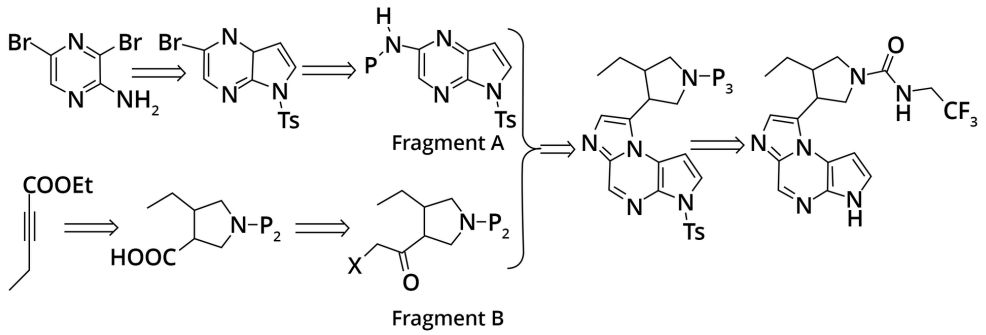
WHITE PAPER

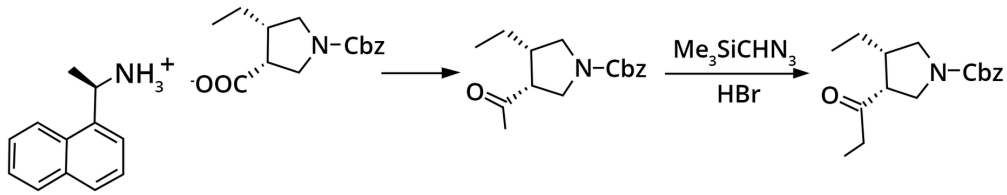
Curia´s patented process for intermediates useful for Upadacitinib

Upadacitinib (also known as ABT-494) is a potent and selective JAK1 inhibitor developed by AbbVie. It has been approved by the FDA for the treatment of rheumatoid arthritis.

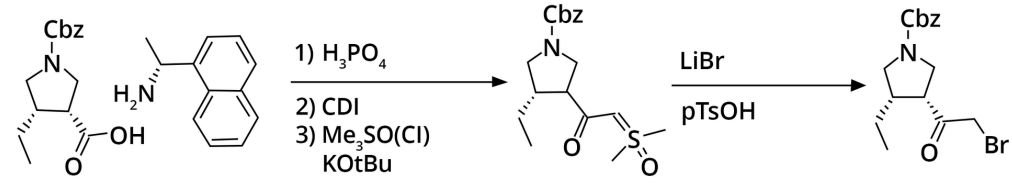
Several methods have been described in the literature for the synthesis of Upadacitinib, but they all are mainly based on the same approach: preparation of what we call Fragment A and Fragment B, which are then joined. Subsequent cyclization to provide the imidazopyrrolopyrazine skeleton and derivatization gives rise to Upadacitinib.



Fragment B could be synthesized according to prior art documents such as: WO2013/043826, by treatment of an intermediate acid chloride with trimethylsilyldiazomethane, which could be considered unstable and highly toxic.

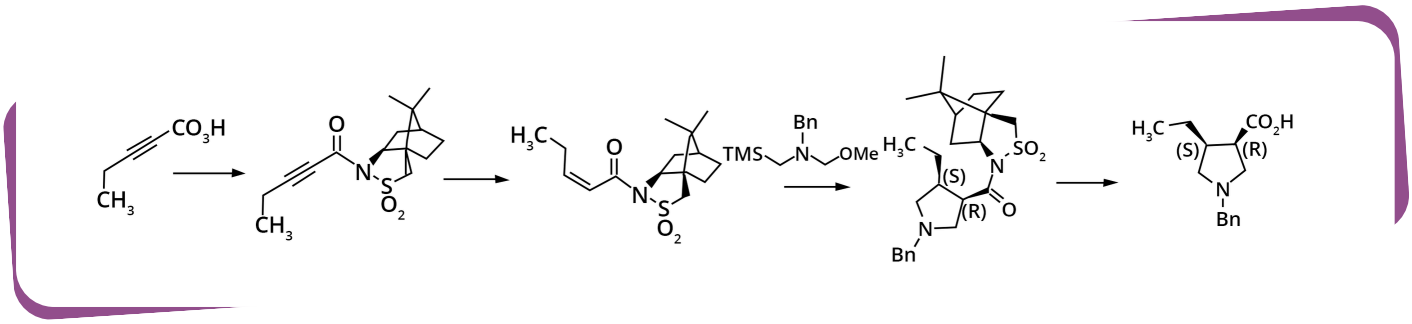


Document WO2017/066775 discloses preparation of cis-(3R,4S)-1- benzyloxycarbonyl-4-ethylpyrrolidine-3-carboxylate through formation of a sulfoxonium salt and subsequent treatment with LiBr.



However, Curia scientists have observed that the basic conditions required for the preparation of the sulfoxonium salt and the subsequent bromination reaction give rise to partial isomerization to the trans isomer, making necessary a further purification to obtain the pure product, which is so obtained in lower yield.

It is disclosed in WO2017/066775 through asymmetric hydrogenation. Finally, document WO2019/016745 discloses a process for the preparation of an analog of Fragment B which comprises the use of (1R)-2,10-camphorsultam as chiral auxiliary.



This approach further requires the use as starting material of 2-pentynoic acid, which is not easy to manufacture, and it increases the cost of the industrial process.

Curia´s patented process

Curia patented a new process for the preparation of useful intermediates in the synthesis of compounds such as Upadacitinib and structurally related compounds. In particular, Curia´s scientists found that compounds of formula (I) can be obtained satisfactorily, in an industrial and economical way and without the need of highly toxic reagents, using Weinreb amide of formula (III) or triazine ester of formula (IV) as key intermediates.

Additionally, Curia´s scientists observed that isomerization to the trans isomer of the pyrrolidine ring does not occur with the patented process. This contrasts with the conditions required by process disclosed in prior art documents.

For further details, please check Curia Spain patent application WO2021/123288.

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