Organic Process Research & Development

Article

pubs.acs.org/OPRD

Evolution of a Manufacturing Route to Omarigliptin, A Long-Acting DPP-4 Inhibitor for the Treatment of Type 2 Diabetes

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ABSTRACT: Development of a convergent synthesis of omarigliptin (MK-3102) suitable for commercial manufacture is described. The target molecule is assembled through a diastereoselective reductive amination of a highly functionalized pyranone with a mesylated pyrazole followed by deprotection of a Boc group. The synthesis of the pyranone relies on three Ru-catalyzed reactions: (1) a DKR reduction of a *rac*-α-aminoketone to set the two contiguous stereogenic centers, (2) a cycloisomerization of a bis-homopropargylic alcohol to a dihydropyran, and, finally, (3) a Ru-catalyzed oxidation of a pyranol to the desired pyranone. The regioselective synthesis of a *N*-Boc-1-mesyl pyrazole fragment was achieved via base-promoted mesyl group isomerization to afford 30:1 selectivity. A highlight of the endgame process development is telescoping a Boc deprotection and reductive amination followed by direct crystallization of the penultimate from the reaction mixture. This avoids handling of an unstable, mutagenic 1-mesylpyrazole BSA salt used in the earlier multikilogram deliveries and improves the overall diastereoselectivity and efficiency of the route.

INTRODUCTION

Type 2 diabetes mellitus is a growing worldwide epidemic affecting more than 366 million people globally, including nearly 26 million people in the United States.[1] Commercial proof of concept for dipeptidyl peptidase-4 (DPP-4) inhibitors has been established with Merck's sitagliptin,[2] which was the first once-daily DPP-4 inhibitor approved by the FDA in October 2006. Subsequently, additional DPP-4 inhibitors have entered the marketplace.[3] Given the clinical success of DPP-4 inhibitors, there has been interest in generating structurally diverse potent drug candidates with longer half-lives that are amenable to once-weekly dosing. Merck Research Laboratories recently discovered **1** (omarigliptin, MK-3102) (Scheme 1), a highly functionalized and structurally differentiated long-acting DPP-4 inhibitor,[4] that recently received marketing authorization in Japan for the once-weekly treatment of type 2 diabetes. The scalable, first-generation synthesis of a forerunner of **1**, namely, **2**, which differs only by a mesyl group, was recently reported.[5] We adopted similar chemistry for the initial kilogram deliveries of **1** by mesylation of **3** followed by Boc deprotection. Although the process was productive and capable of supporting the program through development, this was not a process that met our standards for commercial manufacture. Significant improvements were made to the first-generation synthesis of Boc-ketone **5** to improve the robustness and reduce both process mass intensity and cost of goods. Herein, we report the evolution and development of an efficient process for multikilogram scale synthesis of omarigliptin amenable to manufacturing scale.

RESULTS AND DISCUSSION

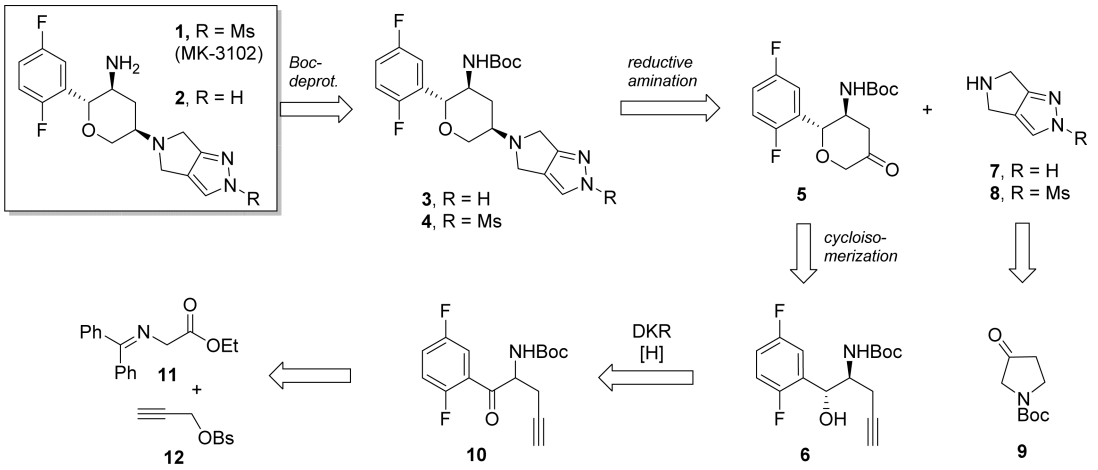
Initial Multikilogram Deliveries of Omarigliptin (1). A critical evaluation of the endgame of the discovery chemistry route indicated that the most salient issue to be addressed was the lack of regiochemical control over the N-sulfonation of the pyrazole moiety embedded within **1** (Scheme 2). An approximately 1:1 mixture of the two N-sulfonated regiochemical isomers, **14** and **15**, was typically obtained when using NaH and MsCl to sulfonate **13**, requiring chromatographic purification,[6] an operation that becomes prohibitive as the scale of operation increases. In addition, as kilogram quantities of the unprotected pyrazole **7** were available for these initial multikilogram deliveries, it was desirable to directly use **7** without the need to reprotect with a Boc group to access **13**. Consequently, we set out to develop a regiochemical sulfonation of known intermediate **3**,[5] which could be accessed by the diastereoselective reductive amination of pyranone **5** with pyrazole **7** (Scheme 1).

Our first kilogram delivery began with the reductive amination of pyranone **5** with pyrazole **7**, which was modified from the previously reported conditions (Scheme 3).[5] Specifically, a switch of solvent from DMAC to DMF was made to suppress formation of acetylated impurity **17** that was observed to form during the subsequent sulfonation step and was attributed to the presence of low levels of residual DMAC within the isolated **3**. Under these modified conditions, the desired **4** was isolated by direct crystallization from the reaction mixture in 80% yield and with 4.5 A% of the undesired

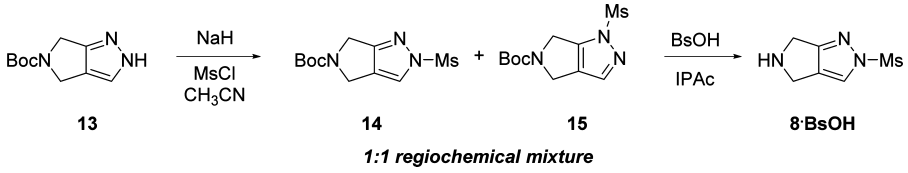
Received: August 18, 2015
Published: October 1, 2015

