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Concept Article

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Route Development and Multikilogram GMP Delivery of a Somatostatin Receptor Antagonist

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Supporting Information

ABSTRACT: Route development and demonstration on multikilogram scale for the first GMP delivery of MK-4256 are described. Key aspects of the convergent route include a regioselective green iodination, one-pot oxadiazole synthesis, and an efficient ketone Pictet–Spengler reaction with diastereomeric upgrade via crystallization to afford 6 kg of API. A recycle procedure augmented the yield of desired diastereomer in the Pictet–Spengler reaction from a mixture of diastereomers heavily enriched in the undesired diastereomer.

INTRODUCTION

Substituted β-carboline derivatives, including MK-4256 (**1**) have been shown to be selective antagonists of the somatostatin subtype receptor (SSTR3) and useful for treatment of type 2 diabetes and its associated conditions. The compounds are also useful for the treatment of depression and anxiety.[1] The discovery synthesis of **1**[2] provided a convergent route to API (Scheme 1) via two key intermediates: tryptamine **2** and ketone **3**. Ketone **3** was, in turn, derived from oxadiazole K-salt **4** and iodopyrazole **5**.

Four key areas were identified to improve the viability of this process on-scale (Scheme 2):

(1) Oxadiazole methyl ester **9** was prepared in only 19% yield over three steps employing $POCl_3$ as solvent for one step, necessitating a new synthesis of this intermediate.[3]

(2) 4-Iodo-*N*-methylpyrazole (**5**) was purchased for earlier efforts; the cost and lead-time on-scale required identification of a cost-effective preparation.

(3) Tryptamine derivative **2** was previously synthesized as the HCl salt with no formal isolation; since this material was to be prepared in bulk in England and used for processing in the United States, identification of an isolable, crystalline salt was critical for shipping.

(4) The final Pictet–Spengler reaction and subsequent chromatography were inefficient, providing **1** in <10% yield; success toward improving the chemical productivity of this reaction and the efficient separation of diastereomers was paramount for the completion of this multikilogram delivery.

RESULTS AND DISCUSSION

Oxadiazoles are known products of the reactions of amidoximes with carboxylic anhydrides, generally in the presence of pyridine. To generate the necessary oxadiazole ethyl ester derivative here, the requisite amidoxime, ethyl α-aminooximinoacetate (**16**), is commercially available on small scale. The anhydride/pyridine conditions used for most oxadiazole formations are known to be less successful with this substrate;[4] in our hands, acetylation proceeded cleanly to generate intermediate **17**, but cyclization to furnish oxadiazole ethyl ester **18** performed poorly under the pyridine conditions. As an alternative approach, after isolation of **17**, acetic acid was identified from a screen of solvents for the desired cyclization reaction. Acetic acid was then examined for the acetylation reaction and found to be suitable for that step as well, allowing for a one-pot process. The cost and availability of ethyl α-aminooximinoacetate on-scale proved prohibitive, necessitating preparation of amidoxime **16**. A literature report described the treatment of ethyl cyanoformate (**15**) with hydroxylamine free base in dichloromethane to provide this intermediate in modest yield.[5] We found acetic acid to be a superior solvent for this reaction as well; hydroxylamine hydrochloride salt could be used in the presence of sodium acetate as base. This result allowed all three reactions to be combined into a one-pot process to convert ethyl cyanoformate to oxadiazole ethyl ester **18** (Scheme 3). Headspace monitoring showed negligible HCN formation during this chemistry, although a cyanide monitor was placed in close proximity to the vessel, and airline hood repirators were employed to avoid potential exposure. In collaboration with our EPSE group, we identified specific safety considerations for this process that are detailed in the Experimental Section. This reaction was run successfully on-scale in a single flask (7.24 kg, 95% assay yield), and an ethyl acetate solution of compound **18** was carried forward for conversion to oxadiazole K-salt **4**.

Replacement of the methyl ester in the medicinal chemistry route with the ethyl ester in the process chemistry route simplified isolation of oxadiazole K-salt **4**. The ethyl acetate solution of oxadiazole ethyl ester **18** was solvent switched to

