Organic Process Research & Development

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Efficient Large-Scale Synthesis of a 2,4,5-Triarylimidazoline MDM2 Antagonist

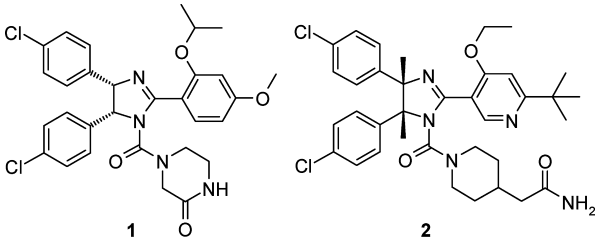
Lianhe Shu,* Chen Gu, Yan Dong, and Robert Brinkman

Process Research and Synthesis, Pharma Research and Early Development (pRED), Hoffmann-La Roche, Inc., 340 Kingsland Street, Nutley, New Jersey 07110, United States

ABSTRACT: An improved, kilogram-scale synthesis of a triarylimidazoline MDM2 antagonist is reported. The nicotinic acid component was prepared in three steps from ethyl 2-dimethylaminomethylene-3-oxo-butyrate. The coupling of the nicotinic acid with the *meso*-diamine selectively produced the monoamide which was cyclized in the presence of *p*-TSA/pyridine to give the imidazoline core. Phosgenation using bis(trichloromethyl) carbonate provided the key carbamoyl chloride intermediate, which was coupled with the side-chain amine, followed by chiral resolution with (*R*)-camphorsulfonic acid to give the final API.

INTRODUCTION

Tumor suppressor p53 is a potent transcription factor that protects cells from malignant transformations.[1] In many human malignancies, MDM2 is overexpressed and effectively impairs p53 functions.[2] Inhibition of MDM2 would reactivate the p53 pathway, thus providing a potential cancer therapy.[3] Since the discovery of the Nutlin series of compounds (e.g., **1**),[4] a number of MDM2 antagonists,[5] including imidazoline **2**, have been identified and evaluated in preclinical/clinical studies.



In the original medicinal chemistry synthesis shown in Scheme 1,[5c] **2** was prepared in 10 steps from commercially available **3**. This process is not suitable for large-scale production due to several reasons: (1) at least five steps required chromatography, including supercritical fluid chromatography (SFC) on a chiral column for the separation of *rac*-**12**; (2) the conversion of **3** to **4** was highly exothermic, with no method of control; (3) the cyclization of **10** using $POCl_3$ gave **11** in only 10% yield along with a large amount of a byproduct; and (4) handling of a phosgene solution is dangerous on a large scale. Therefore, a safe and efficient synthesis is required. Herein, we describe an improved synthesis of **2**, which has been scaled up to the multikilogram scale.

RESULTS AND DISCUSSION

An efficient synthesis of **2** has been developed that is summarized in Scheme 2. The nicotinic acid component was obtained in two steps and 67−80% yield from **3** as a sodium salt, 7-Na. The monoacylation of diamine **9** with **7** cleanly gave **10**, which was cyclized and phosgenated to give *rac*-**12**. The coupling of *rac*-**12** with **13**, followed by resolution with (*R*)-camphorsulfonic acid, produced the desired enantiomer **2** in 36−41% yield and >99% ee.

Synthesis of 7-Na. The synthesis of **4** was originally reported by McCombie et al.,[6] in which a THF solution of **3** and pivaloyl chloride was added simultaneously to a solution of LiHMDS at −70 °C within 1−2 min to give **4** in moderate yield after chromatography. Since the reaction is highly exothermic, it can only be carried out on small scale (a few grams of **3**). In order to control the exotherm, **3** was initially added to a solution of LiHMDS at −70 °C, and then pivaloyl chloride was added dropwise. While the exotherm was well controlled, a new byproduct **14** at various levels (up to 25%) was detected by NMR analysis. This was also obtained by adding LiHMDS to a solution of **3** at −78 °C. A plausible mechanism for the formation of **14** is shown in Scheme 3.[7]

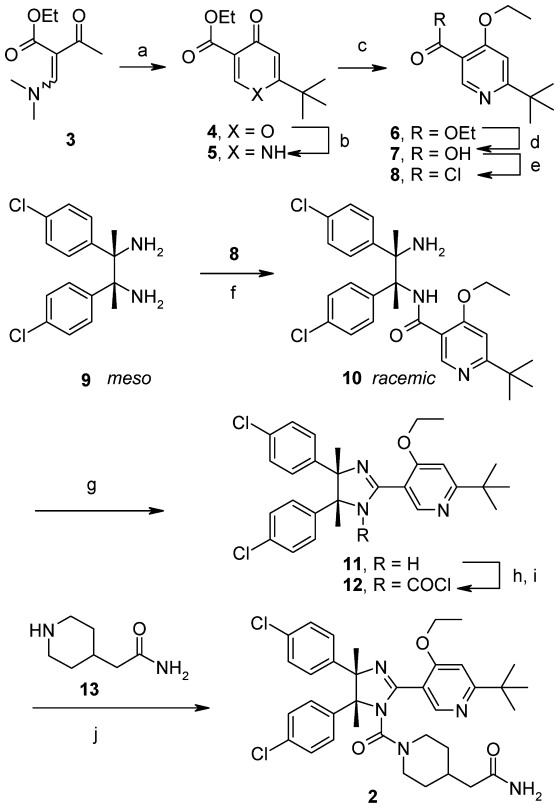
In order to minimize the dimerization of **3**, the addition order was reversed, and pivaloyl chloride was replaced by trimethylacetic anhydride, which could coexist with LiHMDS at low temperature. Compound **3** was thus added dropwise to a premixed solution of LiHMDS and trimethylacetic anhydride at ∼−70 °C. The enolate generated from **3** was immediately trapped by trimethylacetic anhydride. The reaction cleanly gave **4**, with only 0.6% of **14** detected by HPLC analysis.

