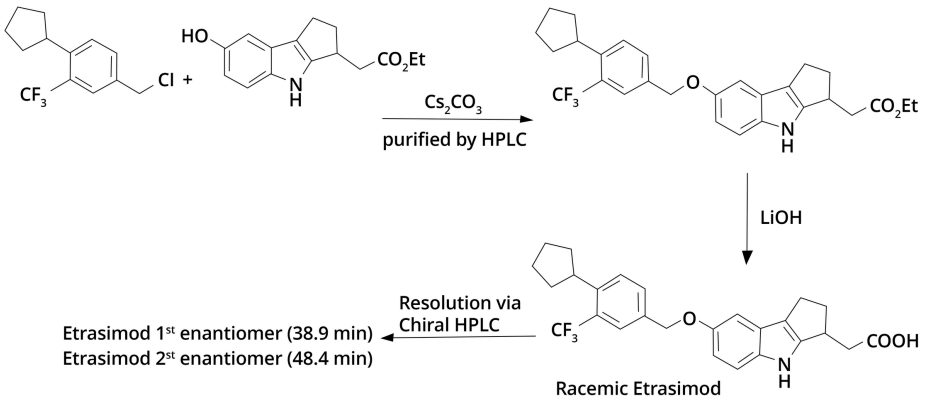
WHITE PAPER

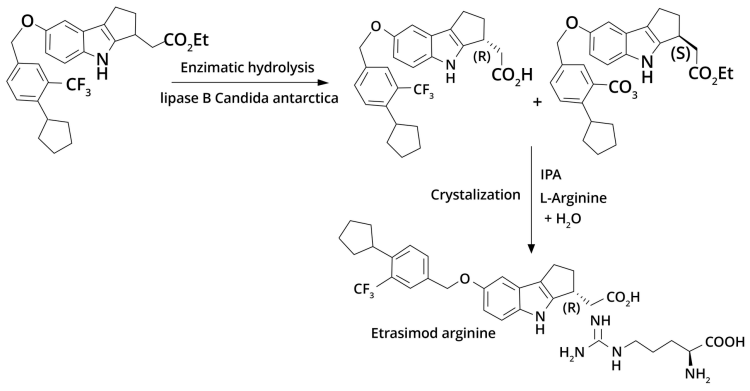
Curia´s patented process for intermediates useful for Etrasimod Arginine

Etrasimod, also known as APD334, is the international non-proprietary name (INN) or common name of (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)- 1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid, a potent, selective and orally available antagonist of the sphingosine-1-phosphate-1 (S1P1) receptor, which was approved on October 2023 by the FDA under the brand name VELSIPITY™ for the treatment of adults with moderately to severely active ulcerative colitis. The active ingredient in VELSIPITY is the L-arginine salt of etrasimod (commonly simply referred to as: etrasimod arginine).

Several synthetic processes for the preparation of this type of compounds and intermediates thereof have been disclosed. WO2010/011316 A1 discloses a process for preparing racemic etrasimod followed by resolution via chiral HPLC to obtain both enantiomers. However, chiral separation by HPLC is not suitable at an industrial scale, especially owing to the high cost of the stationary phase (packing materials).



WO2011/094008 A1 describes the preparation of etrasimod through a process whose last step is the enantioselective enzymatic hydrolysis of the ester which provides a mixture containing etrasimod with the desired (R) configuration and the (S)- 10 ester as an impurity. The process then requires adding seeds of the L-arginine salt of (R)-etrasimod to the mixture to induce the crystallization of etrasimod arginine.



Prior art document WO2016/209809 A1 described the same strategy of enzymatic hydrolysis to prepare a crystalline free-plate habit of etrasimod arginine. Also described the preparation of an allegedly new morphology, however, does not avoid the need of adding the L-arginine salt of (R)-etrasimod for seeding or reworking previously formed crystals by recrystallization.

WO2016/209809 A1 refers to the morphology of etrasimod arginine prepared previously in WO2011/094008 as "spherulite" and "radial cluster", which is defined as a crystal habit consisting of thin plates or flakes whereas the novel crystalline “free-plate habit” is defined as the general shape of an independent substantially flat crystal. According to WO2016/209809 A1, it was observed that the two PXRD patterns for the spherulite and free-plate habits were the same or substantially the same and thus the two habits represent the same crystal phase but are described some parameters such as DSC and BET, and others, to try to differentiate both morphologies. However, the processes reported in WO2011/094008 A1 and WO2016/209809 A1 for obtaining etrasimod in the desired (R)-enantiomeric form (and its L-arginine salt) have important drawbacks in terms of its synthetic efficacy and implementation at an industrial scale.

Curia´s patented process

Curia patented a new process that solves main prior art drawbacks by the provision of a simple, cost-effective and industrially applicable process for the preparation of enantiomeric substituted 2-(1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid derivatives such as etrasimod and to intermediates useful therefor.

Curia´s scientists have surprisingly found that chiral substituted 2-(1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid derivatives such as etrasimod can be obtained through a process involving the enantioselective enzymatic hydrolysis of early synthetic intermediates. This innovative synthetic approach described herein results in better overall molar yield. Moreover, in the process now proposed, if desired, the (S)-isomer ester that remains non-hydrolyzed in the enantioselective hydrolysis may be epimerized and subjected to a second enantioselective hydrolysis.

The fact that the desired chirality is introduced in the structure in the first steps of the synthesis results in lower environmental, operating and material costs.

During the salt formation the final product precipitates from a reaction of a crystalline and pure solid product, having different parameters such as DSC and BET, to try to differentiate to the previously described morphologies.

For further details, please check Curia Spain patent application WO2026/022274.

VELSIPITY is a trademark of Pfizer Inc.

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