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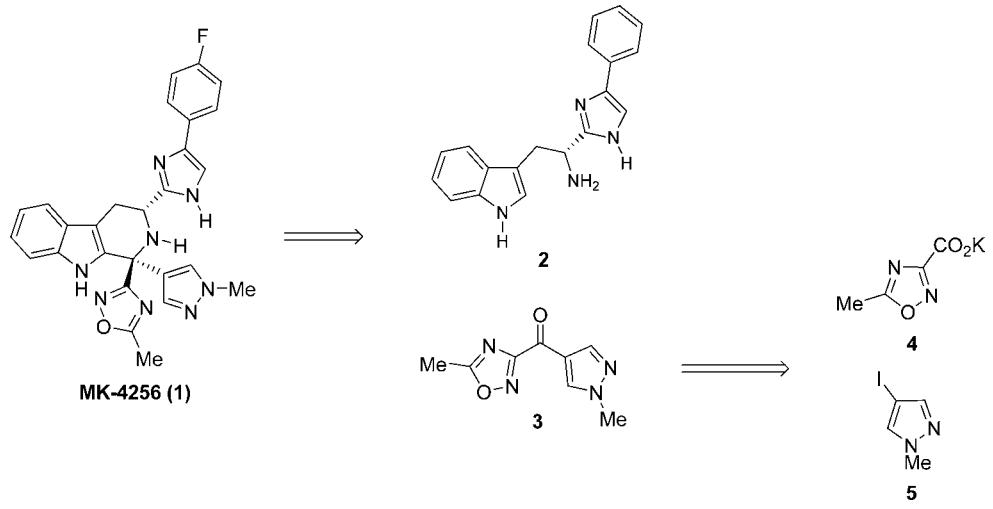
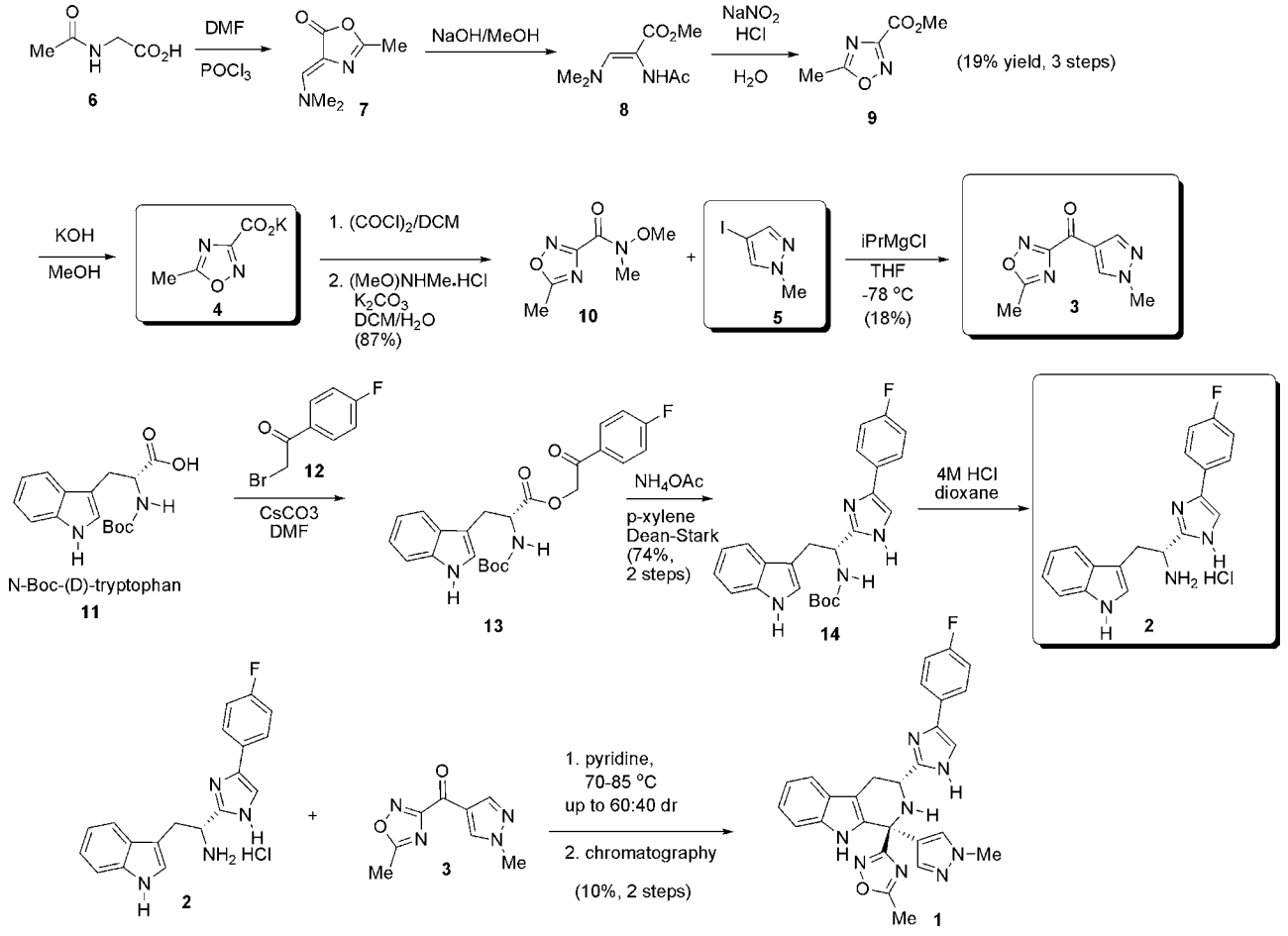
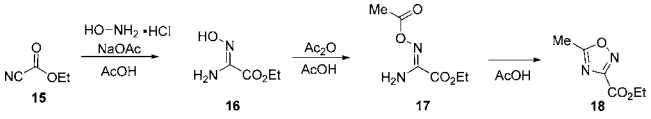
Scheme 1. Convergent synthesis of MK-4256 (1)



Scheme 2. Discovery Chemistry route to 1



Scheme 3. Oxadiazole ethyl ester 18 synthesis



ethanol; great care was taken during this solvent switch as compound **18** was volatile under these conditions in the absence of a hydrogen bond-donating solvent. Maintaining a satisfactory concentration of ethanol served to prevent evaporation of the product. Saponification in ethanol as solvent was efficient, leading to direct crystallization of oxadiazole K-salt **4**. Use of 10 N KOH limited the water concentration, leading to a high recovery (Scheme 4). Oxadiazole K-salt was isolated in 77% yield over two steps (6.33 kg).

The medicinal chemistry route had employed a two-step, one-pot sequence for the preparation of oxadiazole Weinreb

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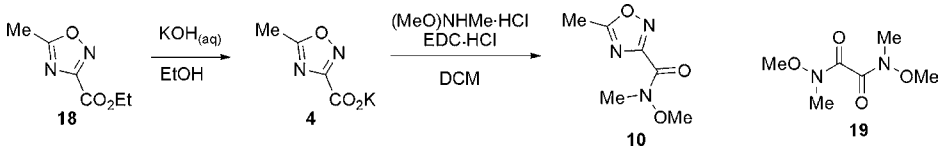
Scheme 4. Preparation of oxadiazole Weinreb amide 10



amide **10**: the K-salt **4** was converted to the corresponding acid chloride, using oxalyl chloride in dichloromethane, and Weinreb amide was formed under Schotten–Bauman conditions. The presence of excess oxalyl chloride led to formation of the corresponding bis-Weinreb amide **19**, which complicated the subsequent ketone formation step; a flushing procedure with toluene was employed to remove excess reagent. Efforts to reproduce this chemistry using one equivalent of oxalyl chloride led to decreased conversion to the acid chloride and low yield of the desired Weinreb amide. It was found that reacting oxadiazole K-salt and Weinreb amine·HCl with EDC·HCl in dichloromethane led to rapid formation of oxadiazole Weinreb amide **10** (Scheme 4). The effectiveness of this reaction using the three salts in DCM was advantageous because of the facile solvent switch to THF for the next step. In one batch, 6.31 kg of oxadiazole Weinreb amide was isolated as a 42 wt % solution in THF after solvent switch (98% assay yield).

4-Iodo-*N*-methylpyrazole (**5**) is commercially available and had been purchased for medicinal chemistry's efforts. The price was high and the lead time prohibitively long for the quantity required for the first GMP delivery (Table 1). Two approaches

Table 1. Cost and lead-time comparison of pyrazole starting materials

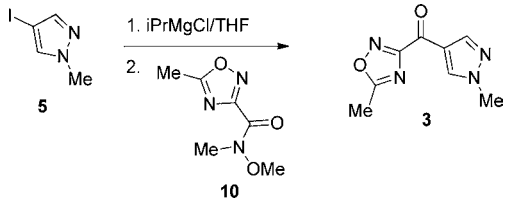
cmpd	lead time (wks)	cost/kg	cost/mol
4-iodo-*N*-methylpyrazole (**5**)	6	$3360	$699
4-iodopyrazole	4	$830	$161
N-methylpyrazole (**20**)	2	$956	$78.50

were considered to rapidly access compound **5**: (1) methylation of 4-iodopyrazole and (2) iodination of 1-methyl pyrazole.[6] The starting material for the former approach also proved expensive, especially since addition of the methyl group does not have much impact on the molecular weight of this intermediate. On the basis of this cost analysis and in-stock availability, *N*-methylpyrazole emerged as the preferred starting material.