Compound **5** was previously prepared from **4** by reaction with ammonium acetate in ethanol at 95 °C.[5c] It can also be prepared in one pot according to the published procedure.[6] The isolation of **4** was therefore skipped, and the reaction mixture was quenched with acetic acid (3 equiv). Ammonium acetate thus generated from LiHMDS and acetic acid was found sufficient for the conversion of **4** to **5**. After the reaction stirred at 60 °C for 30 min, HPLC analysis indicated clean conversion of **4** to **5**. Upon aqueous workup, **5** crystallized and was isolated in 68−82% yield and >99% purity as an off-white solid. The moderate yield was due to the loss of product in the aqueous layer, as **5** has reasonable solubility in water. This process was subsequently transferred to a contract supplier, thus no further optimization was conducted in house.[8]

Received: October 19, 2012

   dx.doi.org/10.1021/op300294g | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

Scheme 1. Original synthesis of 2[a]



[a]Reagents and conditions: a) *t*-BuCOCl, LiHMDS, THF, chromatography, 63%; b) NH_4OAc, EtOH, H_2O, 76%; c) EtI, K_2CO_3, DMF, 80%; d) KOH, EtOH, yield not reported; e) $SOCl_2$, yield not reported; f) TEA, THF, chromatography, 85%; g) $POCl_3$, toluene, chromatography, 10%; h) phosgene, toluene, yield not reported; i) chiral SFC separation, yield not reported; j) TEA, THF, chromatography, yield not reported.

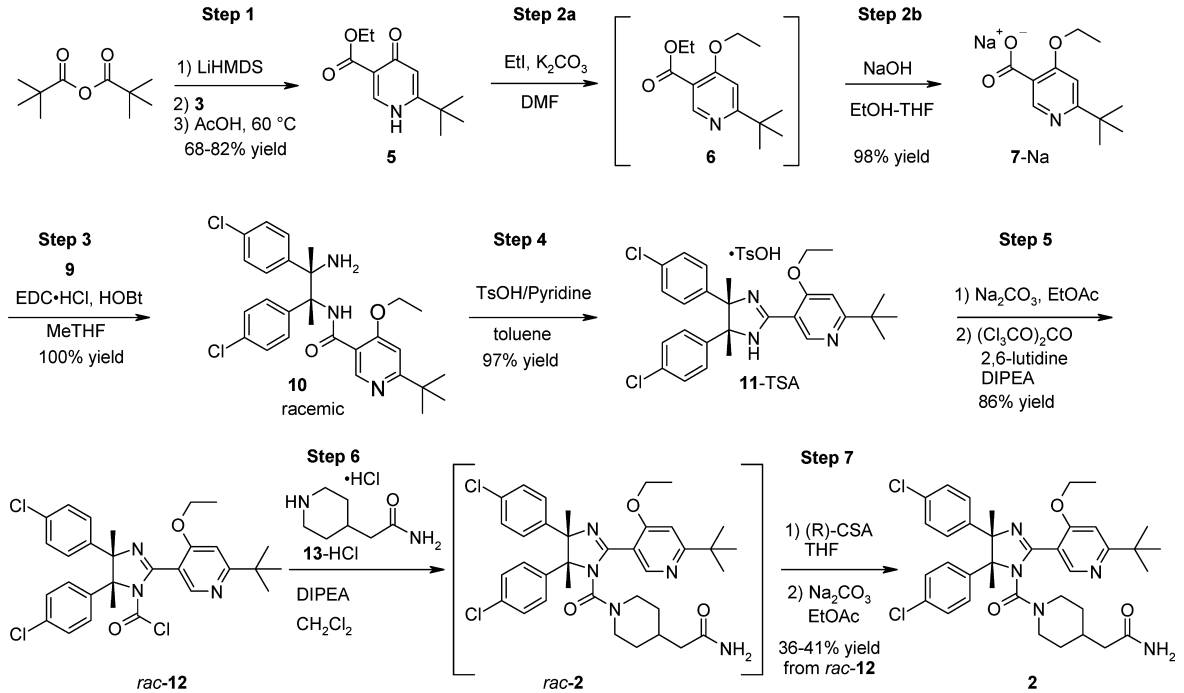
The alkylation of **5** with ethyl iodide was carried out at 60 °C in DMF using potassium carbonate as the base. After extractive workup, **6** was obtained as a solution in methyl *tert*-butyl ether (MTBE). Hydrolysis of **6** was initially performed in aqueous ethanol using sodium hydroxide. However, the isolation of **7** was problematic due to its aqueous solubility. Direct crystallization from the aqueous reaction mixture gave **7** in only moderate yield, contaminated with various levels of sodium chloride. Thus, the hydrolysis was carried out using a minimal amount of water, and the product was isolated as the corresponding sodium salt 7-Na in ≥99% purity and 98% yield from **5**.

