

# Innovation in Route Design, (Bio)Catalysis and Process Development Applied to the Second Generation Synthesis of Sacubitril

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**Abstract:** Commercial manufacturing processes in the pharmaceutical industry need to address numerous goals, ranging from cost effectiveness over process safety to environmental sustainability. While the design of the synthetic route may commonly be considered the centerpiece of chemical process development, only the combination with innovative technologies at scale and in-depth process understanding can unlock the full potential of a synthetic route. The development of a second-generation synthesis of sacubitril, one of the constituent active pharmaceutical ingredients of LCZ696, serves as an example to display how synthesis design can be successfully combined with (bio)catalysis and thorough process development to achieve superior results. In addition, the case at hand highlights the multidisciplinary and team-focused nature of chemical process development.

**Keywords:** Biocatalysis · LCZ696 · Process development · Sacubitril



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both small molecule and oligonucleotide projects. In addition, he extensively supported technical lifecycle management activities of established brands. In early 2024, he took on the role as team lead of the Biocatalysis Team in Chemical & Analytical Development at Novartis.

## 1. Introduction

Life expectancy worldwide has seen a dramatic increase since the mid 1850s.<sup>[1]</sup> Looking at the evolution of life expectancy in Switzerland since 1900, the average values at the time of birth for women and men have increased from 48.9 years and 46.2 years in 1900 to 85.8 years and 82.2 years in 2023, respectively.<sup>[2]</sup> Modern medicine has contributed in a large part to this increase, and life-threatening diseases thought previously to be incurable can today either be controlled like chronic diseases or even be cured.<sup>[3]</sup> Public health therefore highly depends on the reliable and affordable access to drug substances, manufactured by robust and efficient manufacturing processes. The development of such processes forms the heart of chemical development in the pharmaceutical industry, turning the initial synthesis as applied during research and early development into a manufacturing process that can be used for routine manufacture on a commercial scale.<sup>[4]</sup>

Successful process development draws significantly from the creativity, curiosity, resilience and team spirit of the chemists, analysts and engineers involved in the development teams. Besides these soft factors, a clear and concise synthesis strategy on how to assemble the target molecule is equally important and represents a key prerequisite that – in combination with a thorough understanding of the manufacturing process, comprising a detailed assessment of the impact of each parameter and mechanistic insights into the individual chemical transformations, as well as the availability and utilization of state-of-the-art technologies – finally enables the design of a manufacturing process that can be scaled to meet commercial demands.<sup>[5]</sup>

Among the recent Novartis portfolio, the development of a second generation synthesis of LCZ696 (sacubitril valsartan sodium hydrate) may be considered as a prime example in which the combination of an innovative route design, established and new technologies as well as thorough process development resulted in a robust and efficient manufacturing process that was successfully implemented on commercial scale.<sup>[6,7]</sup> LCZ696 was first approved for the treatment of heart failure in the US in July 2015 based on the results of the ground-breaking PARADIGM study and has since then grown into the biggest product in the Novartis portfolio.<sup>[8–10]</sup> Different to a classical small molecule drug substance, LCZ696 combines two active moieties – sacubitril and valsartan – in a crystalline supramolecular complex in a well-defined 1:1 stoichiometric ratio (Fig. 1).<sup>[11]</sup> While valsartan has been marketed independently as a drug substance for a long time,<sup>[12]</sup> sacubitril represented a new chemical structure at the time when LCZ696 was introduced to the market. Efforts for an efficient manufacture of LCZ696 therefore focused on the synthesis and manufacturing process of sacubitril.<sup>[13]</sup> While the first generation synthesis enabled supply during development and early commercialization,<sup>[14,15]</sup> the anticipated large production volumes and the associated challenges made it necessary to embark on a drastically new approach to sacubitril, resulting in the development of a second generation synthesis.<sup>[16,17]</sup>