There are many known conditions for iodination of pyrazoles, though each one suffers from its own drawbacks.[7] Several sets of conditions were shown to be effective for the iodination of *N*-methylpyrazole (**20**). (1) *N*-Iodosuccinimide and catalytic trifluoroacetic acid in acetonitrile were successful reaction conditions, though the cost of NIS was deemed a liability (Scheme 5a). (2) Use of 0.5 equiv each of iodine and ceric ammonium nitrate in acetonitrile also worked, although the considerable quantity of cerium byproduct rendered the workup extremely challenging (Scheme 5b). (3) In the best procedure, the second option was modified to employ 0.6 equiv of hydrogen peroxide as oxidant and water as the only solvent.[8] This result provided a completely green system for the iodination of *N*-methylpyrazole (Scheme 5c); the product is directly filtered from the reaction mixture, and water is the only byproduct. EPSE evaluation of the chemistry identified that the reaction could be conducted safely at a temperature below 70 °C. This procedure was used to prepare 16.2 kg of 4-iodo-*N*-methylpyrazole in a single batch (91% yield). These conditions were subsequently reported for the successful 4-selective iodination of a variety of pyrazole compounds.[9]

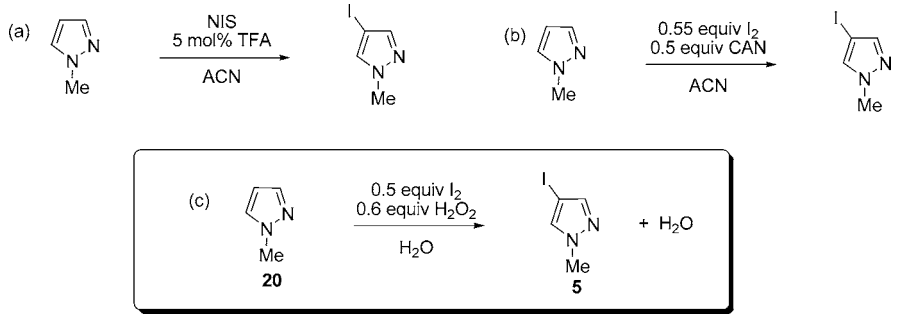
Preparation of ketone **3** followed the medicinal chemistry procedure, with only a minor change to the workup and development of a crystallization protocol that led to a dramatic improvement in yield. 4-Iodo-*N*-methylpyrazole (**5**) underwent magnesium–halogen exchange with isopropylmagnesium chloride. Addition of a THF solution of oxadiazole Weinreb amide **10** led to clean conversion to form pyrazole–oxadiazole ketone **3**. A small amount of direct isopropyl addition was also identified in the reaction mixture (Scheme 6). Dichloro-

Scheme 6. Preparation of ketone 3



methane replaced ethyl acetate as workup solvent, due to low product solubility in ethyl acetate (as well as all other organic solvents considered). Crystallization of the ketone occurred easily from a variety of solvent combinations. Given the

Scheme 5. Iodination of *N*-methylpyrazole 5



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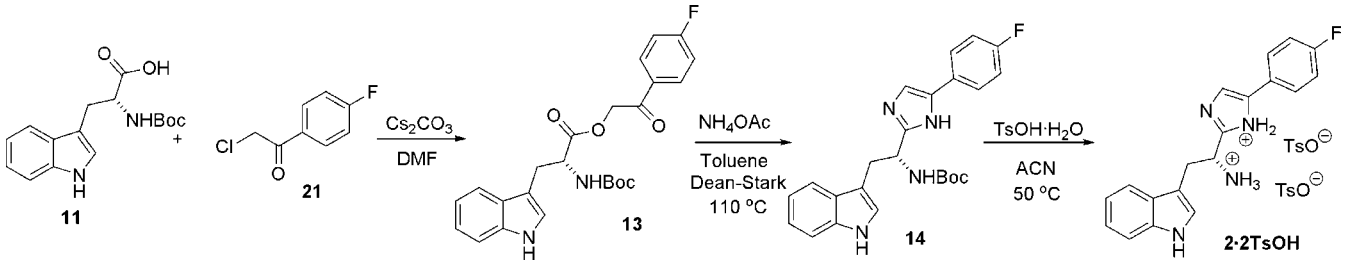
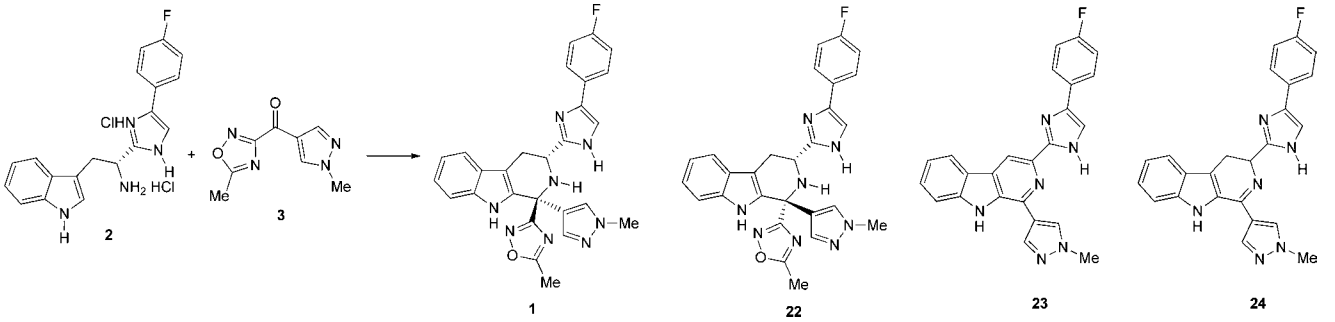
Scheme 7. Tryptamine 2 synthesis



Scheme 8. Pictet–Spengler reaction products formed



presence of THF in the organic extracts from the reaction, a THF/heptane solvent system was employed for crystallization. Two batches of ketone solution were combined for solvent switch to THF and isolation. Pyrazole–oxadiazole ketone **3** was isolated in 87% yield over two steps (6.26 kg).

