9**. The mixture was cooled to 25 °C and a solution of potassium carbonate (4.0 kg, 29.1 mol) in water (30 L) was added. The mixture was stirred for 15 min, the phases were separated, and the aqueous layer was discarded. A solution of sodium chloride (1.5 kg) in water (30.4 L) was added, and the mixture was stirred for 20 min. After the phases were separated, the aqueous layer (bottom) was discarded, and the solution was distilled under reduced pressure at ∼35 °C to volume of ∼22 L. Toluene (61 L) was added, and the distillation was continued under reduced pressure at 35 °C to an end point of <0.5% v/v of ethyl acetate. Toluene (20 L) was charged to adjust the volume to ∼42 L, and the slurry was heated to 70 °C. The light slurry was stirred at ∼70 °C for 30 min and was cooled to 25 °C over 2 h. *n*-Heptane (30 L) was added over 30 min, and the slurry was stirred at 25 °C for 4 h. The slurry was filtered, and the cake was washed with a mixture of toluene (9 L) and *n*-heptane (21 L). The cake was dried by vacuum suction on the filter for ∼1 h and was further dried under vacuum (50 °C, 25 mmHg) to afford methyl (*R*)-2-(benzyloxycarbonylamino)-3-(7-methyl-1*H*-indazol-5-yl)-propanoate (**10**) (3.6 kg, 73% yield, 98.3 area %, 98.0 wt %, >99.9% ee) as an off-white crystalline solid.

A second batch of 6.07 kg input was performed to produce 3.5 kg of **10** in 71% isolated yield and chemical purity (98.1 area %, 97.4 wt %) and chiral purity of 99.9% ee; mp 150.9 °C; $[\alpha]_D^{25}$ +7.89 (*c* 1.03, MeOH). ^{1}H NMR (500 MHz DMSO-d_6) δ 13.08 (s, 1 H), 7.98 (s, 1 H), 7.83 (d, *J* = 8.2 Hz, 1 H), 7.41 (s, 1 H), 7.30−7.22 (m, 5 H), 7.02 (s, 1 H), 4.97 (s, 2 H), 4.31−4.28 (m, 1 H), 3.62 (s, 3 H), 3.10 (dd, *J* = 5.0, 8.9 Hz, 1 H), 2.92 (dd, *J* = 3.5, 10.0 Hz, 1 H), 2.47 (s, 3 H); ^{13}C NMR (125 MHz DMSO-d_6) δ 172.5, 156.0, 139.2, 136.9, 133.4, 129.4, 128.3, 127.7, 127.5, 127.3, 122.7, 119.6, 117.7, 65.3, 56.0, 51.9, 36.5, 16.8; IR (KBr pellet) ν_{max} 3329, 3207, 3154, 3067, 2979, 2947, 2929, 2862, 2837, 2765, 1950, 1746, 1696, 1624, 1604, 1589, 1528, 1453, 1431, 1380, 1362, 1333, 1284, 1260, 1251, 1203, 1179, 1151, 1072, 1037, 1030, 1013, 991, 952, 909, 877, 847, 818, 779, 752, 738, 697, 672, 642; Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.66; H, 5.48; N, 11.59.

Methyl (*R*)-2-Amino-3-(7-methyl-1*H*-indazol-5-yl)-propanoate Dihydrochloride (3 bis-HCl). *Method A.* Palladium on carbon (10%, 0.2 kg, 0.1 mol), **10** (2.6 kg, 7.1 mol), methanol (13 L) and ethyl acetate (7 L) were sequentially charged to a hydrogenation reactor. The reactor was purged repeatedly with nitrogen and then pressurized with hydrogen to 45 psig. The reaction mixture was heated to 25 °C and was stirred for 2 h to complete the consumption of **10**. Ethyl acetate (13 L) was charged, and the mixture was purged with nitrogen for ∼30 min. The mixture was filtered sequentially through a 2 in. bed of Celite 545 (2 kg) and a 10 μm polypropylene filter, rinsing with a solution of ethyl acetate (10 L) and methanol (11 L), and the rinse was combined with the filtrate. The combined filtrate was filtered through a Cuno Zeta pad (R53SP) at a rate of 1.5 L/min to remove the residual metals. The reactor and the Zeta pad were rinsed with ethyl acetate (9 L), and the rinse was combined with the filtrate. An aliquot of the filtrate was taken and analyzed to ensure the residual palladium and rhodium levels were <10 ppm. The solution was polish filtered through a 0.5 μm in-line polish filter and ethyl acetate (27 L) was added to adjust the ethyl acetate/methanol ratio to 3:1. A solution of HCl in IPA (4.5 M, 3.3 kg, 15.6 mol) was added over 1 h, and the resulting slurry was stirred at 20 °C for 3 h. The slurry was filtered, and the cake was washed with ethyl acetate (4 L). The cake was dried by cacuum suction on the filter for 1 h and was further dried under vacuum (35 °C, 25 mmHg) to afford (*R*)-methyl 2-amino-3-(7-methyl-1*H*-indazol-5-yl)propanoate dihydrochloride (**3** bis-HCl) (1.85 kg, 85.6% yield, 99.5 area %, 98