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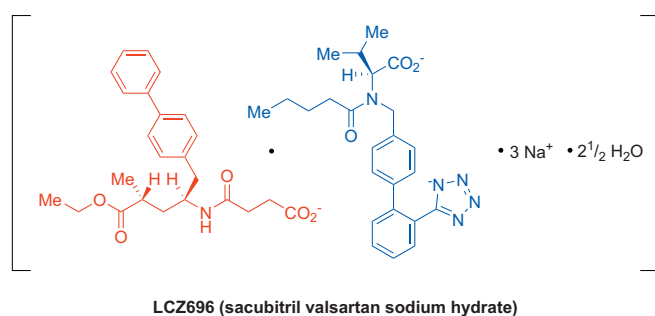


Fig. 1. Structure of LCZ696 (sacubitril valsartan sodium hydrate), with sacubitril shown in red and valsartan shown in blue.

## 2. Second Generation Synthesis of Sacubitril

The second-generation synthesis aimed for a straightforward access to compound **6**, an advanced intermediate in the established manufacturing route of sacubitril (Scheme 1). At this point in the synthesis, all major functional elements, *i.e.* the biphenyl moiety as well as the amino and ester functionalities, have been installed, both stereogenic centers are set, and all bonds to assemble sacubitril – with the exception of the succinyl amide bond – have been formed. Compound **6** is thus considered a key intermediate in the established synthesis of sacubitril and was therefore defined as a target for interception.

Using in-house and external expertise from a broad range of disciplines like synthetic and process chemistry as well as chemical engineering, more than 100 potential routes were evaluated and ranked. The best options had one important feature in common: They all relied on the use of biocatalysis to establish the amino functionality. Biocatalysis offered three distinct advantages in this respect: (1) the nitrogen atom could be introduced late in the synthesis, significantly reducing the chemical challenges by limiting bond formation and bond cleavage to the chemistry of hydrogen, carbon and oxygen; (2) structural complexity could be quickly built up from readily accessible materials, requiring only a few steps to assemble the precursor for the key biocatalytic transformation; and (3) there is an overall pronounced shortening of the synthetic route, in particular due to the avoidance of any protecting groups.

### 2.1 Installation of the First Stereogenic Center by Metal-Catalyzed Asymmetric Hydrogenation

Access to (*R*)-methyl ester **2** was gained by a metal-catalyzed asymmetric hydrogenation of itaconic acid methyl ester **1**, a com-

modity chemical available in large quantities and at low cost due to its use in the polymer industry.<sup>[18]</sup> The application of transition metal catalysis was particularly attractive in this case, as itaconic acid and its derivatives widely serve as benchmarks for the assessment of novel chiral ligands, and ample literature precedent is thus available.<sup>[19–21]</sup> In collaboration with Johnson Matthey, an extensive screening and optimization program resulted in the identification of a chiral Rh catalyst with (*R,R*)-PhBPE as the ligand of choice that fulfilled the pre-defined performance parameters.<sup>[22]</sup> The Rh catalyst could be applied as a pre-formed complex, ensuring the desired 1:1 stoichiometry between the metal and chiral ligand, while simplifying handling of sensitive materials in commercial production. Methanol was used as an environmentally benign solvent, alleviating the use of chlorinated solvents. Due to the high catalytic activity of the catalyst system, a moderate reaction temperature of 30 °C was sufficient to reach full conversion, and the tolerance of a wide range of hydrogen pressures allowed adjustment of the pressure to the specifications of the available manufacturing equipment, with 10 bar finally chosen as the set-point. Under optimized conditions, the catalyst system showed a remarkable efficiency, achieving substrate-to-catalyst ratios of 35,000:1 and higher in routine operations. A dedicated cleaning protocol for the hydrogenation equipment was developed to ensure reliable removal of the residual trace amounts of catalytic species to suppress any racemic background reactivity. Furthermore, levels of coordinating anions like chloride or sulfate, even if only weakly coordinating, had to be kept low to avoid a negative impact on the reaction rate due to catalyst inhibition.<sup>[23]</sup>