The synthesis of tryptamine **2** supplied by medicinal chemistry (identified as the HCl salt of **2**) was deemed fit for purpose, albeit with a few requisite process-related improvements. 2-Bromo-4′-fluoroacetophenone (**12**) had been used as the medicinal chemistry starting material; however, bulk supplies of this reagent were not available in an adequate timeframe for this delivery. Hence, for this campaign, the reaction with the corresponding chloride **21** was investigated. The coupling of Boc-D-Trp-OH (**11**) with chloride **21** proceeded in quantitative yield in less than 2 h at 20 °C in DMF. Compound **13** was isolated on small scale by concentrating the reaction mixture to dryness after aqueous workup. Since this was not an option on scale, we decided to telescope this reaction with the subsequent imidazole formation. This through process was achieved by partitioning the reaction mixture between water and ethyl acetate then switching the organic solvent to toluene: the resulting stream of compound **13** was used directly in the next step. This protocol had two additional benefits: the imidazole formation performed very well in toluene (a more desirable solvent than *p*-xylene previously used), and the equivalents of ammonium acetate required to effect this transformation could be reduced (five vs. ten in the prior procedure). The medicinal chemists partitioned imidazole **14** between water and ethyl acetate then partially concentrated the organics for crystallization. This crystallization was suboptimal: it was necessary to chromatograph the mother liquors to recover product in adequate yield. An alternative process was developed that involved partitioning the reaction mixture between water and ethyl acetate then solvent switch to toluene for crystallization. These changes were implemented on-scale (Scheme 7): Boc-D-Trp-OH (**11**) (19.0 kg) was processed to afford imidazole **14** in 83% yield over two steps with excellent retention of enantiopurity (99.6% ee).

The medicinal chemistry procedure for Boc-deprotection of compound **14** employed HCl in dioxane to afford the corresponding HCl salt. However, isolation was difficult, and it was necessary to dry the product by vacuum over several days to isolate a foam. We decided to investigate whether Boc-deprotection mediated by a sulfonic acid and concomitant salt formation would represent a viable alternative on scale. Initially, a THF solution of **14** was heated to 60 °C in the presence of MSA. These conditions furnished the desired amine after one hour, but the product failed to crystallize from the reaction mixture. When the same protocol was applied using $TsOH·H_2O$, the desired product crystallized to afford a 48% yield of the bis-TsOH salt. The isolated yield of the bis-tosylate salt of **2** was improved to 94% by using toluene as antisolvent; however, the small particle size of the resultant crystals led to a slow filtration that was impractical for large-scale implementation. A solvent screen of this deprotection/salt formation sequence identified acetonitrile as the optimal solvent. Thus, a solution of Boc-amine **14** in acetonitrile was heated to 60 °C in the presence of 3 equiv of $TsOH·H_2O$ until complete deprotection was observed. The reaction mixture was then cooled to 20 °C, leading to crystallization of salt **2**. This solid was composed of much larger particles and was filtered with ease. An 85% isolated yield (29.4 kg) of this bis-tosylate salt of **2** was achieved on-scale without the use of antisolvent.

The Pictet–Spengler reaction represented a convergent method for the construction of **1**. This final step also served to identify the GMP range for this synthesis, with ketone **3** and tryptamine **2** serving as GMP starting materials. There are limited examples of Pictet–Spengler reactions using ketones as substrates in the literature; moreover, these reactions generally require strong acid catalysis and furnish products in poor diastereoselectivities. The original synthesis of **1** employed harsh conditions to effect this transformation: the two reaction components were heated in pyridine at 70–85 °C for 3 d (Scheme 8). An excess of ketone **3** was used because it was removed more easily than the tryptamine **2** during chromatography. The diastereomers **1** and **22** were formed in variable

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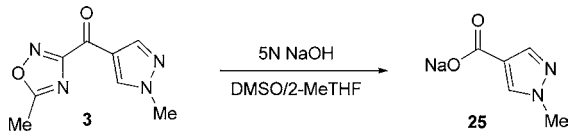
ratios up to a maximum of 1.5:1. At this point, we identified a major impurity (**23**) arising from elimination of the oxadiazole and oxidation to the corresponding pyridine, in addition to many small impurities likely resulting from decomposition of the tryptamine fragment. Assay yield for the Pictet–Spengler reaction was variable from 15 to 30%, a fact potentially attributable to excess HCl present in the unpurified tryptamine·HCl salt. The isolated yield was further compromised by inefficient chromatography to separate the two diastereomers; isolated yields ranged from 5 to 10% of amorphous free base after chromatography and lyophilization from acetonitrile/water.

Extensive screening efforts to identify improved conditions for the Pictet–Spengler reaction identified DMSO and ethanol as viable alternatives to pyridine. A new impurity, corresponding to elimination of the oxadiazole without oxidation (**24**), also formed in some solvents and formed almost exclusively in acetic acid. Ultimately, DMSO was chosen as solvent because the reaction rate was faster relative to that in ethanol, and the reaction itself could be carried out under more concentrated conditions.

The particular acid used to catalyze the Pictet–Spengler reaction played a pivotal role in preventing byproduct formation. Lower pK_a's led to faster reaction rates, but also faster decomposition rates and lower diastereoselectivities. Trifluoromethanesulfonic acid with tryptamine free base and tryptamine·2TsOH emerged as the two best acid candidates. Since tryptamine **2** was isolated as the bis-TsOH salt, there was a driving force to employ this material as-is without the requirement to break the salt. Additionally, this option offered greater ease of handling, making a compelling case for entering into the reaction with tryptamine·2TsOH (**2**) directly. The stoichiometry of acid used was found to have a similar effect on the Pictet–Spengler reaction as the pK_a of the acid used: the presence of more acid led to a faster reaction rate, but also to faster elimination to byproduct **24**. One equivalent of strong acid provided the optimal balance between reaction rate and purity. With two equivalents of *p*-TsOH entering into the system, one equivalent of base was used to attenuate the acidity. Alkali acetates and hydroxides (sodium, potassium, cesium) and *tert*-butoxides (sodium, potassium) were screened, and sodium acetate as base provided the best reaction purity and greatest ease of handling (lowest hygroscopicity) while simultaneously leading to the beneficial formation of one equivalent of the conjugate weak acid.

With base and solvent now identified, final details for the optimization could be set. One equivalent of tetraethyl orthosilicate [Si(OEt)$_4$] served to increase the reaction rate, likely by favoring imine formation and sequestering water.[10] The presence of a silicon byproduct complicated the workup of this reaction: this byproduct exhibited different physical properties at varying pH values. Ultimately, the strongly basic conditions employed for workup led to formation of a dense silicate oil that formed a third layer in the extraction vessel and could be removed from the reaction mixture. The reaction temperature was decreased from 100 to 75 °C, minimizing impurity formation, while still allowing an improved reaction time of 40 h. The final stoichiometry used was one equivalent of tryptamine·2TsOH (**2**) and 1.1 equivalents of pyrazole–oxadiazole ketone **3**. The goal was to maximize consumption of the tryptamine fragment, and 96–97% conversion was achieved under these conditions. The ketone was shown to hydrolyze to the corresponding *N*-methylpyrazole-4-carboxylic acid sodium salt (**25**) under the strongly basic workup conditions and could be washed into the aqueous layer along with water-soluble oxadiazole byproduct (Scheme 9).