Synthesis of 11-TSA. We have previously reported a boric acid-catalyzed direct condensation of *meso*-bis(4-chlorophenyl)-ethane-1,2-diamine with a benzoic acid, which gave a *cis*-4,5-bis(aryl)imidazoline in good yield.[9] The presence of the two methyl groups in **9** significantly impacts the reactivity of **9**, and no reaction was observed when a mixture of **9**, **7** and boric acid in xylenes was heated to reflux. A stepwise approach via **10** was therefore considered.

The monoacylation of **9** was carried out under typical amide preparation conditions using EDC·HCl as the coupling reagent. After a mixture of 7-Na, diamine **9**, a catalytic amount of HOBt or its monohydrate, DIPEA, and EDC·HCl in MeTHF were stirred at room temperature overnight, HPLC analysis indicated a clean conversion to monoamide **10**, which was obtained in nearly quantitative yield after an aqueous wash and crystallization from MeTHF−*n*-heptane. LC−MS analysis indicated the presence of bis-amide **17** in the reaction mixture at a level of 0.89%, but it purged well in the workup and was not observed in isolated **10**.

Cyclization of **10** in the presence of phosphorus oxychloride under the original conditions[5c,10] gave **11** in only 10% yield after chromatography. The major product from this reaction was **18** (Scheme 4). When phosphorus pentoxide was used as the dehydration agent, de-ethylation occurred exclusively to

Scheme 2. New synthesis of 2



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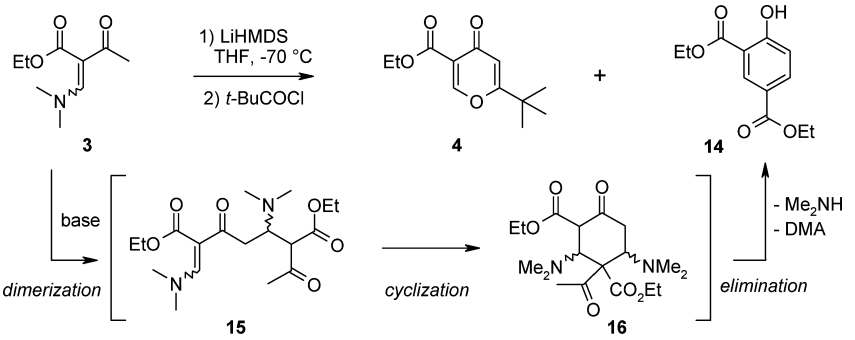
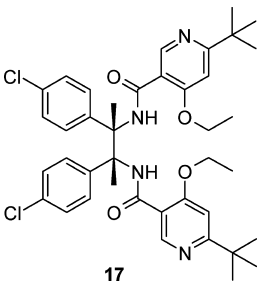
Scheme 3. Plausible mechanism for the formation of byproduct 14

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give **18** as the sole product in 68% yield. Subsequently, the cyclization was found to proceed reasonably cleanly when 1-propylphosphonic acid cyclic anhydride (T3P;[11] 1 equiv) was used, and the reaction was stopped in 2 h. Product **11** was obtained as a hydrochloride salt (**11**-HCl) in 90% yield and ≥96% purity (less than 2% of **18**) after aqueous workup, followed by salt formation with hydrogen chloride generated in situ from methanol and trimethylchlorosilane. This process was successfully scaled up to produce 1.5 kg of **11**-HCl.

In order to test the robustness of this process, the reaction was extended for an additional 20 h. While the cyclization was complete within 2 h, the level of **18** increased almost linearly with reaction time, reaching 50% after 22 h at the expense of product **11**, indicating that **18** was mainly generated from **11** (Figure 1a). Thus, it became critical that the reaction be stopped at the right time point to minimize degradation, a challenge at plant scale. As the de-ethylation is likely acid catalyzed, base additives were considered to slow this process. The addition of 2,6-lutidine (2 equiv) was found to significantly retard the rate of the formation of **18** without a negative impact on the cyclization rate (Figure 1b).

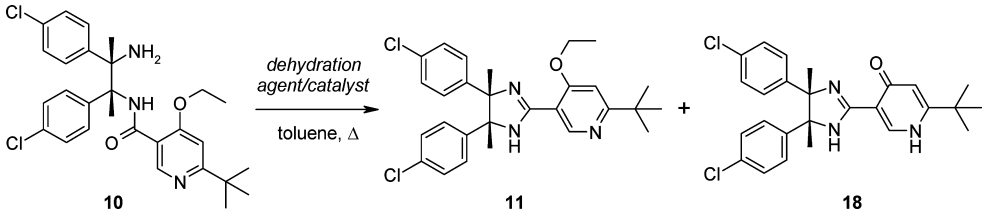
Subsequently, an improved cyclization procedure was developed, using 1 equiv of *p*-toluenesulfonic acid (*p*-TSA) buffered with 3 equiv of pyridine as the catalyst and a Dean–Stark trap to remove water generated during the reaction. The cyclization of **10** was complete within 3 h, and **11** precipitated out from the reaction mixture as the *p*-TSA salt. More importantly, once the reaction was complete, no further decomposition of **11** to **18** was detected (Figure 2); the levels of **11** and **18** remained essentially constant at 94% and 4%, respectively, even after heating the mixture to reflux for an additional 21 h. After cooling to room temperature, **11**-TSA was isolated in 97% yield and 95.8% purity (containing 2.6% of **18**). Material of this quality can be directly used in the next step. Interestingly, pyridine and *p*-TSA were found to be the ideal combination. Reactions catalyzed by *p*-TSA alone or with 2,6-lutidine in place of pyridine were observed to be slower and generated higher levels (4.8–8.8%) of **18**.