A striking feature was the strong dependence of the catalyst performance on the concentration, with improved results obtained at higher concentrations. Consequently, a concentration of 50% based on mass, *i.e.* a 1:1 mass ratio of substrate **1** and methanol, was applied in commercial manufacture. Due to the exothermicity of the transformation, the high concentration of the hydrogenation reaction posed challenges from the perspective of thermal process safety. Inevitably, a large batch size was necessary to meet the minimum stirring volume of the available hydrogenation equipment, and the relatively small area of the reaction mixture exposed to the reactor wall limited the ability to efficiently remove heat by cooling of the reactor wall. A series of calorimetric tests were therefore run to investigate how the system reacted to process changes, in particular to cover potential failure modes like loss of stirring or changes in hydrogen pressure. The hydrogenation reaction showed a pronounced and almost instantaneous reduction of the heat flow when either stirring or hydrogen pressure



Scheme 1. Synthetic route to key intermediate **6** in the second generation synthesis of sacubitril.

were reduced, indicating a slowdown of the reaction rate (Fig. 2). As a result of these investigations, reduction of either the stirring rate or the hydrogenation pressure was finally defined as a potential safety measure in case of incidents during commercial manufacture.

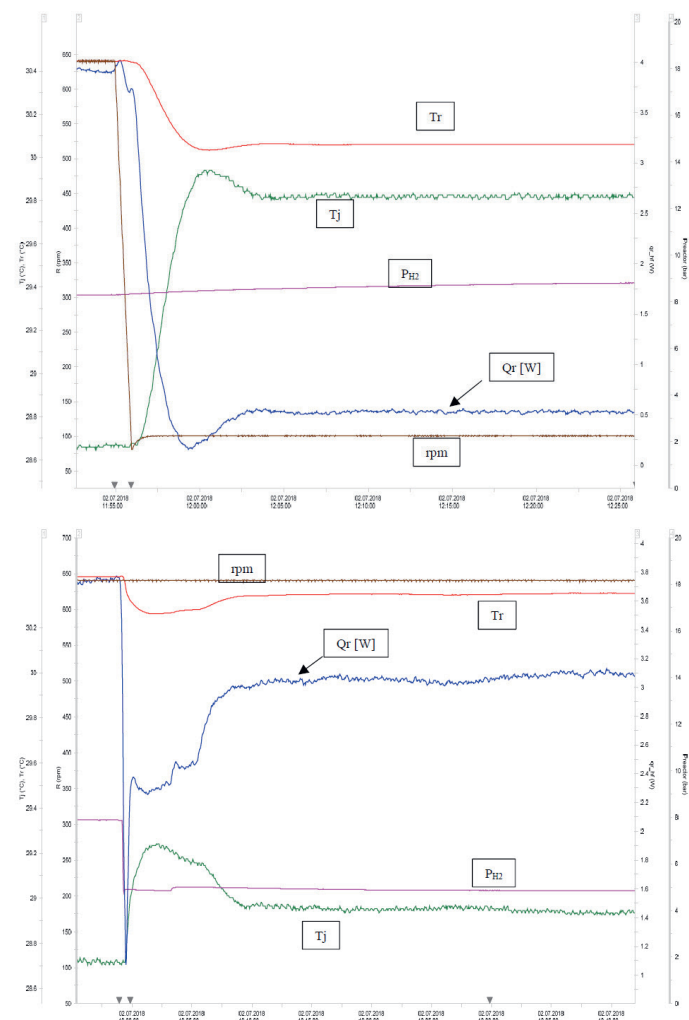
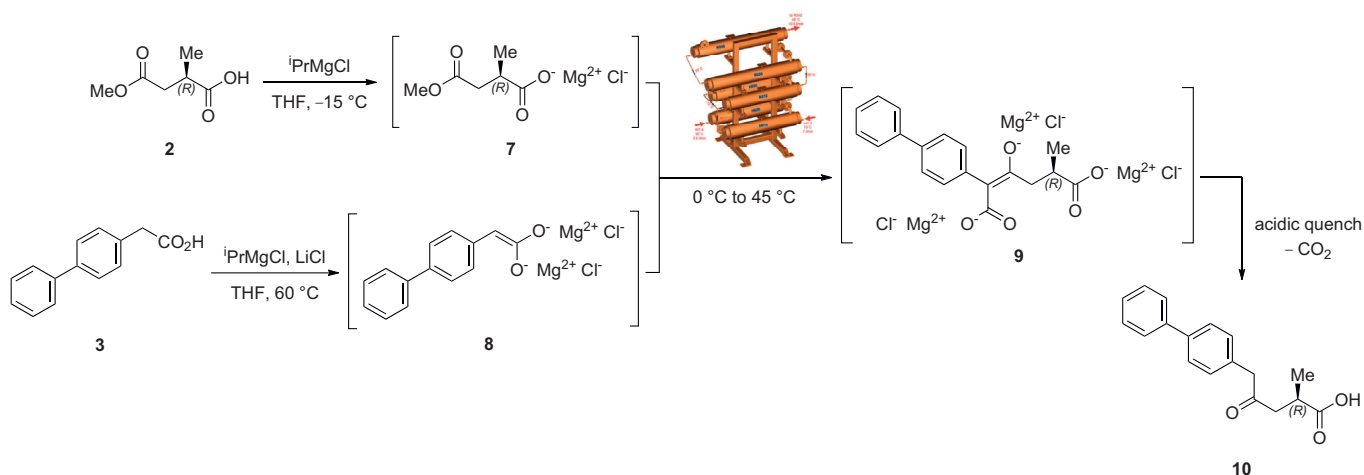