DOI: 10.1021/acs.oprd.5b00267
Org. Process Res. Dev. 2015, 19, 1760−1768

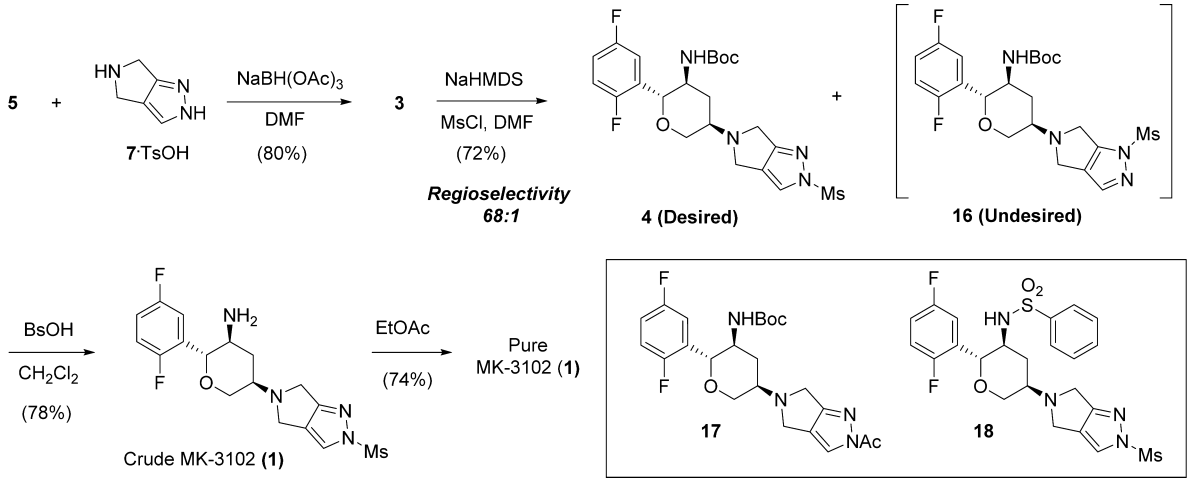
Scheme 1. Retrosynthetic Analysis of Omarigliptin (1)



Scheme 2. Discovery Chemistry Pyrazole N-Sulfonation



Scheme 3. First Multikilogram Delivery of Omarigliptin (1)

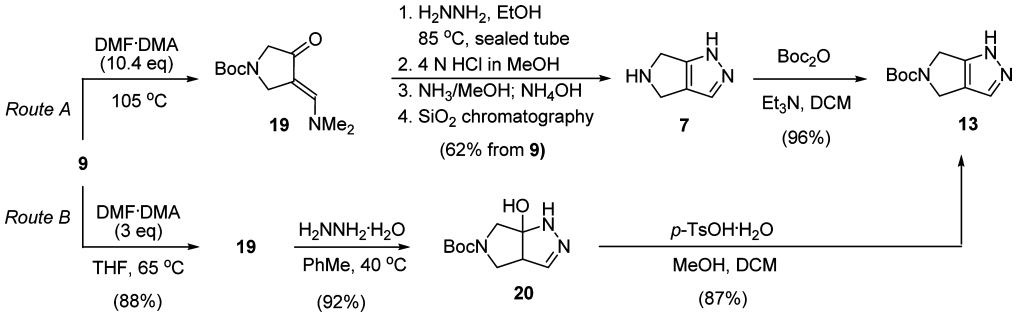


diastereomer present. The diastereoselectvity of the reduction was 16:1.

With intermediate **3** in hand, screening of the mesylation indicated that amine bases such as Et_3N and pyridine when used in combination with mesyl chloride favored *undesired* regioisomer **16** with as high as 9:1 selectivity. Moving to stronger K and Na metal bases provided more encouraging results, with selectivities as high as 1:8 favoring desired isomer **4** under certain conditions. A key observation was made when using NaHMDS, namely, that the selectivity of the reaction improved as long as there remained some **3** present within the reaction mixture (or more specifically the Na anion of **3**, *vide infra*). Once all of **3** had been consumed to **4** and **16**, no further change in the ratio of **4**:**16** occurred on extended aging. Application of DOE to one set of reagents (NaHDMS as base, MsCl as mesylating agent in DMF) indicated that the regioselectivity was not directly dependent on concentration, temperature, or reagent equivalents. In addition, the regioselectivity was not dependent on the age time when preforming the anion prior to MsCl addition. A slow addition of MsCl resulted in high regioselectivity for the desired **4** (up to 1:68 in favor of **4** in the reaction mixture). Our mechanistic hypothesis for these observations is that undesired **16** can serve as a mesylating agent under the reaction conditions and undergoes turnover to the more thermodynamically stable isomer **4**. Optimized conditions required a balance between the amount of unconverted **3** left over at the end of reaction and achieving a high regioselectivity for the penultimate intermediate, **4**. Ultimately, for this first kilogram delivery, conditions of 2.0 equiv of NaHMDS and 1.75 equiv of MsCl in DMF were used, with the addition of MsCl occurring over 4−6 h. The desired **4** crystallized toward the end of addition, and following addition of water as antisolvent, it could be

DOI: 10.1021/acs.oprd.5b00267
Org. Process Res. Dev. 2015, 19, 1760−1768

Scheme 4. Evolution of the Synthesis of Boc Pyrazole 13



isolated in 74% yield (96 A% purity) with regioisomer **16** present at just 0.1 A%.

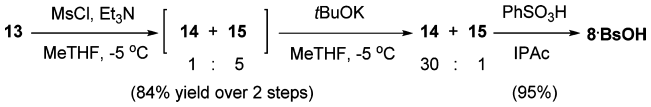
Deprotection of the Boc group within **4** proved to be challenging. This was due to competitive cleavage of the mesyl group to form undesired byproduct **2**. From a screen of acid and solvent combinations, benzenesulfonic acid (BSA) in dichloromethane as solvent emerged as the most promising, with levels of **2** suppressed to around 3.0 A% in the reaction mixture. Extended aging led to an increase in the level of **2**, and as such, the reaction was typically quenched with around less than 2.0 A% of **4** remaining. A further impurity that proved to be problematic was the formation of N-benzenesulfonated **18**, which occurred during basification in the workup and is speculated to occur by besylation with the mixed anhydride formed from benzenesulfonic acid and the mesyl portion cleaved from **4**. The final level of **18** was ultimately controlled through recrystallization, and application of the deprotection conditions afforded crude omarigliptin (**1**) in 78% yield (1.7 A % **18**), followed by recrystallization from EtOAc to give pure **1** in 72% yield with 1.0 A% of **18** present. In a subsequent kilogram campaign, the addition of water (0.2 wt %) was found to suppress the formation of **18**, and omarigliptin could be isolated in an improved 73% yield without the need for recrystallization (vs 56% for the previous campaign).

Process Development for Manufacturing Scale. While significant progress to solving the N-sulfonation regiochemical problem was made during the first kilogram campaign to **1**, specifically on fully elaborated intermediate **3**, it was considered desirable to move back to the more convergent approach, wherein mesylated pyrazole **8** is coupled with pyranone **5**, followed by a final Boc deprotection to form omarigliptin (Scheme 1). In so doing, we expected to be able to utilize our knowledge gained in the sulfonation of **3** to pyrazole **13** and turnover any of the undesired regioisomer **15** that might form to **14**. In addition, focused process development on other steps on the routes to pyrazole **8** and pyranone **5** was pursued to reduce cost, improve processability and scalability, and address safe handling as well as other aspects associated with readiness for manufacturing scale operations.

Process Development of Boc-mesyl-pyrazole 8 for Manufacturing Scale. Before embarking on the development of the selective mesylation of **13**, we needed a scalable synthesis of this intermediate. The discovery chemistry route to **13** (Scheme 4, route A) employed high temperatures, excess *N*,*N*-dimethylformamide dimethylacetal (DMF·DMA),[7] silica gel chromatography, and a Boc reprotection, which were all undesirable. We undertook process development to address these issues, and the revised process to **13** (Scheme 4, route B) used lower reaction temperatures and fewer equivalents of DMF·DMA, eliminated the silica gel chromatography, and utilized mild dehydration conditions to retain the Boc group. In addtion, the levels of mutagenic impurities (such as hydrazine, methyl tosylate) in the downstream steps were estimated through purge factor calculations[8] and/or confirmed by analysis to be significantly below threshold of toxicological concern (TTC) levels.

