Process Chemistry

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Sitagliptin Manufacture: A Compelling Tale of Green Chemistry, Process Intensification, and Industrial Asymmetric Catalysis**

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Dedicated to Professor William Dean Wulff on the occasion of his 61st birthday

Process chemistry is a challenging science. Not only do the practitioners have to make the target molecule efficiently, but they also have to contend with numerous other equally (and often times more) important considerations such as process safety, waste streams, chemical toxicity, recycling of solvents/catalysts, process economics, and a multitude of engineering/technology considerations.[1,2] Nevertheless, despite the challenges, the ideal outcome of these efforts when accomplished is quite satisfying: a simple, efficient, green, robust, and safe manufacturing process.

Sitagliptin is the active ingredient in Januvia, a leading drug for the treatment of type 2 diabetes.[3–5] Researchers from Merck, in collaboration with those from Solvias and Codexis, have recently reported on their process research and development efforts towards the industrial manufacture of sitagliptin phosphate (**1**). A showcase of green chemistry, process intensification, and industrial asymmetric catalysis—the sitagliptin manufacture has garnered wide acclaim.[6,7] More importantly, it has served as a vehicle for discovery in organic synthesis. This highlight will focus on the evolution of the sitagliptin manufacture through three generations of process research and development.

The initial process chemistry route towards **1** is outlined in Scheme 1 a (1st generation process).[8] Starting from achiral β-keto ester **2**, asymmetry was introduced in the form of a hydroxy group in β-hydroxy acid **3** through a ruthenium-catalyzed asymmetric hydrogenation. This was subsequently transformed into the requisite chiral amine center in **4** by using an EDC[9] coupling/Mitsunobu sequence. With a total of eight steps and an overall yield of 52%, this route was used to deliver more than 100 kg of **1** for early clinical studies.

From the perspective of an efficient manufacture, however, the 1st generation process lacked significantly. Of primary concern was the EDC coupling/Mitsonobu sequence, which apart from being a circuitous method for introducing the chiral amine center, generated copious amounts of waste resulting from the poor atom economy inherent to a Mitsunobu reaction. Thus, the realization that the 1st generation process was not slated to be the ultimate sitagliptin manufacture led to additional process development, efforts which pair off well and led to the 2nd generation process (Scheme 1 b).[6,10] This process has subsequently been implemented on the manufacturing scale.

The key feature of the 2nd generation process is a three-step one-pot synthesis of dehydrositagliptin **12**, which contains within its structure the entire carbon skeleton of **1**. Starting from trifluorophenyl acetic acid **8**, sequential and controlled addition of reactants and reagents leads to the formation of **12**;[11] the product crystallizes out during the last step and a simple filtration furnishes **12** in 82% overall yield with 99.6 wt% purity. The researchers then developed a rhodium-catalyzed asymmetric hydrogenation of the unprotected enamine amide **12** to install the chiral amine center in **13**.[12,13] This step utilizes 0.15 mol% of the rhodium catalyst, and affords **13** in 98% yield and 95% *ee*.[10] Nearly all utilized rhodium is subsequently removed and recovered upon treatment of the crude hydrogenation stream of **13** with activated carbon. Crystallization for an upgrade to a greater than 99.9% *ee* and final isolation of **1** as its phosphate monohydrate salt constitutes the endgame of the 2nd generation process.

With a total of three steps and an overall yield of 65%, this 2nd generation protecting-group-free process for the sitagliptin manufacture has led to significant reductions in waste as compared to the 1st generation process—per kg of final product, the total waste produced has been reduced from 250 kg to 50 kg, and the aqueous waste stream has been completely eliminated.[10] This improvement is expected to translate to a waste cutback of at least 150 million kilograms over the entire lifetime of the drug.[14]

Although the β-ketoamide **11** is an intermediate during the one-pot sequence in the 2nd generation process, it is possible to isolate **11** as a crystalline solid.[10] The Merck researchers then developed a ruthenium-catalyzed asymmetric direct reductive amination methodology for preparing unprotected β-amino amides from β-keto amides.[15] This enables them to set the chiral amine center in **13** with