Scheme 9. Ketone workup hydrolysis



The final Pictet–Spengler reaction conditions used for the first GMP delivery are illustrated in Scheme 10. Two batches were completed, each providing **1** and its diastereomer **22** in a better than 58:42 ratio and a combined >88% assay yield.

Identification of an effective crystallization protocol obviated the need for chromatographic separation of diastereomers. The combination of toluene and different cosolvents (methanol, isopropanol, dichloromethane, acetonitrile) provided the first crystalline forms of **1**. On crystallization from 94/6 v/v toluene/acetonitrile, the supernatant contained >5:1 **22**/**1**,[11] efficiently removing **22** to produce **1**, following filtration, in high diastereomeric purity (dr ≈ 99.5:0.5) and good recovery (41–42% isolated yield, 6.01 kg over two batches).

The crystalline solid obtained from the diastereomeric upgrade above was identified as the toluene solvate Form I. On drying in the vacuum oven, Form I lost toluene and converted to a new form characterized as Form III. In our prep lab ovens, this drying procedure was inefficient and required ∼3 w at 69 °C at 120 Torr with a nitrogen sweep to achieve a specification of <0.149 wt % toluene. However, drying at 90 °C led to formation of the oxadiazole elimination byproduct **24**; thus, we decided to retain the lower temperature point. The final process is illustrated in Scheme 11.

The diastereomers **22** and **1** were found to interconvert under acidic conditions without enantiomeric erosion. Acetic acid and acetonitrile were suitable solvents for the epimerization using sulfonic acids or trifluoroacetic acid. Greater than one equivalent of acid was necessary as the first equivalent was neutralized by the basic imidazole group. A procedure was developed in which the filtrate from the initial **1** crystallization, containing ∼5.5:1 ratio of the undesired diastereomer **22** to **1**, was equilibrated to a 1:1 ratio, and a second crop of API was collected by repeating the diastereoselective crystallization. This allowed for recovery of more than 2 kg of additional **1** from the campaign in a single recycle.

■ CONCLUSIONS

We have presented the chemistry toward the first GMP delivery of **1**. Improved chemistry was employed to isolate the tryptamine fragment as a bis-TsOH salt, enabling its direct use in the final Pictet–Spengler reaction. New chemistry was developed for synthesis of the requisite oxadiazole fragment that employed a safe, multicomponent sequence conducted fully in acetic acid. A novel green 4-iodination of *N*-methyl pyrazole was identified and applied to a series of pyrazole compounds. Optimized conditions for the ketone Pictet–Spengler reaction led to a high assay yield, and a diastereoselective crystallization of **1** afforded the desired API in high purity. A recycle protocol was developed to isolate additional **1** from a mixture enriched in the undesired diastereomer. A total of 8 kg of API was obtained using these two methods.

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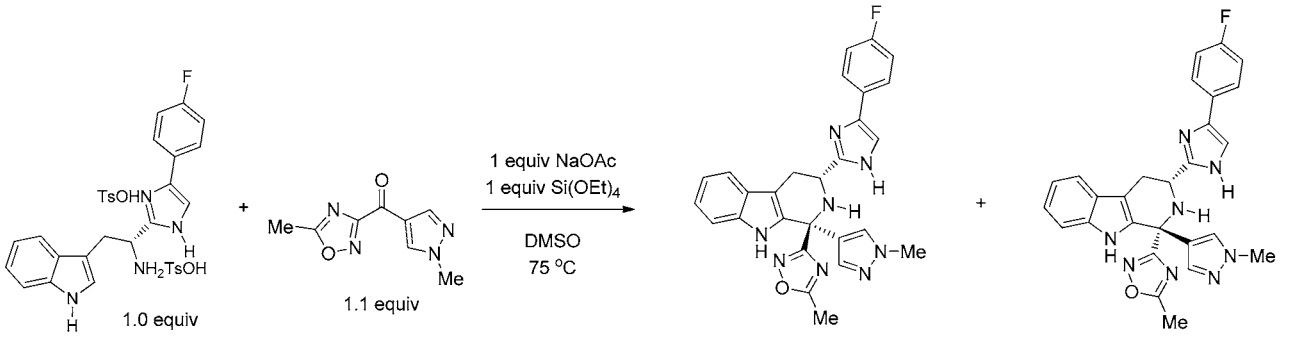
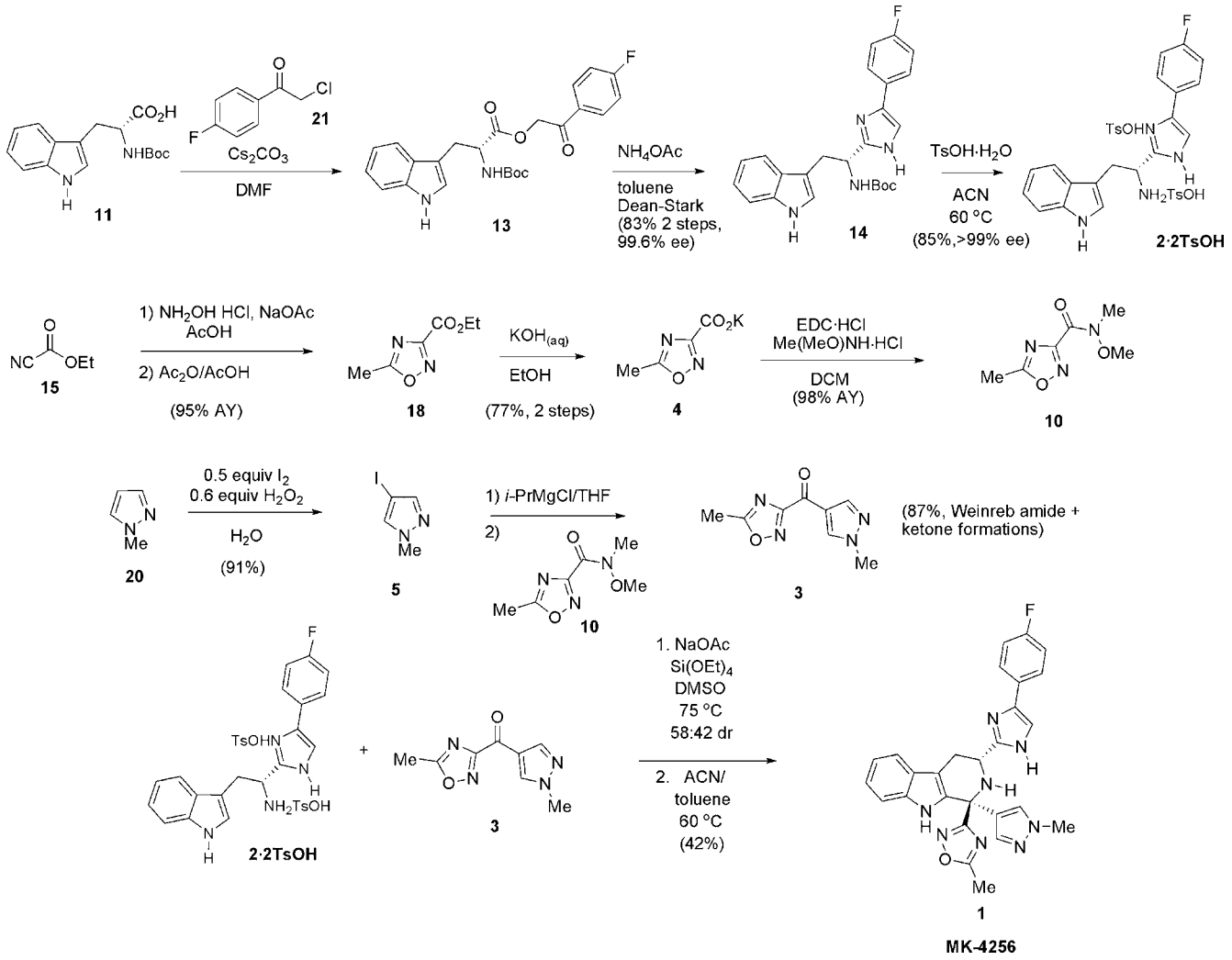
Scheme 10. Final Pictet–Spengler reaction conditions