Fig. 2. Impact of agitation (top) and pressure (bottom) on heat release in the asymmetric hydrogenation of compound **1**;  $T_r$  = reactor temperature (red),  $T_j$  = jacket temperature (green),  $P_H$  = hydrogen pressure,  $Q_r$  = heat flow, rpm = stirring speed.

## 2.2 Ivanov Reaction for Installation of Biphenyl Moiety

Introduction of the biphenyl moiety relied on an Ivanov reaction, in which the dianion of a carboxylic acid serves as a nucleophile that reacts with an ester as an electrophile to form – after decarboxylation during acidic work-up – the corresponding ketone (Scheme 2).<sup>[24,25]</sup> Though the Ivanov reaction is less commonly used on a large scale, it offered various distinct advantages to access intermediate **4**: (1) a fast and straightforward installation of the biphenyl moiety using commercially available biphenylacetic acid; (2) the possibility to readily distinguish the two carboxyl acid moieties present in (*R*)-methyl ester **2**; and (3) compatibility of the reaction conditions with the carboxylate group in compound **2**, thus protecting the adjacent stereogenic center from racemization under the strongly basic reaction conditions.<sup>[26]</sup> However, based on the mechanism of the Ivanov reaction, multiple anionic species are present at the same time in the reaction mixture, and the various anionic species – in particular the dianion of biphenylacetic acid – may react not only as a nucleophile, but also as a base, potentially resulting in their quenching by more acidic species in the reaction mixture. The use of a flow reactor for the reaction offered a possible way out, as the various anionic species and reaction intermediates generated *in situ* could be separated in space and would thus not be present simultaneously. After intensive process development, the Ivanov reaction was found to work well in a flow setup. The feed solutions of carboxylate **7** and dianion **8**, derived from biphenylacetic acid, were prepared in a classical batch setup and subsequently combined in a flow reactor under precisely controlled conditions to ensure the correct stoichiometry and temperature profile for maximum conversion and minimum formation of impurities. The output stream of the flow reactor, containing  $\beta$ -keto acid **9** as the corresponding enolate, was then added to an aqueous solution to quench the reaction. Following acidification by charging of hydrochloric acid, concomitant decarboxylation of compound **9** occurred, and  $\gamma$ -keto acid **10** was obtained after work-up and isolation, utilizing again a classical batch mode.