Preparation of *rac*-12. Due to the limited supply and safety concerns regarding phosgene, alternative reagents, such as *p*-nitrophenyl chloroformate,[12] were tested. However, the resulting intermediates did not react with amine **13**.

Therefore, bis(trichloromethyl) carbonate (triphosgene), was used to generate phosgene in situ. Triphosgene (0.37 equiv) in CH_2Cl_2 was cooled to ≤5 °C and then treated with 0.1 equiv of 2,6-lutidine to give a solution of phosgene. Compound **11**-HCl was then added, followed by the dropwise addition of DIPEA. The reaction was complete within 1 h. Excess phosgene was quenched with water, and *rac*-**12** was isolated in 89–92% yield and >99% purity as a white solid after aqueous workup and crystallization (Scheme 5).

As **11**-TSA was prepared and isolated using the improved cyclization conditions, it was decided to directly use this salt in the phosgenation step following the procedure described above for **11**-HCl. The reaction, however, gave a lower conversion, with a significant amount of *p*-toluenesulfonyl chloride detected by HPLC analysis, indicating that *p*-TSA was also consuming phosgene. Thus, a suspension of **11**-TSA in CH_2Cl_2 was treated with aqueous sodium carbonate to remove the *p*-TSA. The resulting solution of **11** was then added to the in situ-generated phosgene. After aqueous workup and dilution with *n*-heptane, carbamoyl chloride *rac*-**12** crystallized and was obtained as a white solid in 86% yield and 98.5% purity. Based on molecular weight data, the major impurity formed during the reaction was, presumably, the cyclization product **19**, generated from **18**. Although this impurity had good solubility and was removed

Scheme 4. Cyclization of 10



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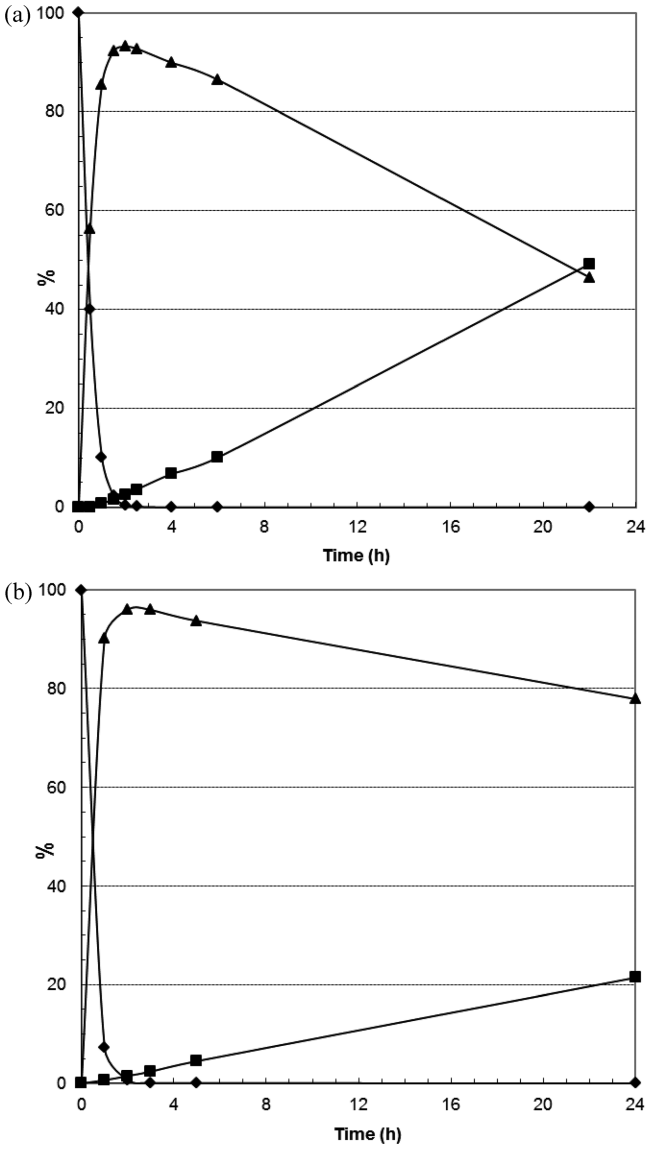


Figure 1. Cyclization of **10** catalyzed by T3P. (a) without an additive; (b) with 2,6-lutidine (2.0 equiv) added; ♦ **10**, ▲ **11**, ■ **18**.

during the crystallization, the loss of *rac*-**12** in the filtrate increased when **19** was present. Therefore, removing **18** from **11** prior to the phosgenation step is highly recommended for further scale up.[13]

Though carbamoyl chloride **12** was compatible with weak bases, such as aqueous sodium bicarbonate, it can be converted back to **11** when treated with aqueous sodium hydroxide. This provides an easy means for recycling the undesired enantiomer. Therefore, a chiral resolution of *rac*-**12** is highly desirable. Unfortunately, crystallization screening with a variety of chiral acids did not produce any fruitful results. The racemic form was thus carried forward into the next step.