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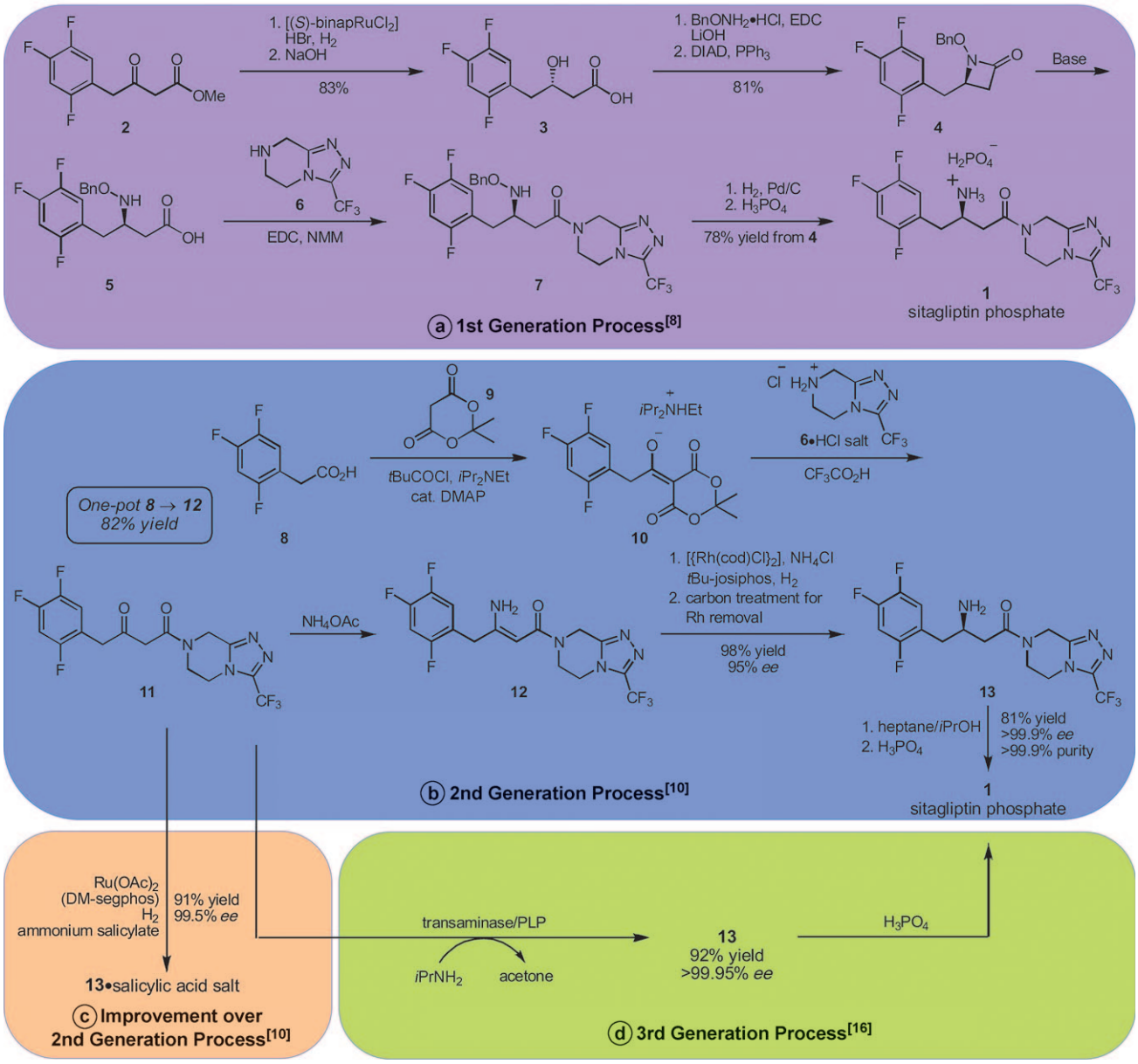

Scheme 1. Three generations of process research and development towards the manufacture of sitagliptin phosphate **1**. a) 1st generation process. b) 2nd generation process. c) Improvement upon the 2nd generation process. d) 3rd generation process. Bn = benzyl, binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, cod = 1,5-cyclooctadiene, DIAD = diisopropyl azodicarboxylate, DMAP = 4-dimethylaminopyridine, NMM = *N*-methylmorpholine, segphos = (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine).

complete stereocontrol directly from **11** (Scheme 1c). Even though the transformation **11**→**12** is embedded in the one-pot sequence in the 2nd generation process, it still represents a unit operation for the process. This is eliminated in the direct reductive amination of **11** into **13**, which thus represents an improvement over the 2nd generation process (Scheme 1c).

Despite the overall brevity and efficiency of the 2nd generation process (Schemes 1b and c), its endgame left open room for improvement because of the inherent drawbacks of utilizing a transition metal mediated hydrogenation step. This necessitated the use of specialized high-pressure equipment and a process for the complete removal of the transition metal from the product stream, both of which were significant cost drivers. Moreover, in the Rh-catalyzed process, the relatively low stereocontrol in the asymmetric hydrogenation step (95% *ee*) necessitated the incorporation of an additional crystallization to obtain optically pure **1**.

To circumvent these drawbacks, Merck and Codexis researchers have recently engineered a highly evolved transaminase biocatalyst to transform **11** into **13** (Scheme 1d; 3rd generation process).[7,16] Starting from an *R*-selective transaminase enzyme for which **11** was not a natural substrate, a combination of computational modeling and iterative directed evolution was utilized to engineer the optimal biocatalyst. This evolved enzyme contains 27 mutations, which are found not only in the active site, but also in the interface of the

enzyme dimer where they presumably aid in the protein stabilization. In the optimized final process, 6 g L^{-1} of the evolved transaminase enzyme tolerates a 200 g L^{-1} concentration of **11** in 50% DMSO at 40 °C, and produces **13** in 92% yield in optically pure form (> 99.95% *ee*; Scheme 1 d). The reaction is run in multipurpose reactors, and thus eliminates all the drawbacks of the 2nd generation process. Not only does their 3rd generation process lead to an increase in the overall yield (13%) and productivity (53%) as compared to the 2nd generation process, but it also results in a reduction of the total waste produced (19%).[16] This process has already been demonstrated in a pilot-scale production.[17]

The sitagliptin manufacture has thus been an important and impressive case study on process chemistry in the pharmaceutical/fine chemical industry. An example of target-driven discovery, it has enabled the development of new and general synthetic methodology.[11–13,15,16,18] Finally, the sitagliptin manufacture is a testament to the power of collaboration in the industry; the efficient processes have been made possible only by pooling the process chemistry work of Merck with the homogeneous catalysis expertise of Solvias and the biocatalysis expertise of Codexis.

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[2] A journal dedicated to developments in this field is *Organic Process Research & Development*.
[3] The phosphate monohydrate salt of sitagliptin is the final required pharmaceutical form.
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[7] The 3rd generation process outlined in Scheme 1 d has received the 2010 Presidential Green Chemistry Challenge Award for Greener Reaction Conditions.
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