Building on the discovery of the regioselective sulfonation of intermediate **3**, whereby an initially formed mixture of regioisomers was converged to the desired isomer **4**, we sought to develop a related process for the sulfonation of Boc-pyrazole **13** (Scheme 5). While application of our previously developed

Scheme 5. Regioselective Pyrazole N-Sulfonylation



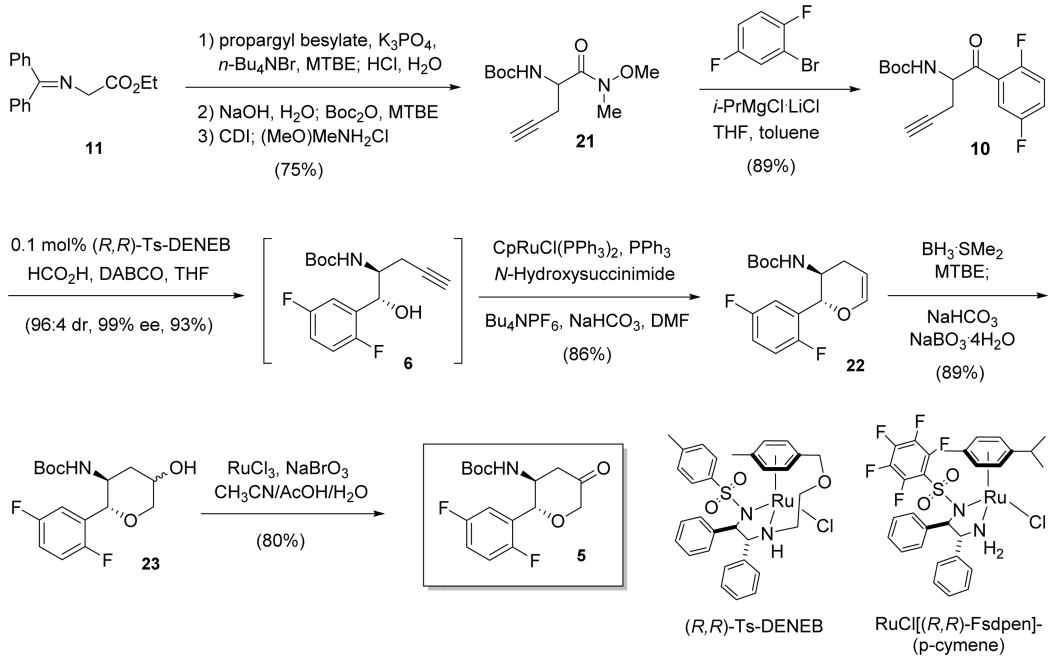
NaHMDS/MsCl conditions was studied first, unacceptably high levels of starting material **13** were typically present, and only a 63% yield of **14** was obtained with a 9:1 regioselectivity. Following screening, a telescoped process was developed whereby a kinetic mesylation with MsCl/Et_3N was carried out in 2-MeTHF to afford a quantitative combined yield of **14** and regioisomer **15** that favored **15** in a 5:1 ratio. Following an aqueous workup to remove triethylamine salts and azeotropic drying, addition of 7 mol % of solid *t*-BuOK to the mixture afforded turnover to a 30:1 mixture that favored the desired **14**. Following a recrystallization of the isolated solids, **14** was obtained in 84% yield from **13** and with <2% of **15** present. Mechanistically, we speculate the isomerization again occurs through mesyl group cleavage of the undesired **15** to the potassium anion of **13**, which then allows for mesylation to the desired **14**. This is supported by the observation of **13** by HPLC under the reaction conditions.

Process Development of Pyranone 5 for Manufacturing Scale. Several areas for improvement in the first-generation synthesis[5] of pyranone **5** were identified (Scheme 6). In step 1, the inorganic base Cs_2CO_3 (2.75 equiv) used for the PTC alkylation of glycine benzophenone imine (**11**) with propargyl besylate was found to be the highest cost reagent in the synthesis of pyranone **5**. After some screening studies, we identified K_3PO_4 (3 equiv) along with an equimolar amount of water to be a suitable inexpensive replacement without sacrificing either yield or purity. The addition of water was beneficial for the reaction kinetics.

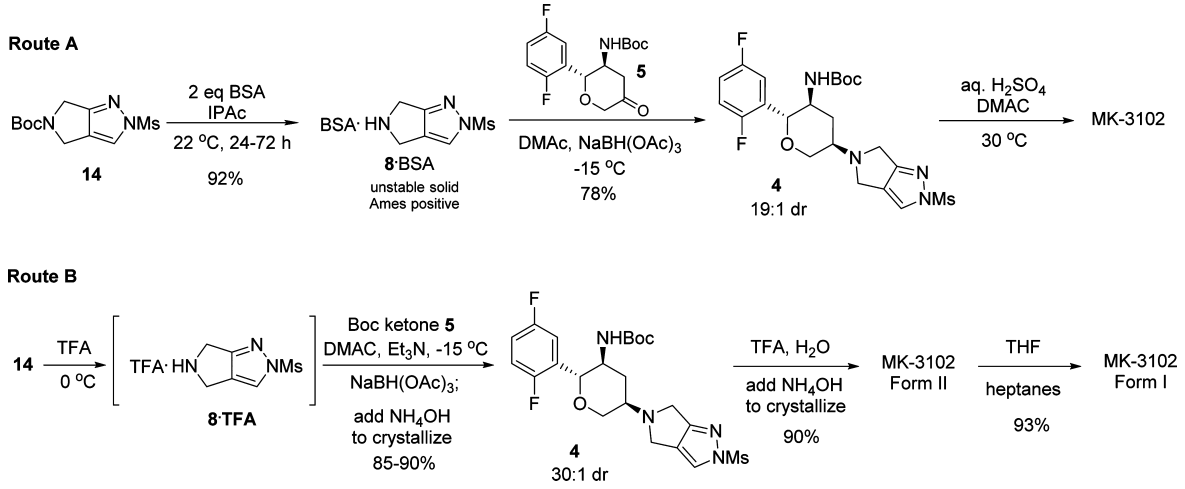
In the first-generation synthesis, the DKR asymmetric transfer hydrogenation of *rac* aminoketone **10** with the catalyst

DOI: 10.1021/acs.oprd.5b00267
Org. Process Res. Dev. 2015, 19, 1760−1768

Scheme 6. Manufacturing Route to Pyranone 5



Scheme 7. Evolution of Omarigliptin Endgame Synthesis



RuCl[(*R*,*R*)-Fsdpen](*p*-cymene) typically produced the anti-aminoalcohol **6** with 8:1 dr and ≥98% ee.[5] In 2011, Takasago International Corporation introduced oxo-tethered ruthenium-(II) catalyst, (*R*,*R*)-Ts-DENEB,[9] as a highly efficient asymmetric transfer hydrogenation catalyst (Scheme 6). We made a switch to this catalyst while maintaining the same reaction conditions and found the performance of this catalyst to be superior in all aspects. In particular, the diastereoselectivity, enantioselectivity, and reaction yield improved to 24:1 dr, >99% ee, and 93% assay yield, respectively. This catalyst proved to be highly active and robust such that we could reduce the catalyst loading from 0.5 to 0.1 mol % without sacrificing selectivity and reaction kinetics. We found that it was critical to apply efficient N_2 sparging during the reaction to remove CO_2; otherwise, the reaction could stall if this was allowed to accumulate. It is hypothesized that the tethered catalyst reduced the dissociation tendency of the arene from the Ru relative to the first-generation catalyst, which, in conjunction with the increased steric hindrance of the linker, contributed to improved stereoselectivity, activity, and robustness. The DKR product **6** work up stream was taken directly into the Ru-catalyzed cycloisomerization step without isolation as previously reported. In order to ensure consistent reaction kinetics and purity profiles in the downstream chemistry, we incorporated activated carbon and silica slurry treatments to the work up streams of DKR product **6** and cycloisomerization product **22**, respectively. Compound **22** was then isolated by crystallization. With these treatments, the subsequent hydroboration of **22** and the $RuCl_3$-catalyzed oxidation of the resulting **23** proceeded smoothly. Boc ketone **5** was crystallized directly from reaction mixture in good purities, and Ru levels in **23** and **5** were <350 and <90 ppm, respectively. This was further reduced to <5 ppm Ru in the next step. Other process intensification changes such as the replacement of high grade *n*-heptane with cheaper grade *n*-heptane containing C7 isomers[10] and reduction of work up solvent volumes[11] and of adsorbents[12] were also developed. All of these changes were