wt %, >99.9% ee) as a white crystalline solid with less than 5 ppm of both palladium and rhodium.

A second batch with a 2.6 kg input was performed to produce 1.80 kg of **3** bis-HCl in 83% isolated yield, chemical purity 98 wt %, and chiral purity >99.9% ee.

*Method B. Step 1: Formation of the bis-HCl Salt of **14**.* Indazolyl amino acid **14** (2.0 kg, 8.8 mol) and methanol (16 L) were charged to a reactor, and the mixture was stirred for 10 min. The mixture was cooled to <10 °C, and acetyl chloride (1.45 kg, 18.5 mol) was charged while maintaining the internal temperature at <20 °C. The charging lines were rinsed with methanol (1 L) into the reactor. The mixture was stirred at 20 °C for 30 min, and MTBE (34 L) was charged over 1 h. The slurry was stirred at 20 °C for 2 h and was filtered. The cake was washed with MTBE (11 L) and was dried by vacuum suction on the filter for 12 h to afford (*R*)-2-amino-3-(7-methyl-1*H*-indazol-5-yl)propanoic acid dihydrochloride (**14** bis-HCl) (2.38 kg, 94.5% yield, 97.5 area %). ^{1}H NMR (400 MHz $CDCl_3$) δ 8.73 (s, 1 H), 7.78 (s, 1 H), 7.48 (s, 1 H), 4.38 (dd, J = 1.9, 5.7 Hz, 1 H), 4.38 (dd, J = 5.6, 8.9 Hz, 1 H), 2.65 (s, 3 H); ^{13}C NMR (400 MHz $CDCl_3$) δ 171.4, 141.4, 133.9, 132.9, 132.2, 124.3, 123.0, 121.7, 55.3, 37.4, 17.4.

Step 2: Fischer Esterification. (*R*)-2-Amino-3-(7-methyl-1*H*-indazol-5-yl)propanoic acid dihydrochloride (**14** bis-HCl) (2.34 kg, 8.0 mol) and methanol (55 L) were charged to a reactor, and the mixture was stirred at 20 °C for 30 min. The resulting solution was recirculated through a 10 μm Cuno polish filter for 1 h. The polish filter and the circulating lines were rinsed with methanol (2 L) into the reactor. The combined solution was cooled to <10 °C, and acetyl chloride (3.1 kg, 40.0 mol) was charged while maintaining the internal temperature at <20 °C. The charging lines were rinsed with methanol (1 L) into the reactor. The reaction mixture was heated to 40 °C and was stirred for 16 h to ensure complete consumption of **14**. The reaction mixture was cooled to <25 °C and was concentrated by distillation under reduced pressure at <30 °C to a volume of ∼21 L. The resulting slurry was warmed to 35 °C and was charged with MTBE (19 L) over 1 h. The slurry was stirred at 20 °C for 2 h and was filtered. The cake was washed with MTBE (5.8 L) and dried by vacuum suction on the filter for ∼1 h. The cake was further dried under vacuum (25 °C, 25 mmHg) to afford methyl (*R*)-2-amino-3-(7-methyl-1*H*-indazol-5-yl)propanoate dihydrochloride (**3** bis-HCl) (2.2 kg, 90.7% yield, 98.6 area %, 74.7 wt %, 99.0% ee) as a white crystalline solid; mp 162.9 °C; $[\alpha]_D^{25}$ −7.06 (c 1.03, MeOH). ^{1}H NMR (500 MHz DMSO-d_6) δ 8.66 (s, 1 H), 7.73 (s, 1 H), 7.43 (s, 1 H), 4.34 (dd, J = 1.9, 5.6 Hz, 1 H), 3.44 (dd, J = 5.7, 9.1 Hz, 1 H), 3.29 (dd, J = 1.9, 6.7 Hz, 1 H), 2.61 (s, 3 H); ^{13}C NMR (125 MHz DMSO-d_6) δ 169.3, 139.5, 133.2, 127.4, 126.7, 122.6, 120.2, 118.4, 53.5, 52.4, 35.7, 16.8; IR (KBr pellet) ν_{max} 3426, 2948, 2841, 2702, 2614, 2535, 2437, 1742, 1637, 1588, 1529, 1448, 1433, 1391, 1360, 1302, 1269, 1238, 1217, 1139, 1113, 1065, 1007, 983, 951, 923, 897, 879, 843, 752, 713, 622; Anal. Calcd for $C_{12}H_{17}Cl_2N_3O_2$: C 47.07, H 5.59, Cl 23.15, N 13.72. Found: C 47.07, H 5.59, Cl 22.94, N 13.70.