The results of design of experiments (DoE) studies on lab scale as well as scale-up trials on kilogram scale, combined with extensive investigations of key physical parameters (*e.g.* temperature profile or mixing) laid the foundation for the design of the custom-made flow reactor for commercial manufacture. In-depth simulations were fundamental to finalize the reactor design and accurately predict performance of the process in the commercial equipment for reliable reproduction of the development results.



Scheme 2. Access to  $\gamma$ -keto acid **10** by reaction of ester **2** and biphenylacetic acid (**3**) in a flow reactor *via* the Ivanov reaction.

The successful scale-up of the equipment was finally confirmed by the results during commercial manufacture.

Screening of a range of bases derived from alkali and alkaline earth metals demonstrated the best results for magnesium as the counterion, with  $^i\text{PrMgCl}$  finally chosen as the stoichiometric base. The presence of  $\text{LiCl}$  in the feedstream of dianion **8** was found to beneficially impact conversion, even when used in sub-stoichiometric quantities. Distinct differences in reactivity were observed between THF and 2-methyltetrahydrofuran as the solvent, which may be potentially attributed to different coordination of the solvent to the magnesium and lithium cations in enolate **8**, as indicated by the observed differences in crystallization behavior between solutions in THF and 2-methyltetrahydrofuran.<sup>[27]</sup>

As a slight excess of biphenylacetic acid (**3**) was applied in the transformation, removal of residual biphenylacetic acid during work-up and isolation was crucial to achieve high product quality and avoid a negative impact on reaction conversion in the subsequent biocatalytic reaction, likely due to competitive binding of biphenyl acetic acid (**3**) and  $\gamma$ -keto acid **10** by the transaminase enzyme.<sup>[28]</sup> When salt forming agents were investigated for isolation of  $\gamma$ -keto acid **10**, high depletion of residual biphenylacetic acid was observed for ammonium salts of  $\gamma$ -keto acid **10**. Serendipitously, the ammonium salt formed from isopropylamine, the amine donor in the following biocatalytic reaction, was among the best performing systems, and  $\gamma$ -keto acid **10** was therefore isolated as the isopropylammonium salt **4**.

### 2.3 Biocatalytic Transamination

A biocatalytic transamination, utilizing a transaminase in combination with pyridoxal 5'-phosphate (PLP, vitamin B<sub>6</sub>) as the co-factor to install the amino functionality, had been originally proposed based on precedent from the preparation of chiral  $\alpha$ -amino acids.<sup>[29]</sup> Nature utilizes this approach as one of the various access routes to chiral  $\alpha$ -amino acids, and internal experience had been gained earlier on the preparation of chiral  $\alpha$ -amino acids with bulky aromatic substituents by transamination.<sup>[30,31]</sup> As the  $\gamma$ -keto acid **10** required as the precursor for the transamination shared – with the exception of the increased distance between the keto and the acid functionalities as well as differences in the electronic properties – all relevant functional aspects with the prior examples for chiral  $\alpha$ -amino acids, confidence was high that a suitable enzyme could either be identified from available libraries or designed by directed evolution. Considering the potential challenge of the task, Codexis was onboarded as a partner.