DOI: 10.1021/acs.oprd.5b00267
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successfully implemented on pilot plant scale, resulting in significant cost reduction in the synthesis of pyranone **5**.

Process Development of Reductive Amination for Manufacturing Scale. The reductive amination of pyranone **5** with mesyl pyrazole BSA salt **8** was typically carried out in DMAC at −15 °C with slow addition of $NaBH(OAc)_3$,[13] affording Boc-amine **4** in a typical 19:1 dr (Scheme 7, route A). During development of this reaction, a number of issues were uncovered. First, the reaction yield proved to be variable, with a range from 50 to 80% observed. An investigation led to the discovery of an instability of starting materials **5** and **8** in DMAC when aged together at RT prior to the $NaBH(OAc)_3$ charge, which was thought to be responsible for the variable yield that was dependent on the aging time. Initial investigation was puzzling given that the combined starting materials in DMAC appeared to be stable based on HPLC A% monitoring. Subsequently, it was discovered that both starting materials in DMAC were decomposing at a rate of ∼2−3 wt % per hour at ambient temperature when monitored by HPLC wt % analysis. This decomposition produced a plethora of low-level impurities near the detection limit as well as polymeric impurities, which made impurity detection challenging. Short-term remedies were to avoid storage or hold the starting materials in DMAC at −15 °C. A second issue, observed during reductive amination, was that Boc-amine **4** precipitated from the reaction mixture in an uncontrolled fashion, yielding a slurry of very fine particles. This led to entrainment of starting materials and incomplete conversion of pyranone **5**. This issue could be partially addressed by applying heat−cool cycles to the reaction mixture, but the improvement was only marginal, and this also lowered the reaction diastereoselectivity. A third issue uncovered was that Boc-amine **4** has very low solubility in typical organic solvents and was not amenable to extraction into organic solvents; therefore, direct precipitation from the reaction mixture by antisolvent addition was the only practical option. Fourth, because of the small particle size, the product slurry filtered very slowly and proved to be difficult to dry. This translated to weeks of filtration and drying time on pilot plant scale. In addition to these issues, mesyl pyrazole BSA salt **8** was found to be a genotoxic,[14] unstable solid that demesylates at a rate of 1−5% per month at ambient temperature. To avoid the handling and storage of mesyl pyrazole salt **8**, we designed a through-process for the Boc deprotection of Boc mesyl pyrazole **14** and *in situ* reductive amination. After screening various acids,[15] we found trifluoroacetic acid to be the best reagent/solvent, as it offered fast deprotection rate, good solubility for both starting materials and product, and negligible demesylation. Interestingly, the resulting mesylpyrazole TFA salt in this TFA solution could be taken directly into the reductive amination reaction by simply adding DMAC and triethylamine, followed by slow addition of $NaBH(OAc)_3$ at −15 °C (Scheme 7, route B). Boc-amine product **4** remained soluble throughout the reaction. This allowed us to develop a controlled crystallization and thereby form larger primary particles, affording significantly improved filtration rate, drying time, and residual solvent levels. Gratifyingly, this new process not only addressed all of the physical problems mentioned above but also improved the diastereoselectivity to ≥30:1 and the isolated yield to 85−90%.

In the initial development of this telescoped process, we were faced with the question of how to transition from end-of-reaction mesyl pyrazole TFA salt in TFA (3 vol or 12 equiv) to DMAC (14 vol) solution for reductive amination with Boc ketone (**5**). Initial attempts involved evaporation of TFA followed by DMAC addition or adding DMAC to the TFA solution followed by concentration. In both cases, we found that the subsequent reductive amination afforded lower yields of product **4** (70−80%) due to increased demesylation of mesyl pyrazole TFA salt during the solvent switch. We therefore simply added DMAC to the post-Boc-deprotected TFA solution without evaporation of TFA and obtained an improved yield of reductive amination product (∼84%). We were encouraged to see that there was negligible Boc deprotection of Boc ketone **5** or product **4**. These observations were consistent with our experience that in the presence of Lewis basic cosolvent the acidity of TFA was significantly reduced, leading to little or no reactivity toward Boc deprotection. The main byproduct in these reactions was pyranol **23** (8−10%) as a result of reduction of Boc ketone **5**. However, it is well-known that $NaBH(OAc)_3$ has low reactivity toward ketones. In several related experiments, where we replaced $NaBH(OAc)_3$ with $NaBH_4$, presumably it would convert to $NaBH_x(TFA)_y$; we also saw elevated levels of **23** (16−20%). We hypothesized that TFA could promote the reduction of Boc ketone **5** by protonation of the carbonyl group and/or that the newly generated trifluoroacetoxy borohydride, being a more reactive, less selective hydride reagent, could be the actual reductant. Therefore, addition of base should suppress this side reaction. Indeed addition of triethylamine led to improved yields. We screened 2.5, 4, 5, and 6 equiv of triethylamine in the reductive amination and found 5 equiv to be the optimum with respect to yield (87−92%) and dr (24−28:1). Although 5 equiv of triethylamine is not enough to neutralize the 12 equiv of TFA, the acidity of TFA is most likely significantly reduced by the 14 vol of Lewis basic DMAC.

Process Development of Final Deprotection for Manufacturing Scale. With penultimate intermediate **4** in hand, what remained to complete the synthesis was deprotection of the Boc group and conversion of omarigliptin to crystalline form I. Various acids were reevaluated in the Boc deprotection of **4**, and we initially settled on H_2SO_4 in aqueous DMAC at 30 °C. Unfortunately, the pilot scale up experienced a foam-out when a subsurface nitrogen blow was introduced to the viscous reaction slurry, which entrained the gaseous byproducts from the Boc cleavage. As a result, alternate Boc deprotection conditions were sought. Previous reported conditions of HCl in aqueous EtOH were unsuitable because of significant demesylation. Again, trifluoroacetic acid proved to be an excellent solution to this problem. The reaction worked well in both neat TFA and aqueous TFA (up to 67 wt % H_2O). It provided excellent solubility, milder conditions (3−5 h at 0−22 °C vs 20 h at 30 °C), fast kinetics, negligible demesylation (0.0−0.3 A%), and improved isolated yield (90 vs 81%) and overall purity. NMR studies found that >90% of *tert*-butyl cation was trapped by TFA and H_2O as *t*-butyl trifluoroacetate and *t*-butanol; thus, <10% of isobutylene gas evolved, which was confirmed by headspace mass spectroscopy. Upon treatment with ammonium hydroxide, trifluoroacetamide was detected, but it was quickly hydrolyzed to trifluoroacetate ammonium salt. Trifluoroacetylated omarigliptin was not detected.