Preparation of Drug Substance 2. The coupling of *rac*-**12** with amine **13** was carried out in CH_2Cl_2 in the presence of DIPEA. The reaction mixture was worked up, and after solvent exchange to THF, the resulting suspension of *rac*-**2** was directly used in the resolution step. When this process was scaled up in the pilot plant, phase separation during the aqueous workup was found to be slow.

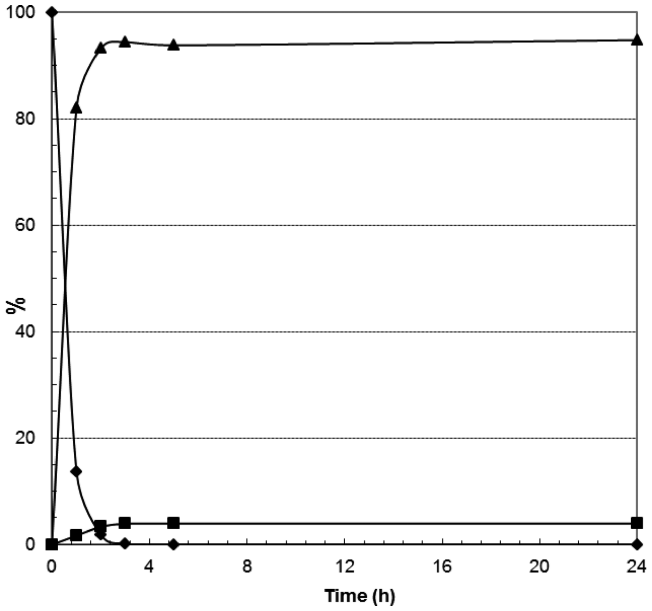


Figure 2. Cyclization of **10** catalyzed by *p*-TSA and pyridine. ♦ **10**, ▲ **11**, ■ **18**.

In order to solve this issue, direct precipitation of *rac*-**2** from the reaction mixture was attempted. Thus, *rac*-**12** was suspended in CH_2Cl_2, and then **13**-HCl was added followed by addition of DIPEA. After stirring at room temperature overnight, the reaction mixture became a thick slurry and HPLC analysis indicated complete reaction. This slurry was then diluted with water and *n*-heptane, worked up and filtered to give the desired product in nearly quantitative yield. This improved process was consistent in small scale test runs and should be more reliable for large scale preparations.

After screening a variety of chiral acids, the resolution of **2** with (*R*)-camphorsulfonic acid (CSA) was the only hit identified. In a solvent effect study,[14] only THF and MTBE gave a crystalline salt of **2**-CSA with up to 20% enantiomer enrichment. In THF, the diastereomeric purity of the salt was significantly improved when only 0.5 equiv of camphorsulfonic acid was used, and **2**-CSA was obtained in 99.5% de and 36.5% yield. In MTBE, however, the stoichiometry of camphorsulfonic acid barely affected the chiral purity of the salt. On scale-up, a solution of *rac*-**2** in THF was treated with 0.5 equiv of (*R*)-CSA at reflux for 1 h and stirred overnight. The resolved salt, **2**-CSA, was collected in 43% yield and 99.7% de.

The undesired enantiomer could be recovered from the mother liquor by basic aqueous workup and crystallization. All efforts to recycle the enantiomer to **11** by hydrolysis under strong acidic or basic conditions were unsuccessful, as the sterically hindered urea was very stable. Attempts to reduce the urea moiety by treatment with lithium aluminum hydride in toluene at reflux resulted in decomposition.

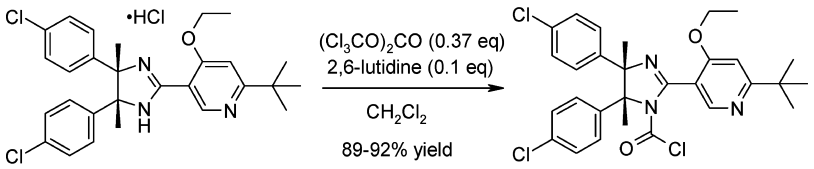
With the resolved salt **2**-CSA in hand, the API was obtained by neutralization with aqueous sodium carbonate in ethyl acetate. The product **2** crystallized from ethyl acetate and *n*-heptane, and was isolated in 98.7% chemical purity, 99.7% ee, and 36.5% overall yield from *rac*-**12**.

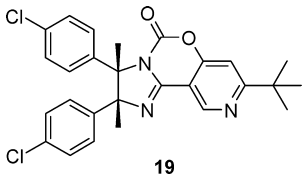
■ CONCLUSION

In summary, we have developed an improved, multikilogram-scale synthesis of **2** in seven steps and 20−27% overall yield

dx.doi.org/10.1021/op300294g | *Org. Process Res. Dev.* XXXX, XXX, XXX−XXX

Scheme 5. Preparation of *rac*-12 from 11-HCl

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from **3**. This process was successfully scaled up in a pilot plant to produce >10 kg of API. While some optimization might be required for a few minor issues, such as the low-temperature reaction and the use of potentially hazardous HOBt, this synthesis is considered adequate for the drug substance supply at this stage. The recycling of the undesired enantiomer or resolution of *rac*-**12** would be the area for further development.

