CONTINUOUS FLOW APPROACH FOR THE SYNTHESIS OF
MAYTANSINOL, AS ADC-BASED THERAPY CYTOTOXIC AGENT

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Maytansinoids are natural compounds extracted from the bark of the African shrub Maytenus ovatus, showing antimitotic activity binding tubulin and inhibiting microtubule assembly. [1] Since their discovery, in vitro and in vivo tests revealed a limited therapeutic window due to high toxicity at therapeutic dosages. [2] Recently, importance of maytansinoids has been re-evaluated, because of the possibility to use them for Antibody Drug Conjugates (ADC) therapy. Ansamitocin P3 (1), produced by a fermentation process, has been considered as the ideal starting material to form maytansinol (2). Transformation of ester in secondary alcohol is feasible through a reductive hydrolysis with LiAlH(OMe) 3, in very strict and drastic reaction conditions, even in good yields (82%). [3] Low reproducibility of this kind of process and potentially high toxicity risk for the operator made us to think about a different approach. Confining the potent cytotoxic agent in a close circuit could represent a convincing solution from the point of view of safety. Therefore, in our attempts, we tried to obtain maytansinol as product of a continuous flow reduction of ansamitocin P3, using LiAlH 4 itself as reducing agent, instead of the methoxylated analogue.

Such a method led to the reductive hydrolysis of isobutyryl ester derivative in good yields (60%), protecting the operator safety and allowing the obtainment of a crude mixture in which maytansinol 2 is present almost exclusively. In-depth studies are ongoing to better understand the possibility to proceed towards the final product by a continuous flow work-up, without any further purification needed.