Omarigliptin was initially crystallized from the reaction mixture by charging ammonium hydroxide into the end of reaction stream and then seeding with form II. Because various salt forms precipitated and redissolved at intermediate pH values during the ammonia addition, hitting a clear seed point

DOI: 10.1021/acs.oprd.5b00267
Org. Process Res. Dev. 2015, 19, 1760−1768

was challenging, and although the desired form (form II) was obtained at the end of each batch, an improved process was desired to improve form control and reproducibility. Ultimately, a semicontinuous crystallization was developed in which the end of the Boc deprotection stream in TFA and NH_4OH was charged simultaneously to an aqueous seed bed (form II) held at low temperature to reduce demesylation. In this process, the crystallization proceeded at a constant pH of ~10−11, eliminating the intermediate salt forms and improving robustness. Additionally, the particle size was generally larger. The process demonstrated excellent rejection of process impurities, in particular, the diastereomer produced from reductive amination, demesylated omarigliptin impurity **2**, mesyl pyrazole **8** (mutagenic impurity), and ammonium trifluoroacetate salt. Therefore, the levels of these impurities were controlled at the crude step and were not dependent on rejection in the final pure step. Finally, omarigliptin form II was converted to form I by recrystallization from THF and heptanes.

In summary, we have described the evolution of a manufacturing route to omarigliptin (**1**) that is amenable to multikilogram scale production. The synthesis of pyranone **5** relies on three Ru-catalyzed reactions both to control stereochemistry and enable bond constructions. Highlights are (1) an improved catalyst for the DKR reduction that delivers 24:1 dr and >99% ee, (2) an improved isomerization-based synthesis of *N*-Boc-1-mesyl pyrazole fragment **14**, which afforded 30:1 regioselectivity, and (3) a telescoped Boc deprotection of **14** and reductive amination to avoid handling of mutagenic 1-mesylpyrazole BSA salt **8**, which also improved the overall diastereoselectivity and efficiency of the route. Starting from glycine ester **11**, the overall yield of this synthesis of **1** is 29%.

EXPERIMENTAL SECTION

All reactions were carried out under a nitrogen atmosphere. All solvents and reagents were purchased from commercial sources and were used without further purification. ^{1}H and ^{13}C NMR chemical shifts were reported relative to residual proton solvent peaks. All yields are corrected for purity and determined by reverse-phase HPLC using purified standards.

***tert*-Butyl (3*E*)-3-[(Dimethylamino)methylidene]-4-oxopyrrolidine-1-carboxylate (19).** To a stirred solution of DMF·DMA (290.5 g, 2.44 mol) in THF (1500 mL) at 65−70 °C was added aminoketone **9** (150 g, 810 mmol) in THF (420 mL). The resultant solution was aged at 65−70 °C for 13−18 h, cooled to 30 °C, and then concentrated *in vacuo* to approximately 2.5 volumes. This concentrated solution was solvent-switched with cyclohexane (4 × 744 g) to a final volume of 4.5 volumes, during which time a slurry formed. The solids were filtered, washed with further cyclohexane, and dried *in vacuo* to afford the product **19** (171 g, 88% yield). Characterization data have been previously reported.[4,7]

***tert*-Butyl 6a-Hydroxy-3a,4,6,6a-tetrahydropyrrolo-[3,4-*c*]pyrazole-5(1*H*)-carboxylate (20).** To a stirred solution of oxopyrrolidine **19** (171 g, 712 mmol) in toluene (818 mL) at 40 °C was added hydrazine monohydrate (41.5 mL, 854 mmol) followed by a further rinse of toluene (55 mL). After aging for 10 h, toluene was introduced (513 mL), and the reaction mixture was concentrated *in vacuo* to a final volume of ~1 L and then cooled to ~5 °C. The resultant slurry was filtered, and the cake was washed with heptanes (296 mL) before drying *in vacuo* at 40 °C to afford the product **20** (148 g, 651 mmol, 92% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22 (1H, s), 6.65 (1H, br s), 6.13 (1H, br s), 3.60 (2H, br s), 3.30 (1H, br s), 3.15 (2H, br s), 1.35 (9H, s); ^{13}C NMR (100 MHz, DMSO-d_6, mixture of rotamers): δ 153.1, 142.2, 100.0, 99.2, 78.7, 56.4, 55.7, 54.8, 48.9, 28.1. HRMS $[M + H]^+$ for $C_{10}H_{18}N_3O_3$ calcd, 228.1348; found, 228.1359.

***tert*-Butyl 4,6-Dihydropyrrolo[3,4-*c*]pyrazole-5(1*H*)-carboxylate (13).** To a solution of pyrazole alcohol **20** (74 g, 326 mmol) in dichloromethane (814 mL) at ~0 °C was added a solution of *p*-TsOH monohydrate (6.3 g, 33 mmol) in MeOH (92 mL) over 1−2 h. After aging for ~4 h, the reaction was quenched with aqueous $NaHCO_3$ (7.4 g in 141 mL water) before warming to ambient. The layers were cut, and the aqueous was back-extracted with dichloromethane (370 mL). The combined organics were washed twice with brine (19 g of NaCl in 351 mL of H_2O) before the organics were treated with activated carbon. Concentration *in vacuo* to ~2 volumes was followed by addition of heptanes (592 mL) to crystallize the batch. Filtration, washing with heptanes (74 mL), and drying *in vacuo* afforded the title compound **13** (59.5 g, 284 mmol, 87% yield). Characterization data have been previously reported.[4]

***tert*-Butyl 2-(Methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazole-5(4*H*)-carboxylate (14).** To a cooled (−5 °C) solution of pyrazole **13** (115 g, 550 mmol) in 2-MeTHF (1.38 kg) and triethylamine (114 mL, 824 mmol) was added a solution of MsCl (75.5 mL, 660 mmol) in 2-MeTHF (99 g). After 30 min aging from end of addition, the resultant mixture was quenched with water (230 mL) followed by brine (34.5 g of NaCl in 311 mL of H_2O). The layers were cut, and the aqueous was back-extracted with 2-MeTHF (492 g). The combined organics were further washed with brine (107 g of NaCl in 966 mL of H_2O) and then diluted with 2-MeTHF (492 g). The resultant solution was concentrated *in vacuo* to ~2.5 vol, flushing with further 2-MeTHF (800 g). Dilution with 2-MeTHF (431 g) and cooling to ~−5 °C was followed by the addition of potassium *tert*-butoxide (4.4 g, 39 mmoL) and aging for ~1 h. The mixture was quenched with brine (46 g in 414 mL of H_2O), and the layers were cut. The organics were further washed with brine, treated with activated carbon, and dried with sodium sulfate. Evaporation *in vacuo* to ~2.5 volumes followed by addition of heptanes (1.15 L) afforded a slurry. Filtering, washing with further heptanes, and drying *in vacuo* afforded the desired mesyl pyrazole **14** (132 g, 459 mmol, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$, ~1:1 mixture of rotamers) δ 7.79 and 7.76 (1H, s), 4.53−4.45 (4H, m), 3.33 and 3.32 (3H, s), 1.51 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6 and 161.2, 154.3 and 154.2, 124.1 and 123.8, 122.7 and 122.2, 80.5, 45.2 and 44.9, 44.7 and 44.3, 41.6, 28.5, and 28.3. HRMS $[M + H]^+$ for $C_{11}H_{18}N_3O_4S$ calcd, 288.1018; found, 288.1021.

