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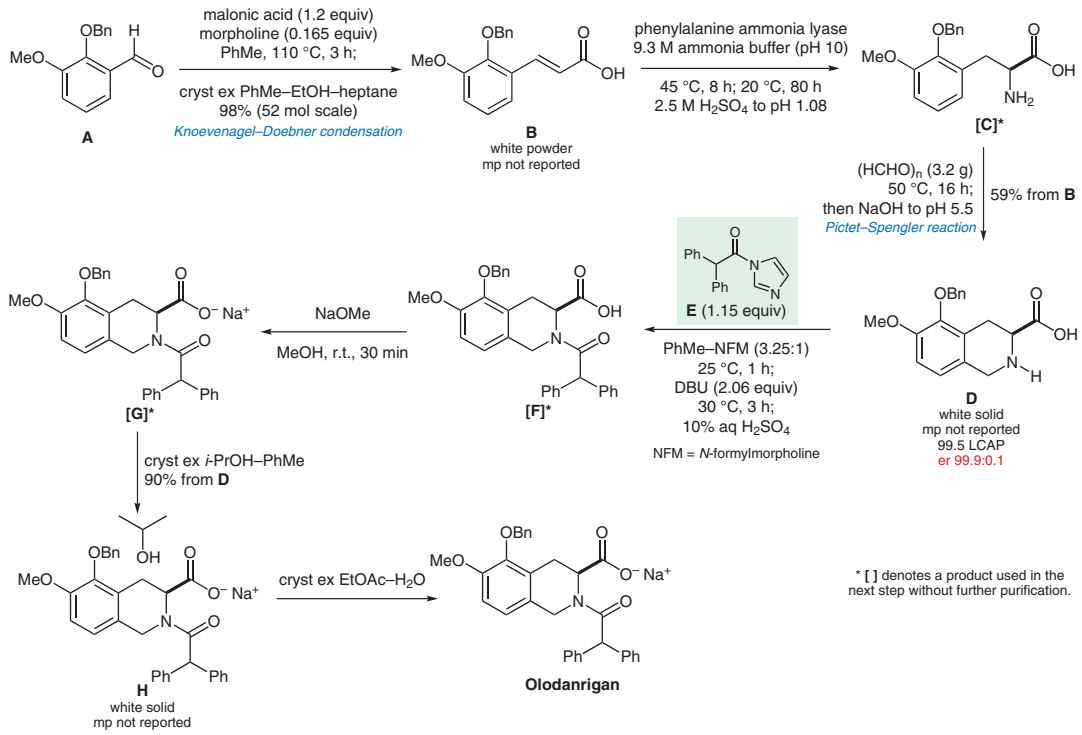
Toward a Scalable Synthesis and Process for EMA401, Part I: Late Stage Process Development, Route Scouting, and ICH M7 Assessment

Org. Process Res. Dev. **2020**, *24*, 1743–1755, DOI: 10.1021/acs.oprd.0c00215.

Synthesis of Olodanrigan



Significance: Olodanrigan (EMA401) is an angiotensin II type 2 antagonist that had been considered for the treatment of postherpetic neuralgia and neuropathic pain. This short synthesis of olodanrigan is presented in detail in three back-to-back papers. Part 1 concerns the optimized conversion of the phenylalanine **C** to the target molecule and includes the search for a suitable polymorph. Part 2 (*Org. Process Res. Dev.* **2020**, *24*, 1756) concerns development of a pyridine- and piperidine-free Knoevenagel–Doebner condensation using a catalytic amount of morpholine that delivered 25 kg of cinnamic acid **C** in 98% yield.

Comment: Part 3 (*Org. Process Res. Dev.* **2020**, *24*, 1763) describes the hydroamination of the cinnamic acid **B** using an engineered phenylalanine ammonia lyase enzyme to afford amino acid **C**. Enzyme loadings as low as 2.5 wt% (E/S = 1:40 w/w) and substrate concentrations between 1.17–0.39 M were compatible with the reaction conditions. The telescoped process from **B** via **C** to tetrahydroisoquinoline **D** was scaled up to a batch size of 2 kg, resulting in 81% conversion to **C** and a 59% isolated yield of **D** with high chiral purity (er = 99.9:0.1).

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Category

Synthesis of Natural Products and Potential Drugs

Key words

olodanrigan

phenylalanine ammonia lyase

hydroamination

tetrahydroisoquinolines

Pictet–Spengler reaction

Synfact of the Month