5-Bromo-7-methyl-1*H*-indazole (17). 4-Bromo-2,6-dimethylaniline, **16** (10.8 kg, 53.7 mol), potassium acetate (8.0 kg, 81.6 mol,) and toluene (162 L) were sequentially charged to a reactor. The mixture was stirred for 30 min and was charged with acetic acid (4.6 kg, 76.8 mol) while maintaining internal temperature at <40 °C. The mixture was stirred at 40 °C and *tert*-butyl nitrite (90% purity, 7.1 kg, 61.8 mol) was charged over 30 min while maintaining the internal temperature at <50 °C. The reaction mixture was stirred at 45 °C for 6 h to ensure the complete consumption of **16**. The reaction mixture was cooled to 25 °C and was charged with ethyl acetate (60 L) followed by water (54 L). The mixture was stirred at 25 °C for 20 min, and aqueous sodium hydroxide solution (4 M, 20 L) was charged to adjust the pH to ∼9.0. The mixture was stirred for an additional 1 h,, and the phases were separated. The aqueous layer was extracted with ethyl acetate (32 L), and the ethyl acetate extract was combined with the organic phase. The combined organic phase was washed with water (54 L), and the solution was distilled under reduced pressure at 55 °C to a volume of ∼43 L. Toluene (63 L) was charged, and the distillation was continued under reduced pressure at 35 °C to an end point of <5% v/v of ethyl acetate. The resulting slurry was heated to 85 °C and *n*-heptane (65 L) was charged over ∼1 h. The slurry was cooled to 25 °C over 2 h and stirred for an additional 6 h. The slurry was filtered, and the cake was washed with *n*-heptane (2 × 32 L). The cake was dried by vacuum suction on the filter for 1 h and was further dried under vacuum (35 °C, 25 mmHg) to afford 5-bromo-7-methyl-1*H*-indazole, **17**, (9.43 kg, 81.7% yield, 99.2 wt %) as a light-brown crystalline solid; mp 185.7 °C. ^{1}H NMR (500 MHz DMSO-d_6) δ 13.52 (br, 1 H), 8.14 (s, 1 H), 7.89 (s, 1 H), 7.36 (s, 1 H), 2.63 (s, 3 H); ^{13}C NMR (125 MHz DMSO-d_6) δ 138.9, 133.3, 128.1, 124.0, 122.6, 120.1, 112.6, 16.6; IR (KBr pellet) ν_{max} 3449, 3151, 3068, 2936, 2875, 2839, 2778, 1712, 1695, 1618, 1592, 1572, 1494, 1449, 1432, 1412, 1374, 1341, 1300, 1277, 1241, 1205, 1165, 1104, 1087, 1070, 1039, 1014, 985, 946, 908, 870, 856, 851, 822, 779, 739, 612; HRMS Calcd for $C_8H_7BrN_2$: 210.9865 [$(M + H)^+$], found 210.9862.

