Title: **Studies related to the optimization of the large-scale synthesis of a peptide of industrial interest.**

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Dipeptide Fmoc-L-Val-L-Leu-OH (**8a**) and its epimer Fmoc-L-Val-D-Leu-OH (**8b**) have been synthesized in solid-phase using Fmoc chemistry and a 2-CTC resin in order to confirm the chemical identity of unwanted by-products found when the synthesis of a peptide of pharmacological interest was scaled up. The occurrence of severe epimerization processes at large-scale was confirmed but they could not be reproduced at small-scale. Additionally, a minor peptide by-product (**11**) arising from residual reagents embedded into the resin was characterized and an optimized washing protocol has been proposed to minimize its impact on the synthesis. Finally, stability of the 2-CTC peptidyl-resins has been evaluated using the SPPS preparation of dipeptide Fmoc-Arg(Pbf)-Leu-OH (Figure 12) as model. It was found that these peptidyl-resins slowly lose peptide chains at rt. This behavior may be responsible of the lack of reproducibility and of the unexpected low yields observed in some large-scale synthesis.

Additionally, compound **10** has been synthesized but the extreme lability of its ester bond has precluded it use as a "soluble" model of the amino acid-resin moiety.

Keywords: peptide chemistry, Fmoc chemistry, solid-phase synthesis, epimerization.