(±)-*tert*-Butyl (1-(Methoxy(methyl)amino)-1-oxopent-4-yn-2-yl)carbamate (21). To a mixture of ethyl *N*-(diphenylmethylene) glycinate (200 g, 0.748 mol), propargyl besylate (161.5 g, 0.823 mol), and Bu_4NBr (24 g, 0.075 mol) in MTBE (2 L), and water (40.5 mL, 2.247 mol) was added K_3PO_4 (476.5 g, 2.245 mol) in portions over 2 h with vigorous stirring. The mixture was stirred at 50 °C for at least 3 h until the ratio of the desired product to starting material was greater than 100, as determined by HPLC. The slurry was then cooled to 5 °C. Water (800 mL) was added slowly. The organic phase was separated, and the aqueous phase was extracted with MTBE (384 mL). The combined organic phase was concentrated to ~1 L. Then, 1 N aqueous HCl (823 mL, 0.823 mol) was added dropwise at 10−20 °C. Upon complete

DOI: 10.1021/acs.oprd.5b00267
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consumption of the imine intermediate, as determined by HPLC analysis of the organic layer, the organic layer was discarded. The aqueous layer was basified with 30% aqueous NaOH (232 mL, 2.319 mol) to pH 10.5−11.5 at ambient temperature. The mixture was stirred at 23−27 °C for at least 2 h until complete consumption of the ester. 30% aqueous NaOH (100 mL, 1.003 mol) and water (1.6 L) were added followed by a solution of di-*tert*-butyl dicarbonate (361 g, 0.827 mol) in MTBE (259 mL) at ambient temperature. The resulting biphasic reaction mixture was stirred for at least 4 h until conversion was >95%. The organic layer was discarded. The aqueous layer was cooled to 10 °C, MTBE (800 mL) was added, and the mixture was acidified with conc. HCl (∼200 mL) to pH 2.5−3.5. The organic layer was separated, and the aqueous layer was extracted with MTBE (600 mL). The combined organic layer was washed with water (213 mL), azeotropically dried, and solvent-switched to DMF (361 mL) to give a crude stream of the Boc-protected acid. 1,1′-Carbonyldiimidazole (133 g, 0.823 mol) was added to above crude stream in portions below 15 °C. The resulting reaction mixture was stirred at 25 °C for several hours until conversion was >99%. *N*,*O*-Dimethylhydroxylamine HCl salt (81 g, 0.827 mol) was added in portions below 25 °C. The resulting reaction mixture was stirred at ambient temperature until the ratio of Weinreb amide **21** to the corresponding *n*-butyl amide was greater than 99, as determined by HPLC [HPLC sample preparation: a small amount of the reaction mixture was quenched in *n*-butylamine at ambient temperature and diluted with acetonitrile and water (about 1:1)]. The mixture was cooled to 0 °C, water (136 mL) was added, and the mixture was stirred for at least 0.5 h at <30 °C to promote spontaneous nucleation; otherwise, the batch was seeded with **21** (0.1 wt %/wt) and stirred for at least 0.5 h. Water was slowly added (766 mL), keeping the internal temperature at <30 °C. The slurry was cooled to 0−5 °C and aged for an additional 2 h before filtration. The wet cake was washed with 5 °C aqueous DMF (DMF/water = 1:9, 298 mL) followed by water (405 mL) and then dried in vacuum oven at 40−45 °C overnight to afford 193.1 g of **21** with 99.3 wt % and 99.6 A% purity in 75% corrected isolated yield. Characterization data have been previously reported.[5]

(±)-*tert*-Butyl (1-(2,5-Difluorophenyl)-1-oxopent-4-yn-2-yl)carbamate (10). To a solution of 1-bromo-2,5-difluorobenzene (207.7 g, 1.08 mol) in toluene (415 mL) between −10 to −5 °C was added *i*-PrMgCl/LiCl solution (1.43 M in THF, 827 mL, 1.18 mol) over 1.5 h. The reaction solution was then aged for 1 h between −10 to −5 °C. A solution of Weinreb amide **21** (137.5 g, 0.536 mol) in THF (540 mL) was added over about 30 min while the internal temperature was maintained between −10 to −5 °C. The reaction mixture was then warmed to 20 °C over 1 h and aged at 20 °C for 1 h. The reaction mixture was quenched by adding an aqueous HCl solution (184.6 g of conc. HCl in 527 mL of H_2O) at 0 to 10 °C over 30 min. The organic phase was washed with 10% NaCl solution (2 × 1000 mL). The organic phase was concentrated to about 400 mL, diluted with *i*-PrOH (2260 mL), and concentrated to a final volume of about 1350 mL. Water (1860 mL) was added over 1 h at 10−15 °C, and the mixture was then aged at the same temperature for 2 h. Solids were filtered and washed with 40% *i*-PrOH in water (730 mL) and then water (385 mL). The wet cake was dried under vacuum at 45 °C to afford 151 g of **10** with 98.1% purity in 89% corrected isolated yield. Characterization data have been previously reported.[5]

***tert*-Butyl ((1*R*,2*S*)-1-(2,5-Difluorophenyl)-1-hydroxypent-4-yn-2-yl)carbamate (6).** To a nitrogen degassed solution of ketone **10** (110 g, 0.356 mol), DABCO (119.7 g, 1.067 mol), and (*R*,*R*)-Ts-DENEB)RuCl (243 mg, 0.37 mmol) in THF (1.1 L) at 10−15 °C was slowly added degassed formic acid (67 mL, 1.778 mol) at <15 °C. The solution was warmed to 35 °C and agitated for 20 h with nitrogen sparging with a condenser set at −20 °C to minimize solvent loss. After ≥99% conversion was attained, the reaction solution was cooled to 20−30 °C and concentrated to ∼800 mL. MTBE (800 mL) was added, and the mixture was cooled to 5−10 °C and washed with 0.5 N HCl (1 L). The organic phase was washed with 4% aqueous $NaHCO_3$ (910 mL) followed by 7.4% aqueous NaCl (460 mL). A slurry of activated carbon (10 g) in MTBE (200 mL) was added to the organic phase, and the mixture was stirred at 20−25 °C for at least 0.5 h. The mixture was filtered and washed with MTBE (320 mL) and then heptane (415 mL). The organic solution was concentrated to about 140 mL, diluted with heptane (275 mL), and concentrated to 140 mL (target KF < 800 ppm). This solution was used directly for the next step and had 93% assay yield with 24:1 dr and >99% ee. Characterization data have been previously reported.[5]