While initial library screenings were met with limited success, detailed studies and optimization of the screening conditions allowed the identification of transaminase ATA-217 with measurable activity for the desired transformation.<sup>[7]</sup> Surprisingly, transaminase ATA-217, though derived from a panel known to generally provide products with the *S*-configuration, turned out to be selective for the undesired *R*-diastereoisomer. However, the desired *S*-diastereoisomer was obtained for other transaminases in the screening, yet with lower activity. Interestingly, these transaminases were known to typically deliver products with the *R*-configuration. The decision was taken to benefit from the higher starting activity of transaminase ATA-217 – though selective for the undesired *R*-diastereoisomer – and introduce mutations from the *S*-selective transaminases that are favorable for the desired *S*-selectivity in the subsequent evolution rounds. This strategy worked out well, and over only two rounds of evolution, the diastereoselectivity could be completely reversed from *dr* 0:100 to *dr* 98:2 (Fig. 3), while concomitantly increasing the activity almost 40-fold. Though generation of variants in the libraries that favored the undesired *R*-diastereoisomer could not be completely suppressed until round 5, the subsequent evolution rounds eventually locked the diastereoselectivity.<sup>[32]</sup> Activity increased round by round (Fig. 4), achieving a total activity increase from the starting

transaminase ATA-217 up to the final variant CDX-043 of approximately 500,000-fold after 11 evolution rounds.<sup>[7,17]</sup> Over the course of the evolution program, thermal stability was significantly improved, with evolution round 6 dedicated to tolerance of higher temperature as evolutionary pressure. Though the more thermally stable variant sacATA-6 was less active at 58 °C than the precursor variant sacATA-5 at 50 °C, the drop in activity was completely recovered in the subsequent evolution round.

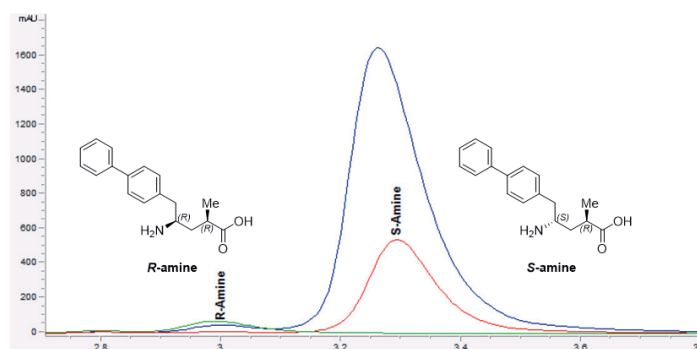


Fig. 3. Reversal of diastereoselectivity in enzyme evolution rounds 1 and 2 with a concomitant increase of activity (green: starting enzyme variant ATA-217; red: enzyme variant sacATA-1 after first evolution round; blue: enzyme variant sacATA-2 after second evolution round).

Process development for the transamination reaction proceeded in parallel to the enzyme evolution program.<sup>[6]</sup> In the final manufacturing process, the reaction was performed at 58 °C under mildly basic conditions at pH 8.6.<sup>[16]</sup> The pH value was found to remain stable after initial adjustment to the target value, with only a minor drift over the course of the reaction observed, thus making the use of a buffer system or active pH control obsolete. As organic co-solvents were not found to positively influence conversion, the reaction was finally performed utilizing pure water as the solvent.<sup>[33]</sup> Despite the low solubilities of both substrate **4** and product **5** in water due to the highly apolar biphenyl moiety, requiring the process to be operated in a slurry-to-slurry mode, the trace quantities of substrate **4** present in solution in combination with sufficiently fast dissolution kinetics ensured an adequate reaction rate. A highly concentrated aqueous solution of isopropylamine instead of widely used isopropylammonium salts was applied as the amine donor for ease of handling on a commercial scale.

Transaminase-catalyzed reactions are equilibrium reactions, often favoring the substrate, *i.e.* ketone, over the product, *i.e.* amine. High conversion therefore generally requires to actively shift the equilibrium towards the product.<sup>[34]</sup> A common and straightforward approach is the use of a significant excess of the amine donor, which is not preferred in a commercial setting primarily for environmental considerations, as the high nitrogen load of the aqueous waste streams often prevents treatment in standard wastewater treatment plants. Most notably, in the transamination at hand, the reaction was found to be ‘self-driven’ as a result of the lower solubility of product **5** compared to substrate **4**, which led to the constant removal of product **5** from the equilibrium by crystallization.<sup>[28]</sup> Consequently, actively shifting the equilibrium was not required, and the required excess of isopropylamine could be limited to approximately 3.5 equivalents.

