Asymmetric synthesis of telcagepant, a CGRP receptor antagonist for the treatment of migraine

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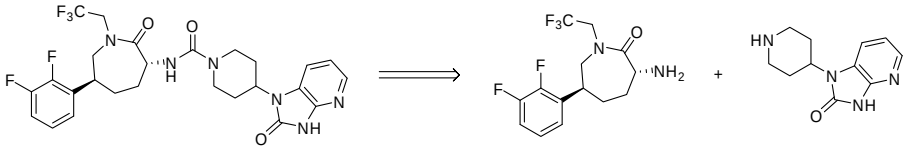
Process Research Department at Merck supports all Merck drug development programs by defining viable synthetic route to supply bulk API (Active Pharmaceutical Ingredient) for safety studies and clinical trials. For late stage program, a long-term synthetic route or a manufacturing route is designed and developed by aiming at "the ultimate synthesis", which needs to be efficient, practical, scalable, cost effective and environmentally benign, in order to supply larger quantities of API. In the long-term process, the quality of the final product also has to be strictly controlled to meet the high purity standards (e.g., no unqualified impurities >0.10%).

Migraine is a highly prevalent and disabling disorder[1] characterized by severe headache and associated symptoms such as nausea, vomiting, photophobia, and phonophobia. Triptans, 5-$HT_{1B/1D}$ agonists, are used as effective therapy for migraine. However, these compounds are contraindicated in patients with some types of cardiovascular disease,[2] and a substantial number of patients are unresponsive to this type of therapy.[3] It has more recently been suggested that calcitonin gene-related peptide (CGRP) may play a key role in the migraine pathophysiology as CGRP levels were shown to be elevated during migraine attacks.[4] Selective antagonists of CGRP receptor could therefore prove to be a new type of migraine treatment without the cardiovascular effects associated with the triptan compounds.[5] Telcagepant (**1**) is a novel, orally active CGRP receptor antagonist,[6] being evaluated by Merck for acute treatment of migraine. This investigational drug has been demonstrated to significantly relieve migraine pain and associated symptoms in phase III clinical trials.[7]

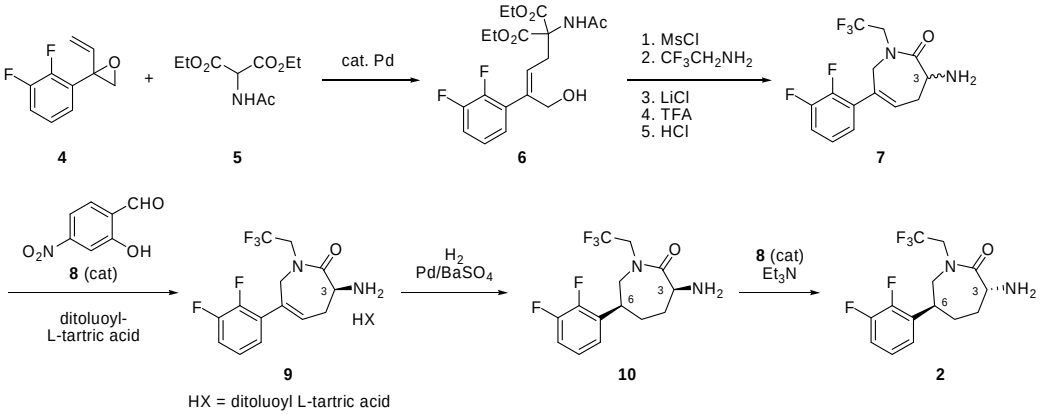
Telcagepant (**1**) is synthesized by a coupling reaction of two heterocyclic components **2** and **3** (Scheme 1).[8] While an efficient and practical synthesis of the piperidine piece **3** was recently established in our laboratories,[9] there remained a need for a better synthesis of the caprolactam component **2**.



1: telcagepant **2** **3**

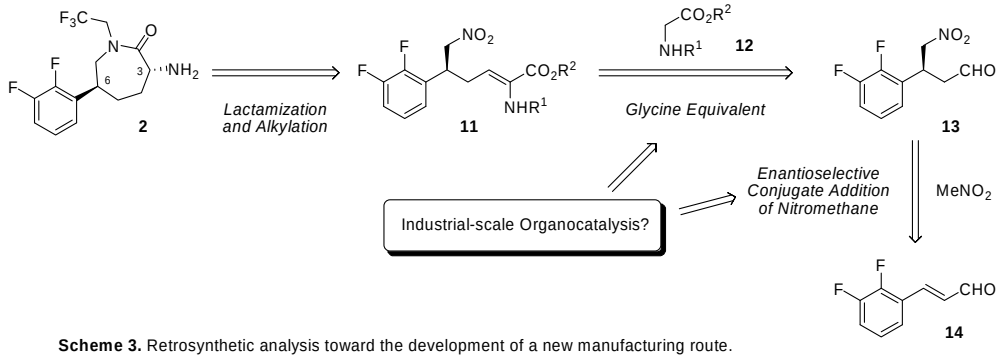
Scheme 1.

