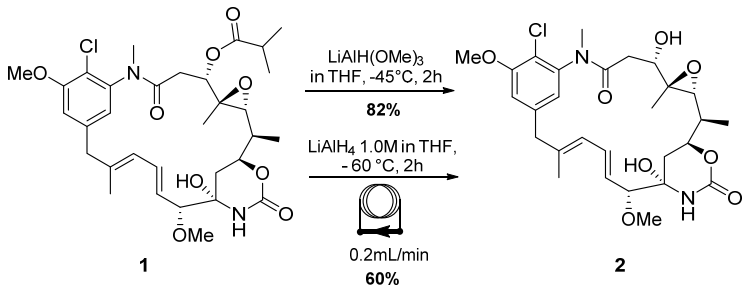
CONTINUOUS FLOW APPROACH FOR THE SYNTHESIS OF MAYTANSINOL, AS ADC-BASED THERAPY CYTOTOXIC AGENT

S. Princiotto [a], M. Taddei [a], L.Vaccaro [b], G. Fontana [c] and P. Allegrini [c]

[a] Dip. di Biotecnologie, Chimica e Farmacia, Università di Siena, Via Aldo Moro 2, 53100, Siena
[b] Dipartimento di Chimica, Università di Perugia, Via Elce di Sotto, 8, 06123, Perugia
[c] Indena spa, Viale Ortles 12, 20139, Milano

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.

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