***tert*-Butyl ((2*R*,3*S*)-2-(2,5-Difluorophenyl)-3,4-dihydro-2*H*-pyran-3-yl)carbamate (22).** To the heptane solution of DKR alcohol **6** from the previous step under a nitrogen atmosphere was added anhydrous DMF (617 mL) to reach a final volume of about 757 mL (target KF < 800). This solution was degassed by N_2 sparging for at least 1 h. In an another vessel, tetrabutylammonium hexafluorophosphate (17.93 g, 46.28 mmol), *N*-hydroxysuccinimide (20.08 g, 174.48 mmol), and $NaHCO_3$ (15.25 g, 181.56 mmol) were charged, and it was degassed with at least three vacuum/N_2 cycles, followed immediately by $CpRuCl(PPh_3)_2$·EtOH (5.93 g, 7.68 mmol) and PPh_3 (6.02 g, 22.95 mmol), and degassed with at least three vacuum/N_2 cycles. The DKR alcohol solution was transferred into the vessel containing the cycloisomerization reagents (then rinsed with 20 mL of DMF and combined). The reaction mixture was heated at 80 °C for at least 16 h until ≥99% conversion was achieved. The reaction mixture was cooled to ∼15 °C, and water (845 mL) was added at <30 °C, followed by MTBE (960 mL). The organic phase was separated, and the aqueous layer was back-extracted with MTBE (2 × 680 mL). The combined organic phase was washed with 20% NaCl solution (4 × 640 mL) and then concentrated to about 275 mL. To this solution were added MTBE (120 mL), heptanes (1275 mL), and silicon dioxide (90 g, 60−200 mesh), and the mixture was stirred at 20 °C for at least 2 h. The mixture was filtered, and the spent silica was stirred in a mixture of MTBE (680 mL) and heptanes (3380 mL) for at least 1 h and then filtered. The combined filtrates solution was concentrated to ∼385 mL and then solvent-switched to heptanes with 2 × 160 mL of heptanes to a final volume of ∼385 mL. The mixture was heated at 90−110 °C until all solids dissolved, cooled to ∼5 °C over at least 2 h, and then aged at this temperature for at least 2 h. The slurry was filtered and washed with 5 °C heptanes (80 mL). The wet cake was dried under vacuum at 50 °C to afford dihydropyran **22**. HPLC: 80% corrected yield from **10**, 99.2% dr, 99.8% ee, 92% purity. Characterization data have been previously reported.[5]

***tert*-Butyl ((2*R*,3*S*)-2-(2,5-Difluorophenyl)-5-hydroxytetrahydro-2*H*-pyran-3-yl)carbamate (23).** To a solution

DOI: 10.1021/acs.oprd.5b00267
Org. Process Res. Dev. 2015, 19, 1760−1768

of dihydropyran **22** (100 g by assay, 321.21 mmol) in MTBE (1000 mL), cooled to 0 °C, was slowly added $BH_3{\cdot}SMe_2$ (72.2 mL, 812.66 mol) while maintaining the internal temperature at <5 °C. After aging for an additional 2 h, the reaction achieved >99% conversion. Water (59 mL) was added to the reaction while the internal temperature was maintained at <15 °C, and the mixture was then stirred at 10−15 °C for at least 0.5 h until H_2 off-gassing has ceased. 3% $NaHCO_3$ aqueous solution (790 mL) was added, keeping the temperature at <15 °C. Sodium perborate tetrahydrate (148.3 g, 963.86 mmol) was then added in portions while maintaining the internal temperature at <15 °C. After aging at 25 °C for at least 1 h, the organic phase was separated and washed with H_2O (2 × 500 mL). The organic phase was concentrated at ambient pressure at <80 °C to ∼450 mL. Toluene (600 mL) was added and concentrated to ∼450 mL at <80 °C. This was repeated with 300 mL of toluene until MTBE was removed. The batch temperature was raised to 80−85 °C, and the reaction stirred until a clear solution was obtained. Heptane (894 mL) was added over 0.5 h. The resulting slurry was aged for an additional 0.5 h at 80−85 °C, cooled to 20−25 °C gradually, and aged for at least 3 h before filtration. The wet cake was washed with heptanes/toluene (2:1, 500 mL) and dried in vacuum oven at 45 °C. The solid was collected and combined with toluene (433 mL) and tributylphosphine (15 g) and heated at 85 °C for 0.5 h. Heptanes (865 mL) was added over 1 h at 85 °C, and the resulting slurry was cooled to 5 °C over 1 h and then stirred for 1 h before filtration. The wet cake was washed with 5 °C 4:1 heptane/toluene (250 mL) and then dried under vacuum at 45 °C for at least 8 h to give 97.6 g of off-white solid **23**. 96.5% purity, 89% corrected yield. Pyranol **23** is a mixture of two diastereoisomers in about 55:45 ratio. Characterization data have been previously reported.[5]

***tert*-Butyl ((2*R*,3*S*)-2-(2,5-Difluorophenyl)-5-oxotetrahydro-2*H*-pyran-3-yl)carbamate (5).** To a solution of alcohol **23** (90.0 g, 273.27 mmol) in CH_3CN (369 mL), AcOH (45 mL), and water (45 mL) was added a solution of $RuCl_3{\cdot}3H_2O$ (308 mg, 1.37 mmol) in water (72 mL) at 20−25 °C, which was rinsed with H_2O (18 mL) and transferred to the reaction mixture. The mixture was cooled to 0 °C, and $NaBrO_3$ (22.68 g, 150 mmol) was added in portions at <2 °C. The resulting reaction mixture was stirred at 0 °C until >99% consumption of alcohol **23** was achieved, as monitored by HPLC. 2-Propanol (32.5 g) was added over 0.5 h at 0 °C. Water (1350 mL) was added over at least 1.5 h at 0 °C. The resulting slurry was aged at 0 °C for at least 2 h. The product was collected by filtration, washed with a 0 °C solution of CH_3CN/H_2O (1:9, 2 × 450 mL), and vacuum-dried at 50 °C to give 81.5 g of **5**. 97.7% purity, 89% corrected yield. Characterization data have been previously reported.[5]

***tert*-Butyl ((2*R*,3*S*,5*R*)-2-(2,5-Difluorophenyl)-5-(2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl)tetrahydro-2*H*-pyran-3-yl)carbamate (4).** A vessel equipped with an overhead stirrer was charged with trifluoroacetic acid (314 mL) and cooled to −5 to 0 °C under N_2. Boc-mesyl-pyrazole **14** (121 g, 0.420 mol) was added over 3 min; the temperature rose from −2 to 3 °C over 3−4 min with CO_2 evolution. The charging funnel was rinsed with TFA (63 mL). The solid slowly dissolved over 15 min to give a clear solution. After stirring for 2 h at 0 °C, precooled (−10 °C) DMAc (1.71 L) at <10 °C was slowly added to the TFA solution, followed by precooled (5 °C) triethylamine (292 mL, 2.092 mol) at <10 °C and then by a rinse with precooled DMAC (53.4 mL). The solution was cooled to −15 °C. Precooled (−20 °C) solution of Boc-ketone **5** (125 g, 0.375 mol) in DMAC (53.4 mL) was then added at <10 °C, and the mixture was then rinsed with DMAc (72.5 mL). $NaHB(OAc)_3$ (124.5 g, 0.587 mol) was added in 3 portions at 30 min intervals. The solution was aged at −15 to −16 °C overnight (22 h). The reaction was warmed to 22 °C over 1 h to give a clear solution that was then aged for 5 h. Seed (1 wt %, 1.5 g) was added to give a hazy mixture, which was then heated at 40 °C. A solution of 30% NH_4OH (43.3 mL) and water (3.5 mL) was then added over 2 h at 40 °C, followed by a solution of 30% NH_4OH (432 mL) and water (35 mL) over 5 h at 40 °C. The batch was cooled to 20−25 °C and aged until supernatant concentration was ∼1 mg/mL. The batch was filtered and washed with 5:1 DMAc/H_2O (419 mL DMAc + 84 mL of H_2O) and then H_2O (502 mL). The wet cake was vacuum-dried at 40 °C for at least 12 h, affording 167.8 g of Boc-amine **4** as a white solid (87% isolated yield, 97 wt %, 96.7 A%, dr = 96.9:3.1 (31:1); KF = 0.56%). Compound **4** has two rotamers in DMSO in about a 5:1 ratio at ambient temperature. For the major rotamer of **4**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.94 (s, 1H), 7.16 (m, 3H), 6.93 (d, J = 9.7 Hz, 1H), 4.27 (d, J = 10.0 Hz, 1H), 4.17 (m, 1H), 3.80 (s, 2H), 3.75 (s, 2H), 3.68 (m, 1H), 3.46 (s, 3H), 3.24 (t, J = 10.7 Hz, 1H), 2.95 (m, 1H), 2.24 (m, 1H), 1.61 (dd, J = 23.9, 12.0 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.5, 157.9 (d, J = 238.4 Hz), 156.4 (d, J = 241.0 Hz), 154.4, 128.4 (dd, J = 16.8, 7.9 Hz), 124.2, 124.1, 116.5 (dd, J = 25.4, 9.1 Hz), 115.9 (dd, J = 24.0, 8.0 Hz), 115.3 (dd, J = 24.3, 4.6 Hz), 77.6, 76.5, 70.6, 58.8, 49.7, 48.0, 47.7, 41.2, 35.6, 27.9; HRMS $[M + H]^+$ for $C_{22}H_{29}F_2N_4O_5S$ calcd, 499.1827; found, 499.1830.