Among several different syntheses of **2** developed to date,[6,10,11] the first-generation large-scale synthesis[11] that was utilized to supply **1** for the early safety studies and clinical trials is summarized in Scheme 2. All the carbons in the caprolactam ring were installed by the coupling of vinyl epoxide **4** and amino malonate **5**. The C-6 stereogenic center in the caprolactam was established by a *cis*-selective hydrogenation of **9** based on the C-3 stereogenic center that was temporarily set to *R*-configuration via dynamic kinetic resolution (DKR) crystallization of racemic **7**. Once the C-6 center had been established, the C-3 center was flipped to the requisite *S*-configuration by epimerization of **10**, which was promoted by a catalytic amount of **8**. Although this synthesis allowed for the supply of bulk API to support clinical trials, there were some drawbacks that rendered this synthesis unsuitable for a manufacturing process. The overall yield of the synthesis to caprolactam **2** was only approximately 12% in hundred kilogram scale runs, and the installation of the stereogenic centers had to rely on laborious manipulation including the resolution of a racemic intermediate.



Scheme 2. The first-generation large-scale synthesis of the caprolactam piece.

Scheme 3 depicts the retrosynthesis proposed for a new manufacturing process. In order to aim for "the ultimate synthesis", it was crucial to identify a more straightforward method to construct the C-6 stereogenic center. To this end, we envisioned that the conjugate addition of nitromethane to α,β-unsaturated aldehyde **14** would be most suitable. This approach was very attractive for us because of the excellent atom economy, which is a key element of a long-term process. Over the past decade, the field of organocatalysis has emerged as a powerful tool and has made a significant impact on synthetic organic chemistry.[12] Indeed, there were several examples of enantioselective addition of nitroalkanes to α,β-unsaturated aldehydes promoted via the formation of iminium species using organocatalysts, at the time of development.[13] However, to the best of our knowledge, application of organocatalysis technology based on the iminium activation on an industrial scale was unprecedented. Another key step in the new synthetic route was the subsequent condensation of glycine enolate equivalent **12** with nitroaldehyde **13** to form enamine **11**. Although this transformation has typically been performed by utilizing Horner-Wadsworth-Emmons method, we were required to identify the most atom-economical, cost-effective and environmental benign chemistry for this step.