EXPERIMENTAL SECTION

General. Achiral HPLC analyses were performed on an Agilent Zorbax XDB-C8 (100 mm × 3 mm, 3.5 μm) column with 30−100% CH_3CN/H_2O (+0.1% TFA) as mobile phase over 15 min at flow rate of 0.5 mL/min. Chiral HPLC analysis were performed on Chiralcel OD (250 mm × 4.6 mm, 5 μm) column using EtOH/hexane (1:4) as mobile phase at flow rate of 1 mL/min. Compound **9** was prepared in three steps and 54% yield from 1,2-bis(4-chlorophenyl)ethane-1,2-dione using an optimized process based on a previously described route.[5c] Bulk quantities of 7-Na were prepared by a CMO using a process based on the procedures described below.

Ethyl 6-*tert*-Butyl-4-oxo-1,4-dihydropyridine-3-carboxylate (5). A solution of LiHMDS[15] (1.6 M in THF, 210 mL, 336 mmol) was cooled to −50 °C, and then trimethylacetic anhydride (30.0 g, 161 mmol) was added over 15 min at ≤−50 °C. The resulting mixture was further cooled to about −75 °C. Then, **3** (30.1 g, 163 mmol) was added over 40 min at ≤−70 °C. After stirring for an additional 20 min, the mixture was warmed to room temperature, and AcOH (30.0 mL, 500 mmol) was added over 5 min. The mixture was stirred at 60 °C for 30 min and then concentrated under reduced pressure to remove THF. The residual aqueous mixture was diluted with EtOAc (240 mL) and water (90 mL). The organic phase was separated, washed with sat. Na_2CO_3 (120 mL) and water (90 mL), concentrated to ∼100 mL, and diluted with *n*-heptane (240 mL). The resulting suspension was further concentrated to ∼220 mL, cooled to ∼5 °C, and stirred for 1 h. The solid was collected by filtration, washed with cold *n*-heptane (50 mL), and dried by suction to give **5** (24.5 g, 68% yield, >99% HPLC purity) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 6.82 (s, 1H), 4.10 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 H, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.53, 175.53, 169.35, 167.63, 150.75, 107.85, 61.61, 37.66, 29.59, 14.08; HRMS calcd for $C_{12}H_{18}O_3N$ [M + H] 224.1287, found 224.1280.

Sodium 6-*tert*-Butyl-4-ethoxynicotinate (7-Na). A mixture of **5** (25.0 g, 112 mmol), DMF (75 mL), and K_2CO_3 (25.0 g, 181 mmol) was stirred at 60 °C for 30 min, and then iodoethane (12.5 mL, 155 mmol) was added. After stirring at 60 °C overnight, the resulting suspension was diluted with water (125 mL) and extracted with MTBE (200 mL). The extract was washed with water (200 mL), concentrated to ∼100 mL, and diluted with ethanol (25 mL) and THF (200 mL). Then, 50% sodium hydroxide (6.2 mL, 118 mmol) was added. After stirring at 50 °C for 2 h, the mixture was cooled to room temperature and diluted with MTBE (100 mL). The resulting solid was collected by filtration, washed with MTBE (100 mL), and dried to give 7-Na (27.0 g, 98% yield, 99% HPLC purity) as a white solid; mp 303−304 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 6.82 (s, 1H), 4.10 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.11, 168.02, 161.11, 148.28, 126.09, 102.83, 62.83, 37.10, 30.07, 14.18; HRMS calcd for $C_{12}H_{17}O_3NNa$ [M + H] 246.1106, found 246.1103.

rac*-*N*-[(1*R*,2*S*)-2-Amino-1,2-bis(4-chlorophenyl)-1-methylpropyl]-6-*tert*-butyl-4-ethoxynicotinamide (10).** Two flasks were each charged with **9** (1.20 kg, 3.88 mol), 7-Na (1.06 kg, 4.32 mol),[16] HOBt (97.3 g, 0.72 mol) (CAUTION***: HOBt can be explosive under certain conditions), MeTHF (12 L), and DIPEA (622 g, 4.81 mol). The resulting suspension was stirred for 10 min, and then EDC·HCl (870 g, 4.53 mol) was added to each flask in one portion. After stirring overnight, the contents of the two flasks were combined, diluted with MeTHF (12 L), and washed with water (3 × 7.2 L). The organic phase was then equally divided into two portions, and each portion was concentrated to remove ∼12 L of solvent. The residues were each diluted with *n*-heptane (4.8 L) and further concentrated to remove 4.8 L of solvent. The residues were again each diluted with *n*-heptane (4.8 L), and the resulting suspensions were stirred at 50 °C for 30 min and at room temperature overnight. The contents of the two flasks were combined and filtered. The filter cake was washed with *n*-heptane (2 × 4.8 L) and dried to give **10** (3.99 kg, quantitative yield, 96.2% HPLC purity) as a light-brown solid; mp 184−185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 8.68 (s, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.14 (s, 1H), 7.11 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 7.8 Hz, 2H), 4.47 (m, 2H), 2.19 (s, 2H), 1.86 (s, 3H), 1.59 (s, 3H), 1.58 (t, J = 7.0 Hz, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.20, 162.57, 162.35, 151.20, 143.66, 140.99, 131.24, 130.73, 129.79, 129.12, 126.60, 126.48, 116.08, 103.02, 64.87, 63.74, 60.58, 37.68, 29.79, 24.69, 20.72, 14.65; HRMS calcd for $C_{28}H_{34}O_2N_3Cl_2$ [M + H] 514.2028, found 514.2019.