	1	22
Batch 1	3.78 kg (*50.9% AY*)	2.69 kg (*36.3% AY*)
Batch 2	3.63 kg (*51.8% AY*)	2.56 kg (*36.5%AY*)

Scheme 11. Final GMP delivery route



EXPERIMENTAL SECTION

General. HPLC analysis was performed on an Agilent 1100 instrument with Zorbax Eclipse Plus C18 4.6 mm × 50 mm; MeCN/H_2O (0.1% H_3PO_4) 10/90 to 90/10 0–5 min: hold at 90/10 5–6 min; 1.5 mL/min; 210 nm; 25.0 °C, 8 min run time. All compounds described are fully characterized in the literature, and data obtained here matched literature information; relevant references are provided.

*1,2,4-Oxadiazole-3-carboxylic acid, 5-methyl-ethyl ester (**18**).*[12] A 100-L RBF in a water bath was charged with

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hydroxylamine·HCl (4.23 kg, 60.8 mol), followed by acetic acid (24.86 L). Ethyl cyanoformate (4.95 kg, 49.4 mol) was added, then sodium acetate (4.99 kg, 60.8 mol) was added over 75 min.

CAUTION: *Ethyl cyanoformate is typically used as an acylating agent with cyanide as byproduct.* Even though headspace monitoring suggested the absence of this competing pathway, this reaction sequence was conducted in the presence of a cyanide monitor to ensure avoidance of exposure to HCN.

On the basis of the decomposition temperature of α-hydroxylamine·HCl in the presence of sodium acetate, our EPSE group identified that this step was safe to run at $T < 35$ °C. The reaction was complete after 2 h at 18−28 °C. The reaction mixture was cooled in an ice bath to 15 °C and then exhibited a slow exotherm during acetylation; our EPSE group recommended that the addition be conducted at $T < 30$ °C, and that heatup proceed slowly and under well-vented conditions to avoid pressure buildup. Acetic anhydride (8.76 kg, 86 mol) was added via addition funnel over 90 min. The temperature increased to 26 °C during the addition. The reaction mixture was stirred for an additional 15 min. Acetylation to form **17** was complete, with no detectable oxime **16**. The reaction mixture was heated at 99 °C for 12 h. HPLC analysis of the reaction mixture showed 99.66% conversion to oxadiazole **18** (call point: >99% conversion). The slurry was cooled to room temperature, and acetic acid was removed under vacuum. Evaporation was discontinued when a ratio of 1.6:1 of acetic acid/**18** was observed in the reaction mixture by ^{1}H NMR spectroscopy. Ethyl acetate (25 L) and water (5 L) were added to the reaction mixture. The solution was neutralized with 30% K_2CO_3 (17.5 L) to pH 7. The batch was transferred to a 100-L glass extraction vessel via an inline filter. The flask was rinsed twice with ethyl acetate (7.5 L, 5 L), and the rinses were also transferred to the glass extraction vessel. The aqueous layer was removed. The organic layer was washed with water (5 L). The organic layer was determined to contain 7.24 kg (95%) product by HPLC. Compounds **16**, **17**, and **18** are all commerically available, with spectra matching those provided in the literature[11] and of known authentic material.

*1,2,4-Oxadiazole-3-carboxylic acid, 5-methyl-, potassium salt (**4**).*[13] The isolated organic layer containing oxadiazole ester **18** (7.24 kg, 46.4 mol) was transferred to a 100-L RBF with ethanol (20 L), and the solution was solvent switched to ethanol. When the ratio of product: ethyl acetate was 8.6:1 by ^{1}H NMR spectroscopy, distillation was stopped. The total ethanol volume was adjusted to 46.8 L. The batch was heated to 56 °C, and 10 N KOH (430 mL) was added via addition funnel over 5 min. White crystals immediately began to form in the reaction mixture. After the first addition was complete, 10 N KOH (3.87 L) was added over 10 min; the temperature increased to 76 °C. Additional 10 N KOH (350 mL) was added, and the slurry was left to age and cool to room temperature overnight. Supernatant HPLC assay showed approximately 206 g (2.5%) product and 823 g (10.7%) ethyl ester. The batch was filtered and rinsed with ethanol, followed by heptane. The product was dried under vacuum and nitrogen for 2 d, affording 6.33 kg (77% over two steps) of oxadiazole K-salt as a white crystalline solid matching spectroscopic data from the literature[14] and that of material purchased commercially. The mother liquor contained 185 g (2.2%) product and 626 g (8%) unreacted ethyl ester by HPLC assay.