7-Methyl-1*H*-indazole-5-carbaldehyde (18). 5-Bromo-7-methyl-1*H*-indazole, **17**, (8.6 kg, 40.5 mol) and THF (128 L) were charged to a reactor. The mixture was stirred for 20 min, and the resulting solution was cooled to −70 °C. A solution of *n*-butyllithium in hexanes (2.5 M, 16.9 kg, 60.8 mol) was charged while maintaining the internal temperature at <−60 °C. The charging lines were rinsed with THF (3 L) followed by cyclohexane (2 L) into the reactor. The mixture was stirred at −70 °C for ∼1 h, and a solution of *sec*-butyllithium in cyclohexane (2.0 M, 54.1 kg, 101.3 mol) was charged while maintaining the internal the temperature <−60 °C. The charging lines were rinsed with cyclohexane (3 L) followed by THF (2 L) into the reactor. The mixture was stirred at −70 °C for ∼1 h to ensure the complete consumption of **17**. Dimethylformamide (11.8 kg, 162.0 mol,) was charged while maintaining the internal temperature <−55 °C. The reaction mixture was warmed to 5 °C over 2 h and was charged with water (86 L) while maintaining the internal temperature <20 °C. The mixture was stirred for 15 min, and the phases were separated. The organic layer was concentrated by distillation at reduced pressure and 40 °C to a final volume of ∼55 L. The concentrated solution was extracted with aqueous sodium bisulfite solution (10%, 5 × 26 L). The product rich aqueous extracts were combined. Ethyl acetate (128 L) was charged, and the pH of the mixture was adjusted to between pH 8 to 9 with aqueous sulfuric acid (2 M, 17 L). Sodium chloride (43 kg) was charged and mixture was stirred for 30 min. After the phases were separated, the aqueous layer (bottom) was discarded. The solution was concentrated by distillation at reduced pressure at 45 °C to a volume of ∼26 L. *n*-Heptane (60 L) was charged, and the distillation was continued under reduced pressure at ∼45 °C to an end point of <5% v/v of ethyl acetate. *n*-Heptane

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(34 L) was charged to adjust the volume to ~60 L. The slurry was cooled to 5 °C over 2 h and stirred for an additional 2 h. The slurry was filtered, and the cake was washed with *n*-heptane (9 L). The cake was dried by vacuum suction on the filter for ~1 h and was further dried under vacuum (40 °C, 25 mmHg) to afford 7-methyl-1*H*-indazole-5-carbaldehyde, **18**, (5.84 kg, 90.3% yield, 98.5 wt %) as a white crystalline solid; mp 183.5 °C; ^{1}H NMR (500 MHz DMSO-d_6) δ 13.61 (s, 1 H), 9.97 (s, 1 H), 8.32 (s, 1 H), 8.24 (s, 1 H), 7.59 (s, 1 H), 2.56 (s, 3 H); ^{13}C NMR (125 MHz DMSO-d_6) δ 192.5, 142.8, 136.5, 130.6, 125.7, 123.6, 122.5, 121.4, 16.9; IR (KBr pellet) ν_{max} 3516, 3354, 3250, 3075, 2937, 2827, 2797, 2717, 1816, 1798, 1688, 1669, 1620, 1602, 1503, 1489, 1462, 1440, 1383, 1376, 1351, 1333, 1324, 1283, 1243, 1213, 1125, 1083, 1060, 998, 941, 889, 860, 834, 802, 760, 705, 613; Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.17; H, 4.85; N, 17.53.

4-((7-Methyl-1*H*-indazol-5-yl)methylene)-2-phenyloxazol-5(4*H*)-one (19). 7-Methyl-1*H*-indazole-5-carbaldehyde, **18**, (5.4 kg, 33.9 mol) and potassium acetate (4.6 kg, 47.1 mol) were charged to a reactor. Acetic anhydride (86.5 kg, 847 mol) was charged to the mixture while maintaining the internal temperature at <40 °C. The mixture was stirred at 25 °C for 1 h, and hippuric acid (12.2 kg, 67.8 mol) was charged. The reaction mixture was heated to 60 °C over 30 min and was stirred at 60 °C for 3 h to ensure the complete consumption of **18**. The reaction mixture was cooled to 25 °C and water (38 L) was charged while maintaining the internal temperature at <40 °C. The slurry was heated to 60 °C and was stirred for at 2 h. The slurry was cooled to ~20 °C over 1 h and filtered. The cake was washed with a (1:1) methanol/water mixture (109 L) and dried by vacuum suction on the filter for 1 h. The cake was further dried under vacuum (40 °C, 25 mmHg) to afford 4-((7-methyl-1*H*-indazol-5-yl)methylene)-2-phenyloxazol-5(4*H*)-one, **19**, (10.95 kg, 93.9% yield, 99.3 wt %) as a yellow crystalline solid.; mp 224.8 °C; ^{1}H NMR (500 MHz DMSO-d_6) δ 13.49 (s, 1 H), 8.52 (s, 1 H), 8.25 (s, 1 H), 8.19 (s, 1 H), 8.13 (s, 1 H), 8.12 (d, J = 1.3 Hz, 1 H), 7.72−7.69 (m, 1 H), 7.65−7.62 (m, 2 H), 7.41 (s, 1 H), 2.58 (s, 3 H); ^{13}C NMR (125 MHz DMSO-d_6) δ 167.1, 161.8, 141.0, 135.8, 133.3, 132.7, 130.7, 129.3, 128.8, 127.8, 126.5, 125.3, 125.2, 123.2, 120.7, 17.0; IR (KBr pellet) ν_{max} 3434, 3232, 3146, 3057, 2939, 2851, 1789, 1770, 1755, 1650, 1609, 1597, 1583, 1557, 1501, 1491, 1450, 1369, 1325, 1298, 1258, 1209, 1173, 1144, 1106, 1085, 1062, 1009, 979, 943, 913, 888, 877, 858, 776, 757, 719, 699, 686, 673, 655, 632, 619; Anal. Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85. Found: C, 70.80; H, 3.85; N, 13.77.