For work-up and isolation, the reaction mixture was acidified at the end of the reaction with hydrochloric acid, and the resulting  $\gamma$ -keto acid product was extracted as the hydrochloride salt into 2-methyltetrahydrofuran (2-MeTHF).<sup>[35]</sup> After removal of water by distillation, accounting for the detrimental impact of residual water on the isolated yield due to product loss into the mother li-

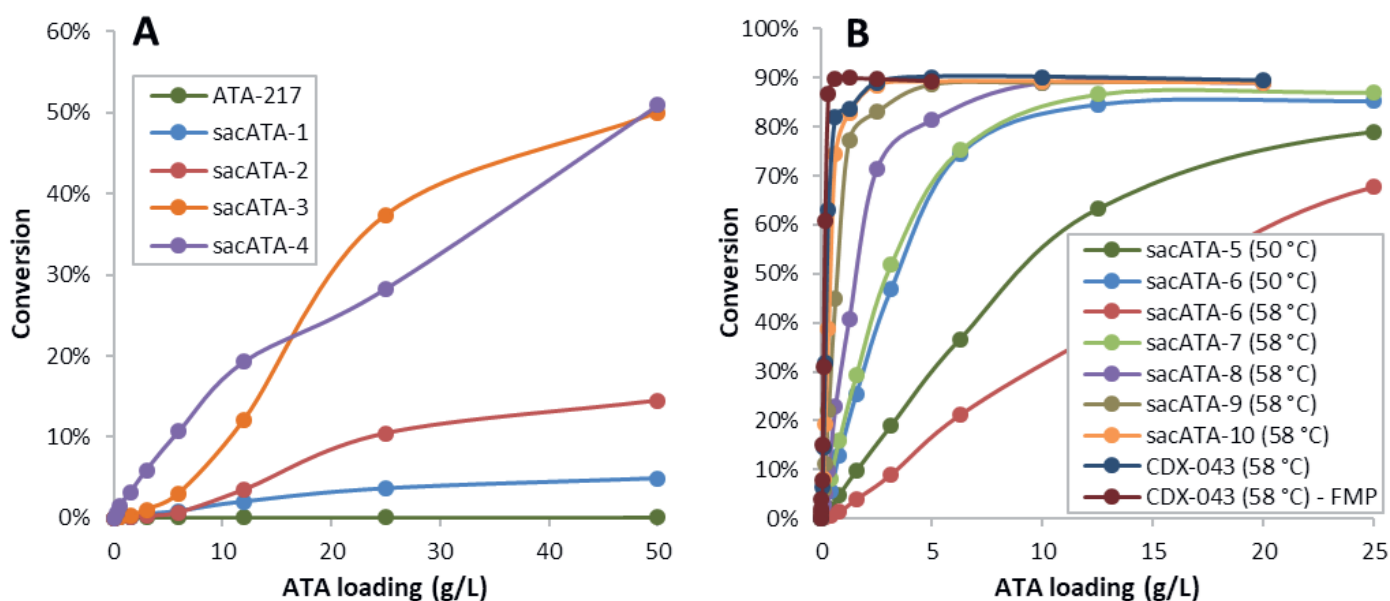


Fig. 4. Activity comparison of the enzyme variants over the evolution program up to the final variant CDX-043 (A: backbones from rounds 1–5; B: backbones from rounds 6–11). Reprinted with permission from *ACS Catalysis* **2021**, *11*, 3762. Copyright 2025 American Chemical Society.