*1,2,4-Oxadiazole-3-carboxamide,N-methoxy-N,5-dimethyl- (**10**).*[1,2] A 100-L glass extraction vessel was charged with dichloromethane (20 L), followed by oxadiazole K-salt **4** (6.25 kg, 37.6 mol). *N*,*O*-Dimethylhydroxylamine·HCl (4.68 kg, 47.0 mol) was added to the slurry. Additional dichloromethane (11.25 L) was added to rinse the vessel, and the batch temperature was lowered to 8 °C. EDC·HCl (8.29 kg, 43.3 mol) was added portionwise over 1.5 h, with the temperature increasing to 22 °C. After an additional 10 min, Weinreb amide formation was complete by HPLC (>97% conversion, Weinreb amide/carboxylic acid); DCM (11.6 L) and H_2O (18.6 L) were added to the reaction mixture which was stirred vigorously. The layers were separated. The DCM layer was returned to the glass extraction vessel and washed with 4.2% $NaHCO_{3(aq)}$ (14.6 L). The DCM solution was then transferred, via an inline filter, to a 100-L RBF and concentrated under vacuum. THF was added during the distillation to complete the solvent switch. The Weinreb amide was isolated as a solution in THF (total mass = 14.9 kg, 42.3 wt %). Spectroscopic data were consistent with that reported in the literature.[1,2]

*4-Iodo-1-methylpyrazole (**5**).*[10] A 100-L RBF with a water bath was charged with *N*-methylpyrazole (7.0 kg, 85.3 mol) and water (30 L), followed by iodine (11.0 kg, 43.5 mol). After a 10 min age, 4-iodo-*N*-methylpyrazole (15 g) was charged as seed. 30% H_2O_2 (5.2 L, 51.2 mol) was charged over 30 min, the temperature increasing from 18 to 32 °C. After 42 h of stirring, the slurry was cooled to 10 °C. Ten percent $NaHSO_{3(aq)}$ (20 L) was slowly charged as quench, keeping the internal temperature below 20 °C. The resulting light-tan slurry was stirred at room temperature for 3 h and isolated by filtration. The wet cake was washed with water (5 × 20 L). The wet cake was dried in the vacuum oven (30−35 °C, ∼200 mm vac, N_2 sweep) for 3 d.[15] The isolated yield was 91% (16.2 kg, 98.1 wt % by HPLC). This compound is commercially available; spectroscopic data were consistent with that of authentic material.

*Methanone, (5-methyl-1,2,4-oxadiazol-3-yl)(1-methyl-1H-pyrazol-4-yl)- (**3**).*[1,2] A 100-L glass extraction vessel was charged with 1-methyl-4-iodo-pyrazole (4.49 kg, 21.2 mol) and THF (9.0 L) under N_2. The reaction mixture was cooled to −19 °C. Isopropylmagnesium chloride (2.0 M in THF, 11.1 L, 22.1 mol) was added over 1.75 h; the temperature was maintained below 5 °C during the addition. The solution was assayed by quench of a sample into methanol for 100% conversion of the iodo compound to the protio compound by HPLC. Oxadiazole Weinreb amide **10** (3.15 kg, 18.4 mol) was then added as a solution in THF (5.33 L) over 25 min, the temperature increasing from −9 to 21 °C. After the addition, the reaction mixture was stirred at room temperature. Ketone formation was complete by HPLC after 10 min; the reaction mixture was cooled to 8 °C. HCl (2 N, ∼3 L) was added, the temperature increasing to 21 °C. DCM (4.0 L) was added to aid stirring, and the slurry was recooled to 14 °C. Additional HCl (2 N, 9.1 L) was added over 5 min. DCM (20.0 L) and H_2O (11.0 L) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with additional DCM (8.0 L). The combined organic layers were returned to the glass extraction vessel and washed with H_2O (4.0 L). This procedure was performed in two batches; the organic extracts from both batches were combined for solvent switch to afford 6.78 kg of ketone (95.8% yield).[16] The ketone solution was transferred via an inline filter to a 100-L RBF. The solution was concentrated under vacuum and flushed with additional THF (∼40 L) to a low volume (16.75 L). The RBF

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was placed under N_2 and warmed to 44 °C. Heptane (36 L) was added via addition funnel in 4-L portions, allowing the slurry to cool during addition. Crystallization of off-white needles occurred immediately. The slurry was stirred at room temperature overnight, then filtered, washing with 5:4 heptane/THF (18.0 L) followed by heptane. The solid was dried under nitrogen and vacuum overnight. Assay of the dried, off-white crystals showed 6.26 kg of product (88.4% yield, 100 LCAP). The yield over two steps, from oxadiazole K-salt **4** to ketone **3**, was 86.6%. Spectroscopic data were consistent with that previously reported in the literature.[1,2]

*Carbamic acid, N-[(1R)-1-[5-(4-fluorophenyl)-1H-imidazol-2-yl]-2-(1H-indol-3-yl)ethyl]-, 1,1-dimethylethyl ester (**14**).*[1,2] Boc-D-Trp-OH **11** (19.0 kg, 62.4 mol) was dissolved in DMF (89.7 kg). Cesium carbonate (10.2 kg, 31.2 mol) was added, followed by 2-chloro-4′-fluoroacetophenone (10.8 kg, 62.4 mol). The mixture was aged at 20 °C for 16 h. Water (95.0 kg) was charged such that the temperature was less than 25 °C. Ethyl acetate (84.9 kg) was added, and the resulting phases were separated. The aqueous phase was extracted with ethyl acetate (84.9 kg). The combined organic layers were then washed with a 5% aqueous LiCl solution (4.8 kg LiCl in 95.0 kg of water) to aid in removal of DMF. Toluene (164.7 kg) was added and the solution distilled under vacuum until approximately 100 L remained in the vessel. Ammonium acetate (24.1 kg, 312.2 mol) was added and the reaction heated at 110 °C under Dean−Stark conditions for 2.5 h (>99% conversion by HPLC). The reaction was cooled to 20 °C and diluted with ethyl acetate (84.9 kg) and water (95.0 kg). Product crystallised in the upper organic layer at this point. The lower aqueous phase was cut away. NaOH (1 N aq.) solution was added to the batch such that the temperature was less than 35 °C. The organics were washed with half-saturated brine (95.0 kg) followed by water (10 kg). The reaction mixture was distilled under vacuum until approximately 95 L remained in the vessel. The mixture was cooled to 20 °C and aged for 30 min. The batch was sampled, and the mother liquors were found to contain approximately 3% of the theoretical product yield by HPLC assay. The slurry was filtered and the cake washed with toluene (20 kg). The solid was pumped dry on the filter for 12 h. A total of 23.9 kg of a white solid was isolated (91.2 LCWP due to residual toluene); 21.8 kg of product were isolated in 83% corrected yield over two steps. The enantiopurity of the solid was 99.6%. Spectroscopic data were consistent with that previously reported in the literature.[1,2]