Methyl 2-Benzamido-3-(7-methyl-1*H*-indazol-5-yl)-acrylate (20). 4-((7-Methyl-1*H*-indazol-5-yl)methylene)-2-phenyloxazol-5(4*H*)-one, **19**, (10.9 kg, 31.4 mol) and methanol (163 L) were charged to a reactor. The mixture was stirred for 10 min, and a 30% solution of sodium methoxide in methanol (0.6 kg, 3.1 mol) was charged while maintaining the internal temperature at <30 °C. The reaction mixture was stirred at 25 °C for 3 h to ensure complete consumption of **19**. Acetic acid (0.4 kg, 6.3 mol) was charged to the reaction mixture, and the mixture was stirred for 30 min. The mixture was charged with water (163 L) while maintaining the internal temperature at <30 °C. The resulting slurry was cooled to 5 °C and was stirred for 1 h. The slurry was filtered, and the cake was washed with water (43 L). The cake was dried by vacuum suction on the filter for 1 h and was further dried under vacuum (50 °C, 25 mmHg) to afford methyl 2-benzamido-3-(7-methyl-1*H*-indazol-5-yl)acrylate, **20**, (10.3 kg, 94.8% yield, 96.6 wt %) as white crystalline solid; mp 225.2 °C. ^{1}H NMR (500 MHz DMSO-d_6) δ 13.32 (s, 1 H), 10.06 (s, 1 H), 8.11 (s, 1 H), 8.03 (s, 1 H), 8.02 (s, 1 H), 7.97 (s, 1 H), 7.64−7.61 (m, 1 H), 7.58−7.55 (m, 3 H), 7.53 (s, 1 H), 3.75 (s, 3 H), 2.46 (s, 3 H); ^{13}C NMR (125 MHz DMSO-d_6) δ 166.3, 165.8, 140.2, 134.9, 134.8, 133.6, 131.9, 128.6, 127.7, 127.2, 126.2, 124.4, 122.8, 121.2, 120.0, 52.2, 17.0; IR (KBr pellet) ν_{max} 3426, 3231, 3061, 2945, 2850, 2784, 1731, 1718, 1646, 1615, 1580, 1509, 1483, 1437, 1373, 1361, 1318, 1248, 1191, 1160, 1134, 1104, 1084, 1027, 979, 946, 915, 902, 871, 835, 797, 766, 750, 714, 692, 633, 616; Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.03; H, 5.12; N, 12.59.

2-Hydroxy-3-(7-methyl-1*H*-indazol-5-yl)acrylic Acid (15). Methyl 2-benzamido-3-(7-methyl-1*H*-indazol-5-yl)-acrylate, **20**, (1.8 kg, 5.1 mol), water (2 L), and 30% aqueous hydrochloric acid (49 kg) were sequentially charged to a reactor. The reaction mixture was heated to ~100 °C and was stirred for 6 h to ensure a complete consumption of **20**. The reaction mixture was cooled to 10 °C over 2 h, and the slurry was filtered. The cake was washed with water (17 L) and was charged back to the reactor. Water (20 L) was charged, and the mixture was warmed to 90 °C. The slurry was stirred at 90 °C for 2 h and was filtered through a preheated filter (90 °C). The cake was washed with hot water (90 °C, 10 L) and was dried by vacuum suction on the filter for 1 h. The cake was dried under vacuum (50 °C, 25 mmHg) to afford an *E*/*Z* mixture of 2-hydroxy-3-(7-methyl-1*H*-indazol-5-yl)acrylic acid (**15**) (0.89 kg, 74.6% yield, 97.2 area %, 96.10 wt %) as a white solid. ^{1}H NMR (500 MHz $CDCl_3$) *E*-isomer: 8.11 (s, 1 H), 8.0 (d, J = 1.3 Hz, 1 H), 7.68 (d, J = 1.9 Hz, 1 H), 7.54 (t, J = 1.9, 5.0 Hz, 1 H), 6.57 (s, 1 H), 2.56 (s, 3 H); *Z*-isomer: 8.13 (s, 1 H), 8.02 (d, J = 1.0 Hz, 1 H), 7.69 (s, 1 H), 7.58 (t, J = 1.6, 8.8 Hz, 1 H), 2.56 (s, 3 H); ^{13}C NMR (125 MHz $CDCl_3$) 167.4, 166.6, 140.2, 139.4, 134.3, 132.9, 130.8, 129.3, 128.6, 127.8, 127.7, 123.0, 119.6, 119.0, 110.9, 16.9; IR (KBr pellet) ν_{max} 3473, 3445, 3071, 2972, 2838, 2670, 2603, 2557, 1788, 1687, 1617, 1602, 1583, 1518, 1496, 1453, 1424, 1369, 1327, 1291, 1258, 1240, 1186, 1152, 1128, 1095, 1073, 1026, 993, 963, 945, 890, 876, 845, 833, 810, 768, 751, 707; HRMS Calcd for $C_{11}H_{11}N_2O_3$: 219.0764 [$(M + H)^+$], found 219.0764.