quor, *tert*-butylmethylether (TBME) was added as an anti-solvent, the formed suspension was cooled, and the product was finally isolated by filtration in 89% yield, > 99.9% chemical purity by HPLC and as a single diastereomer with > 99.9:0.1 *dr*. Studies on the depletion of the enzyme CDX-043 during work-up and isolation of compound **5** as well as in downstream steps demonstrated complete removal of the residual enzyme as well as smaller peptide fragments and single amino acids to levels well below 0.10%, in line with ICH guidelines.<sup>[30]</sup>

### 2.4 Esterification to Intercept Intermediate **6**

Esterification to convert  $\gamma$ -amino acid **5** into the corresponding ethyl ester **6** was achieved under standard conditions using thionyl chloride in ethanol.<sup>[14]</sup> The acidic reaction conditions allowed isolation of the product as the corresponding hydrochloride salt in high purity after solvent exchange to *n*-heptane, with protonation of the amino functionality in ethyl ester **6** preventing intramolecular cyclization to the corresponding lactam.

## 3. Environmental Sustainability

Improvements of key parameters associated with environmental sustainability like process mass intensity (PMI),<sup>[36]</sup> total carbon dioxide release (TCR),<sup>[37–39]</sup> or avoidance of transition metals had been defined as development goals from the very beginning, and advances were thus routinely assessed against the targets during process development. Introduction of the second-generation synthesis of sacubitril finally resulted in a significant reduction of the environmental impact of the manufacturing process. Compared to the established synthesis of sacubitril,<sup>[14,40]</sup> the total carbon dioxide release was reduced by 50% or – with inclusion of solvent recovery and recycling, already considered during the design phase – to one third of the original value (Fig. 5). The application of biocatalysis was a decisive factor for the achieved TCR reduction, making synthetic strategies accessible that would otherwise have been out of reach using traditional chemical approaches and, in the end, allowed a reduction in the overall number of steps up to intermediate **6** from ten steps in the original synthetic route to only five steps in the second-generation synthesis.

## 4. Conclusion

The second-generation synthesis of compound **6**, a key intermediate in the synthesis of sacubitril as one of the two active phar-

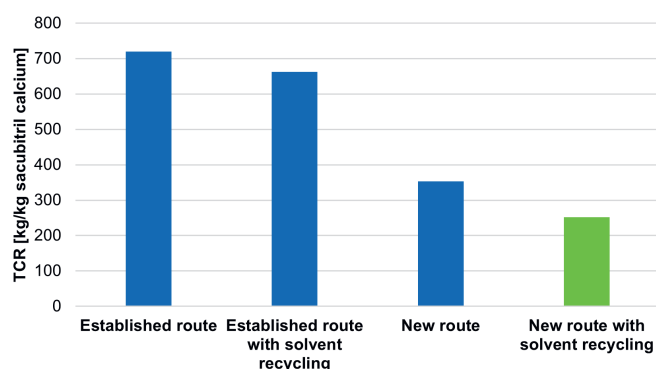


Fig. 5. Improved environmental sustainability of the second generation synthesis based on the assessment of the total carbon dioxide release (TCR). Reprinted with permission from *J. Org. Chem.* **2020**, *85*, 6844. Copyright 2025 American Chemical Society.

maceutical ingredients of LCZ696, was successfully achieved by combining strategic route design with in-depth and comprehensive process development. Utilization of metal catalysis, flow chemistry and – in particular – biocatalysis as state-of-the-art technologies enabled the development of a significantly improved manufacturing process that met all pre-defined performance targets for efficiency and environmental sustainability for large-scale commercial manufacture.

The case at hand equally serves as an excellent showcase for the major improvements that are achievable when skilled and dedicated colleagues with diverse technical backgrounds join forces in the process development of drug substances. With new modalities of constantly increased structural complexity entering the portfolio of the pharmaceutical industry, and development targets – particularly on environmental sustainability – becoming more ambitious, chemical process development will not run out of new challenges to address. Routine utilization of state-of-the-art technologies like biocatalysis and implementation of currently emerging technologies like photocatalysis on a commercial scale hold great promise in order to meet these challenges.

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