*1H-Indole-3-ethanamine, α-[5-(4-fluorophenyl)-1H-imidazol-2-yl]-, (α-R)- (**2**).*[1,2] The Boc-imidazole compound **14** (21.8 kg, 51.9 mol) was slurried in acetonitrile (85.7 kg). *p*-Toluenesulfonic acid monohydrate (29.6 kg, 155.5 mol) was added and the mixture heated to 60 °C. Bubbling, but no foaming, was observed. Greater than 99% conversion to product was achieved within 45 min by HPLC; the batch was cooled to 20 °C. The slurry was aged for a further 30 min at this temperature. The slurry was filtered and the cake washed with acetonitrile (17.1 kg). The solid was dried under vacuum at 45 °C under a sweep of nitrogen to constant mass. A total of 29.6 kg of a white solid was isolated in high purity (99.3 LCWP). This corresponds to 29.4 kg of product in 85% yield. The enantiopurity was >99%. Spectroscopic data were consistent with that previously reported in the literature.[1,2]

*1H-Pyrido[3,4-b]indole, 3-[5-(4-fluorophenyl)-1H-imidazol-2-yl]-2,3,4,9-tetrahydro-1-(5-methyl-1,2,4-oxadiazol-3-yl)-1-(1-methyl-1H-pyrazol-4-yl)-, (1R,3R)- (**1**).*[1,2] A 100-L glass extraction vessel was charged with pyrazole−oxadiazole ketone **3** (2.96 kg, 15.4 mol), tryptamine·2TsOH **2** (9.42 kg, 14.2 mol), and sodium acetate (1.16 kg, 14.2 mol). DMSO (14.1 L) and tetraethyl orthosilicate (2.95 kg, 14.2 mol) were added, and heating was applied to 73.5−75.5 °C. The reaction mixture was homogeneous above 58 °C. The reaction proceeded to 96% conversion after 40 h (dr = 58.7:41.3). The reaction mixture was cooled to room temperature. 2-Methyltetrahydrofuran (38 L) was added, and the mixture was cooled to 18.5 °C. $NaOH_{(aq)}$ (5 N, 30 L) was added in 4 L portions, the temperature rising to 32 °C. The mixture was stirred for 3 h, until no white solid remained. On settling, three layers formed: the bottom silicon layer was removed, and $NaOH_{(aq)}$ (1N, 16 L) was added to the biphasic mixture with additional stirring. The aqueous layer was separated. The organic layer was washed with 2.5% brine (16 L) The organic layer contained 3.63 kg **1** (51.8% assay yield by HPLC); it also contained 2.56 kg of L-274 (36.5%) for a dr of 58.7:41.3 and a combined yield of 6.19 kg (88.3%). The solution was recharged into a 100-L RBF via inline filter. The solution was solvent-switched into toluene. Aceteonitrile (3.55 L) was charged; the amount equal to ∼6% of toluene volume. KF was 50 ppm. The batch was heated to 60 °C, crystallization occurred, and the batch was allowed to cool to room temperature overnight. Supernatant assay showed a 5.5:1 ratio of **22**/**1**. The batch was filtered, washing with 3% acetonitrile/toluene (60 L), to afford **1** as a white crystalline solid. The wet cake was 99.6:0.4 **1**/**22** by LC. The solid was transferred to trays and placed in a vacuum oven at 69 °C and ∼120 Torr for 3 w to remove toluene to 0.11 wt %. **1** was isolated as a white crystalline solid (2.97 kg, 6.01 mol, 42.4% yield). Spectroscopic data were consistent with that previously reported in the literature.[1,2] Residual metals were <10 ppm. Chiral method: Chiralcel OD-H, 250 mm × 4.6 mm, 40 °C, 1 mL/min, 260 nm, 30 min run time, 20% (1:1 IPA/MeOH) in heptane +0.1% TEA isocratic: rt (**1**): 7.61 min, rt (**enantiomer-1**): 14.45 min. By HPLC assay, final product was 99.60 LCAP **1**, 0.17 LCAP **22**, 0.24 LCAP **enantiomer-22**, **enantiomer-1** was undetectable.

*Epimerization of Filtrate and Crystallization of Second Crop of **1**.* The filtrates and initial washes from **1** crystallization batches 1 and 2 contained about 1 kg of **1** and about 5.4 kg of the diastereomer for a total of about 6.4 kg (12.9 mol) in about 160 L of toluene/acetonitrile. This solution was concentrated to a volume of 35−40 L. Acetonitrile (32 L) was added, and the solution was transferred to a 100-L glass extraction vessel, and trifluoroacetic acid (3.68 kg, 32.3 mol) was added, causing the temperature to rise from 19 to 28 °C. The solution was heated to 55 °C for 18 h, giving an approximate 48:52 ratio of isomers. The solution was cooled to 17 °C and quenched with aqueous 2.5 N NaOH (26 L, mild exotherm caused a 5 °C temperature rise). The aqueous layer was removed. The organic layer was washed with water (26 L). The final organic layer was drummed off and assayed to contain 6.05 kg of the combined diastereomers (51.3 kg at 11.8 wt % by HPLC). The solution was transferred through an inline filter into a 100-L round-bottom flask and solvent switched into toluene. Acetonitrile was used to rinse the drums forward and keep the product in solution until water was azeotropically removed. Distillation was completed at a volume of 60 L (KF = 19 ppm), and the acetonitrile content was adjusted to 5.5 vol %. The mixture was

heated to 65 °C, with crystallization initiating during heatup at around 50 °C. The suspension was allowed to cool to room temperature. HPLC assay of the supernatant showed a 1:5 ratio of **1** to its diastereomer in solution. The crystalline **1** was collected by filtration, rinsing with 3% acetonitrile in toluene (56 L). Solid was dried in a vacuum oven at 70 °C, giving 2.2 kg (34%).

XRPD Data of ***1****.* Slurry analysis (green, Form I) and evaluation of Form III (red) and mixture (blue) (see Figure 1).

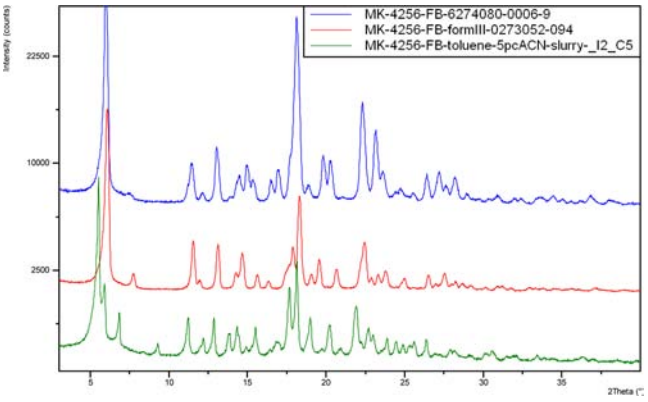

Figure 1.

■ ASSOCIATED CONTENT

Supporting Information

Additional HPLC parameters. This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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