Preparation of (*R*)-Amino Acid 14 from Keto Acid 15. [Note: this procedure was previously reported in ref 13 but is reproduced here for the convenience of the reader.] Water (445 mL), keto acid **15** (30 g, 0.14 mol), DL-alanine (120 g, 1.35 mol), K_2HPO_4 (6.97 g, 0.04 mol), and KH_2PO_4 (1.36 g, 0.01 mol) were charged to a 2-L reactor followed by 30% sodium hydroxide (8 M, 17.3 mL), and the suspension was stirred at 200 rpm for 10 min to dissolve most of the solids. Additional water (445 mL) was added to bring the total volume to 1 L, and stirring was continued for 20 min to completely dissolve the solids. The pH was adjusted to 7.5 with a few drops of 25% NaOH. Dithiothreitol (154 mg, 1 mmol) in water (2 mL) and pyridoxal phosphate monohydrate (26.5 mg, 0.1 mmol) in pH 7.5 buffer (2 mL) were then added to the solution which was stirred at 50 rpm and 30 °C. D-Transaminase (300 mg, 4.4 U/mg, Biocatalytics) dissolved in 25 mL of 0.1 M potassium phosphate buffer pH 7.5 was then added to the stirred solution. After precipitation of **14** commenced (~3 h), stirring was periodically increased to 150 rpm so that aliquots for HPLC analysis could be obtained. Reaction was continued until the area % of **15** was <10 area % relative to that for **14**, which took about 72 h. The pH was adjusted to 1 with sulfuric acid at which point product **14**

redissolved. The solution was filtered, and the filtrate was passed through a 2.5 cm i.d. × 9.1 cm column of Amberlite F XAD-16 resin, washing with 0.1 M H_2SO_4 to remove nonpolar impurities. The column effluent was heated to 100 °C, and the pH was slowly adjusted to 7 with NaOH. The mixture was cooled to room temperature, stirred for 15 h, and filtered, washing the cake with deionized water. The cake was dried in vacuum at room temperature, giving 24.6 g of **14** as the monohydrate. The yield from keto acid **15** was 77%, correcting for the purity of the keto acid (94.2 wt %) and isolated product (96.5 wt %). $[\alpha]_D^{29}$ +17.3 (*c* 0.08, HOAc); ^{1}H NMR (400 MHz, acetic acid-d_4) 2.54 (s, 3H), 3.27 (dd, *J* = 14.5, 8.2 Hz, 1H), 3.45 (dd, *J* = 14.7, 4.6 Hz, 1H), 4.39 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.16 (s, 1H), 7.54 (s, 1H), 8.11 (s, 1H). Anal. Calcd for $C_{11}H_{13}N_3O_2.H_2O$: C, 55.68, H, 6.37, N, 17.71; found: C, 55.62; H, 6.45, N, 17.63. Water, calculated for monohydrate 7.59; found: 7.50 (Karl Fischer).