***tert*-Butyl ((2*R*,3*S*,5*S*)-2-(2,5-Difluorophenyl)-5-(2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl)tetrahydro-2*H*-pyran-3-yl)carbamate (Diastereomer of 4).** The minor diastereomer could be isolated from above the crude reaction mixture on a silica gel column eluting with EtOAc/hexanes. For the major rotamer, ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.96 (s, 1H), 7.12 (m, 3H), 6.85 (d, J = 8.8 Hz, 1H), 4.39 (d, J = 9.8 Hz, 1H), 4.12 (d, J = 12.6 Hz, 1H), 3.91 (m, 2H), 3.80 (m, 3H), 3.55 (d, J = 12.2 Hz, 1H), 3.48 (s, 3H), 2.91 (m, 1H), 2.15 (m, 1H), 1.84 (m, 1H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 158.1 (d, J = 239 Hz), 156.2 (d, J = 241 Hz), 154.6, 129.0 (dd, J = 14, 4 Hz), 124.6, 124.3, 116.6 (dd, J = 25, 9 Hz), 115.9 (dd, J = 24, 8 Hz), 115.2 (dd, J = 24, 5 Hz), 77.6, 76.1, 68.7, 58.5, 48.6, 48.1, 46.3, 41.2, 34.0, 28.0; HRMS $[M + H]^+$ for $C_{22}H_{29}F_2N_4O_5S$ calcd, 499.1827; found, 499.1827.

(2*R*,3*S*,5*R*)-2-(2,5-Difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]-tetrahydro-2*H*-pyran-3-amine, Crude Omarigliptin (1). A vessel was charged with trifluoroacetic acid (TFA) (550 mL) and water (220 mL) and cooled to 5−10 °C. Omarigliptin Boc amine **4** (227 g, 0.441 mol) was charged while maintaining a temperature of 5−15 °C. Trifluoroacetic acid (TFA) (110 mL) was added. The batch temperature was adjusted to 20−25 °C, and the reaction was aged for 2−6 h. A sample was taken to confirm completion of the Boc deprotection reaction, and the batch was cooled to 5−10 °C in preparation for the crystallization. A seed bed containing omarigliptin crude (form II) (2.2 g) in water (1.08 L), dimethylacetamide (110 mL), and 30% ammonia−water (22.5 mL) at 5−10 °C was prepared. The batch stream and 30% ammonia−water (845 mL) were simultaneously added over a minimum of 3 h to the

DOI: 10.1021/acs.oprd.5b00267
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seed bed at 5−10 °C. Water (220 mL) was charged to the batch at 5−10 °C, and the batch was aged for a minimum of 0.5 h. The batch was filtered at 0−10 °C and washed with water (1.32 L). The wet cake was dried at ≤50 °C, resulting in 162 g (90% yield, 99.2 A%, dr = 99.7:0.3) omarigliptin crude (form II).

(2*R*,3*S*,5*R*)-2-(2,5-Difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]-tetrahydro-2*H*-pyran-3-amine, Pure Omarigliptin (1). Omarigliptin crude (70.0 as-is g; 68.6 assay g) was charged with THF (1.4 L). The resulting solution at 20−25 °C was filtered and then concentrated at ≤30 °C under vacuum to 690 mL. THF was charged so that the final level of the batch was 820 mL. The batch was heated at 42−46 °C for dissolution and subsequently cooled to 35−38 °C. Omarigliptin seed (form I) (0.70 g) was charged and aged for a minimum of 1 h. The batch was cooled to 20−25 °C over a minimum of 3 h and then concentrated at ≤30 °C under vacuum to 340 mL. The temperature of the batch was adjusted to 20−25 °C. Heptanes (544 mL) was charged over minimum 5 h to the batch at 20−25 °C. The batch was subsequently wet milled, filtered, and washed with 2:1 heptanes/THF (210 mL) followed by 1:1 heptanes/THF (210 mL). The wet cake was dried at ≤40 °C, resulting in 64.1 g (93% yield, 99.6 wt %, 99.9 A%) omarigliptin (**1**). Characterization data for **1** have been previously reported.[4]

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank F. Bernadino, P. Zhuang, N. McGachy, P. Skrdla, K. Eckenroad, T. Florez, S. Thomas, K. McNamara, E. Emmett, R. Petrova, A. Zelellow, and I. Z. Arroyo for chemical and analytical support, V. R. Capodanno, R. M. Flessner, S. Jones, C. Jordan, and E. Margelefsky for engineering support, and C. Chen, J. Limanto, S. Dolman, J. Janey, and C. Cowden for helpful discussions. We gratefully acknowledge the Fabbrica Italiana Sintetici (FIS) team for the pilot manufacturing and Takasago International Corporation for helpful discussions.

ABBREVIATIONS

DABCO, 1,4-diazabicyclo[2.2.2]octane; DMA, dimethylacetal; DMAC, *N*,*N*-dimethylacetamide; DMF, *N*,*N*-dimethylformamide; DOE, design of experiment; MsCl, methanesulfonyl chloride; NaHMDS, sodium bis(trimethylsilyl)amide; BSA, benzenesulfonic acid; DKR, dynamic kinetic resolution

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(10) Replacement of *n*-heptane by a heptane isomer mixture was carried out without issues in the workup stages of step 4 (cycloisomerization) and step 5 (hydroboration/oxidation).

(11) Step 1 was modified in the azeodrying and solvent switch from MTBE to DMF. Previously, azeodrying was performed by repetitive vacuum distillation of MTBE. In the new process, the drying stage was performed by adding *n*-heptane to the concentrated MTBE solution. This proved to be advantageous in terms of cycle time and solvent consumption.

(12) The amounts of activated carbon and silica gel used in the DKR and cycloisomerization steps were reduced to 9 and 80 wt %, respectively, from larger quantities used in the previous version of the process without issues.

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(14) Mesyl pyrazole besylate salt, **8**·BsOH, was found to be AMES-positive in the standard bacterial reverse mutation (mutagenicity) assay carried out according to ICH S2(R1) and OECD 471 guidelines.

(15) HCl and HBr are not suitable acids for Boc deprotection of Boc mesyl pyrazole (**14**) due to a significant demesylation side reaction mediated by nucleophilic chloride and bromide anions. Sulfonic acid (H_2SO_4, MsOH, BsOH) mediated Boc deprotection in organic solvents tended to be slow due to poor substrate solubility, and the product salts tended to be unstable in the solid state.

DOI: 10.1021/acs.oprd.5b00267
Org. Process Res. Dev. 2015, 19, 1760−1768