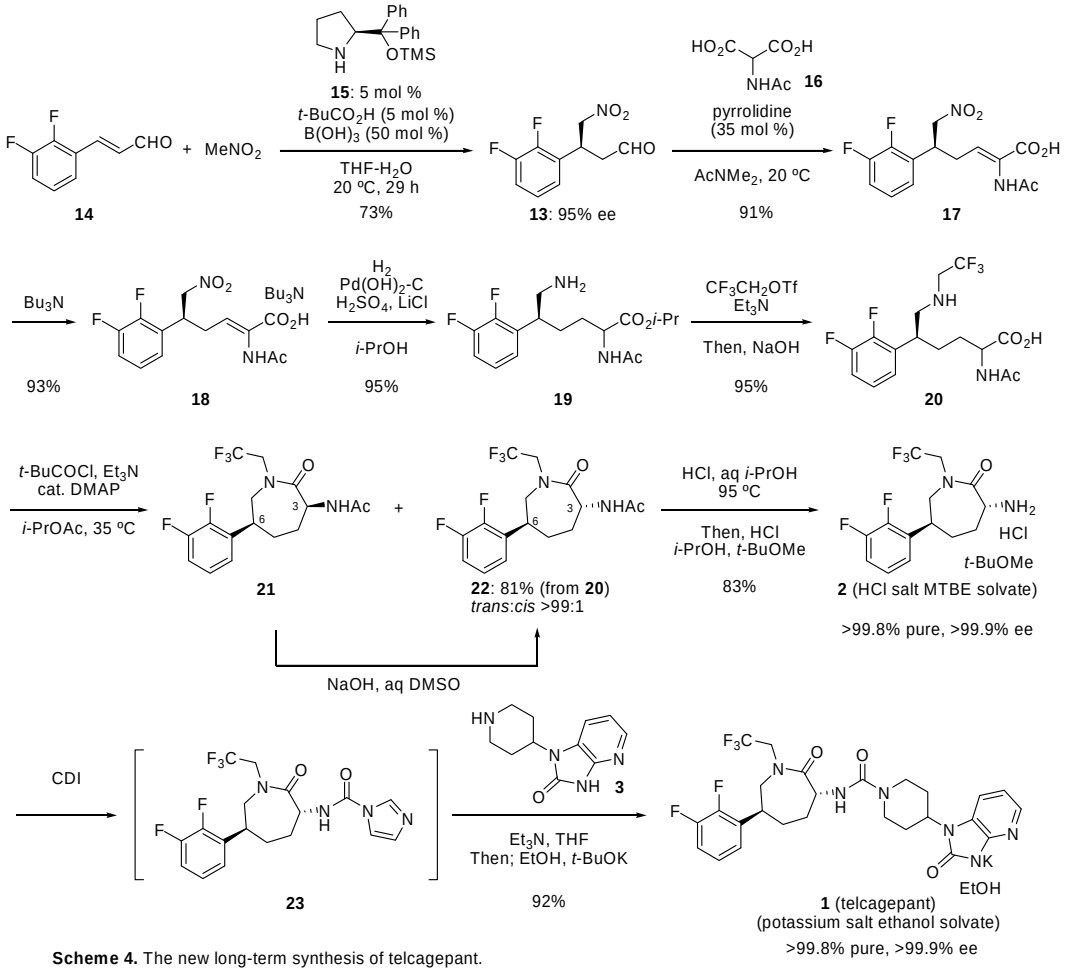


Scheme 3. Retrosynthetic analysis toward the development of a new manufacturing route.

In order to prove the concept of the new synthetic approach, we first examined the nitromethane addition reaction of our substrate **14** under Hayashi's conditions[13d] using a proline-derived catalyst **15**[14] with benzoic acid as a co-catalyst in MeOH. Although the reaction afforded the desired product **13** with excellent enantioselectivity (95% ee), we observed the competitive reaction of substrate **14** with solvent (MeOH) to generate considerable amounts of the corresponding dimethyl acetal as byproduct. A quick screening proved that the use of alcoholic solvents was essential to obtain a high yield and a reasonable reaction rate for the desired transformation. Nevertheless, we concluded that alcoholic solvents had to be eliminated from the system in order to avoid the risk of acetal formation, which would pose a serious concern for scale up. After extensive screening, we were able to discover a new "cocktail" catalytic

system consisting of the prolinol catalyst **15**, pivalic acid and boric acid that worked effectively in aqueous THF without introducing any alcoholic solvents (Scheme 4).

The subsequent condensation of **13** with a glycine enolate equivalent was investigated by evaluating various methods. Although the Horner-Wadsworth-Emmons reaction of **13** with the corresponding amino phosphonate reagent (ethyl *N*-acetyl-2-(dimethoxyphosphoryl)glycinate) worked efficiently as expected, this approach had the disadvantage of generating phosphate side products along with metal waste. On the other hand, Doebner-Knoevenagel-type condensation[15] of **13** with an amino malonate half ester or free acid substrate **16** would provide a direct access to the same transformation with excellent atom economy; however, this type of transformation using a glycine enolate equivalent had been little explored.[16] It should also be noted that the reaction conditions had to be extremely mild to avoid potential side reactions caused by the two labile functionalities in **13**, the nitro and aldehyde groups. After careful evaluation using several different malonate reagents and mechanistic analyses, we were able to develop a highly efficient condensation of **13** with 2-acetamidomalonic acid (**16**). The reaction was promoted by using 35 mol % of pyrrolidine as the catalyst under very mild conditions to afford the desired enamine **17** in 91% yield, which was isolated as the tributylamine salt **18**. Our data supported that this transformation was likely to be promoted by the same iminium-activation as in the nitromethane addition step.



Scheme 4. The new long-term synthesis of telcagepant.

In the subsequent hydrogenation of **18**, the most serious issue was the formation of desfluorinated byproducts, which were difficult to reject in the downstream of the synthesis and could affect the

impurity profile of the final product. Extensive screening of reaction conditions identified LiCl as an effective additive, and the desfluorinated impurities were successfully suppressed below 0.2% under the optimized conditions. The hydrogenation reaction was conducted using $Pd(OH)_2$-C as catalyst in *i*-PrOH in the presence of LiCl and H_2SO_4, and the product was converted to the isopropyl ester **19** in the same pot in order to avoid undesired *O*-alkylation reaction in the subsequent trifluoroethylation step. After installation of a trifluoroethyl group followed by saponification of the ester, the caprolactam ring formation was effected in an extremely efficient manner by the use of *t*-BuCOCl as the activating reagent.

At this point, the C-3 stereogenic center was not defined yet as the caprolactam intermediate was obtained as a diastereomeric mixture (**21** and **22**). Interestingly, treatment with NaOH in aqueous DMSO selectively epimerized the C-3 center to the desired *S*-configuration without using any other promoters like **8**. While the thermodynamic equilibrium ratio was 97:3 (**22**:**21**), the desired *trans*-isomer **22** was selectively crystallized out of the reaction system with the ratio of >99:1 (**22**:**21**) in the isolated product. Deprotection of the acetamide with HCl followed by crystallization in the presence of HCl and *t*-BuOMe (MTBE) afforded the desired caprolactam piece **2** as the monohydrochloride MTBE solvate. The synthesis of telcagepant (**1**) was completed by the CDI coupling of **2** with **3**.[8]

The new synthesis, which requires isolation of only three intermediates and no chromatographic purification, has been successfully demonstrated on large scales (>10 kg) in pilot plant. This highly efficient, cost effective process reproducibly gives telcagepant (**1**) with high purity (>99.8%, >99.9% ee).[17] This lecture describes our efforts toward the development of this novel process in more detail.

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