Telescoped Preparation of (*R*)-3-(7-Methyl-1*H*-indazol-5-yl)-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)-piperidine-1-carboxamido)propanoic Acid (11). *Step 1: CDI Activated Urea Coupling.* Methyl (*R*)-2-amino-3-(7-methyl-1*H*-indazol-5-yl)propanoate hydrochloride, **3** bis-HCl, (1.4 kg, 4.6 mol), *N*,*N*-dimethylformamide (DMF, 6 L), and *N*,*N*-diisopropylethylamine (DIPEA, 1.2 kg, 9.6 mol) were sequentially charged to a reactor. The mixture was stirred for 20 min, and the resulting solution was cooled to −20 °C. A slurry of 1,1′-carbonyldiimidazole (CDI, 0.9 kg, 5.5 mol) in DMF (4 L) was charged while maintaining the temperature at <−10 °C. The mixture was stirred at −10 °C for 15 min to ensure the complete consumption of **3**. A solution of water (0.4 kg, 22.9 mol) in DMF (1 L) was charged while maintaining the temperature at <−10 °C. The resulting mixture was stirred at −10 °C for 15 min to ensure the complete quench of CDI. 3-(Piperidin-4-yl)quinolin-2(1*H*)-one hydrochloride (**4** HCl salt) (1.3 kg, 4.7 mol), DIPEA (0.7 kg, 5.0 mol), and methylene chloride (3 L) were sequentially charged to the reactor. The reaction mixture was heated to 40 °C and was stirred for 12 h to ensure the complete consumption of **24**. The reaction mixture was cooled to 20 °C and was charged with aqueous hydrochloric acid (2 M, 6.5 kg, 13.1 mol) to adjust the pH of the mixture to 2. The resulting mixture was extracted with methylene chloride (8 L), and the product-rich methylene chloride phase was washed with water (14 L).

Step 2: Saponification. A solution of lithium hydroxide (0.16 kg, 7.1 mol) in water (4 L) was charged to the product-rich methylene chloride solution. The mixture was stirred at 20 °C for 40 min to ensure complete hydrolysis. After the phases were separated, the methylene chloride phase was discarded. Water (8 L) was charged, and the diluted aqueous phase was transferred into aqueous hydrochloric acid (1 M, 10.2 kg, 10.1 mol) while maintaining the temperature below 15 °C. The resulting slurry with pH between 1 and 2 was stirred at <20 °C for 2 h and was filtered. The cake was washed with water (4 × 14 L) to reduce the conductivity of the filtrate to below 2.0 mS. The cake was further washed with MTBE (14 L) and was deliquored (20 °C, 25 mmHg) in an agitation drier with minimum stirring for 16 h. The drying was continued under vacuum (35 °C, 25 mmHg) to afford (*R*)-3-(7-methyl-1*H*-indazol-5-yl)-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)-piperidine-1-carboxamido)propanoic acid, **11**, (1.90 kg, 84% yield, 95.6 wt %, 99.3% ee) as a white amorphous solid; $[\alpha]_D^{25}$ +28.7 (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.4−13.4 (br, 2H), 11.76 (s, 1H), 7.97 (s, 1H), 7.61 (d, *J* = 6.9 Hz, 1H), 7.54 (s, 1H), 7.37−7.47 (m, 2H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.11−7.2 (m, 1H), 7.04 (s, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 4.03−4.14 (m, 2H), 3.04−3.14 (m, 1H), 2.94−3.03 (m, 1H), 2.83−2.94 (m, 1H), 2.61−2.79 (m, 2H), 2.46 (s, 3H), 1.67−1.81 (m, 2H), 1.18−1.38 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 160.6, 156.0, 138.4, 136.6, 136.2, 133, 132.6, 129.8, 128.6, 126.9, 126.8, 122.0, 121, 118.7, 117, 114, 55.8, 44.2, 44, 36.6, 35.5, 30.8, 17.1; IR (KBr pellet) ν_{max} 3215 (br), 2930, 2856, 1716, 1646, 1615, 1571, 1517, 1426, 1314, 1267, 1222, 1084, 983, 944, 870, 755, 714, 590, 467; HRMS Calcd for $C_{26}H_{28}N_5O_4$: 474.2136 [(M + H)$^+$], found 474.2063.

