With asymmetric hydrogenation towards a scalable, stereoselective syntheses of Aleglitazar and Bitopertin

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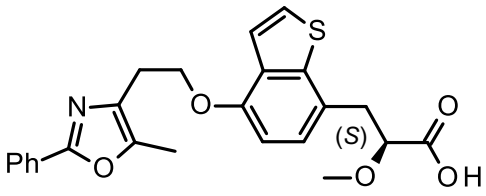
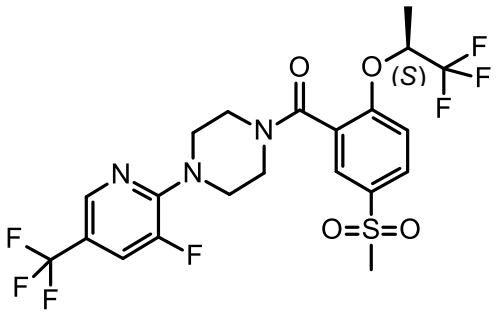
In recent years new drug candidates containing one or more chiral centers are developed almost exclusively as pure enantiomers. Their increasing structural complexity together with the public pressure on drug pricing has made cost of goods a critical issue. In this context, the task of a synthesis & process research chemist is to find shorter synthetic routes in which the chiral centers are directly and selectively established in the desired configuration in order to avoid labor- and equipment-intensive resolution processes, as well as to develop the synthesis in the limited time frame available.

The presentation gives an insight into the role of Roche's Process Research & Catalysis units in the development of new drugs. In the first part of the presentation, the process towards the potential commercial API route, started with the optimization of the existing Medicinal Chemistry route and concluded with the creation of an entirely new route, will be exemplified with Roche's dual PPAR agonist Aleglitazar. Particularly, the stereoselective synthesis of (2S)-alkoxy propionic acids via Lewis acid-mediated diastereoselective aldol reaction and asymmetric (transfer) hydrogenation will be presented.

In the second part of the presentation, the enantioselective hydrogenation of 1,1,1-trifluoroacetone to (S)-1,1,1-trifluoro-2-propanol - key building block in Bitopertin - will be highlighted. The relevant criteria associated with the application of the asymmetric hydrogenation technology will be addressed, such as the activity, the selectivity and the accessibility of the catalysts, as well as of the availability and the quality of hydrogenation substrates. Successful laboratory and pilot plant campaigns will be described.



Aleglitazar



Bitopertin