5-[(4*S*,5*R*)-4,5-Bis(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-2-*tert*-butyl-4-ethoxypyridine *p*-Toluenesulfonic Acid Salt (11-TSA). Two flasks were each charged with **10** (1.38 kg, 2.69 mol), *p*-TSA·H_2O (538 g, 2.82 mol), pyridine (692 mL, 8.56 mol) and toluene (13.8 L). Each reaction mixture was stirred at reflux for 4.5 h, and water was removed via a Dean−Stark trap. After cooling to room temperature, the contents of the two flasks were combined and filtered. The filter cake was washed with MTBE (2 × 8 L)

dx.doi.org/10.1021/op300294g | Org. Process Res. Dev. XXXX, XXX, XXX−XXX

and dried to give **11**-TSA (3.50 kg, 97% yield, 95.8% HPLC purity) as a white solid; mp 303 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 2H), 8.86 (s, 1H), 7.46 (m, 2H), 7.31 (s, 1H), 7.20−7.16 (m, 4H), 7.11 (m, 2H), 7.10−7.06 (m, 4H), 4.42 (q, J = 7.0 Hz, 2H), 2.28 (s, 3H), 1.95 (s, 6H), 1.45 (t, J = 7.0 Hz, 3H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.66, 163.64, 160.06, 149.87, 145.61, 138.83, 137.60, 132.14, 128.11, 128.00, 127.64, 125.46, 106.26, 103.74, 72.64, 65.29, 38.30, 29.63, 22.67, 20.78, 14.02; HRMS calcd for $C_{28}H_{32}ON_3Cl_2$ [M + H] 496.1922, found 496.1912.

***rac*-(4*S*,5*R*)-2-(6-*tert*-Butyl-4-ethoxypyridin-3-yl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl Chloride (*rac*-12).** Compound **11**-TSA (6.83 kg, 10.22 mol) was suspended in CH_2Cl_2 (34 L) and toluene (19.5 L). The mixture was stirred at room temperature, and a solution of Na_2CO_3 (1.13 kg) in water (11.3 L) was added over 30 min. The resulting solution was stirred for 30 min. The organic layer was then separated, washed with water (19.5 L), and concentrated under reduced pressure to remove ∼36 L of solvent. The residue was diluted with CH_2Cl_2 to 10 L and equally divided into four portions.

Four flasks were each charged with triphosgene (285 g, 0.96 mol) and CH_2Cl_2 (8.5 L). The resulting solutions were cooled to −7 °C. To each flask was added 2,6-lutidine (26 mL, 0.22 mol) over 15 min. Then, the solution of **11** (2.5 L each, 2.55 mol in theory) in CH_2Cl_2 from above was added over 45 min, followed by the addition of DIPEA (597 mL, 3.43 mol). The resulting four reaction mixtures were stirred below 0 °C for 2.5 h and at room temperature overnight and then were quenched with water (5 L each). The contents of the four flasks were combined and washed with water (2 × 20 L). The organic phase (∼60 L) was concentrated to remove ∼25.6 L of solvent and then was diluted with *n*-heptane (31.2 L). The resulting solution was further concentrated to remove an additional 22 L of solvent. The suspension was filtered, and the collected solid was washed with *n*-heptane (2 × 6.8 L) and dried to give *rac*-**12** (4.92 kg, 86% yield, 98.4% HPLC purity) as a white solid; mp 202−204 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.65 (s, 1H), 7.25−7.00 (m, 9H), 4.53 (m, 1H), 4.31 (m, 1H), 2.23 (s, 3H), 1.79 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.72, 163.09, 154.36, 150.23, 144.56, 139.55, 133.08, 127.91, 127.78, 127.65, 114.35, 101.89, 64.45, 38.09, 30.05, 24.66, 21.65, 14.50; HRMS calcd for $C_{29}H_{31}O_2N_3Cl_3$ [M + H] for 558.1482, found 558.1474.

2-{1-[(4*S*,5*R*)-2-(6-*tert*-Butyl-4-ethoxypyridin-3-yl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]piperidin-4-yl}acetamide (*R*)-Camphorsulfonic Acid Salt (2-CSA). Two flasks were each charged with *rac*-**12** (1.23 kg, 2.20 mol), CH_2Cl_2 (12 L), DIPEA (1.93 L, 11.08 mol), and **13**-HCl (492 g, 2.75 mol). After stirring overnight, the reaction mixtures were combined and diluted with water (20 L). The organic layer was separated, washed with 0.4 M HCl (20 L), diluted with additional CH_2Cl_2 (20 L), and washed with water (20 L). After concentrating essentially to dryness, the residue was suspended in THF (5 L) and reconcentrated to near dryness. This operation was repeated one more time, and the resulting wet solid *rac*-**2** was divided equally into three portions. To each portion was added THF (11 L), and the resulting mixtures were warmed to 50−55 °C to give clear solutions. Then, (*R*)-CSA (148 g each, 0.64 mol) was added, and the mixtures were heated to reflux for 1.5 h and at room temperature overnight. The contents of three flasks were combined and filtered. The filter cake was washed with THF (3 × 2.4 L) and dried to give **2**-CSA (1.70 kg, 43% yield, 98.5% chemical purity, and 99.7% de) as a white solid; mp 176−178 °C.