(*R*)-*N*-(3-(7-Methyl-1*H*-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (1 HCl salt). (*R*)-3-(7-methyl-1*H*-indazol-5-yl)-2-(4-(2-oxo-1,2-dihydroquinolin-3-yl)-piperidine-1-carboxamido)propanoic acid, **11**, (1.81 kg, 3.8 mol), 1-hydroxybenzotriazole monohydrate (HOBT, 0.6 kg, 3.8 mol), dimethylacetamide (DMAc, 3 L), diisopropylethylamine (DIPEA, 1.0 kg, 7.6 mol) and piperazine **2** (0.84 kg, 4.6 mol) were sequentially charged to a reactor while maintaining the temperature <45 °C. The mixture was stirred at 45 °C for 15 min, and 1-[3-(dimethylamine)-propyl]-3-ethylcarbodiimide (EDAC-HCl, 1.0 kg, 4.6 mol) was added portionwise to ensure a good dispersion, rinsing with DMAc (1 L). The reaction mixture was cooled to 25 °C and was stirred for ∼24 h to consume **11**. The reaction mixture was polish filtered through a 10 μm in-line polypropylene filter, rinsing the reactor and the filter lines with ethanol (200 proof, 2 L). The combined filtrate was heated to 45 °C over 30 min. Acetone (11 L) was charged while maintaining the temperature >41 °C. The solution was seeded with a slurry of **1** (HCl salt) (4.5 g, 0.3 wt %) in acetone (0.2 L), and the mixture was stirred at 45 °C for ∼1 h. Acetone (43 L) was charged over 30 min, and the resulting slurry was stirred at 45 °C for 1 h. The slurry was cooled to 20 °C over 30 min and was stirred for 3 h. The slurry was filtered, and the cake was washed with acetone (7 L). The cake was dried by vacuum suction on the filter for 1 h and was further dried under vacuum (45 °C, 25 mmHg) to afford crude (*R*)-*N*-(3-(7-methyl-1*H*-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (**1** HCl salt) (2.32 kg, 90% yield, 95.5 wt %, 99.9% ee) as a white crystalline solid.

A second batch with a 1.81 kg input of **11** was performed to produce 2.24 kg of **1** (HCl salt) in 86% isolated yield and chemical purity (98.8 area %, 95.5 wt %) and chiral purity of 99.9% ee.

Recrystallization of 1 (HCl salt). Crude (*R*)-*N*-(3-(7-methyl-1*H*-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)-piperidine-1-carboxamide (2.0 kg, 3.0 mol) and ethanol (40 L) were charged to a reactor, and the mixture was heated to 73 °C over 30 min. The resulting solution was cooled to 45 °C and was polish filtered through a 10 μm Cuno in-line filter, rinsing with EtOH (2 L), and the combined filtrate was heated to 45 °C over 30 min and was charged with acetone (3 L). The solution was stirred for 15 min and was seeded with a slurry of **1** HCl salt (15 g, 0.8 wt %) and acetone (367 mL). The mixture was stirred at 45 °C for 1 h, and acetone (39 L) was charged over 30 min. The slurry was stirred at 45 °C for 1 h, cooled to 20 °C over 30 min, and stirred for 12 h. The slurry was filtered, and the cake was washed with acetone (3 × 10 L). The cake was dried by vacuum suction on the filter for 1 h and was

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further dried under vacuum (65 °C, 25 mmHg) to afford (*R*)-*N*-(3-(7-methyl-1*H*-indazol-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2-dihydroquinolin-3-yl)piperidine-1-carboxamide (**1**, HCl salt) (1.81 kg, 89% yield, 99.8 wt %, >99.9% ee) as a white crystalline solid; mp 276.6 °C; $[\alpha]_D^{25}$ −27.3 (*c* 1.04, MeOH); ^{1}H NMR (400 MHz DMSO-d_6) δ 13.07 (s, 1 H), 11.78 (s, 1 H), 7.97 (s, 1 H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.60 (s, 1 H), 7.43 (t, *J* = 7.4 Hz, 1 H), 7.38 (s, 1 H), 7.38 (s, 1 H), 7.29 (d, *J* = 8.3 Hz, 1 H), 7.15 (t, *J* = 7.8 Hz, 1 H), 7.03 (s, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 4.79 (dd, *J* = 7.3, 7.8 Hz, 1 H), 4.15 (d, *J* = 12.2 Hz, 1 H), 3.55−2.67 (m, 15 H), 2.62 (s, 3 H), 2.49 (s, 3 H), 2.35−2.00 (m, 4 H), 1.79−1.75 (m, 2 H), 1.71−1.45 (m, 5 H), 1.38−1.29 (m, 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.8, 164.7, 159.6, 141.5, 139.0, 138.1, 137.0, 135.7, 131.6, 131.5, 130.4, 129.3, 125.0, 124.2, 122.4, 122.1, 120.2, 116.6, 59.7(br), 55.2(br), 53.6, 47.3, 46.2, 44.0(br), 43.6, 40.4, 37.6, 32.6, 26.8(br), 26.7(br), 17.7; IR (KBr pellet) ν_{max} 3600−3200 (br), 1658, 1637, 1627, 1611, 1533, 1469, 1227 Anal. Calcd for $C_{36}H_{47}ClN_8O_3$: C, 64.03; H, 7.02; Cl, 5.25; N, 16.59. Found: C, 64.07; H, 7.76; Cl, 5.30; N, 16.50.

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Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

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