Synthesis of Telcagepant

Significance: Telcagepant is a selective antagonist of calcitonin gene related peptide (CGRP) that is in phase clinical trials for the treatment of migraine. The synthesis featured an enantioselective 1,4-addition of nitromethane, which is the first application of iminium organocatalysis on an industrial scale and a highly stereoselective Doebner–Knoevenagel condensation that created the enamide F.

Comment: The formation of desfluoro impurities that accompanied the hydrogenation of F was minimized by conducting the reaction in the presence of LiCl. The mixture of caprolactams I and J (2:1) was converted into pure J by crystallization-induced diastereoselection. The synthesis was accomplished in 27% overall yield and involved only three isolated crystalline intermediates (F, J and K).