2-{1-[(4*S*,5*R*)-2-(6-*tert*-Butyl-4-ethoxypyridin-3-yl)-4,5-bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroimidazole-1-carbonyl]piperidin-4-yl}acetamide (2). Compound **2**-CSA (3.00 kg, 3.34 mol) was charged portionwise to an extractor containing a mixture of EtOAc (39 L) and Na_2CO_3 (975 g, 9.20 mol) in water (19.5 L). The suspension was stirred for 2 h, and then the layers were separated. The organic phase was washed with water (2 × 19.5 L) and then filtered through a pad of Celite (200 g). The pad was washed with EtOAc (2 × 3 L), and the combined filtrate and washes were concentrated while *n*-heptane (39 L) was added. The resulting suspension was further concentrated to ∼21 L, then filtered. The filter cake was washed with *n*-heptane (2 × 3 L) and dried to give **2** (1.88 kg, 85% yield, 98.7% chemical purity and 99.7% ee) as a white solid; mp 206−209 °C; ^{1}H NMR (400 MHz, DMSO-d_6)[17] δ 8.65 (s, 0.4H), 8.64 (s, 0.6H), 7.23−6.90 (m, 10H), 6.73 (s, 0.4H), 6.68 (s, 0.6H), 4.33 (m, 1H), 4.05 (m, 1H), 3.57 (m, 0.4H), 3.50 (m, 0.6H), 3.42−3.25 (m, 1H), 2.66 (m, 0.6H), 2.52 (m, 0.6H), 2.21 (m, 0.4H), 1.99 (m, 0.4H), 1.90 (s, 1.2H), 1.88 (s, 1.8H), 1.72−1.18 (m, 20H), 0.99 (m, 0.4H), 0.88 (m, 0.4H), 0.27 (m, 0.6H), −0.58 (m, 0.6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.06, 172.43, 172.22, 162.94, 162.44, 155.08, 154.93, 153.02, 149.79, 141.40, 140.72, 140.64, 130.59, 130.15, 128.23, 128.14, 126.66, 126.14, 113.72, 102.01, 101.59, 76.38, 76.25, 74.93, 64.09, 47.45, 45.07, 41.81, 40.91, 37.63, 32.17, 31.97, 31.56, 30.61, 30.45, 30.07, 29.86, 29.70, 23.71, 20.09, 19.85, 13.82, 13.73; HRMS calcd for $C_{36}H_{44}Cl_2N_5O_3$ [M + H] 664.2816, found 664.2818.

***rac*-5-[(4*S*,5*R*)-4,5-Bis-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazol-2-yl]-2-*tert*-butyl-1*H*-pyridin-4-one (18).** Compound **10** (500 mg, 0.97 mmol) was dissolved in toluene (10 mL), then P_2O_5 (138.0 mg, 0.97 mmol) was added. The mixture was stirred at reflux overnight, then cooled to room temperature and quenched with water, followed by 2 M sodium hydroxide (2.9 mL, 5.8 mmol). The organic phase was separated, washed with water (2 × 10 mL), and concentrated. The resulting foam was crystallized from MTBE−*n*-heptane (1:2, v/v, 15 mL) to give **18** (310 mg, 68% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 7.09 (d, J = 8.7 Hz, 4H), 6.97 (d, J = 8.7 Hz, 4H), 6.42 (s, 1H), 3.50 (br, 1H), 3.39 (s, 1H), 1.77 (s, 6H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.48, 163.13, 149.19, 141.45, 131.12, 127.99, 127.26, 111.09, 71.82, 62.77, 36.58, 29.57, 23.14; HRMS calcd for $C_{26}H_{28}ON_3Cl_2$ [M + H] 468.1609, found 468.1600.

4-Hydroxyisophthalic Acid Diethyl Ester (14):[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (s, 1H), 8.57 (d, J = 2.5 Hz, 1H), 8.12 (dd, J = 9.0, 2.5 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H), 4.45 (q, J = 7.2 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.79, 165.61, 165.11, 136.45, 132.38, 121.69, 117.67, 112.37, 61.91, 60.98, 14.35, 14.18.

AUTHOR INFORMATION

Corresponding Author

*E-mail: lshu@verizon.net

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Masami Okabe for helpful discussion and Ms. Rui Yu and Bojana Nedjic for analytical support. We thank Dr. Hanspeter Michel of Formulation Research Department for HRMS analysis.

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(13) Compound **18** partially precipitated from CH_2Cl_2 when **11**-TSA was neutralized with base. Thus, level of **18** in **11** could be reduced by in-line filtration.

(14) The following solvents were screened: 2-propanol, ethyl acetate, acetonitrile, toluene, MTBE, and THF.

(15) LiHMDS from commercial sources was used as received.

(16) Early batches of compound **7**-Na supplied by CMO appeared to be lower in quality as 10% excess of **7**-Na was required for a complete reaction, while for small-scale test runs with in-house prepared **7**-Na, one equivalent was sufficient.

(17) NMR showed a 2:3 mixture of rotamers of **2**.

(18) Compound **14** was isolated from **4** by flash column chromatography on silica gel.