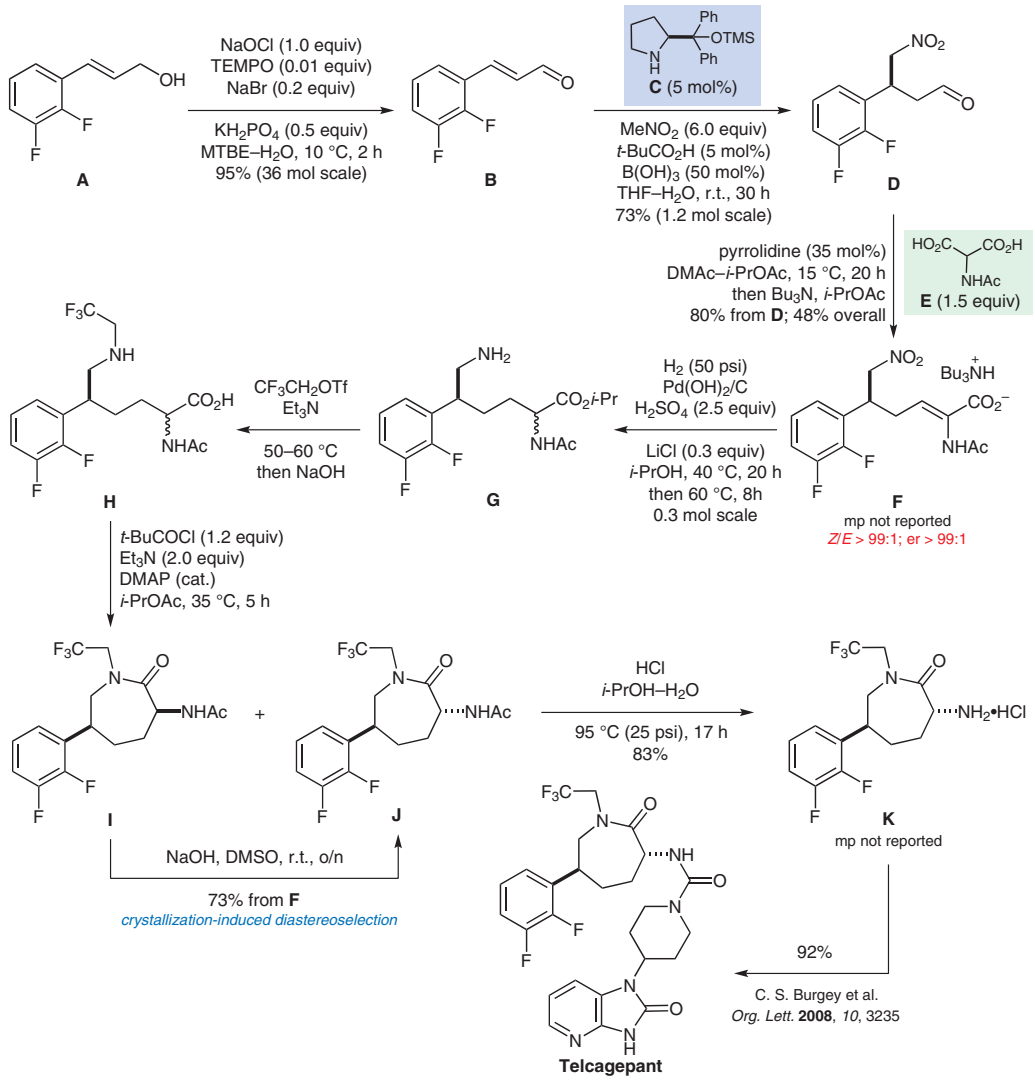
F. XU ET AL.* (MERCK RESEARCH LABORATORIES, RAHWAY, USA)

Asymmetric Synthesis of Telcagepant, a CGRP Receptor Antagonist for the Treatment of Migraine
J. Org. Chem. **2010**, *75*, 7829-7841.

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 (**B** → **D**) 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**).

SYNFACTS Contributors: Philip Kocienski
Synfacts 2011, 2, 0119-0119 Published online: 19.01.2011
DOI: 10.1055/s-0030-1259212; **Reg-No.:** K09110SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

telcagepant

CGRP receptors

iminium organocatalysis

asymmetric conjugate addition

crystallization-induced diastereoselection

Doebner–Knoevenagel condensation

SYNFACT of the month